Predictors of underexpansion after transcatheter aortic valve implantation with the ACURATE *neo* valve

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Editorial note:

On 28 May 2025, the manufacturer announced the global discontinuation of sales of its ACURATE neo2 and ACURATE Prime aortic valve systems. The following article, submitted and accepted prior to the market withdrawal, discusses clinical experience with this device. Though no longer relevant for current practice, the Editorial Board believes it is important to document these findings in the interest of transparency and completeness of the scientific record. Accordingly, we publish this work with acknowledgement of the device's discontinued status.

ABSTRACT

BACKGROUND: Transcatheter heart valve (THV) deformation after transcatheter aortic valve implantation (TAVI) using the self-expanding ACURATE platform has been associated with impaired clinical outcomes in a randomised trial. Procedural factors associated with THV deformation remain incompletely understood.

AIMS: We aimed to investigate procedural factors associated with valve underexpansion, mainly derived from preprocedural computed tomography angiography (CTA) imaging.

METHODS: A single-centre, retrospective, observational study was carried out, including patients who underwent TAVI with an ACURATE THV between January 2014 and December 2022, with available CTA and procedural fluoroscopy. Aortic calcium volume was quantified using 3mensio software. Fluoroscopy was used to determine valve frame underexpansion.

RESULTS: Of 3,027 patients, 480 were eligible (74 [15.4%] with an underexpanded and 406 [84.6%] with an expanded ACURATE THV). There were no differences regarding baseline clinical and procedural characteristics. Preprocedural CTA assessment showed more calcium at the annulus level in underexpanded versus expanded THVs (60.3 [interquartile range {IQR} 21.3; 135.2] mm^3 vs 45.3 [IQR 15.8; 96.1] mm^3, respectively; p=0.042), while post-dilatation was less frequently performed in underexpanded compared to expanded THVs (44.6% vs 64.8%, respectively; p=0.001). Multivariable regression analysis revealed that annulus calcium volume (odds ratio [OR] 2.333, 95% confidence interval [CI]: 1.331-4.089; p=0.003) and post-dilatation (OR 0.350, 95% CI: 0.203-0.602; p<0.001) were significantly associated with underexpanded THVs. Sensitivity analysis using annulus calcium volume as a dichotomised variable (>54 mm^3) confirmed the significant association with valve frame underexpansion (OR 2.38, 95% CI: 1.37-4.19; p=0.002).

CONCLUSIONS: Annular calcium volume was shown to be associated with underexpanded ACURATE THVs, while post-dilatation may reduce valve deformation.

Transcatheter aortic valve implantation (TAVI) has become the standard procedure for patients with severe calcific aortic valve stenosis[1], and its indication has now been extended to younger and lower-risk patients[2-4].

Self-expanding supra-annular transcatheter heart valves (THVs) were shown to provide favourable haemodynamics due to their configuration when compared to balloon-expandable intra-annular THVs[5-8], albeit with an increased risk of pacemaker need after TAVI[9,10] and the disadvantage of sometimes intricate coronary access after valve implantation[11,12]. However, the self-expanding supra-annular ACURATE (Boston Scientific) THV platform has the advantage of facilitating coronary cannulation after implantation due to the wide axial stabilisation arches and the absence of a continuous tall inner frame reaching beyond the coronary ostia. Furthermore, the ACURATE THV was shown to exhibit a comparably low risk of pacemaker implantation owing to the reduced radial strength of its nitinol frame, thereby mitigating compressive forces to the conduction system[13-15].

In contrast to these findings, the relatively lower radial strength of the valve might increase the risk of valve underexpansion and its associated clinical risks, as previously described, compared with fully-expanded THVs[16]. The mechanism behind this phenomenon is incompletely understood to date, but it has been hypothesised that underexpanded THVs augment turbulent flow and stasis in the neosinus because of inefficient leaflet functionality, including the presence of pinwheeling. The result might be increased shear stress, creating leaflet fissures, and microthrombus formation, with consequently higher risks of stroke, myocardial infarction, and probably early degeneration of the THV[17,18]. Despite the immediate and fundamental investigation of this association after release of the ACURATE IDE trial[16], with accompanying data from European centres supporting the association between underexpansion of the ACURATE *neo/neo*2 and impaired clinical outcome[19], causal inference remains to be established.

Against this background, we aimed to investigate the procedural factors associated with underexpansion of the ACURATE *neo/neo*2 in a large clinical database of real-world cases.

Methods

STUDY POPULATION AND ENDPOINTS

The current study included patients from a single high-volume centre in Germany (German Heart Center, Munich) who underwent successful TAVI using the ACURATE *neo* or *neo*2 devices after multidisciplinary Heart Team evaluation, between January 2014 and December 2022. All patients with available high-quality computed tomography angiography (CTA) for TAVI were included in the present study. Patients were treated according to local standards, and the decision regarding THV type was at the discretion of the operators.

The study was performed based on the principles of the Declaration of Helsinki. All patients provided written informed consent. Ethical approval was obtained by the ethical committee from the Technical University Munich under the registry OBSERVTAVI (525/17). CTA measurements were performed and recorded in a specific database before THV implantation. Baseline clinical characteristics, procedural characteristics, and laboratory values were entered into a customised database. For Valve Academic Research Consortium 3 (VARC-3)-defined clinical outcomes[20], in-hospital and discharge follow-up was monitored and registered. The composite endpoint including all-cause mortality, stroke, and congestive heart failure rehospitalisation at 1 year was also recorded. Follow-up was performed via telephone contact, hospital visit, or follow-up letter. Electrocardiograms and biomarkers regarding periprocedural myocardial infarction after TAVI were also analysed in the underexpanded THV population according to VARC-3 definitions.

THV UNDEREXPANSION ANALYSIS

For the purpose of the study, the analysis of valve underexpansion was performed using fluoroscopic imaging by an independent observer at the same centre. Angiographic studies of the TAVI procedure were retrospectively reviewed, using the latest fluoroscopic acquisition in which the degree of frame expansion could be assessed. Valve midframe underexpansion was assessed on post-implantation fluoroscopic images in an imaging plane providing the least parallax view where at least two of the three posts of the implanted THV were considered parallel to each other.

For reference, a box was drawn, delimited at the top by the lower part of the valve posts, at the bottom by the lower edge of the valve crown, and at the sides by the lateral edge of the crown portion of the valve. Once the frame was drawn, the same frame was duplicated and inserted below the first frame, and two more frames were inserted above the reference frame. Three parallel lines were drawn across the middle of the three valve posts, and the degree of parallelism of the lines was assessed in the last box, at the bottom. If two of the lines crossed in the lower box, the valve was considered to be underexpanded **(Central illustration A)**. If none of the lines
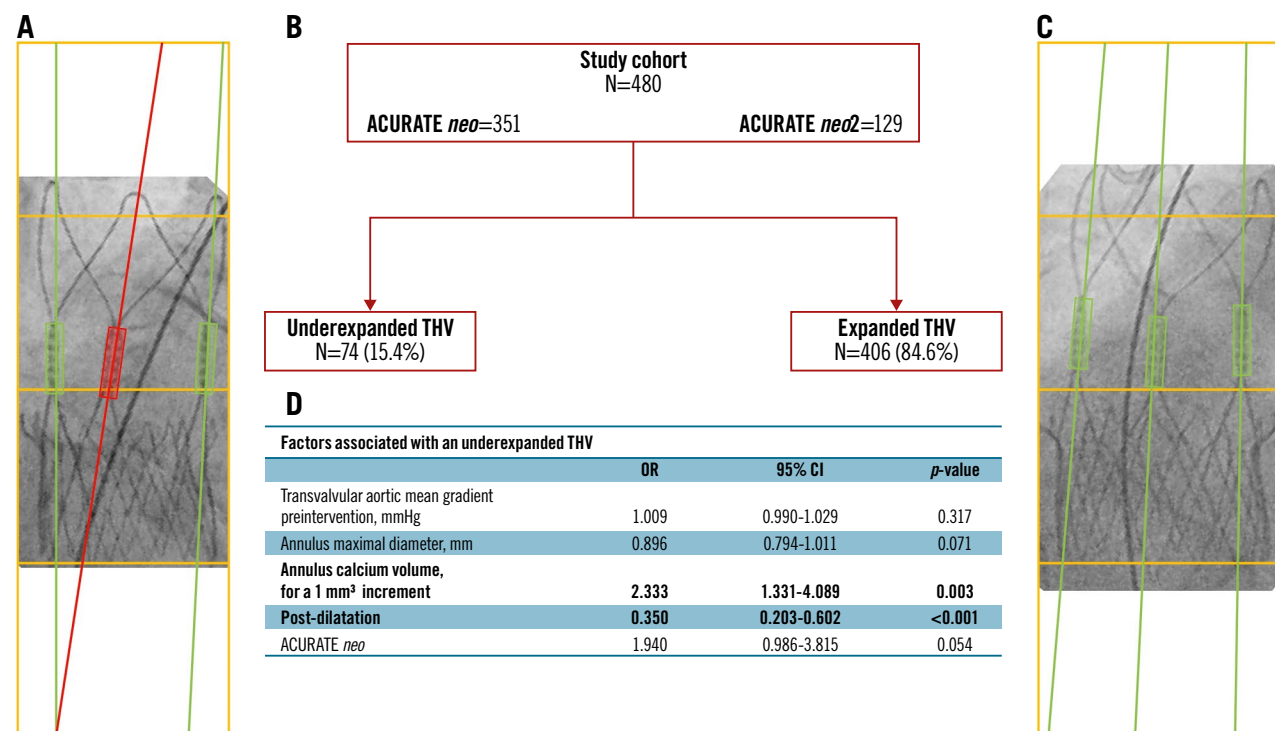
Impact on daily practice

Valvular deformation or underexpansion of the supra-annular ACURATE *neo/neo*2 self-expanding valve following transcatheter aortic valve implantation is associated with prosthesis malfunction and increased risk of clinical events. Excessive annular calcium volume is associated with a higher likelihood of underexpansion of the ACURATE prosthesis, and post-dilatation reduces the risk of underexpansion. Whether valve frame underexpansion is observed at a similar frequency in other transcatheter heart valve platforms and whether this is also associated with adverse clinical outcome needs to be studied in dedicated clinical trials.

Abbreviations

CTA	computed tomography angiography	**TAVI**	transcatheter aortic valve implantation	**THV**	transcatheter heart valve

Factors associated with an underexpanded ACURATE transcatheter heart valve.

A

B

Study cohort
N=480

ACURATE *neo*=351   **ACURATE** *neo2*=129

Underexpanded THV
N=74 (15.4%)

Expanded THV
N=406 (84.6%)

C

D

Factors associated with an underexpanded THV

	OR	95% CI	*p*-value
Transvalvular aortic mean gradient preintervention, mmHg	1.009	0.990-1.029	0.317
Annulus maximal diameter, mm	0.896	0.794-1.011	0.071
Annulus calcium volume, for a 1 mm³ increment	**2.333**	**1.331-4.089**	**0.003**
Post-dilatation	**0.350**	**0.203-0.602**	**<0.001**
ACURATE *neo*	1.940	0.986-3.815	0.054

A) ACURATE neo prosthesis with some degree of deformation (underexpanded), shown by the red line in the middle which intersects with the lateral line at the bottom within the box. B) Simple study flowchart. C) ACURATE neo prosthesis with no deformation (expanded), shown by the parallelism of the three green lines through the image. D) The factors found to be associated with THV underexpansion. CI: confidence interval; OR: odds ratio; THV: transcatheter heart valve

crossed, the valve was considered to be properly expanded **(Central illustration C).**

COMPUTED TOMOGRAPHY ANGIOGRAPHY ANALYSIS

All contrast-enhanced CTA studies were evaluated using 3mensio software (Pie Medical Imaging) to assess the size of the aortic valve, the level and the distribution of valvular calcification load in cubic millimetres (mm³). Aortic valve and valvular calcification measurements were obtained according to a previous publication[21]. In brief, the device landing zone calcium volume (DLZ-CV) was measured semiautomatically within a prespecified region of interest (above the level of the commissures including the leaflets and the left ventricular outflow tract 5 mm below the annular plane) using a scan-specific individual threshold derived from the mean attenuation of the ascending aorta plus 4 standard deviations and an additional volume filter with a threshold of 5 mm³ [22]. Calcium volume measurements were determined for the aortic valve (from the basal plane to above the commissures), aortic annulus (3 mm above the basal plane and 2 mm below the basal plane) and the left ventricular outflow tract (from the basal plane to 5 mm below it). Calcification was also measured separately for each cusp, and values were obtained in mm³, according to a previous publication where the calcium volume was validated against the standard Agatston unit[21]. Aortic valve measurements were obtained 0.5 mm below the basal plane to determine maximal, minimal, and mean diameter, perimeter, area, and perimeter-derived mean diameter.

AIMS AND ENDPOINTS

The aim of the current study was to investigate procedural factors associated with valve underexpansion, mainly derived from CTA imaging. Composite (all-cause mortality, stroke, and congestive heart failure rehospitalisation) and isolated clinical endpoints at 1 year were also evaluated. VARC-3 definitions were applied to describe procedural and follow-up outcomes.

STATISTICAL ANALYSIS

Categorical variables are summarised using frequencies and proportions and were compared using the chi-square test. Continuous data were tested for normality with the Shapiro-Wilk test and are summarised using mean (±standard

deviation) or median (interquartile range [IQR]) depending on data distribution. Differences between groups were evaluated using the Student's t-test or Mann-Whitney U test for continuous variables as appropriate and the chi-square test or Fisher's exact test for categorical variables.

Logistic binary regression analysis was performed to fit a univariate model for the association between calcification volume and valve underexpansion. Subsequently, receiver operating characteristic (ROC) curve analysis was performed to find a binary cutoff for the calcification volume best associated with valve underexpansion (Youden index). Adjusted multivariable analysis was performed for variables significantly associated with valve expansion by univariate analysis and those included mean aortic gradient prior to TAVI, total annulus calcification (as a continuous parameter), annulus maximum diameter, and post-dilatation. Factors inducing significant collinearity such as aortic valve orifice area and individual components of annulus calcification (at the right, left, and non-coronary cusps) were omitted to avoid model overfitting. Sensitivity analysis was performed using total annulus calcification as a binary variable after dichotomisation according to the previously established cutoff (Youden index).

Statistical analysis was performed using SPSS Statistics, Version 29 (IBM), JMP Pro, version 17.02 (SAS Institute) and RStudio (Posit Software, PBC) with R software, version 4.1 (R Foundation for Statistical Computing).

Results
BASELINE AND PROCEDURAL CHARACTERISTICS

A total of 3,207 patients underwent TAVI between January 2014 and December 2022. Of these cases, 627 patients received an ACURATE *neo* or *neo*2 THV platform. From those, 480 cases were eligible (ACURATE *neo*=351, ACURATE *neo*2=129) with sufficient fluoroscopic and high-quality CTA imaging allowing for valve expansion analysis as previously described. After valve deployment, 135 cases (28.1%) were identified as having an underexpanded THV and 315 (65.6%) as having an expanded THV; in 30 cases (6.3%), it was initially impossible to determine valve expansion because of a lack of proper fluoroscopic imaging to evaluate parallelism of the posts. From the study cohort (480 patients) after post-dilatation, 74 (15.4%) were identified as having underexpanded valves and 406 (84.6%) as having well-expanded valves **(Figure 1)**.

Baseline clinical, echocardiographic, and CTA characteristics are described in **Table 1**. The patients' median age was 82 (IQR 78; 85) years, 57.9% were female, and the median European System for Cardiac Operative Risk Evaluation (EuroSCORE) II was 4.26 (IQR 2.58; 7.36). Patients with underexpanded versus expanded valves showed similar echocardiographic parameters, except their significantly higher mean aortic gradients prior to TAVI (all=41 [IQR 32; 48] mmHg, underexpanded=44 [IQR 36;
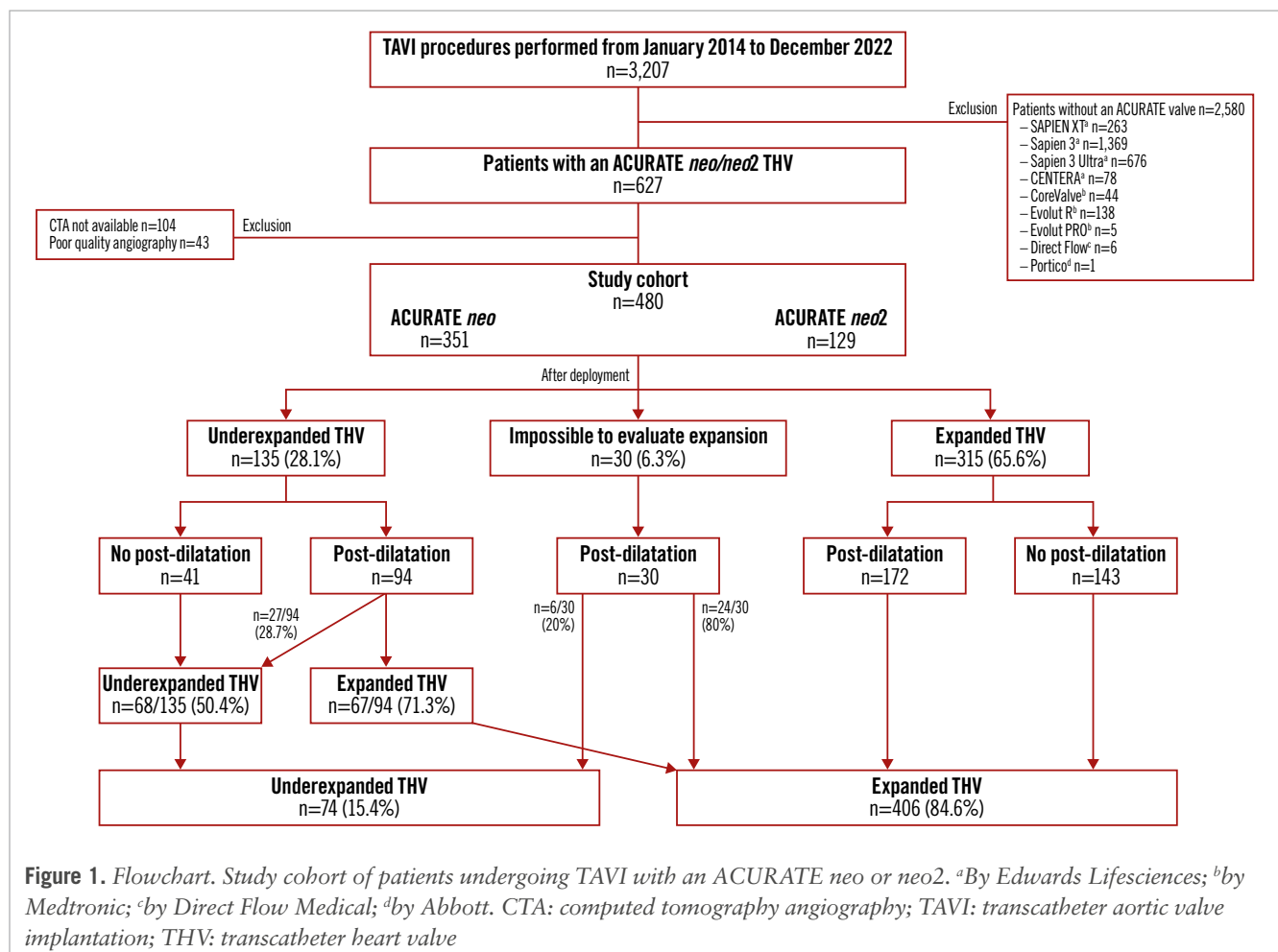
Figure 1. *Flowchart. Study cohort of patients undergoing TAVI with an ACURATE neo or neo2. [a]By Edwards Lifesciences; [b]by Medtronic; [c]by Direct Flow Medical; [d]by Abbott. CTA: computed tomography angiography; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve*

Table 1. Baseline characteristics.

	All (n=480)	Underexpanded (n=74)	Expanded (n=406)	*p*-value
Age, years	82 [78; 85]	83 [79; 86]	82 [78; 85]	0.138
Female	278 (57.9)	46 (62.2)	232 (57.1)	0.445
BSA, m²	1.82±0.20	1.86±0.24	1.82±0.19	0.119
NYHA				0.010
I	35 (7.3)	7 (9.5)	28 (6.9)	
II	148 (30.8)	19 (25.7)	129 (31.8)	
III	270 (56.3)	38 (51.4)	232 (57.1)	
IV	27 (5.6)	10 (13.5)	17 (4.2)	
Hypertension	443 (92.3)	65 (87.8)	378 (93.1)	0.151
Diabetes	141 (29.4)	20 (27.0)	121 (29.8)	0.679
Dyslipidaemia	373 (77.7)	55 (74.3)	318 (78.3)	0.450
COPD	27 (5.8)	8 (10.8)	19 (4.9)	0.057
PAD	61 (12.7)	5 (6.8)	56 (13.8)	0.127
Pacemaker	46 (9.6)	6 (8.1)	40 (9.9)	0.679
CAD	399 (83.1)	60 (81.1)	339 (83.5)	0.614
Previous PCI	187 (39)	28 (37.8)	159 (39.2)	0.897
Previous MI	49 (10.2)	4 (5.4)	45 (11.1)	0.151
Previous CABG	50 (10.4)	11 (14.9)	39 (9.6)	0.212
Stroke/TIA	63 (13.1)	5 (6.8)	58 (14.3)	0.092
History of cancer	98 (20.4)	11 (14.9)	87 (21.4)	0.214
AF	200 (41.7)	25 (33.8)	175 (43.1)	0.159
Dialysis	7 (1.5)	1 (1.4)	6 (1.5)	>0.999
EuroSCORE I	12.93 [8.41; 20.08]	14.86 [8.61; 20.55]	12.63 [8.28; 20.03]	0.273
EuroSCORE II	4.26 [2.58; 7.36]	5.44 [2.21; 9.16]	4.18 [2.62; 7.25]	0.359
STS-PROM score	3.84 [2.66; 5.64]	4.27 [2.84; 6.92]	3.71 [2.63; 5.41]	0.026
Laboratory parameters				
Creatinine, mg/dL	1.05 [0.89; 0.132]	1.06 [0.90; 1.36]	1.05 [0.89; 1.31]	0.770
Creatinine clearance, mL/min	53.5 [41.0; 67.0]	51.5 [38.0; 64.2]	54.0 [41.9; 68.0]	0.292
NT-proBNP, ng/L	1,350 [657; 3,220]	1,120 [712; 3,232]	1,380 [646; 3,227]	0.555
CK, U/L	81 [59; 128]	96 [63; 145]	81 [59; 125]	0.211
CK-MB, U/L	14.5 [11.8; 18.4]	15.2 [11.6; 19.2]	14.4 [11.8; 18.3]	0.498
Hs-troponin I, ng/L	0.04 [0.02; 0.14]	0.03 [0.02; 0.27]	0.04 [0.02; 0.15]	0.103
CRP, mg/L	1.97 [0.98; 5.33]	2.41 [1.31; 8.67]	1.82 [0.95; 4.98]	0.030
LDH, U/L	206 [181; 236]	218 [182; 241]	205 [181; 235]	0.198
WBC, 10^9/L	6.92 [5.93; 8.25]	6.87 [5.89; 8.27]	6.92 [5.94; 8.27]	0.981
Platelets, 10^9/L	221 [188; 268]	212 [175; 271]	223 [191; 268]	0.263
Echocardiographic parameters				
AVA, cm²	0.71 [0.58; 0.84]	0.64 [0.56; 0.80]	0.72 [0.59; 0.85]	0.119
AVA indexed, cm²/BSA	0.38 [0.32; 0.45]	0.34 [0.30; 0.42]	0.39 [0.32; 0.46]	0.041
LVEF, %	60 [51; 60]	60 [50; 60]	60 [51; 60]	0.861
Aortic mean gradient, mmHg	41 [32; 48]	44 [36; 52]	41 [32; 47]	0.032
Aortic maximal gradient, mmHg	66 [54; 78]	70 [57; 82]	66 [54; 78]	0.220
Systolic pulmonary artery pressure, mmHg	40 [33; 48]	37 [29; 49]	40 [33; 48]	0.367

Table 1. Baseline characterisitics (cont'd).

	All (n=480)	Underexpanded (n=74)	Expanded (n=406)	*p*-value
Tomographic parameters				
Bicuspid	21 (4.4)	2 (2.7)	19 (4.7)	0.555
Valvular calcium volume on NCC, mm³	229.8 [123.8; 389.9]	232.4 [130.5; 466.2]	229.4 [122.8; 381.5]	0.379
Valvular calcium volume on RCC, mm³	146.5 [67.1; 261.0]	158.7 [66.9; 297.8]	139.6 [66.9; 258.1]	0.172
Valvular calcium volume on LCC, mm³	132.3 [73.0; 257.5]	163.3 [81.1; 262.8]	129.5 [72.8; 258.5]	0.237
Total valvular calcium volume, mm³	553.1 [299.1; 889.6]	586.5 [298.8; 998.3]	543.5 [298.2; 883.2]	0.251
Annular calcium volume on NCC, mm³	15.3 [0.0; 41.5]	18.5 [0.0; 49.0]	14.7 [0.0; 41.1]	0.538
Annular calcium volume on RCC, mm³	0.0 [0.0; 16.9]	7.8 [0.0; 49.0]	0.0 [0.0; 16.0]	0.001
Annular calcium volume on LCC, mm³	11.9 [0.0; 39.6]	20.8 [0.0; 47.2]	10.1 [0.0; 38.2]	0.039
Total annular calcium volume, mm³	46.0 [16.4; 100.5]	60.3 [21.3; 135.2]	45.3 [15.8; 96.1]	0.042
LVOT calcium volume on NCC, mm³	0.0 [0.0; 0.0]	0.0 [0.0; 1.6]	0.0 [0.0; 0.0]	0.167
LVOT calcium volume on RCC, mm³	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.227
LVOT calcium volume on LCC, mm³	0.0 [0.0; 13.0]	0.0 [0.0; 8.6]	0.0 [0.0; 14.2]	0.938
Total LVOT calcium volume, mm³	0.0 [0.0; 29.4]	2.5 [0.0; 37.6]	0.0 [0.0; 27.2]	0.321
Total calcium volume, mm³	577.0 [310.4; 908.5]	605.0 [333.8; 1,006.1]	560.5 [309.3; 900.3]	0.238
Calcium asymmetry	184 (38.4)	29 (39.2)	155 (38.3)	0.897
Annulus minimum diameter, mm	20.2±1.9	20.1±1.9	20.3±1.9	0.399
Annulus maximum diameter, mm	26.4 [24.8; 28.0]	25.8 [24.1; 27.6]	26.5 [24.8; 28.1]	0.039
Annulus mean diameter, mm	23.3 [22.0; 24.7]	23.1 [21.5; 24.3]	23.4 [22.1; 24.8]	0.106
Annulus perimeter, mm	74 [70; 78]	73 [68; 77]	74 [70; 78]	0.094
Annulus mean diameter derived from perimeter, mm	23.5 [22.3; 24.9]	23.2 [21.7; 24.6]	23.5 [22.3; 24.9]	0.094
Annulus area, mm²	415 [373; 467]	404 [357; 458]	417 [375; 469]	0.138
Annulus mean diameter derived from area, mm	23.0 [21.8; 24.4]	22.7 [21.3; 24.1]	23.0 [21.8; 24.4]	0.137
Eccentricity index	0.23 [0.19; 0.27]	0.22 [0.19; 0.26]	0.23 [0.19; 0.28]	0.381
Sinotubular junction height, mm	21.7 [20.0; 23.7]	21.0 [19.3; 23.2]	21.9 [20.0; 23.9]	0.074
Sinotubular junction width, mm	26.3 [24.8; 28.7]	26.0 [24.2; 28.2]	26.5 [24.8; 28.8]	0.118
Ascending aorta width, mm	34.0 [31.5; 36.7]	33.2 [31.4; 36.7]	34.0 [31.5; 36.8]	0.338
Left main height, mm	13 [12; 15]	13 [11; 15]	14 [12; 16]	0.074
RCA height, mm	17 [15; 19]	17 [14; 19]	17 [15; 19]	0.503

Data are presented as median [IQR], mean±SD, or number (%) as appropriate. AF: atrial fibrillation; AVA: aortic valve area; BSA: body surface area; CABG: coronary artery bypass graft; CAD: coronary artery disease; CK: creatine kinase; CK-MB: creatine kinase-myocardial band; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; EuroSCORE: European System for Cardiac Operative Risk Evaluation; hs: high-sensitivity; IQR: interquartile range; LCC: left coronary cusp; LDH: lactate dehydrogenase; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MI: myocardial infarction; NCC: non-coronary cusp; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; RCA: right coronary artery; RCC: right coronary cusp; SD: standard deviation; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TIA: transient ischaemic attack; WBC: white blood cell

52] mmHg vs expanded=41 [IQR 32; 47] mmHg; p=0.032). CTA parameters showed no significant differences regarding overall valvular calcium volume (all=553.1 [IQR 299.1; 889.6] mm³, underexpanded=586.5 [IQR 298.8; 998.3] mm³ vs expanded=543.5 [IQR 298.2; 883.2] mm³; p=0.251), left ventricular outflow tract calcium volume (all=0.0 [IQR 0.0; 29.4] mm³, underexpanded=2.5 [IQR 0.0; 37.6] mm³ vs expanded=0.0 [IQR 0.0; 27.2] mm³; p=0.321), or total aortic calcium volume (all=577.0 [IQR 310.4; 908.5] mm³, underexpanded=605.0 [IQR 333.8; 1,006.1] mm³

vs expanded=560.5 [IQR 309.3; 900.3] mm³; p=0.238). However, there was significantly greater calcium volume at the annulus level in underexpanded versus expanded valves (60.3 [IQR 21.3; 135.2] mm³ vs 45.3 [IQR 15.8; 96.1] mm³, respectively; p=0.042).

Procedural characteristics are presented in **Table 2**. No differences were observed regarding procedural time (all=54 [IQR 45; 65] min, underexpanded=51 [IQR 42; 62] min vs expanded=54 [IQR 45; 65] min; p=0.095), technical success (all=93.3%, underexpanded=94.6% vs expanded=93.1%; p=0.802) or predilatation (all=99.4%, underexpanded=100% vs expanded=99.3%; p>0.999). Post-dilatation was performed significantly less frequently in underexpanded compared with expanded THVs (44.6% vs 64.8%; p=0.001). No differences regarding in-hospital cardiac biomarkers were observed between underexpanded and expanded THVs (creatine kinase

Table 2. Procedural characteristics.

	All (n=480)	Underexpanded (n=74)	Expanded (n=406)	*p*-value
Cerebral protection device	9 (1.9)	0 (0)	9 (2.2)	0.196
Procedural time, min	54 [45; 65]	51 [42; 62]	54 [45; 65]	0.095
Contrast media, mL	150 [120; 196]	140 [110; 182]	150 [120; 200]	0.075
Fluoroscopy time, min	12.7 [10.2; 16.5]	12.2 [9.4; 16.9]	12.8 [10.3; 16.3]	0.381
Fluoroscopy dose, cGy*cm²	1,885 [793; 3,077]	2,133 [873; 3,387]	1,842 [774; 3,044]	0.457
ACURATE				0.032
neo	351 (73.1)	62 (83.8)	289 (71.2)	
neo2	129 (26.9)	12 (16.2)	117 (28.9)	
Size of valve implanted				0.186
23 mm	139 (29)	28 (37.8)	111 (27.3)	
25 mm	209 (43.5)	29 (39.2)	180 (44.3)	
27 mm	132 (27.5)	17 (23.0)	115 (28.3)	
THV over- or undersizing, %	−6 [−9; −3]	−6 [−8; −3]	−6 [−9; −3]	0.664
Predilatation	477 (99.4)	74 (100)	403 (99.3)	>0.999
Semicompliant balloon	312 (65.4)	51 (68.9)	264 (65.5)	0.550
Non-compliant balloon	165 (34.6)	23 (31.1)	139 (34.5)	0.550
Predilatation balloon size, mm	23 [20; 24]	22 [20; 23.3]	23 [21; 24]	0.082
Balloon-to-annulus ratio	0.96 [0.93; 0.98]	0.95 [0.93; 0.99]	0.96 [0.93; 0.98]	0.433
Post-dilatation	296 (61.7)	33 (44.6)	263 (64.8)	0.001
Semicompliant balloon	201 (67.9)	25 (75.8)	176 (66.9)	0.280
Non-compliant balloon	95 (32.1)	8 (24.2)	87 (33.1)	0.280
Post-dilatation balloon size, mm	23 [22; 24]	23 [20.5; 24]	23 [22; 24]	0.593
Balloon-to-annulus ratio	0.97 [0.94; 0.99]	0.95 [0.93; 0.98]	0.97 [0.94; 0.99]	0.034
Technical success	448 (93.3)	70 (94.6)	378 (93.1)	0.802
Tamponade	2 (0.4)	0 (0)	2 (0.5)	>0.999
Annulus rupture	1 (0.2)	0 (0)	1 (0.2)	>0.999
Conversion to surgery	2 (0.4)	0 (0)	2 (0.5)	>0.999
Aortic insufficiency ≥2	14 (2.9)	2 (2.8)	12 (3.0)	>0.999
Mean gradient post-intervention, mmHg	8 [6; 11]	8 [6; 11]	8 [6; 11]	0.387
In-hospital mortality	1 (0.2)	0 (0)	1 (0.2)	>0.999
Days in ICU	1 [1; 1]	1 [1; 1]	1 [1; 2]	0.010
In-hospital laboratory parameters				
NT-proBNP, ng/L	1,680 [566; 3,400]	1,340 [566; 2,957]	1,690 [565; 4,900]	0.537
CK, U/L	105 [77; 162]	102 [70; 180]	106 [77; 162]	0.786
CK-MB, U/L	18.4 [14.5; 24]	19.1 [15.5; 25.7]	18.4 [14.5; 24.1]	0.680
Hs-troponin I, ng/L	0.13 [0.08; 0.47]	0.12 [0.08; 0.15]	0.17 [0.08; 1.44]	0.220
CRP, mg/L	55.8 [33.8; 83.3]	59.4 [37.9; 78.8]	54.8 [33.6; 83.6]	0.585
LDH, U/L	239 [209; 283]	244 [205; 298]	238 [209; 282]	0.350
WBC, 10^9/L	10.4 [8.68; 12.5]	9.8 [8.26; 11.13]	10.6 [8.74; 12.63]	0.029
Platelets, 10^9/L	197 [165; 239]	189 [154; 226]	198 [167; 240]	0.126

Data are presented as median [IQR] or number (%) as appropriate. CK: creatine kinase; CK-MB: creatine kinase-myocardial band; CRP: C-reactive protein; hs: high-sensitivity; ICU: intensive care unit; IQR: interquartile range; LDH: lactate dehydrogenase; NT-proBNP: N-terminal pro-brain natriuretic peptide; THV: transcatheter heart valve; WBC: white blood cell

[CK]: 102 [IQR 70; 180] U/L vs 106 [IQR 77; 162] U/L; p=0.786; CK-myocardial band [MB]: 19.1 [IQR 15.5; 25.7] U/L vs 18.4 [IQR 14.5; 24.1] U/L; p=0.680; high-sensitivity [hs] troponin [Tn] I: 0.12 [IQR 0.08; 0.15] ng/L vs 0.17 [IQR 0.08; 1.44] ng/L for underexpanded vs expanded valves, respectively; p=0.220). After analysing all the underexpanded THVs, no cases of periprocedural myocardial infarction (MI) were observed. There were no differences regarding procedural complications between groups.

POST-DILATATION EFFECT IN THV EXPANSION

Of the 296 patients that received a post-dilatation strategy, angiographic images before and after post-dilatation were available in 266 (89.9%) patients. Underexpanded THVs were modified to expanded THVs from 94 (35.3%) to 67 patients (25.2%) after post-dilatation. Among the 30 patients (6.3%) without fluoroscopic imaging before post-dilatation, 6 patients (20%) were identified as having underexpanded THVs, while 24 (80%) had expanded THVs after post-dilatation.

CLINICAL AND ECHOCARDIOGRAPHIC OUTCOMES AT FOLLOW-UP

Clinical outcomes at 1 year are shown in **Supplementary Table 1**. No differences between underexpanded and expanded THVs were detected regarding the composite endpoint (all-cause mortality, stroke, and congestive heart failure; 12.2% vs 11.8%; p>0.999), all-cause mortality (8.1% vs 6.4%; p=0.611), stroke (1.4% vs 1.5%; p>0.999), or congestive heart failure (5.4% vs 5.2%; p>0.999) at 1-year follow-up; mortality at the longest available follow-up (802 [413; 1,374] days) was also similar between groups (33.8% vs 27.1%; p=0.239) **(Supplementary Figure 1)**. No significant differences between New York Heart Association (NYHA) heart failure classification were observed at 30 days or 1 year between underexpanded and expanded THVs **(Figure 2)**. No differences regarding laboratory parameters (N-terminal pro-brain natriuretic peptide, CK, CK-MB, hsTnI) at 30 days or 1 year between underexpanded and expanded THVs were observed **(Supplementary Table 2)**. Echocardiographic outcomes at 30 days and 1 year are summarised in **Figure 3**

and **Supplementary Table 1**. There was a significantly higher transvalvular mean gradient at 30 days in underexpanded compared to expanded THVs (8.9±4.1 mmHg vs 7.4±3.6 mmHg; p=0.006), but there was no difference at 1 year. No differences were observed regarding aortic valve area at 30 days or 1 year. Aortic insufficiency that was more than moderate was not significantly different between underexpanded and expanded THVs at 30 days (0% vs 1.0%; p>0.999) or at 1 year (5.7% vs 1.6%; p=0.172).

FACTORS ASSOCIATED WITH AN UNDEREXPANDED THV

Unadjusted binary logistic regression analysis showed that annulus calcium volume (per 1 mm³ increment of calcium volume; odds ratio [OR] 1.003, 95% confidence interval [CI]: 1.000-1.005; p=0.024), the ACURATE *neo* THV platform (OR 2.092, 95% CI: 1.087-4.024; p=0.027), and post-dilatation (OR 0.438, 95% CI: 0.265-0.723; p=0.001) were associated with underexpanded valves. Annulus calcium volume was also dichotomised using a cutoff value (>54 mm³) derived from ROC analysis **(Supplementary Table 3)**, with an OR of 1.804, 95% CI: 1.094-2.975; p=0.022. After multivariable analysis **(Table 3)**, only annulus calcium volume (per 1 mm³ of calcium volume, OR 2.333, 95% CI: 1.331-4.089; p=0.003), and post-dilatation (OR 0.350, 95% CI: 0.203-0.602; p<0.001) remained significant **(Central illustration)**. Sensitivity analysis using annulus calcium volume as a dichotomised variable (>54 mm³) confirmed the significant association with valve frame underexpansion (OR 2.38, 95% CI: 1.37-4.19; p=0.002) **(Supplementary Figure 2)**.

Discussion

This single-centre observational study sought to investigate factors associated with underexpanded ACURATE *neo* and ACURATE *neo*2 THVs in patients with severe aortic valve stenosis and an indication for TAVI. The main findings of the current study can be summarised as follows: (1) higher annular calcium volume increased the risk of underexpansion of the ACURATE *neo/neo*2 THV; (2) post-dilatation decreased the risk of underexpansion of the ACURATE *neo/neo*2 THV; and (3) 1-year mortality appeared to be numerically higher in patients with underexpanded THVs, yet without reaching
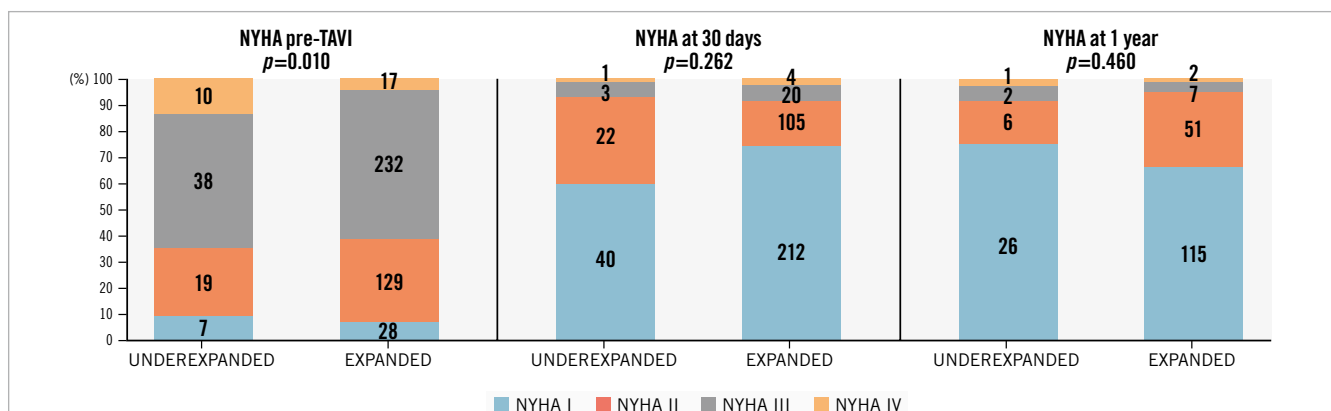
Figure 2. *Heart failure symptoms. NYHA classification before, at 30 days, and at 1 year after aortic valve implantation in both groups: underexpanded and expanded transcatheter heart valves. NYHA: New York Heart Association; TAVI: transcatheter aortic valve implantation*
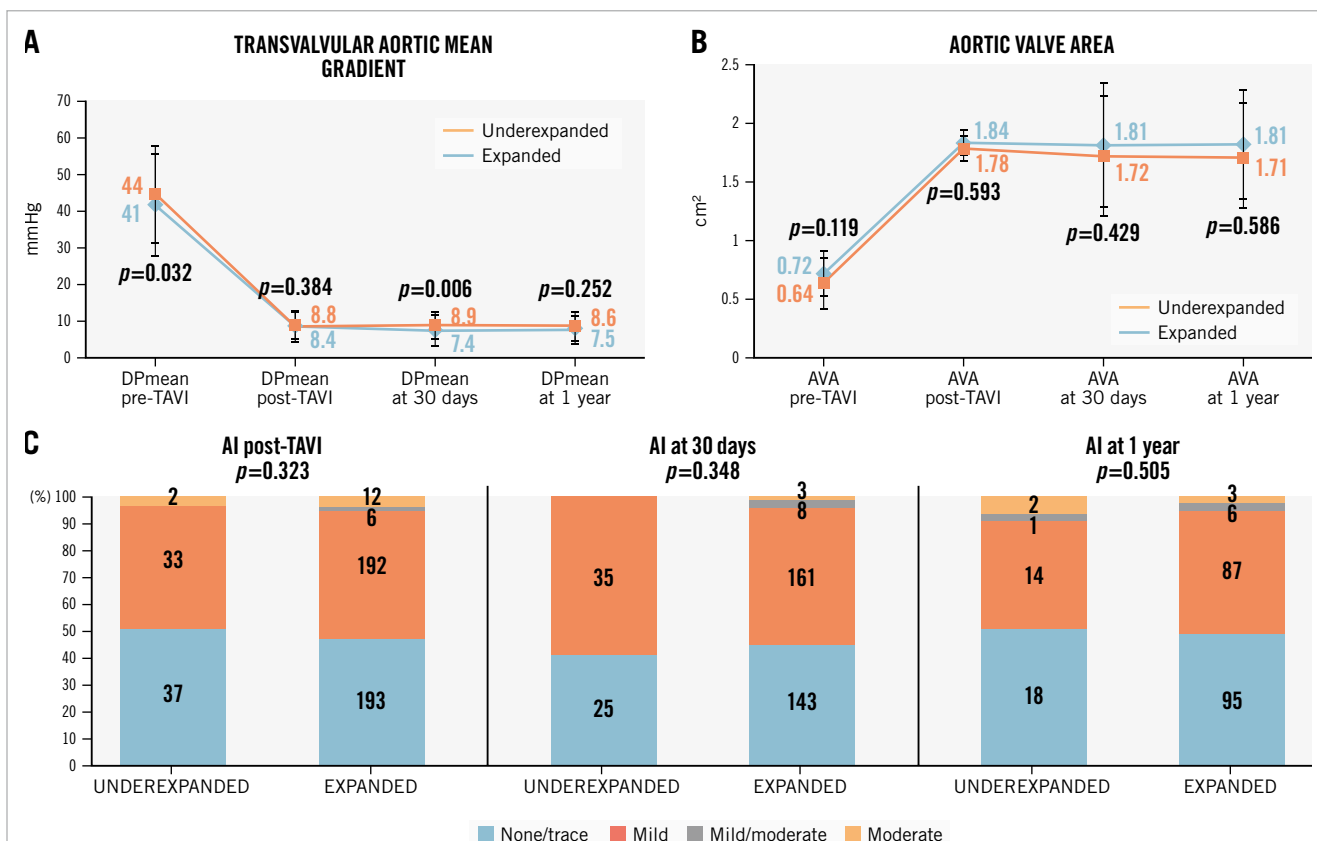
Figure 3. *Echocardiographic aortic valvular parameters during follow-up (30 days and 1 year). A) Transvalvular aortic mean gradient; (B) aortic valve area; (C) aortic insufficiency. AI: aortic insufficiency; AVA: aortic valve area; DPmean: delta pressure mean gradient; TAVI: transcatheter aortic valve implantation*

Table 3. Multivariable analysis for underexpanded valves.

	OR	95% CI	*p*-value
Transvalvular aortic mean gradient preintervention, mmHg	1.009	0.990-1.029	0.317
Annulus maximal diameter, mm	0.896	0.794-1.011	0.071
Annulus calcium volume, for a 1 mm³ increment	2.333	1.331-4.089	0.003*
Post-dilatation	0.350	0.203-0.602	<0.001*
ACURATE *neo*	1.940	0.986-3.815	0.054

*Indicates statistical significance. CI: confidence interval; OR: odds ratio

statistical significance. Importantly, this study identified the relevance of annulus calcium volume evaluation when considering which ACURATE *neo/neo*2 THV should be selected to treat degenerative calcific aortic valve stenosis (CAVS). This finding may have relevance to determine individualised treatment approaches for patients suffering CAVS. Importantly, post-dilatation was found to be an effective measure to correct underexpanded ACURATE *neo/neo*2 valves, modifying the frame deformation to expanded frames in 71.3% of patients.

In the ACURATE IDE randomised controlled trial[16], the ACURATE *neo*2 failed to meet non-inferiority for the primary endpoint of all-cause mortality, stroke, or rehospitalisation at 1 year using a Bayesian approach against a control group composed of U.S. Food and Drug Administration-approved THVs (SAPIEN 3/3 Ultra [Edwards Lifesciences] and Evolut R/PRO/PRO+/FX [Medtronic]): ACURATE *neo*2: 16.16%, control: 9.53%; posterior median difference 6.63% (95% Bayesian credible interval: 3.04-10.20%)[16]. Given the unexpected outcome of this study, an in-depth investigation into potential root causes of this failure was immediately initialised and reported[16]; approximately 20% of the ACURATE *neo*2 valves in the IDE trial were found to be underexpanded, which is higher compared to previously reported studies evaluating this valve[19] and also compared with the 15.4% of underexpanded ACURATE *neo/neo*2 valves in our cohort. In the ACURATE IDE trial, underexpansion was associated with a 1-year composite event rate (death, stroke, and rehospitalisation) of 18.8% versus 12.4% in the adequate expansion group. In contrast, we observed a 1-year composite event rate of 12.2% in the underexpanded valve group and 11.8% in the adequately expanded valve group.

While this difference was not statistically significant, a trend towards higher event rates in the underexpanded group was apparent. This may be explained by the smaller sample size in our study and the fact that it was not specifically powered to evaluate composite clinical outcomes. This trend of increased 1-year event rates in the underexpanded valve group was also observed in the individual outcomes of mortality and heart failure-related hospitalisation but not in stroke, possibly due to underdiagnosis. Nevertheless, the overall 1-year mortality rate in our cohort was comparable to that reported in previous studies[23]. In aggregate, these data for the first time suggest a direct link between valve frame underexpansion of the ACURATE *neo/neo*2, malfunctioning of the valve leaflets causing microembolism, and consequently, increased rates of ischaemic events such as myocardial infarction and stroke. Despite the seemingly intuitive pathophysiology behind the increased clinical event rates of underexpanded ACURATE *neo/neo*2 valves, direct evidence for the mechanistic interaction is missing to date, and careful future investigation is warranted in this regard. This proposition is also fuelled by the observation in the ACURATE IDE trial of increased ischaemic event rates after 30 days, suggesting microembolism occurring beyond this time frame and not in the periprocedural phase. This is confirmed by the absence of periprocedural MI according to VARC-3 definitions in our study.

Interestingly, midframe underexpansion of the ACURATE *neo/neo*2 did not affect aortic valve area or haemodynamic mean gradients at 1-year follow-up in the studied population. No major differences in heart failure symptoms or aortic insufficiency were observed between patients with underexpanded and expanded valves. Although no statistically significant differences were observed, there was a tendency towards higher mean transvalvular gradients, a smaller valve area, as well as greater functional class impairment and moderate aortic insufficiency, in patients with an underexpanded valve. These might be considered the haemodynamic consequences of underexpanded valve frames.

Our findings demonstrated that annular calcification increased the risk of prosthetic valve deformation, implying that a higher calcium burden at the aortic annulus level was associated with a greater likelihood of prosthesis deformation after implantation. Valvular calcification has previously been evaluated as a predictor of mortality[21] and as a risk factor for annulus rupture[24] and paravalvular regurgitation[25]. Furthermore, in certain CTA-based assessment models, valvular calcium has been shown to impair optimal expansion of balloon-expandable THVs[26,27] and also to distort self-expanding THVs at the annular level[28]. Until recently, the clinical relevance of detecting prosthetic valve deformation was based on the theoretical association with hypoattenuated leaflet thickening, which may in turn compromise prosthesis function and durability, while also increasing the risks of thrombosis, mortality, and hospitalisation[29,30]. To address this, appropriate implantation strategies should be considered, including adequate predilatation, careful selection of the prosthetic valve tailored to patient-specific anatomy, guided in part by quantification of valvular calcium volume, and the use of post-dilatation when appropriate.

In this regard, we observed that post-dilatation was more frequently performed in patients with adequately expanded prostheses, suggesting that this approach should be considered in recipients of the ACURATE THV. Importantly, the decision to post-dilate should be based on angiographic confirmation of valve expansion as previously established[16]. In a stringent way, the company has advocated a simplified onsite assessment of valve expansion using two different c-arm angulations. Should underexpansion be detected in one of these two projections, post-dilatation is warranted. Post-dilatation of self-expanding valves has already been associated with reduced underexpansion and, consequently, with a lower incidence of leaflet thickening[31], findings in clear support of the current study.

Limitations

The present study is limited by the observational nature of the investigation, selection bias of patients assigned to procedures, and it is limited to 1-year follow-up. The number of patients included in the study was not sufficient to observe a statistically significant difference in clinical events at 1 year, although there is a trend of higher events in the underexpanded valve population.

Conclusions

Annular calcium volume was shown to be associated with underexpanded ACURATE *neo/neo*2 THVs, and a post-dilatation strategy may reduce this valve deformation. Future studies will need to address this association in a prospective controlled way and determine whether the use of this specific THV system is reasonable for treating severely calcified aortic valve stenosis.

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Conflict of interest statement

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Supplementary data

Supplementary Table 1. One-year follow-up.
Supplementary Table 2. Laboratory parameters during follow-up.
Supplementary Table 3. Receiver operating characteristic analysis of annulus calcium volume for the association with an underexpanded valve.
Supplementary Figure 1. Survival at longest available follow-up.
Supplementary Figure 2. Forest plot of factors associated with an underexpanded valve.

The supplementary data are published online at:
https://eurointervention.pcronline.com/
doi/10.4244/EIJ-D-25-00489

Supplementary data

Supplementary Table 1. One-year follow-up.

	All (n = 480)	Under-expanded (n = 74)	Expanded (n = 406)	*p* value
Composite end-point (mortality, stroke or congestive heart failure)	57 (11.9)	9 (12.2)	48 (11.8)	>0.999
Mortality	32 (6.6)	6 (8.1)	26 (6.4)	0.611
Stroke	7 (1.5)	1 (1.4)	6 (1.5)	>0.999
Congestive heart failure	25 (5.2)	4 (5.4)	21 (5.2)	>0.999
Pacemaker	37 (7.7)	6 (8.1)	31 (7.6)	>0.999
Valve dysfunction	7 (1.5)	3 (4.1)	4 (1.0)	0.078
NYHA, n=210, [*missing=238 (49.6%)]				0.460
I	141 (67.1)	26 (74.3)	115 (65.7)	
II	57 (27.1)	6 (17.1)	51 (29.1)	
III	9 (4.3)	2 (5.7)	7 (4.0)	
IV	3 (1.4)	1 (2.9)	2 (1.1)	
AI, n=226, [*missing=222 (46.2%)]				0.505
Non/trace	113 (50.0)	18 (51.4)	95 (49.7)	
Mild	101 (44.7)	14 (40)	87 (45.5)	
Mild/moderate	7 (3.1)	1 (2.9)	6 (3.1)	
Moderate	5 (2.2)	2 (5.7)	3 (1.6)	
Transvalvular mean gradient, mmHg, n=193, [*missing=2555 (53.1%)]	7.6 ± 4.0	8.6 ± 3.9	7.5 ± 4.0	0.252

Aortic valve area, mm^2, n=37, [*missing=411 (85.6%)]	1.80 ± 0.40	1.71 ± 0.60	1.81 ± 0.40	0.586

*One-year mortality of 32 patients were not included in the missing patients.

AI = Aortic insufficiency; mm2 = square millimeters; mmHg = millimeters mercury; NYHA = New York Hear Association functional class.

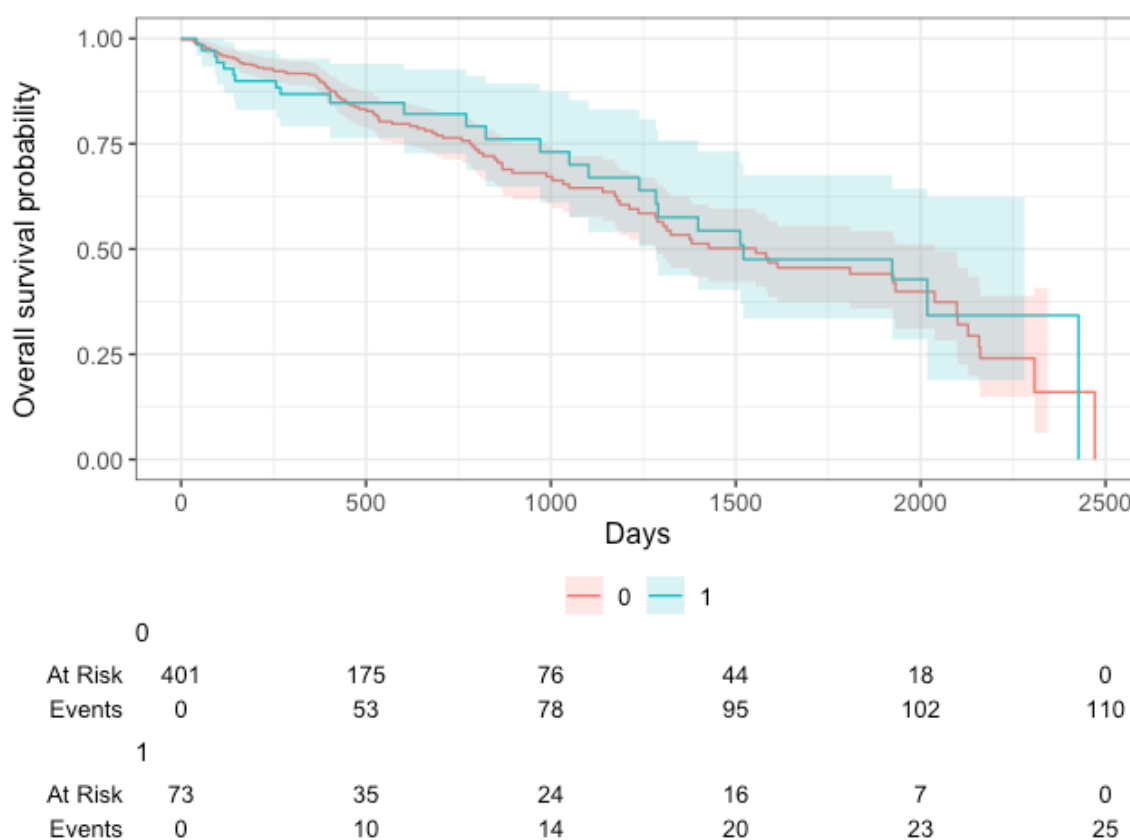**Supplementary Table 2.** Laboratory parameters during follow-up.

	30-days				One-year			
	All (n = 480)	Under-expanded (n =74)	Expanded (n = 406)	*p* value	All (n = 480)	Under-expanded (n =74)	Expanded (n = 406)	*p* value
NT-proBNP, ng/L	720 [329; 1600]	834 [350; 2150]	716 [327; 1532]	0.537	1320 [526; 3640]	6720 [2320; 6720]	807 [464; 3195]	0.057
CK, U/L	87 [52; 151]	62 [44; 195]	88 [57; 147]	0.772	102 [73; 159]	90 [68; 279]	109 [74; 157]	0.912
CK-MB, U/L	17.2 [13.3; 24.2]	13.6 [12.5; 24.2]	17.2 [13.5; 24.3]	0.522	16.6 [12.4; 20.3]	18.6 [12.9; 22.1]	16.5 [12.3; 20.1]	0.460
hsTroponin I, ng/L	0.11 [0.03; 24.0]	0.06 [0.03; 20.4]	0.11 [0.03; 24.5]	0.920	0.06 [0.02; 15.3]	0.03 [0.02; 0.08]	0.08 [0.02; 19.0]	0.069
CRP, mg/L	2.1 [1.1; 4.8]	1.8 [1.1; 4.5]	2.1 [1.1; 4.8]	0.805	3.0 [0.9; 16.0]	3.8 [1.5; 14.8]	2.8 [0.9; 16.2]	0.612
LDH, U/L	246 [222; 287]	265 [237; 301]	244 [222; 282]	0.011	240 [210; 280]	252 [222; 303]	238 [205; 277]	0.232
WBC, 10^9/L	7.24 [6.32; 9.03]	7.53 [6.44; 9.69]	7.20 [6.22; 8.85]	0.185	7.77 [6.70; 9.77]	8.34 [7.19; 10.29]	7.66 [6.61; 9.77]	0.375
Platelet, 10^9/L	227 [189; 266]	213 [176; 260]	230 [190; 268]	0.211	216 [172; 263]	206 [164; 241]	218 [173; 263]	0.418

CK = creatinine kinase; CRP = C reactive protein; hs = high sensitivity; LDH = Lactate dehydrogenase; mg/L = milligrams per liter; ng/L = nanograms per liter; NT-proBNP = N terminal pro brain natriuretic peptide; U/L = Units per liter; WBC = White blood cells.

Supplementary Table 3. Receiver operating characteristic analysis of annulus calcium volume for the association with an underexpanded valve.
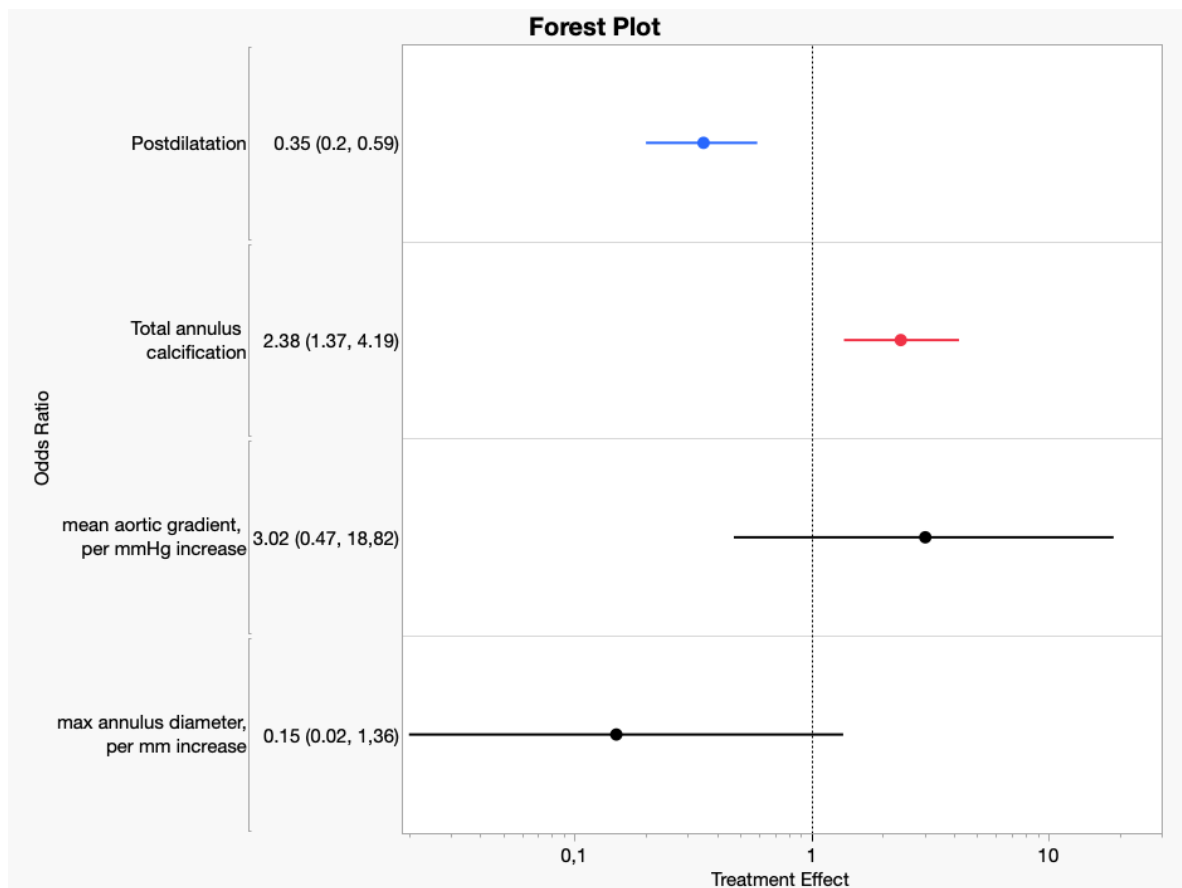
	AUC	95% CI	p	Se	Sp
Annulus calcium volume of 54mm^3	0.574	0.501 – 0.647	0.042	0.581	0.576

AUC = Area under the curve; CI = Confidence interval; mm^3 = cubic millimeters; Se = Sensitivity; Sp = Specificity

0						
At Risk	401	175	76	44	18	0
Events	0	53	78	95	102	110
1						
At Risk	73	35	24	16	7	0
Events	0	10	14	20	23	25

Supplementary Figure 1. Survival at longest available follow-up.

0 = Expanded; 1 = Under-expanded.

Supplementary Figure 2. Forest plot of factors associated with an underexpanded valve.

mm = millimeters; mmHg = millimeters mercury.