

Haemodynamic performance and clinical outcomes of transcatheter aortic valve replacement with the self-expanding ACURATE neo2

Andrea Scotti^{1,2}, MD; Matteo Pagnesi³, MD; Won-Keun Kim⁴, MD; Ulrich Schäfer⁵, MD; Marco Barbanti⁶, MD; Giuliano Costa⁶, MD; Sara Baggio⁷, MD; Matteo Casenghi⁸, MD; Federico De Marco⁸, MD; Maarten Vanhaverbeke⁹, MD, PhD; Lars Sondergaard⁹, MD; Alexander Wolf¹⁰, MD; Joachim Schofer¹¹, MD; Marco Bruno Ancona¹², MD; Matteo Montorfano¹², MD; Ran Kornowski¹³, MD; Hana Vaknin Assa¹³, MD; Stefan Toggweiler¹⁴, MD; Alfonso Ielasi¹⁵, MD; David Hildick-Smith¹⁶, MD; Stephan Windecker¹⁷, MD; Albrecht Schmidt¹⁸, MD; Andrea Buono¹⁹, MD; Diego Maffeo¹⁹, MD; Dimytri Siqueira²⁰, MD; Francesco Giannini²¹, MD; Marianna Adamo³, MD; Mauro Massussi³, MD; David A. Wood²², MD; Jan-Malte Sinning²³, MD; Jan Van der Heyden²⁴, MD; Dirk-Jan van Ginkel²⁵, MD; Nicholas Van Mieghem²⁶, MD; Verena Veulemans²⁷, MD; Darren Mylotte²⁸, MD; Vasileios Tzalamouras²⁹, MD; Maurizio Taramasso³⁰, MD; Rodrigo Estévez-Loureiro³¹, MD, PhD; Antonio Colombo⁷, MD; Antonio Mangieri⁷, MD; Azeem Latib^{1*}, MD; on behalf of the NEOPRO & NEOPRO-2 investigators

The authors' affiliations can be found in the Appendix paragraph.

GUEST EDITOR: Franz-Josef Neumann, MD; Department of Cardiology and Angiology II, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany

This paper also includes supplementary data published online at: <https://eurointervention.pconline.com/doi/10.4244/EIJ-D-22-00289>

KEYWORDS

- aortic stenosis
- atrio-ventricular block
- conduction abnormalities
- TAVR

Abstract

Background: Transcatheter aortic valve replacement (TAVR) with the ACURATE *neo* device has been associated with a non-negligible incidence of paravalvular aortic regurgitation (AR). The new-generation ACURATE *neo2* has been designed to mitigate this limitation.

Aims: The aim of the study was to compare TAVR with the ACURATE *neo* and *neo2* devices.

Methods: The NEOPRO and NEOPRO-2 registries retrospectively included patients undergoing transfemoral TAVR with self-expanding valves at 24 and 20 centres, respectively. Patients receiving the ACURATE *neo* and *neo2* devices (from January 2012 to December 2021) were included in this study. Predischarge and 30-day VARC-3 defined outcomes were evaluated. The primary endpoint was predischarge moderate or severe paravalvular AR. Subgroup analyses per degree of aortic valve calcification were performed.

Results: A total of 2,026 patients (*neo*: 1,263, *neo2*: 763) were included. Predischarge moderate or severe paravalvular AR was less frequent for the *neo2* group (2% vs 5%; $p < 0.001$), resulting in higher VARC-3 intended valve performance (96% vs 90%; $p < 0.001$). Furthermore, more patients receiving the *neo2* had none/trace paravalvular AR (59% vs 38%; $p < 0.001$). The reduction in paravalvular AR with *neo2* was mainly observed with heavy aortic valve calcification. New pacemaker implantation and VARC-3 technical and device success rates were similar between the 2 groups; there were more frequent vascular and bleeding complications for the *neo* device. Similar 1-year survival was detected after TAVR (*neo2*: 90% vs *neo*: 87%; $p = 0.14$).

Conclusions: TAVR with the ACURATE *neo2* device was associated with a lower prevalence of moderate or severe paravalvular AR and more patients with none/trace paravalvular AR. This difference was particularly evident with heavy aortic valve calcification.

*Corresponding author: Section Head, Interventional Cardiology, Montefiore Medical Center/Albert Einstein College of Medicine, 1825 Eastchester Road, Bronx NY 10461, USA. E-mail: alatib@gmail.com

Abbreviations

AR	aortic regurgitation
PPI	permanent pacemaker implantation
TAVR	transcatheter aortic valve replacement
THV	transcatheter heart valve
VARC	Valve Academic Research Consortium

Introduction

Transcatheter aortic valve replacement (TAVR) is an established treatment option for patients with symptomatic severe aortic stenosis^{1,2}. As TAVR candidates are increasingly younger and at lower surgical risk, it has become crucial to minimise potential procedural complications and to provide surgical-like long-term outcomes. Post-procedural moderate or severe paravalvular aortic regurgitation (AR) is a relevant complication after TAVR that has been found to be associated with adverse short- and long-term outcomes³. In the last few years, the first-generation ACURATE *neo* (Boston Scientific) transcatheter heart valve (THV) has emerged as a widely adopted self-expanding device for TAVR, associated with good procedural and clinical outcomes⁴⁻⁹. However, 2 randomised trials have recently reported a higher rate of moderate or severe paravalvular AR with the ACURATE *neo* as compared to other new-generation self-expanding and balloon-expandable THVs^{10,11}. This complication was more frequent with increased device landing zone calcification⁵. For this reason, careful patient selection, proper sizing, and appropriate positioning were proposed to optimise procedural outcomes⁹.

In September 2020, the new-generation ACURATE *neo2* THV was commercially released in Europe. This latest iteration of the ACURATE *neo* platform has been specifically designed to minimise the occurrence of paravalvular AR by utilising a 60% larger sealing skirt. Quantitative aortographic assessments have shown promising results in terms of paravalvular AR reduction with the ACURATE *neo2* device¹². However, no large, real-world data have compared the performance of ACURATE *neo* and *neo2*. With this background, our study aimed to investigate the haemodynamic performance and clinical outcomes after transfemoral TAVR with the ACURATE *neo2* compared to the first-generation ACURATE *neo* THV.

Methods

STUDY POPULATION

The observational, retrospective NEOPRO (A Multicenter Comparison of Acurate NEO Versus Evolut PRO Transcatheter Heart Valves) registry included a total of 1,551 patients who underwent transfemoral TAVR with either ACURATE *neo* (n=1,263) or Evolut PRO (n=288; Medtronic) devices between January 2012 and March 2018 at 24 centres⁴. The NEOPRO-2 registry was designed to expand the previous registry to include procedures performed with the new-generation ACURATE *neo2* (n=763) and Evolut PRO or PRO+ (n=1,412) devices up to December 2021 at 20 centres. All consecutive patients treated with transfemoral TAVR for symptomatic, severe aortic stenosis of the native

aortic valve (AV) with the implantation of the aforementioned self-expanding devices were included in the registries. For the purposes of the present study, only patients treated with ACURATE *neo* or *neo2* THVs were analysed. The number of patients included from each participating centre is detailed in **Supplementary Table 1**. The treatment period was from January 2012 to March 2018 for the *neo* THV and from September 2020 to December 2021 for the *neo2* device. Data obtained from 29 participating centres were included in the present analysis: 18 centres implanting the ACURATE *neo* (NEOPRO) and 16 centres using the *neo2* device (NEOPRO-2). Local multidisciplinary Heart Teams evaluated each case and confirmed eligibility for transfemoral TAVR. All patients provided written informed consent for the procedure and subsequent data collection per local practice for retrospective data. The study complied with the Declaration of Helsinki and was approved by local ethics committees. Preprocedural screening was performed by means of clinical assessment (patient demographics, symptoms, comorbidities, laboratory examinations, and risk evaluation), echocardiography and multidetector computed tomography.

DEVICE DESCRIPTION

The ACURATE *neo2* bioprosthesis is a self-expanding THV with a supra-annular leaflet design. Three sizes are currently available (small, medium, and large) and correspond to annular diameters of 21-23, 23-25, and 25-27 mm, respectively. The *neo2* THV is implanted using a dedicated transfemoral delivery system inserted through a 14 Fr expandable sheath (iSleeve [Boston Scientific]). The deployment is performed in a top-down sequence, starting with the release of the stabilisation arches, and does not require rapid pacing. The self-expanding nitinol frame is wrapped with a pericardial sealing skirt on the outer and inner surface of the stent body that extends 60% higher from the inflow part of the stent frame as compared to the first-generation ACURATE *neo*. The skirt's extended dimensions have the potential of providing a more synchronous adaptation to the native aortic annulus during the different phases of the cardiac cycle, especially in irregular and calcified anatomies. Furthermore, a radiopaque marker has been added to the delivery system to navigate accurate positioning of the THV at the aortic annulus.

STUDY ENDPOINTS AND DEFINITIONS

The primary study endpoint was the occurrence of moderate or severe paravalvular AR at predischarge transthoracic echocardiography. Secondary endpoints were Valve Academic Research Consortium (VARC)-3 defined clinical outcomes at 30 days¹³, including the need for permanent pacemaker implantation (PPI), and 1-year overall survival.

Paravalvular AR severity was assessed with Doppler echocardiography according to VARC-3 criteria and classified as follows: none or trace, mild, moderate, and severe¹³. Native aortic valve and left ventricular outflow tract calcifications from multidetector computed tomography scans were classified and graded using a semiquantitative scoring system, as previously described^{6,14}.

STATISTICAL ANALYSIS

Continuous variables are reported as mean±standard deviation or median (interquartile range [IQR]) and compared with the Student's unpaired t-test (parametric test) or the Wilcoxon rank-sum test (non-parametric test), according to their distribution. Categorical variables were reported as absolute and relative frequencies and compared with the χ^2 test with Yates' correction for continuity or Fisher's exact test, as appropriate. Survival curves with their 95% confidence interval (CI) were plotted using the Kaplan-Meier estimator and compared with the log-rank test. A subgroup analysis testing the primary and secondary endpoints across different degrees of aortic valve calcification was also performed. For all analyses, a two-sided p-value <0.05 was considered to be significant. Statistical analyses were performed using R, version 4.0.2 (R Foundation).

Results

BASELINE PATIENT CHARACTERISTICS

A total of 2,026 patients in the NEOPRO and NEOPRO-2 registries underwent transfemoral TAVR with the self-expanding ACURATE *neo* or *neo2* THVs and were included in this study. Of these, 1,263 patients received the first-generation ACURATE *neo*, whereas 763 were treated using the new ACURATE *neo2* device. Baseline characteristics of the study population are reported in **Table 1**. The mean age was 82.0±5.8 years, and 66% of patients were women. Patients treated with the ACURATE *neo* were more frequently in New York Heart Association (NYHA) Functional Class III or IV (78% vs 55%; p<0.001), and were deemed at higher surgical risk (STS score: 4.1 [IQR 2.9-6.1] vs 3.5 [IQR 2.5-5.0], EuroSCORE II: 4.4 [IQR 2.7-7.2] vs 3.1 [IQR 2.1-5.1]; p<0.001). Patients receiving the ACURATE *neo2* were characterised by smaller anatomies of the aortic valve (area and perimeter) and of the TAVR femoral access (minimal diameter: 7.14±1.13 vs 7.95±1.37; p<0.001). The severity of aortic valve calcification was higher in the *neo* group, whereas mild and moderate left ventricular outflow tract calcifications were more frequent in *neo2* patients.

PROCEDURAL RESULTS

Procedural characteristics are depicted in **Table 2**. Valve sizes were equally distributed within the 2 groups. Implantation of the *neo* THV was more frequently performed under general anaesthesia (13% vs 1%; p<0.001) and completed with final post-dilatation (42% vs 31%; p<0.001). The prevalence of procedural complications (namely: death, valve embolisation, the need for a second THV, annular rupture, pericardial tamponade, aortic dissection, coronary occlusion, and conversion to open-heart surgery) was low with no differences between the *neo* and *neo2* groups.

CLINICAL OUTCOMES

Clinical outcomes assessed at 30 days post-TAVR are shown in **Table 3** and the **Central illustration**. VARC-3 defined technical (*neo*: 91% vs *neo2*: 93%; p=0.117) and device success (*neo*: 81% vs *neo2*: 84%; p=0.119) were similar in the 2 groups. The

Table 1. Baseline characteristics.

	Total (2,026)	ACURATE <i>neo</i> (1,263)	ACURATE <i>neo2</i> (763)	p-value
Clinical characteristics				
Age, years	82±5.8	82±5.8	82±5.9	0.822
Male	694 (34)	444 (35)	250 (33)	0.303
BMI	27±5	27±5	27±5	0.281
BSA	1.82±0.21	1.82±0.21	1.82±0.22	0.314
Hypertension	1,726 (87)	1,079 (88)	647 (85)	0.055
Diabetes mellitus	598 (30)	379 (30)	219 (29)	0.571
Atrial fibrillation	648 (32)	408 (33)	240 (32)	0.772
Previous stroke	209 (10)	126 (10)	83 (11)	0.719
Peripheral vascular disease	271 (13)	156 (12)	115 (15)	0.093
Previous myocardial infarction	220 (11)	138 (12)	82 (11)	0.689
Previous PCI	582 (29)	370 (29)	212 (28)	0.496
Previous CABG	194 (10)	147 (12)	47 (6)	<0.001
COPD	369 (18)	244 (19)	125 (16)	0.114
eGFR, ml/min/1.73m ²	60±25	58±22	64±29	<0.001
Prior PM/ICD	219 (11)	158 (12)	61 (8)	0.002
NYHA Class III/IV	1,397 (69)	981 (78)	416 (55)	<0.001
EuroSCORE II	3.9 [2.5-6.6]	4.4 [2.7-7.2]	3.1 [2.1-5.1]	<0.001
STS score (mortality)	4.0 [2.8-5.8]	4.1 [2.9-6.1]	3.5 [2.5-5.0]	<0.001
Echocardiographic data				
Mean aortic gradient, mmHg	44±16	43±17	45±14	0.057
AVA, cm ²	0.71±0.22	0.71±0.19	0.71±0.26	0.523
Indexed AVA, cm ² /m ²	0.39±0.10	0.39±0.11	0.39±0.09	0.891
LVEF, %	57±11	57±12	58±10	0.032
CT analysis				
Aortic valve area, mm ²	429±64	432±67	424±59	0.015
Aortic valve perimeter, mm	74±6	75±6	74±5	<0.001
Aortic valve calcification	None or mild	470 (29)	286 (29)	0.02
	Moderate	739 (46)	428 (44)	
	Heavy	396 (25)	263 (27)	
LVOT calcification	None	693 (53)	541 (56)	0.01
	Mild	379 (29)	265 (27)	
	Moderate	152 (12)	107 (11)	
	Severe	78 (6)	62 (6)	
Femoral access*, mm	7.78±1.36	7.95±1.37	7.14±1.13	<0.001

*Minimal lumen diameter of the femoral artery used to deliver the valve. Values are n (%), mean±standard deviation, or median [interquartile range]. AVA: aortic valve area; BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; CT: computed tomography; eGFR: estimated glomerular filtration rate; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PM: pacemaker; STS: Society of Thoracic Surgeons

VARC-3 defined intended performance of the valve was more frequently met in the *neo2* group (96% vs 90%; p<0.001). This result was mainly driven by a lower rate of moderate or severe paravalvular AR in the *neo2* group (2% vs 5%; p<0.001). The prevalence of none/trace paravalvular AR was significantly higher

Table 2. Procedural characteristics.

		Total (2,026)	ACURATE <i>neo</i> (1,263)	ACURATE <i>neo2</i> (763)	<i>p</i> -value
Valve size, mm	23	533 (26)	348 (28)	185 (24)	0.255
	25	847 (42)	520 (41)	327 (43)	
	27	645 (32)	394 (31)	251 (33)	
General anaesthesia		175 (9)	168 (13)	7 (1)	<0.001
Predilatation		1,706 (84)	1,051 (83)	655 (86)	0.141
Post-dilatation		759 (38)	526 (42)	233 (31)	<0.001
Death		2 (0.3)	0 (0.0)	2 (0.3)	1.000
Valve embolisation		21 (1)	13 (1)	8 (1)	1.000
Second THV implanted		20 (1)	14 (1)	6 (1)	0.634
Annular rupture		5 (0.2)	4 (0.3)	1 (0.1)	0.656
Pericardial tamponade		27 (1)	20 (2)	7 (1)	0.286
Aortic dissection		1 (0.0)	1 (0.1)	0 (0.0)	1.000
Coronary occlusion		4 (0.2)	2 (0.2)	2 (0.3)	1.000
Conversion to open-heart surgery		16 (1.0)	13 (1.0)	3 (0.4)	0.191

Values are expressed as n (%). THV: transcatheter heart valve

after TAVR with the *neo2* THV (59% vs 38%; $p<0.001$). Slightly increased mean aortic gradients were found in the *neo2* group (*neo*: 8.0 ± 3.3 mmHg vs *neo2*: 8.9 ± 4.1 mmHg; $p<0.001$), and no

differences were found in terms of aortic valve area. The need for a new PPI was similar in the 2 groups (*neo*: 9% vs *neo2*: 8%; $p=0.46$). Patients receiving the *neo2* THV experienced fewer vascular ($p<0.001$) and bleeding ($p=0.020$) complications.

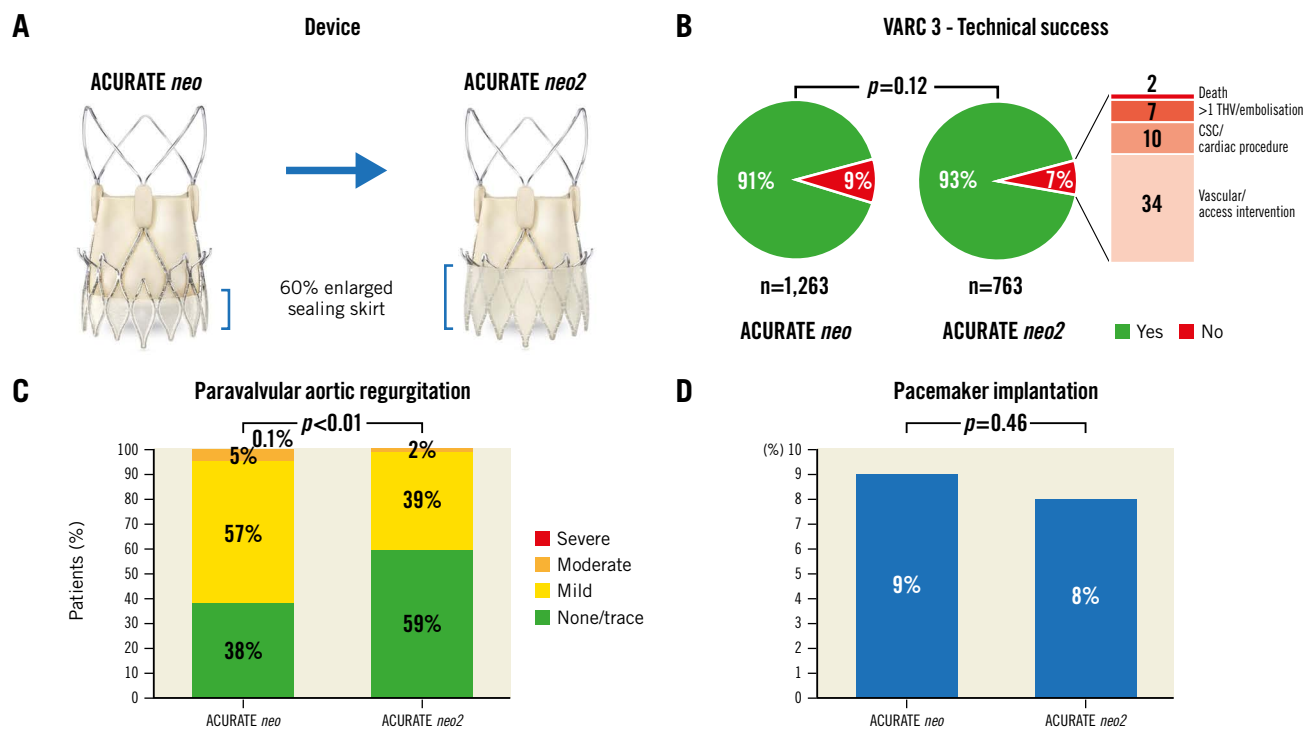
Patients were followed up for a median time of 83 [IQR 30-261] days. As shown in the Kaplan-Meier analysis (**Figure 1**), all-cause mortality at 1-year follow-up was not significantly different between the *neo2* and *neo* groups (90%, 95% CI: 83-98 vs 87%, 95% CI: 84-90; $p=0.14$).

SUBGROUP ANALYSIS ON AORTIC VALVE CALCIFICATION SEVERITY

As shown in **Table 4**, clinical outcomes were further analysed stratifying the overall population for baseline aortic valve calcification grades (none or mild, moderate, and heavy). The significant reduction of moderate or severe paravalvular AR in the *neo2* group was observed in the subgroup of patients with heavy aortic valve calcification (2% vs 9%; $p=0.018$); consequently, VARC-3 intended performance of the valve was more frequently met among patients receiving *neo2* THV in the heavy aortic valve calcification subgroup (97% vs 88%; $p=0.005$). No significant differences were observed for these 2 endpoints between the *neo* and *neo2* groups in the other calcification subgroups (**Table 4**).

EuroIntervention

CENTRAL ILLUSTRATION Comparison of the ACURATE *neo* and the ACURATE *neo2* THVs.



A) Device characteristics, B) VARC-3 technical success, C) predischARGE paravalvular aortic regurgitation, and D) the need for permanent pacemaker implantation after transcatheter aortic valve replacement. Device illustrations reproduced with permission from Boston Scientific. CSC: cardiac structural complication; THV: transcatheter heart valve; VARC: Valve Academic Research Consortium

Table 3. 30-day outcomes.

		Total (2,026)	ACURATE <i>neo</i> (1,263)	ACURATE <i>neo2</i> (763)	p-value
All-cause death		61 (3)	39 (3)	22 (3)	0.903
VARC 3 – technical success		1,859 (92)	1,149 (91)	710 (93)	0.117
VARC 3 – device success		1,630 (82)	1,024 (81)	606 (84)	0.119
VARC 3 – intended performance		1,286 (93)	572 (90)	714 (96)	<0.001
PM implantation		147 (8)	96 (9)	51 (8)	0.460
Acute kidney injury (stage 2-3)		58 (3)	37 (3)	21 (3)	0.953
Vascular complications	None	1,700 (87)	1,032 (83)	668 (94)	<0.001
	Minor	156 (8)	138 (11)	18 (2)	
	Major	98 (5)	75 (6)	23 (3)	
Bleeding complications	None	1,638 (86)	1,011 (85)	627 (88)	0.020
	Type 1	104 (6)	65 (6)	39 (6)	
	Type 2	79 (4)	56 (5)	23 (3)	
	Type 3	74 (4)	56 (5)	18 (2)	
	Type 4	2 (0.1)	0 (0.0)	2 (0.3)	
Mean aortic gradient, mmHg		8.5±3.8	8±3.3	8.9±4.1	<0.001
AVA, cm ²		1.8±0.4	1.8±0.4	1.8±0.4	0.826
Indexed AVA, cm ² /m ²		0.96±0.20	0.96±0.20	0.96±0.20	0.769
Moderate or severe paravalvular AR*		75 (4)	62 (5)	13 (2)	<0.001

*Predischarge assessment. Values are n (%) or mean±standard deviation. AR: aortic regurgitation; AVA: aortic valve area; PM: pacemaker; VARC: Valve Academy Research Consortium

All the remaining clinical outcomes were consistent with the primary analysis with no significant differences between both groups across all aortic valve calcification subgroups. In detail, the rates of new PPI were similar between *neo* and *neo2* THVs in each subgroup (none/mild: 9% vs 7%, moderate: 10% vs 9%, heavy: 8% vs 6%; all p-values >0.05, p for interaction=0.982).

Discussion

The main findings of our multicentre, observational, real-world comparison between ACURATE *neo* and *neo2* devices in a total of 2,026 patients undergoing transfemoral TAVR (from the

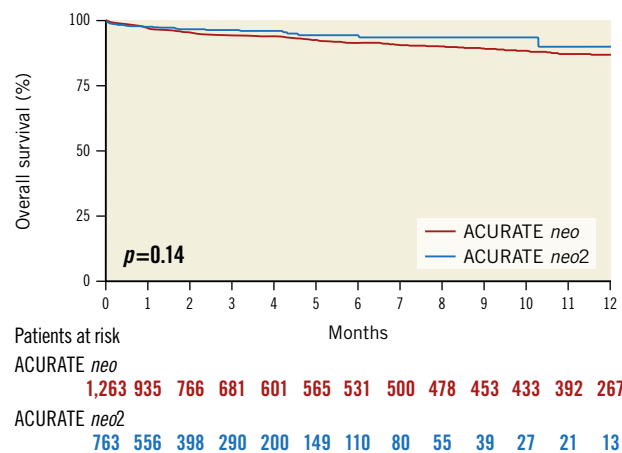


Figure 1. Kaplan-Meier analysis of overall survival in ACURATE *neo* vs ACURATE *neo2* transcatheter aortic valves.

NEOPRO/NEOPRO-2 registries) are as follows: 1) the latest-generation ACURATE *neo2* THV was associated with a significant reduction in post-procedural moderate or severe paravalvular AR as compared to the first-generation *neo* THV; 2) a similar need for new PPI was observed between *neo2* and *neo* devices; 3) the superior performance of the ACURATE *neo2* THV was particularly evident in severely calcified aortic valve anatomies; 4) TAVR with the ACURATE *neo2* in combination with the expandable iSleeve is associated with reduced rates of vascular complications.

In our study, procedural outcomes after ACURATE *neo2* THV implantation suggest acceptable safety and efficacy with rates of 3% for 30-day mortality, 93% for VARC-3 technical success, 84% for VARC-3 device success, and 96% for VARC-3 intended performance of the valve. These results compare favourably with available evidence on the first-generation *neo* device reporting an equal 30-day mortality rate (3%) and similar rates of procedural complications^{5,10,11}. Interestingly, we observed fewer vascular and bleeding complications in the *neo2* group as compared to the *neo* group. It must be acknowledged that all the procedures were transfemoral

Table 4. 30-day outcomes stratified per aortic valve calcification grade.

	None or mild calcification			Moderate calcification			Heavy calcification			p-value for interaction
	ACURATE <i>neo</i> (286)	ACURATE <i>neo2</i> (184)	p-value	ACURATE <i>neo</i> (428)	ACURATE <i>neo2</i> (311)	p-value	ACURATE <i>neo</i> (263)	ACURATE <i>neo2</i> (133)	p-value	
All-cause death	9 (3)	6 (3)	1.000	11 (3)	9 (3)	0.962	9 (4)	0 (0)	0.070	0.418
VARC 3 – technical success	250 (87)	167 (91)	0.332	390 (91)	287 (92)	0.669	240 (91)	128 (96)	0.105	0.404
VARC 3 – device success	229 (80)	150 (84)	0.311	346 (81)	244 (83)	0.524	203 (78)	100 (85)	0.172	0.691
VARC 3 – intended performance	262 (97)	178 (97)	0.937	377 (93)	293 (95)	0.298	214 (88)	127 (97)	0.005	0.899
PM implantation	21 (9)	11 (7)	0.605	40 (10)	23 (9)	0.535	17 (8)	6 (6)	0.705	0.982
Mean aortic gradient, mmHg	7.6±3.4	8.5±4.2	0.023	8.0±3.2	9.0±4.1	0.001	8.2±3.6	8.9±3.9	0.023	0.141
AVA, cm ²	1.7±0.4	1.7±0.4	0.867	1.7±0.4	1.7±0.4	0.731	1.8±0.4	1.9±0.4	0.867	0.135
Indexed AVA, cm ² /m ²	0.96±0.20	0.96±0.20	0.979	0.93±0.20	0.94±0.20	0.589	0.96±0.20	1.0±0.2	0.979	0.208
Moderate or severe paravalvular AR*	6 (2)	1 (0.5)	0.317	21 (5)	7 (2)	0.077	23 (9)	3 (2)	0.018	0.671

*Predischarge assessment. Values are n (%) or mean±standard deviation. AR: aortic regurgitation; AVA: aortic valve area; PM: pacemaker; VARC: Valve Academic Research Consortium

with smaller accesses for *neo2* recipients (minimal lumen diameter 7.14 ± 1.13 vs 7.95 ± 1.37 ; $p<0.001$), similar baseline patient characteristics (age: 82 ± 6 years, atrial fibrillation: 33% vs 32%, peripheral vascular disease: 12% vs 15%), and lower surgical risk scores for the *neo2* group, in accordance with TAVR indication expanding to lower-risk patients over time. Even if speculative, the fewer bleeding and vascular complications observed with the implantation of the *neo2* THV may be explained by a combination of the redesigned expandable introducer with a low-profile (iSleeve; Boston Scientific), increased operator experience with the ACURATE system, and improved vascular access/complication management.

The only VARC-3 defined outcome that was significantly different between the *neo* and *neo2* devices was the intended performance of the valve (*neo2*: 96% vs *neo*: 90%; $p<0.001$). This composite endpoint is achieved with a mean transvalvular gradient <20 mmHg, peak velocity <3 m/s, Doppler velocity index ≥ 0.25 , and less than moderate AR¹³. The improved performance of the *neo2* THV was driven by a reduction in moderate or severe paravalvular AR compared to the first-generation *neo* THV. In the overall population, the 5% rate of moderate or severe paravalvular AR that occurred after the ACURATE *neo* implantation was significantly higher than the 2% rate observed with the *neo2* THV ($p<0.001$). The rate of paravalvular AR in our *neo* group (5%) is lower than those reported by the randomised SCOPE 1 (9.4%) and SCOPE 2 (9.6%) trials^{10,11}. This finding may be explained by differences in outcome adjudication (core lab vs centre-reported) and baseline patient characteristics. Although these trials excluded severe eccentric aortic valve calcifications, they did not report the degrees of overall calcifications which have been demonstrated by Kim et al as having a significant impact on moderate or severe paravalvular AR rates (mild: 0.8%, moderate: 5%, severe: 13%)⁵. Accordingly, our subgroup analysis reported a similarly increasing trend for paravalvular AR in the *neo* group, starting from 2% for none/mild aortic valve calcifications, up to 5% for moderate and 9% for heavy calcifications. On the contrary, the rate of moderate or severe paravalvular AR after TAVR with the *neo2* THV was consistent among these 3 calcification subgroups (none/mild: 0.5%, moderate: 2%, heavy: 2%). Similar rates of moderate or severe paravalvular AR (1.7-2.5%) were reported in other exploratory analyses evaluating TAVR with the ACURATE *neo2* device^{12,15}. Furthermore, 59% of patients treated with the new-generation *neo2* device showed none/trace paravalvular AR after TAVR, which is significantly higher than the 38% obtained with the *neo* THV ($p<0.001$). This finding also compares favourably with the frequency of none/trace paravalvular AR observed after *neo* implantation in the SCOPE 1 (40%) and SCOPE 2 trials^{10,11}. These results are promising as they demonstrate how the engineering refinements translate into better performance of the ACURATE *neo2* THV. Moreover, they indicate that the caveat of avoiding patients with severe aortic calcifications may no longer be appropriate for the ACURATE *neo2* system⁹. Pending further supporting evidence, it seems that this new-generation device can provide favourable performance with a low rate of significant paravalvular AR, even in the more challenging calcific anatomies. The observed gradient with *neo2* in

our population (8.9 ± 4.1 mmHg) is similar to the one reported in patients with small annuli included in the TAVI-SMALL registry and receiving the *neo* device (9.6 ± 0.3 mmHg)¹⁶. An inverse correlation between annular dimensions and post-procedural gradients has been previously demonstrated with better haemodynamic performance of self-expanding supra-annular THVs in this anatomical setting^{17,18}.

Another relevant clinical outcome after TAVR is represented by the need for new PPI. Previous studies investigating the ACURATE *neo* system reported a 10-11% rate of PPI^{5,10,11}, which was found to be independent of device landing zone calcification⁵. Our analysis confirms these findings for the *neo2* THV, showing a rate of new PPI equal to 8% with no significant differences across the aortic valve calcification subgroups. These results are even more meaningful when compared with the 17-18% of PPI after TAVR with the self-expanding CoreValve Evolut platform (Medtronic)^{10,19}. A stable and precise (less protrusion in the left ventricular outflow tract) valve implantation with top-down deployment and radiopaque positioning markers, a moderate device radial force, and the temporal shift from the left anterior oblique to cusp overlap view for the THV implantation are the technical factors explaining this relatively low PPI rate. Keeping this figure as low as possible has a great clinical value and may be used to guide device selection in patients at high risk of permanent conduction disturbances after TAVR²⁰.

At 1-year follow-up, we did not observe a significant difference in all-cause mortality between the *neo2* and *neo* groups (10% vs 13%; $p=0.14$). The 1-year mortality rate observed in this real-world experience with ACURATE *neo* is in line with rates recently reported by the randomised SCOPE 1 (11%) and SCOPE 2 (13%) trials^{10,11}. Given the prognostic impact of moderate or severe paravalvular AR³ and its significant reduction using the ACURATE *neo2*, further analyses with larger sample sizes and longer follow-up are eagerly awaited to better explore long-term outcomes after TAVR with this new self-expanding platform.

Limitations

The main limitation of this study is related to its retrospective observational design, with no core laboratory analysis of procedural results and echocardiographic readings or independent adjudication of clinical events. The investigated THVs were implanted in consecutive time periods, and unmeasured confounding factors (e.g., operator experience, valve preference) may have affected the presented results. The use of multiple different sheaths with the ACURATE *neo* may be a major contributor to the differences in peripheral vascular characteristics compared to the *neo2*, which was implanted through a redesigned expandable introducer with a low-profile (iSleeve; Boston Scientific). Given the recent release of the ACURATE *neo2* device (September 2020), available follow-up time is currently limited, and future studies will be needed to assess if lower paravalvular AR is sustained over time and how it impacts on long-term clinical outcomes. Whilst waiting for the results of ongoing registries (Early *neo2* Registry of the Acurate *neo2* TAVI Prosthesis [ClinicalTrials.gov: NCT04810195]) and randomised controlled trials (ACURATE IDE: Safety and Efficacy

Study of Acurate Valve for Transcatheter Aortic Valve Replacement [ClinicalTrials.gov: NCT03735667]), these exploratory analyses can provide immediate assistance in THV selection for TAVR.

Conclusions

The latest-generation ACURATE *neo2* THV is associated with a lower rate of moderate or severe paravalvular AR, when compared to the first-generation ACURATE *neo*, in patients undergoing transfemoral TAVR. As a result, a greater percentage of patients receiving the *neo2* THV have none/trace paravalvular AR. The superior performance of the *neo2* device is particularly evident among patients with heavy aortic valve calcification.

Impact on daily practice

TAVR with the ACURATE *neo* THV was associated with a non-negligible rate of moderate or severe paravalvular AR, which is known to have an adverse prognostic impact. TAVR with the ACURATE *neo2* device is associated with a lower rate of moderate or severe paravalvular AR when compared with the first-generation ACURATE *neo*. The superior performance of the *neo2* device is particularly evident among patients with heavy aortic valve calcification. Further studies with larger sample sizes and longer follow-up are needed to confirm these preliminary findings.

Appendix. Authors' affiliations

1. Montefiore Einstein Center for Heart and Vascular Care, Montefiore Medical Center; Albert Einstein College of Medicine, Bronx, NY, USA; 2. Cardiovascular Research Foundation, New York, NY, USA; 3. ASST Spedali Civili di Brescia and Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; 4. Department of Cardiology and Cardiac Surgery, Kerckhoff Heart and Lung Center, Bad Nauheim, Germany; 5. Department of Cardiology, University Heart & Vascular Center, Hamburg, Germany; 6. Department of Cardiology, C.A.S.T. Policlinic G. Rodolico Hospital, University of Catania, Catania, Italy; 7. Cardio Center, Humanitas Research Hospital, Rozzano-Milan, Italy; 8. Department of Cardiology, IRCCS Policlinico San Donato, Milan, Italy; 9. The Heart Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; 10. Contilia Heart and Vascular Centre, Elisabeth-Krankenhaus Essen, Essen, Germany; 11. Department for Percutaneous Treatment of Structural Heart Disease, Albertinen Heart Center, Hamburg, Germany; 12. Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Milan, Italy; 13. Department of Cardiology, Rabin Medical Center-Beilinson Hospital, Petah Tikva, Israel; 14. Department of Cardiology, Heart Center Lucerne, Luzerner Kantonsspital, Lucerne, Switzerland; 15. Clinical and Interventional Cardiology Unit, Istituto Clinico Sant'Ambrogio, Milan, Italy; 16. Department of Cardiology, Royal Sussex County Hospital, Brighton, UK; 17. Department of Cardiology, Inselspital, Bern University Hospital, University of Bern,

Bern, Switzerland; 18. Division of Cardiology, Medical University of Graz, Graz, Austria; 19. Interventional Cardiology Unit, Fondazione Poliambulanza, Brescia, Italy; 20. Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil; 21. GVM Care and Research, Maria Cecilia Hospital, Cotignola, Italy; 22. Centre for Heart Valve Innovation, St. Paul's and Vancouver General Hospital, Vancouver, BC, Canada; 23. Department of Cardiology, Heart Center Bonn, University Hospital Bonn, Bonn, Germany; 24. Sint-Jan Hospital, Bruges, Belgium; 25. Department of Cardiology, St Antonius Hospital, Nieuwegein, the Netherlands; 26. Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands; 27. Division of Cardiology, Pulmonology, and Vascular Medicine, University Hospital Düsseldorf, Düsseldorf, Germany; 28. Department of Cardiology, Galway University Hospital, Galway, Ireland; 29. Cardiology, King's College Hospital, London, UK; 30. Division of Cardiothoracic Surgery, Arzt bei HerzZentrum Hirslanden Zürich, Zürich, Switzerland; 31. Cardiology Department, University Hospital Alvaro Cunqueiro, Galicia Sur Health Research Institute, Vigo, Spain

Guest editor

This paper was guest edited by Franz-Josef Neumann, MD, Department of Cardiology and Angiology II, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany.

Conflict of interest statement

A. Latib has served on advisory boards or as a consultant for Medtronic, Boston Scientific, Philips, Edwards Lifesciences, and Abbott. W-K. Kim is a proctor for Boston Scientific and Abbott Vascular; and has received speaker fees from Edwards Lifesciences. U. Schäfer is proctor for Boston Scientific and Medtronic and has received lecture fees and travel support from both companies. M. Barbanti has served as a consultant for Edwards Lifesciences. D. Hildick-Smith is an advisor and a proctor for Boston Scientific, Symetis, and Medtronic. A. Wolf is a proctor for Medtronic and Boston Scientific. N. Van Mieghem has received research grant support from Boston Scientific, Abbott Vascular, Medtronic, Claret, and Essential Medical. S. Toggweiler is a consultant and proctor for Boston Scientific, Medtronic, Abbott, and Biosensors; is a consultant for Medira, Atheart Medical, Veosource, Shockwave, and Teleflex; has received institutional research grants from Boston Scientific and Fumedica AG; and holds equity in Hi-D Imaging. D. Mylotte is a proctor for Medtronic and Microport. V. Veulemans has received lecture fees and travel support from Medtronic and Edwards Lifesciences. S. Windecker has received grants from Abbott Vascular, Biotronik, Boston Scientific, Edwards Lifesciences, and Medtronic. D. Siqueira is proctor for Medtronic, Symetis, and Edwards Lifesciences. M. Adamo reports speaker honoraria from Abbott Vascular and Medtronic. J-M. Sinning is a proctor for Medtronic and Boston Scientific; and has received speaking honoraria and research grants from Medtronic, Edwards Lifesciences, and Boston Scientific. D.A. Wood has received grant support from Boston Scientific; and is a consultant for Medtronic. L. Sondergaard has received consultant

fees and institutional research grants from Boston Scientific. The other authors have no conflicts of interest to declare. 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.

References

- Writing Committee Members, Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:e25-197.
- Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Haugaa KH, Jeppsson A, Juni P, Pierard L, Prendergast BD, Sadaba JR, Tribouilloy C, Wojakowski W. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *EuroIntervention*. 2022;17:e1126-96.
- Athappan G, Patvardhan E, Tuzcu EM, Svensson LG, Lemos PA, Fraccaro C, Tarantini G, Sinning JM, Nickenig G, Capodanno D, Tamburino C, Latib A, Colombo A, Kapadia SR. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. *J Am Coll Cardiol*. 2013;61:1585-95.
- Pagnesi M, Kim WK, Conradi L, Barbanti M, Stefanini GG, Zeus T, Pilgrim T, Schofer J, Zweiker D, Testa L, Taramasso M, Hildick-Smith D, Abizaid A, Wolf A, Van Mieghem NM, Sedaghat A, Wöhrle J, Khogali S, Van der Heyden JAS, Webb JG, Estévez-Loureiro R, Mylotte D, MacCarthy P, Brugaletta S, Hamm CW, Bhadra OD, Schäfer U, Costa G, Tamburino C, Cannata F, Reimers B, Veulemans V, Asami M, Windecker S, Eitan A, Schmidt A, Bianchi G, Bedogni F, Saccocci M, Maisano F, Alsanjari O, Siqueira D, Jensen CJ, Naber CK, Ziviello F, Sinning JM, Seeger J, Rottbauer W, Brouwer J, Alenezi A, Wood DA, Tzalamouras V, Regueiro A, Colombo A, Latib A. Transcatheter Aortic Valve Replacement With Next-Generation Self-Expanding Devices: A Multicenter, Retrospective, Propensity-Matched Comparison of Evolut PRO Versus Acurate neo Transcatheter Heart Valves. *JACC Cardiovasc Interv*. 2019;12:433-43.
- Kim WK, Möllmann H, Liebetau C, Renker M, Rolf A, Simon P, Van Linden A, Arsalan M, Doss M, Hamm CW, Walther T. The ACURATE neo Transcatheter Heart Valve: A Comprehensive Analysis of Predictors of Procedural Outcome. *JACC Cardiovasc Interv*. 2018;11:1721-9.
- Pagnesi M, Kim WK, Conradi L, Barbanti M, Stefanini GG, Schofer J, Hildick-Smith D, Pilgrim T, Abizaid A, Zweiker D, Testa L, Taramasso M, Wolf A, Webb JG, Sedaghat A, Van der Heyden JAS, Ziviello F, MacCarthy P, Hamm CW, Bhadra OD, Schäfer U, Costa G, Tamburino C, Cannata F, Reimers B, Eitan A, Alsanjari O, Asami M, Windecker S, Siqueira D, Schmidt A, Bianchi G, Bedogni F, Saccocci M, Maisano F, Jensen CJ, Naber CK, Alenezi A, Wood DA, Sinning JM, Brouwer J, Tzalamouras V, Van Mieghem NM, Colombo A, Latib A. Impact of Predilatation Prior to Transcatheter Aortic Valve Implantation With the Self-Expanding Acurate neo Device (from the Multicenter NEOPRO Registry). *Am J Cardiol*. 2020;125:1369-77.
- Mangieri A, Chieffo A, Kim WK, Stefanini GG, Rescigno G, Barbanti M, Tamburino C, Rück A, Pagnesi M, Linder R, Toggweiler S, Montorfano M, Colombo A. Transcatheter aortic valve implantation using the ACURATE neo in bicuspid and tricuspid aortic valve stenosis: a propensity-matched analysis of a European experience. *EuroIntervention*. 2018;14:e1269-75.
- Kim WK, Hengstenberg C, Hilker M, Kerber S, Schäfer U, Rudolph T, Linke A, Franz N, Kuntze T, Nef H, Kappert U, Zembala MO, Toggweiler S, Walther T, Möllmann H. The SAVI-TF Registry: 1-Year Outcomes of the European Post-Market Registry Using the ACURATE neo Transcatheter Heart Valve Under Real-World Conditions in 1,000 Patients. *JACC Cardiovasc Interv*. 2018;11:1368-74.
- Kim WK, Hengstenberg C, Hilker M, Schäfer U, Rudolph TK, Toggweiler S, Rück A, Sondergaard L, Conradi L, Hamm C, Walther T, Möllmann H; Collaborators. Transcatheter aortic valve implantation with the ACURATE neo valve: Indications, procedural aspects and clinical outcomes. *EuroIntervention*. 2020;15:e1571-9.
- Tamburino C, Bleiziffer S, Thiele H, Scholtz S, Hildick-Smith D, Cunningham M, Wolf A, Barbanti M, Tchetché D, Garot P, Pagnotta P, Gilard M, Bedogni F, Van Belle E, Vasa-Nicotera M, Chieffo A, Deutsch O, Kempfert J, Sondergaard L, Butter C, Trillo-Nouche R, Lotfi S, Möllmann H, Joner M, Abdel-Wahab M, Bogaerts K, Hengstenberg C, Capodanno D. Comparison of Self-Expanding Bioprostheses for Transcatheter Aortic Valve Replacement in Patients With Symptomatic Severe Aortic Stenosis: SCOPE 2 Randomized Clinical Trial. *Circulation*. 2020;142:2431-42.
- Lanz J, Kim WK, Walther T, Burgdorf C, Möllmann H, Linke A, Redwood S, Thilo C, Hilker M, Joner M, Thiele H, Conzelmann L, Conradi L, Kerber S, Schymik G, Prendergast B, Husser O, Stortecky S, Heg D, Juni P, Windecker S, Pilgrim T; SCOPE I investigators. Safety and efficacy of a self-expanding versus a balloon-expandable bioprosthesis for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: a randomised non-inferiority trial. *Lancet*. 2019;394:1619-28.
- Rück A, Kim WK, Kawashima H, Abdelshafy M, Elkoumy A, Elzomor H, Wang R, Meduri CU, Verouhis D, Saleh N, Onuma Y, Mylotte D, Serruys PW, Soliman O. Paravalvular aortic regurgitation severity assessed by quantitative aortography: ACURATE neo2 versus ACURATE neo Transcatheter Aortic Valve Implantation. *J Clin Med*. 2021;10:4627.
- VARC-3 WRITING COMMITTEE, Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, Bax JJ, Leipsic JA, Blanke P, Blackstone EH, Finn MT, Kapadia S, Linke A, Mack MJ, Makkar R, Mehran R, Popma JJ, Reardon M, Rodes-Cabau J, Van Mieghem NM, Webb JG, Cohen DJ, Leon MB. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. *J Am Coll Cardiol*. 2021;77:2717-46.
- Barbanti M, Yang TH, Rodés Cabau J, Tamburino C, Wood DA, Jilaihawi H, Blanke P, Makkar RR, Latib A, Colombo A, Tarantini G, Raju R, Binder RK, Nguyen G, Freeman M, Ribeiro HB, Kapadia S, Min J, Feuchter G, Gurtvich R, Alqoofi F, Pelletier M, Ussia GP, Napodano M, De Brito FS Jr, Kodali S, Norgaard BL, Hansson NC, Pache G, Canovas SJ, Zhang H, Leon MB, Webb JG, Leipsic J. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. *Circulation*. 2013;128:244-53.
- Möllmann H, Holzhey DM, Hilker M, Toggweiler S, Schäfer U, Treede H, Joner M, Sondergaard L, Christen T, Allocco DJ, Kim WK. The ACURATE neo2 valve system for transcatheter aortic valve implantation: 30-day and 1-year outcomes. *Clin Res Cardiol*. 2021;110:1912-20.
- Regazzoli D, Chiarito M, Cannata F, Pagnesi M, Miura M, Ziviello F, Picci A, Reifart J, De Marco F, Bedogni F, Adamo M, Currello S, Teles R, Taramasso M, Barbanti M, Tamburino C, Stefanini GG, Mangieri A, Giannini F, Pagnotta PA, Maisano F, Kim WK, Van Mieghem NM, Colombo A, Reimers B, Latib A; TAVI-SMALL Investigators. Transcatheter Self-Expandable Valve Implantation for Aortic Stenosis in Small Aortic Annuli: The TAVI-SMALL Registry. *JACC Cardiovasc Interv*. 2020;13:196-206.
- Abdelghani M, Mankierous N, Allali A, Landt M, Kaur J, Sulimov DS, Merten C, Sachse S, Mehilli J, Neumann FJ, Frerker C, Kurz T, El-Mawardi M, Richardt G, Abdel-Wahab M. Bioprosthetic Valve Performance After Transcatheter Aortic Valve Replacement With Self-Expanding Versus Balloon-Expandable Valves in Large Versus Small Aortic Valve Annuli: Insights From the CHOICE Trial and the CHOICE-Extend Registry. *JACC Cardiovasc Interv*. 2018;11:2507-18.
- Mauri V, Kim WK, Abumayaleh M, Walther T, Moellmann H, Schaefer U, Conradi L, Hengstenberg C, Hilker M, Wahlers T, Baldus S, Rudolph V, Madershahian N, Rudolph TK. Short-Term Outcome and Hemodynamic Performance of Next-Generation Self-Expanding Versus Balloon-Expandable Transcatheter Aortic Valves in Patients with Small Aortic Annulus: A Multicenter Propensity-Matched Comparison. *Circ Cardiovasc Interv*. 2017;10:e005013.
- Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL 3rd, Forrest JK, Tchetché D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ; Evolut Low Risk Trial Investigators. Transcatheter Aortic Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med*. 2019;380:1706-15.
- Nai Fovino L, Cipriani A, Fabris T, Massusi M, Scotti A, Lorenzoni G, Guerra MC, Cardaioli F, Rodinò G, Matsuda Y, Masiero G, Leoni L, Zorzi A, Fraccaro C, Tarantini G. Anatomical Predictors of Pacemaker Dependency After Transcatheter Aortic Valve Replacement. *Circ Arrhythm Electrophysiol*. 2021;14:e009028.

Supplementary data

Supplementary Table 1. NEOPRO and NEOPRO-2 participating centres.

The supplementary data are published online at:

<https://eurointervention.pronline.com/>

doi/10.4244/EIJ-D-22-00289



Supplementary data

Supplementary Table 1. NEOPRO and NEOPRO2 participating centres.

Centre, City, Country	Number of included patients		
	Overall (n=2,026)	ACURATE <i>neo</i> (n=1,263)	ACURATE <i>neo2</i> (n=763)
Kerckhoff Heart and Lung Center, Bad Nauheim, Germany	785	524	261
University Heart Center Hamburg, Hamburg, Germany	161	161	0
University of Catania, Catania, Italy	129	105	24
Humanitas Research Hospital, Rozzano-Milan, Italy	114	73	41
Policlinico San Donato, Milan, Italy	110	33	77
Rigshospitalet, Copenhagen, Denmark	81	0	81
Elisabeth-Krankenhaus Essen, Essen, Germany	59	20	39
Albertinen Heart Center, Hamburg, Germany	57	57	0
San Raffaele Scientific Institute, Milan, Italy	55	55	0
Rabin Medical Center, Petah Tikva, Israel	49	0	49
Heart Center Lucerne, Lucerne, Switzerland	49	0	49
Istituto Clinico Sant' Ambrogio, Milan, Italy	44	0	44
Royal Sussex County Hospital, Brighton, United Kingdom	43	43	0
Bern University Hospital, Bern, Switzerland	41	41	0
Medical University of Graz, Graz, Austria	40	40	0
Fondazione Poliambulanza, Brescia, Italy	40	0	40
Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil	40	40	0
University Hospital of Zürich, Zürich, Switzerland	24	24	0
Maria Cecilia Hospital, Cotignola, Italy	16	0	16
Spedali Civili, Brescia, Italy	16	0	16
St. Paul's & Vancouver General Hospital, Vancouver, Canada	13	13	0
University Hospital Bonn, Bonn, Germany	12	12	0
AZ Sint-Jan, Bruges, Belgium	11	0	11
St. Antonius Hospital, Nieuwegein, the Netherlands	10	10	0
Erasmus Medical Center, Rotterdam, the Netherlands	8	8	0
University Hospital Düsseldorf, Düsseldorf, Germany	7	0	7

Galway University Hospitals, Galway, Ireland	4	0	4
King's College Hospital, London, United Kingdom	4	4	0
Hospital Álvaro Cunqueiro, Vigo, Spain	4	0	4