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ORIGINAL RESEARCH

Valve Underexpansion and Clinical Outcomes With ACURATE neo2

Findings From the ACURATE IDE Trial

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ABSTRACT

BACKGROUND In the ACURATE IDE (Safety and Effectiveness Study of ACURATE Valve for Transcatheter Aortic Valve Replacement) randomized controlled trial, ACURATE neo2 failed to show noninferiority to commercially available balloon-expandable (SAPIEN 3/3 Ultra) and self-expanding (Evolut R/PRO/PRO+/FX) valves for the primary endpoint of all-cause mortality, stroke, or rehospitalization at 1 year. A retrospective investigation was undertaken to evaluate potential factors contributing to these outcomes.

OBJECTIVES The goal of this study was to assess the impact of ACURATE neo2 valve expansion on clinical outcomes in the ACURATE IDE trial.

METHODS Post hoc case review identified angulated (nonparallel) commissure posts in a few implanted ACURATE neo2 valves, indicating valve underexpansion. Procedural angiograms for all ACURATE neo2 valves implanted in the trial's main randomized cohort (n = 752) were inspected by an independent core laboratory. An exploratory analysis was performed to evaluate the association between valve expansion and clinical outcomes.

RESULTS Of the 624 patients who underwent implantation with the ACURATE neo2 and had evaluable procedural angiograms, 135 (21.6%) had underexpanded valves. Greater aortic valve leaflet and annulus calcification at baseline was independently associated with ACURATE neo2 valve underexpansion (OR: 1.92; 95% CI: 1.27-2.91; $P = 0.002$). Procedural techniques, including frequency of predilation (100% in both groups) and postdilation (26.7% vs 25.2%; $P = 0.72$), and balloon sizing did not differ between the underexpanded and expanded valve groups. ACURATE neo2 underexpansion was associated with a higher 1-year rate of death, stroke, or rehospitalization (underexpanded: 18.7%; expanded: 11.8%; $P = 0.04$), which was confirmed in a multivariable analysis (HR: 1.92; 95% CI: 1.27-2.91; $P = 0.002$).

CONCLUSIONS Underexpansion of the ACURATE neo2 valve in the ACURATE IDE study was associated with a higher risk of the composite endpoint of death, stroke, or rehospitalization. Given the post hoc nature of these analyses, the study findings should be considered hypothesis generating. Whether achieving optimal valve expansion of the ACURATE neo2 valve with improvement in device design and procedural iterations will translate into improved clinical outcomes remains to be studied. (JACC. 2025;86:225-238) © 2025 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BAV = balloon aortic valvuloplasty

LVOT = left ventricular outflow tract

PVL = paravalvular leak

TAVR = transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is a well-established, minimally invasive alternative to surgery for patients with severe aortic stenosis across all risk categories.[1-5] The open-cell, self-expanding supra-annular ACURATE neo2 transcatheter heart valve (Boston Scientific) was designed to provide superior hemodynamics, preserve coronary access after TAVR, pose minimal risk of conduction disturbance, and minimize paravalvular leak (PVL) through the addition of an extended pericardial skirt.[6,7]

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The ACURATE IDE (Safety and Effectiveness Study of ACURATE Valve for Transcatheter Aortic Valve Replacement) randomized controlled trial evaluated TAVR outcomes with ACURATE neo2 vs a control group treated with commercially available balloon-expandable (SAPIEN 3/3 Ultra; Edwards Lifesciences) and self-expanding (Evolut R/PRO/PRO+/FX; Medtronic) valves, with the goal of supporting submission for U.S. Food and Drug Administration approval in the United States. The primary findings from the ACURATE IDE randomized controlled trial are published simultaneously in *The Lancet*.[8] The study failed to show noninferiority for the primary endpoint of composite of all-cause mortality, stroke, or rehospitalization at 1 year using a Bayesian approach (ACURATE neo2: 16.16%; Control: 9.53%; posterior median difference: 6.63%; 95% Bayesian credible interval: 3.04%-10.20%).[8] Although observational European clinical studies and registries have reported comparable clinical performance of the ACURATE valve,[9-12] two previous randomized trials evaluating the ACURATE neo valve also did not achieve noninferiority of the ACURATE neo valve compared with the SAPIEN (SCOPE 1 [Safety and Efficacy of the Symetis ACURATE Neo/TF Compared to the Edwards SAPIEN 3 Bioprosthesis] trial)[13] and the Evolut (SCOPE 2 [Safety and Efficacy Comparison of Two TAVI Systems in a Prospective Randomized Evaluation II] trial) valves.[14] As such, a detailed retrospective investigation was undertaken to evaluate potential factors associated with worse clinical outcomes with the ACURATE neo2 valve in the ACURATE IDE trial. A leading procedural factor that emerged from this review of cases was underexpansion of the ACURATE neo2 valve.

Valve underexpansion has the potential to compromise the mechanics of leaflet function and impair valve hemodynamics.[15-17] Previous studies in both balloon-expandable and self-expanding valves have shown that suboptimal expansion or deformation of the prosthesis can result in leaflet thickening and/or restricted leaflet mobility, increasing thromboembolic risk.[18-20] Periprocedural assessment of valve expansion is possible[21] but is not routinely done in current clinical practice. Also, techniques to optimize bioprosthesis expansion through predilation and postdilation of the aortic valve have been described but may be performed selectively.[22]

In the observational post hoc analyses described here, we present a method to detect underexpansion of the ACURATE neo2 valve with fluoroscopy images obtained during the index TAVR procedure. Exploratory analyses were performed to evaluate procedural factors, anatomical variables, and deployment techniques associated with ACURATE neo2 valve frame underexpansion. We also explored the association between ACURATE neo2 valve frame expansion and echocardiographic and clinical outcomes in the ACURATE IDE trial.

METHODS

TRIAL DESIGN AND OVERSIGHT. The ACURATE IDE trial was a multicenter, randomized controlled, noninferiority study conducted at 71 centers across the United States and Canada (NCT03735667). The protocol was designed in collaboration with Boston Scientific (sponsor) and the principal investigators, and it received approval from Institutional Review Boards at each participating site. The trial adhered to the principles of Good Clinical Practice and the Declaration of Helsinki. The sponsor provided funding and managed site selection, data collection, and statistical analyses. An independent steering committee

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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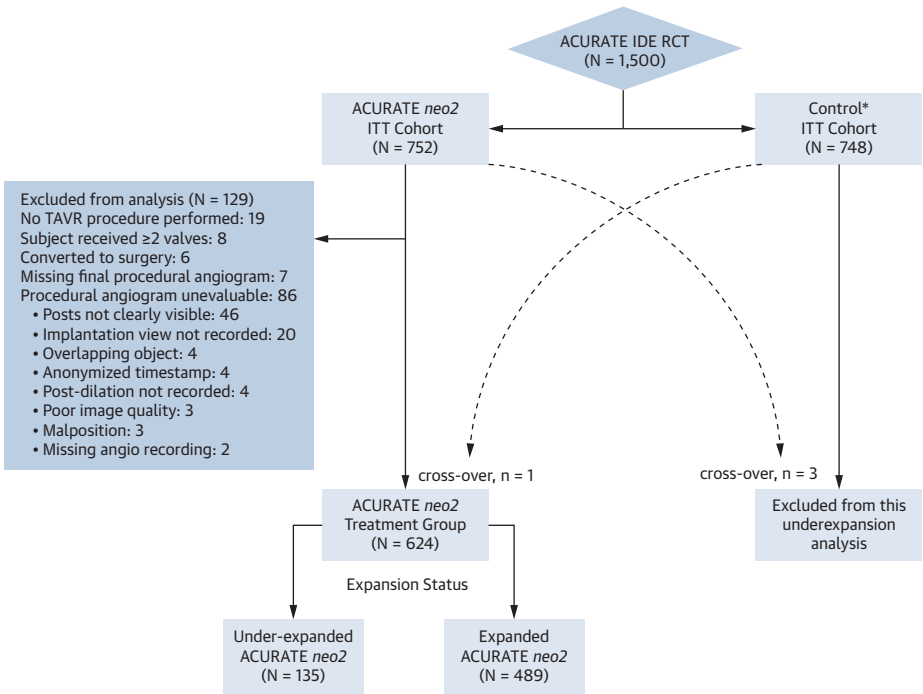
FIGURE 1 ACURATE IDE Expansion Analysis Population



The ACURATE IDE trial enrolled 1,500 patients, who were randomized 1:1 to undergo transcatheter aortic valve replacement (TAVR) with either ACURATE neo2 or a commercially available valve (Control). The ACURATE IDE Expansion Analysis population (n = 624) comprises the ACURATE neo2 Treatment Group, which excludes patients who did not undergo a TAVR procedure after randomization, underwent implantation with >1 valve, underwent conversion to open heart surgery, or did not have an evaluable final procedural aortogram. There were 4 cross-over subjects: 1 subject assigned to the Control arm received an ACURATE valve; 3 subjects assigned to the ACURATE arm received a Control valve. *Control devices included balloon-expandable (SAPIEN 3/3 Ultra) or self-expanding (Evolut R/PRO/PRO+/FX) valves. ITT = intention-to-treat; RCT = randomized controlled trial.

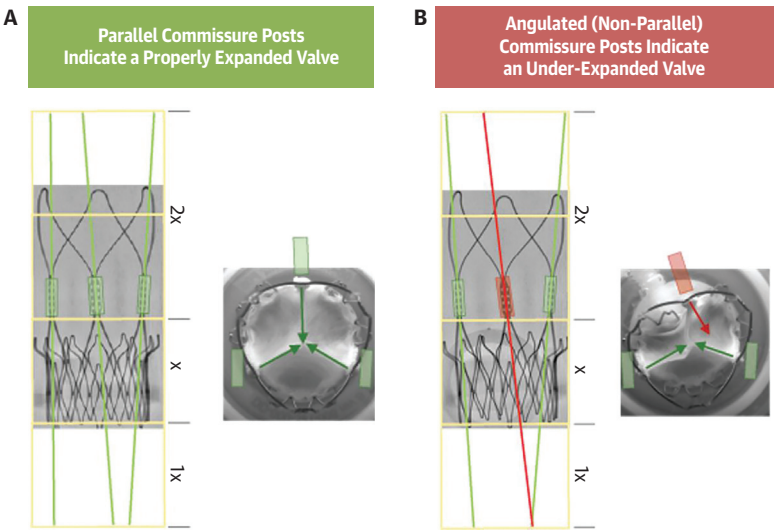
provided scientific oversight; clinical events were adjudicated by an independent clinical events committee; and safety was reviewed by an independent data monitoring committee.

Trial participants were randomized 1:1 to receive either the ACURATE neo2 valve or a commercially available balloon-expandable (SAPIEN 3/3 Ultra) or self-expanding (Evolut R/PRO/PRO+/FX) valve using a block randomization approach stratified according to center and intended control device (ie, the intended control valve type was selected by the operator before randomization to treatment arm).

PATIENT POPULATION. The ACURATE IDE trial enrolled 1,500 patients with symptomatic severe aortic stenosis who were deemed by the heart team to be eligible for transfemoral TAVR. Details on the full ACURATE IDE trial population have been reported previously.[8] The analyses described here exclude patients randomized to the Control arm. From among patients randomized to the ACURATE neo2 arm, these analyses exclude patients who did not undergo a TAVR procedure after randomization, underwent implantation with >1 valve, or underwent conversion to open heart surgery (Figure 1). Patients were stratified based on the actual valve received, regardless of the randomized group to which they were assigned (ie, crossovers from Control to ACURATE neo2 were included, and from ACURATE neo2 to Control were excluded). Assessment of ACURATE neo2 valve expansion was undertaken for patients with one ACURATE neo2 valve implanted in the correct anatomical position and who had an evaluable final procedural aortogram; this group comprises the ACURATE IDE Expansion analysis population.

VALVE DEPLOYMENT AND IMAGING PROTOCOL. The TAVR procedure was performed as per standard techniques established at the start of the trial. CT angiograms were performed per the CT angiography core laboratory procedure guidelines. An independent case review committee provided valve size

FIGURE 2 Visual Criteria to Define Commissure Post Angulation and Underexpansion of ACURATE neo2 Valves in a Bench-Top Model



Easily identifiable visual criteria to define commissure post angulation were established as follows: a line drawn through the longitudinal axis of a single commissure post of the ACURATE neo2 valve crossing over lines drawn through the longitudinal axis of one of the other two commissure posts, within a defined boundary, which is defined as the length of the stent frame plus 1× the length of the lower stent frame (yellow boxes). (A) In a properly expanded valve, the lines drawn through the commissure posts (green lines) do not cross over each other within the boundary box (yellow boxes); the en face view of the valve confirms the valve stent frame is circular and properly expanded, with good leaflet coaptation/apposition (inset, green arrows). (B) In an underexpanded valve, 2 of the lines drawn through the posts (green lines) are nearly parallel within the boundary box (yellow boxes), while the third (red dashed line) crosses over one of the others; as seen in the en face view, the nonparallel post contributes to poor circularization and underexpansion of the valve stent frame, and results in leaflet pin-wheeling and creasing (inset, red arrow).

recommendations based on CT imaging-derived annulus measurements at baseline; however, final selection of valve size implanted was at the operators' discretion. Predilation of the native valve via balloon aortic valvuloplasty (BAV) was mandatory before ACURATE neo2 implantation; training materials for the ACURATE IDE study recommended predilation of ACURATE neo2 with a BAV balloon sized up to 1 mm smaller than the CT perimeter-derived diameter of the aortic valve annulus. In the Control group, predilation was performed according to the commercial valve instructions for use. A postprocedure aortogram was recommended for all patients. A subset of patients were enrolled in the CT substudy and underwent cardiac CT imaging with contrast at 30 days and 1 year after TAVR.

ASSESSMENT OF ACURATE NEO2 VALVE UNDEREXPANSION. The evaluable aortograms of the ACURATE neo2 valves obtained during the index TAVR procedures were analyzed by an independent angiographic core laboratory (CORRIB Research Centre for Advanced Imaging and Core Laboratory [directed by O.S.]) to evaluate valve frame expansion. Detailed methodology is described in **Figure 2**, Supplemental Material, and Supplemental Figures 2 to 4.

A boundary box was drawn from the bottom of the lowest valve commissure post(s) to the bottom of the lower crowns of the valve (noted by dimension "X" in **Figure 2**). The lowest valve commissure post(s) was selected to ensure that the correct boundary was drawn in cases in which there was parallax visible on the implanted valve. This box was replicated twice on top (2X in **Figure 2**) and once on the bottom (1X in **Figure 2**) of the stent body, with this full area defining the "boundary" of the assessment area. Once the boundary was set (yellow lines in **Figure 2**), a straight line was drawn through the center of each of the commissural posts and extended to the top and bottom of the box boundaries. If any 2 of these lines intersected within the boundary conditions, the valve was deemed to be underexpanded. All other configurations of lines within the boundary conditions were deemed to be fully expanded. To understand how commissure post angulation might correlate with overall valve conformation, the condition was replicated and evaluated in a bench-top model, in which the nonparallel post was found to contribute to poor

circularization and underexpansion of the valve stent frame, resulting in leaflet pin-wheeling and creasing.

To assess the validity of the valve frame underexpansion analysis, 3-dimensional models were created from the 30-day CT scans available in 10 cases: n = 5 from the small group with worst case valve frame underexpansion on aortogram and CT imaging; and n = 5 from the group with normally expanded valve frames on aortogram and CT imaging. The review of these 3-dimensional models confirmed the different degrees of valve frame underexpansion (Supplemental Figure 5).

CLINICAL AND ECHOCARDIOGRAPHIC OUTCOMES. The primary endpoint of the ACURATE IDE trial was a composite of death, stroke, or rehospitalization due to valve-related symptoms or worsening heart failure (classified as NYHA functional class III or IV) at 1 year. Key secondary endpoints prespecified in the ACURATE IDE trial, including the individual components of the primary endpoint, composite of death or stroke, cardiovascular death, myocardial infarction, bleeding, vascular complications, acute kidney injury, repeat procedure for valve-related dysfunction, permanent pacemaker implantation, clinical valve thrombosis, and new-onset atrial fibrillation, were assessed according to Valve Academic Research Consortium-2 criteria.[23] Clinical outcomes at 1 year in patients treated with the ACURATE neo2 were stratified according to valve expansion status. Both prespecified 30-day and 1-year secondary clinical outcomes were analyzed. Echocardiographic assessments were performed by an independent core laboratory and included effective orifice area, mean transvalvular gradient, doppler velocity index, and the presence and severity of paravalvular aortic regurgitation. The clinical and echocardiographic outcomes were assessed to determine the clinical significance of valve underexpansion. The impact of device learning curve on valve expansion was assessed in multiple ways, stratifying patients based on terciles of patient enrollment according to the procedure date, sites performing less than the median or greater than or equal to the median number of cases, or sites enrolling <5 or ≥5 patients.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD, and categorical variables are reported as percentages. Differences between groups were evaluated by using the Student's *t*-test for continuous variables and the chi-square or Fisher exact test for categorical variables. Comparisons of clinical outcomes on a time-to-event basis were performed by using the Kaplan-Meier method, with group comparisons made by using the log-rank test. Multivariable Cox proportional analyses were performed to evaluate the association between valve underexpansion and clinical outcomes, with a *P* value <0.05 considered statistically significant.

TABLE 1 Baseline Characteristics Stratified According to ACURATE neo2 Expansion Status; ACURATE IDE Expansion Analysis Population (N = 624)

	Underexpanded ACURATE neo2 (n = 135)	Expanded ACURATE neo2 (n = 489)	*P* Value
Age, y	77.7 ± 7.2	78.0 ± 6.9	0.61
Male	66 (48.9)	225 (46.0)	0.55
Risk assessment			
NYHA functional class			
I	0 (0.0)	0 (0.0)	-
II	68 (50.4)	247 (50.5)	0.98
III	62 (45.9)	236 (48.3)	0.63
IV	5 (3.7)	6 (1.2)	0.07
STS score, %	2.6 ± 1.8	2.7 ± 1.9	0.53
EuroSCORE II, %	2.8 ± 2.4	2.6 ± 2.5	0.60
Operative risk (per heart team assessment)			
High/extreme operative risk	33 (24.4)	122 (24.9)	0.90
Intermediate operative risk	52 (38.5)	188 (38.4)	0.99
Low operative risk	50 (37.0)	179 (36.6)	0.93
Medical history			
Diabetes mellitus, medically treated	48 (35.6)	148 (30.3)	0.24
Hyperlipidemia	120 (88.9)	412 (84.3)	0.18
Hypertension	123 (91.1)	434 (88.8)	0.43
Peripheral vascular disease	9 (6.7)	55 (11.2)	0.12
Chronic obstructive pulmonary disease	13 (9.6)	62 (12.7)	0.33
Coronary artery disease	72 (53.3)	253 (51.7)	0.74
Prior myocardial infarction	14 (10.4)	41 (8.4)	0.47
Congestive heart failure	37 (27.4)	159 (32.5)	0.26
Prior percutaneous coronary intervention	28 (20.7)	103 (21.1)	0.94
Prior coronary artery bypass graft	16 (11.9)	55 (11.2)	0.84
Atrial fibrillation/atrial flutter	35 (25.9)	109 (22.3)	0.37
Prior stroke	8 (5.9)	36 (7.4)	0.56
Echocardiographic measures (core laboratory assessed)			
Aortic valve area, cm^2	0.66 ± 0.14	0.68 ± 0.14	0.15
Mean aortic valve pressure gradient, mm Hg	41.9 ± 12.0	39.1 ± 10.6	0.01
LVEF, %	53.9 ± 9.5	56.9 ± 7.0	0.005
Doppler velocity index	0.23 ± 0.05	0.24 ± 0.05	0.03
CT measures (core laboratory assessed)			
Annulus			
Maximum, mm	26.4 ± 2.1	26.2 ± 1.9	0.35
Perimeter, mm	75.4 ± 5.1	74.5 ± 5.1	0.07
Area, mm^2	442.9 ± 59.2	431.4 ± 58.9	0.05
LVOT			
Maximum, mm	27.2 ± 2.2	26.8 ± 2.2	0.04
Perimeter, mm	74.7 ± 6.0	73.3 ± 6.4	0.03
Area, mm^2	424.3 ± 70.6	409.6 ± 73.7	0.04
Total volume of leaflet and annulus calcification, mm^3	556.9 ± 367.1	455.1 ± 297.6	<0.001

Values are mean ± SD or n (%).

EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; STS = Society of Thoracic Surgeons.

TABLE 2 Procedural Characteristics Stratified by ACURATE neo2 Expansion Status; ACURATE IDE Expansion Analysis Population (N = 624)

	Underexpanded ACURATE neo2 (n = 135)	Expanded ACURATE neo2 (n = 489)	*P* Value
Total procedure time, min	60.5 ± 27.1	59.2 ± 25.0	0.59
Total time with study valve delivery system, min	9.1 ± 7.3	9.8 ± 8.5	0.43
Anesthesia type			
General anesthesia	50 (37.0)	163 (33.3)	0.42
Conscious sedation	85 (63.0)	326 (66.7)	0.42
Total contrast media used for procedure, mL	116.6 ± 63.4	115.7 ± 61.8	0.89
Total fluoroscopy time, min	18.2 ± 8.2	18.0 ± 7.7	0.75
Predilation information			
BAV used during index procedure	135 (100.0)	489 (100.0)	-
Predilation maximum balloon diameter, mm	22.2 ± 1.8	21.9 ± 1.9	0.11
Difference of predilation balloon diameter from annulus-derived diameter			
0-1 mm	19 (14.1)	79 (16.2)	
1-2 mm	57 (42.2)	219 (44.8)	
2-3 mm	40 (29.6)	138 (28.2)	
3-4 mm	11 (8.1)	24 (4.9)	
>4 mm	3 (2.2)	16 (3.3)	
No. of predilations			0.52
1	123 (91.1)	451 (92.4)	0.62
2	10 (7.4)	33 (6.8)	0.79
≥3	2 (1.5)	4 (0.8)	0.62
New conduction disturbance after BAV	16 (11.9)	66 (13.5)	0.62
New requirement for pacing	3 (2.2)	8 (1.6)	0.71
New LBBB	7 (5.2)	38 (7.8)	0.30
New RBBB	1 (0.7)	2 (0.4)	0.52
AV block I	1 (0.7)	2 (0.4)	0.52
AV block II	0 (0.0)	0 (0.0)	-
Other	4 (3.0)	16 (3.3)	1.00
Postdilation information			
Postdilation performed	36 (26.7)	123 (25.2)	0.72
Postdilation maximum balloon diameter, mm	22.9 ± 1.9	23.1 ± 1.8	0.52
No. of postdilations			0.36
1	33 (91.7)	108 (87.8)	0.77
2	3 (8.3)	11 (8.9)	1.00
≥3	0 (0.0)	4 (3.3)	0.58
Valve size implanted			
23 mm (small)	22 (16.3)	113 (23.1)	0.09
25 mm (medium)	50 (37.0)	181 (37.0)	1.00
27 mm (large)	63 (46.7)	195 (39.9)	0.16

Values are mean ± SD or n (%).

AV = atrioventricular; BAV = balloon aortic valvuloplasty; LBBB = left bundle branch block; RBBB = right bundle branch block.

Multivariable logistic regression was used to identify baseline patient and procedural characteristics associated with valve underexpansion, defined as a binary procedural outcome.

Analyses were performed by using SAS version 9.4 or later (SAS Institute, Inc).

RESULTS

BASELINE AND PROCEDURAL DATA IN ACURATE NEO2 GROUP. The ACURATE IDE trial enrolled 1,500 patients, randomly assigning 752 patients to the ACURATE neo2 arm and 748 to the Control arm. Of the 752 patients randomized to the ACURATE neo2 group, 19 did not undergo TAVR, 8 required implantation of >1 valve, and 6 converted to surgery. In addition, 93 patients either lacked a final angiogram (n = 7) or had angiograms unsuitable for evaluation (n = 86), leaving 624 patients available for the valve frame expansion analysis presented in this article (Figure 1). ACURATE neo2 frame underexpansion was noted in 21.6% (135 of 624) of patients.

Table 1 summarizes the baseline clinical, echocardiographic, and CT imaging-assessed aortic valve annular characteristics of patients with underexpanded and expanded ACURATE neo2 valves. The overall mean age was 78 years, and 53% were female. There was no significant difference between expansion groups in terms of Society of Thoracic Surgeons score, NYHA functional class, or heart team-assessed surgical risk.

CT characteristics are also summarized in Table 1. The underexpanded group, compared with the expanded group, was associated with significantly larger aortic valve annular measurements (area 442.9 ± 59.2 mm^2 vs 431.4 ± 58.9 mm^2; $P = 0.046$). Left ventricular outflow tract (LVOT) measurements were also significantly greater in patients with underexpanded valves compared with expanded group (LVOT area 424.3 ± 70.6 mm^2 vs 409.6 ± 73.7 mm^2 [$P = 0.039$] and LVOT perimeter (74.7 ± 6.0 mm vs 73.3 ± 6.4 mm [$P = 0.03$]). The total leaflet and annulus calcification volume was significantly greater in the underexpanded group compared with the expanded group (556.9 ± 367.1 mm^3 vs 455.1 ± 297.6 mm^3; $P < 0.001$). In multivariable analysis, greater total valve calcification (ie, leaflet and annulus calcification >75th percentile) at baseline was independently associated with underexpansion (OR: 1.92; 95% CI: 1.27-2.91; $P = 0.002$) (Supplemental Table 1).

On echocardiography, the mean aortic valve area was not different between the 2 groups at baseline. There were statistically significant differences in the mean aortic valve gradient (41.9 ± 12.0 mm Hg vs 39.1 ± 10.6 mm Hg; $P = 0.01$), left ventricular ejection fraction (53.9% ± 9.5% vs 56.9% ± 7.0%; $P = 0.005$),

TABLE 3 Clinical Outcomes Stratified by ACURATE neo2 Expansion Status; ACURATE IDE Expansion Analysis population (N = 624)

	30 Days			1 Year		
	Underexpanded ACURATE neo2 (n = 135)	Expanded ACURATE neo2 (n = 489)	*P* Value	Underexpanded ACURATE neo2 (n = 135)	Expanded ACURATE neo2 (n = 489)	*P* Value
Death, stroke, or rehospitalization[a]	5 (3.7)	11 (2.3)	0.36	25 (18.7)	57 (11.8)	0.04
Death	0 (0.0)	3 (0.6)	1.00	9 (6.8)	18 (3.7)	0.14
Cardiovascular	0 (0.0)	2 (0.4)	1.00	7 (5.3)	14 (2.9)	0.19
Noncardiovascular	0 (0.0)	1 (0.2)	1.00	2 (1.5)	4 (0.8)	0.49
Stroke	2 (1.5)	4 (0.8)	0.62	10 (7.7)	20 (4.2)	0.11
Disabling	1 (0.7)	2 (0.4)	0.52	2 (1.5)	8 (1.7)	0.91
Nondisabling	1 (0.7)	3 (0.6)	1.00	8 (6.2)	13 (2.7)	0.06
Death or stroke	2 (1.5)	7 (1.4)	1.00	18 (13.5)	35 (7.3)	0.02
Rehospitalization[a]	3 (2.2)	4 (0.8)	0.18	7 (5.3)	24 (5.0)	0.89
Myocardial infarction	3 (2.2)	1 (0.2)	0.03	4 (3.0)	11 (2.3)	0.61
Periprocedural (within 72 h of procedure)	2 (1.5)	0 (0.0)	0.05	2 (1.5)	0 (0.0)	0.01
Spontaneous (>72 h after procedure)	1 (0.7)	1 (0.2)	0.39	2 (1.5)	11 (2.3)	0.59
Bleeding	6 (4.4)	12 (2.5)	0.25	9 (6.7)	25 (5.2)	0.46
Life-threatening or disabling	2 (1.5)	6 (1.2)	0.69	3 (2.2)	14 (2.9)	0.70
Major	4 (3.0)	6 (1.2)	0.24	6 (4.5)	12 (2.5)	0.21
Major vascular complication	6 (4.4)	10 (2.1)	0.13	7 (5.2)	10 (2.0)	0.05
Access site related	5 (3.7)	9 (1.8)	0.20	6 (4.4)	9 (1.8)	0.08
Non-access site related	1 (0.7)	1 (0.2)	0.39	1 (0.7)	1 (0.2)	0.33
Acute kidney injury (stage 2/3)	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Repeat procedure for valve-related dysfunction	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (0.2)	0.60
TAVR	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Valvuloplasty	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (0.2)	0.60
Surgical AVR	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (0.2)	0.60
New permanent pacemaker implantation	7 (5.2)	43 (8.8)	0.17	9 (6.7)	55 (11.3)	0.12
Clinical valve thrombosis	1 (0.7)	0 (0.0)	0.22	2 (1.5)	2 (0.4)	0.16
New onset of atrial fibrillation or atrial flutter	2 (1.5)	12 (2.5)	0.74	2 (1.5)	12 (2.5)	0.49

Values are binary rates at 30 days and time-to-event rates at 1 year, and are presented as n (%). The event rates at 1 year are Kaplan-Meier rates. [a]Rehospitalization due to valve-related symptoms or worsening heart failure (classified as NYHA functional class III or IV), according to Valve Academic Research Consortium-2 criteria.

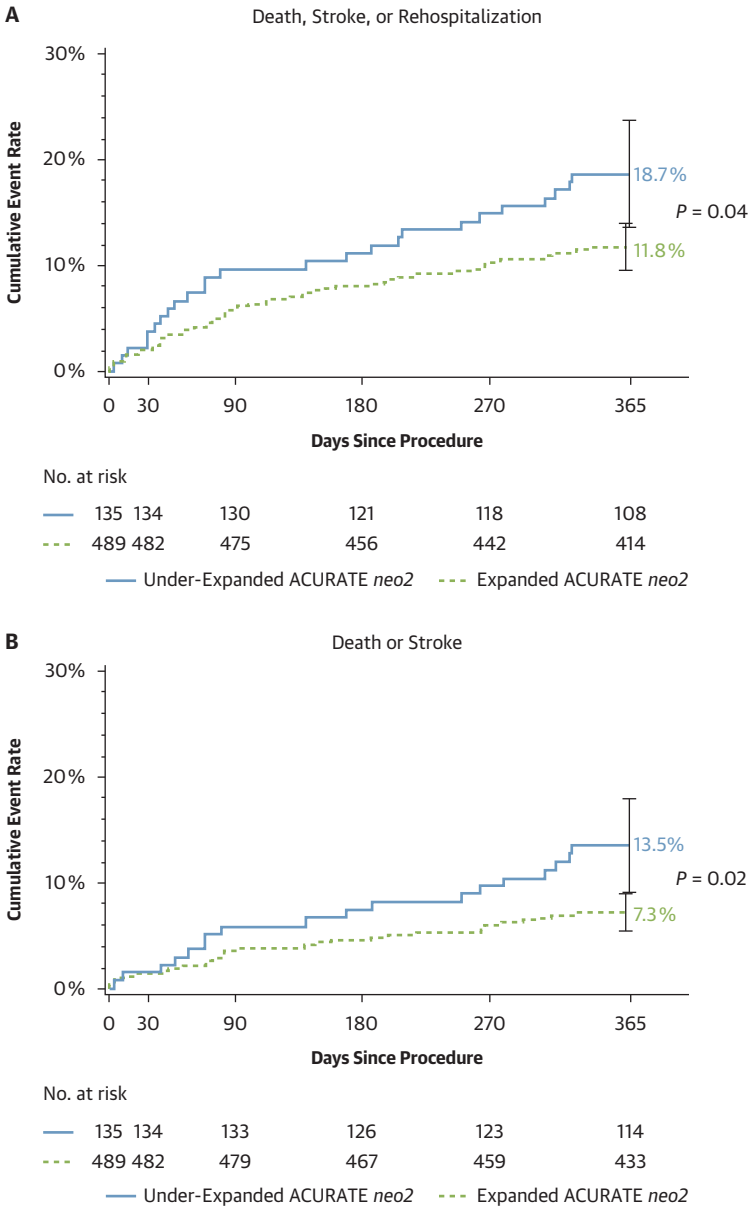
AVR = aortic valve replacement; TAVR = transcatheter aortic valve replacement.

and Doppler velocity index ratio (0.23 ± 0.05 vs 0.24 ± 0.05; $P = 0.03$) between the underexpanded and expanded groups.

Procedural characteristics of the underexpanded and expanded ACURATE neo2 groups are summarized in Table 2. The distribution of implanted valve sizes was similar between groups. Predilation of the aortic valve was performed in 100% of patients treated with ACURATE neo2. Predilation of ACURATE neo2 with a BAV balloon sized up to 1 mm smaller than the aortic valve annulus diameter was followed in 15.7% of cases overall, with similar rates in the underexpanded (14.1%) and expanded (16.2%) groups. Predilation with a BAV balloon sized >1 mm smaller, but <2 mm smaller, than the aortic valve annulus diameter was performed in 44.2% of cases (underexpanded group: 42.2%; expanded group: 44.8%). There was no difference in the incidence of ACURATE neo2 valve expansion in patients who underwent predilation with the balloon diameter within 1 mm of the aortic valve annulus diameter (underexpanded group 14.1% [19 of 125] vs expanded group 16.2% [79 of 489]). There was no difference in the frequency of postdilation between underexpanded and expanded valve groups (26.7% vs 25.2%; $P = 0.72$). The incidence of new conduction disturbance after predilation was similar in the underexpanded and expanded groups (11.9% vs 13.5%; $P = 0.62$).

CLINICAL AND ECHOCARDIOGRAPHIC OUTCOMES. Clinical outcomes of the underexpanded and expanded ACURATE neo2 groups are summarized in Table 3, Figure 3, and the Central Illustration. At 30 days, there was no significant difference between ACURATE neo2 expansion groups for the combined endpoint of death, stroke, or rehospitalization (3.7% vs 2.3%; $P = 0.36$), or for its individual components. At 1 year, patients with underexpanded valves, compared with expanded valves, had a significantly higher risk for the composite of death, stroke, or

FIGURE 3 Clinical Outcomes Through 1 Year in the ACURATE IDE Expansion Analysis Population (N = 624)

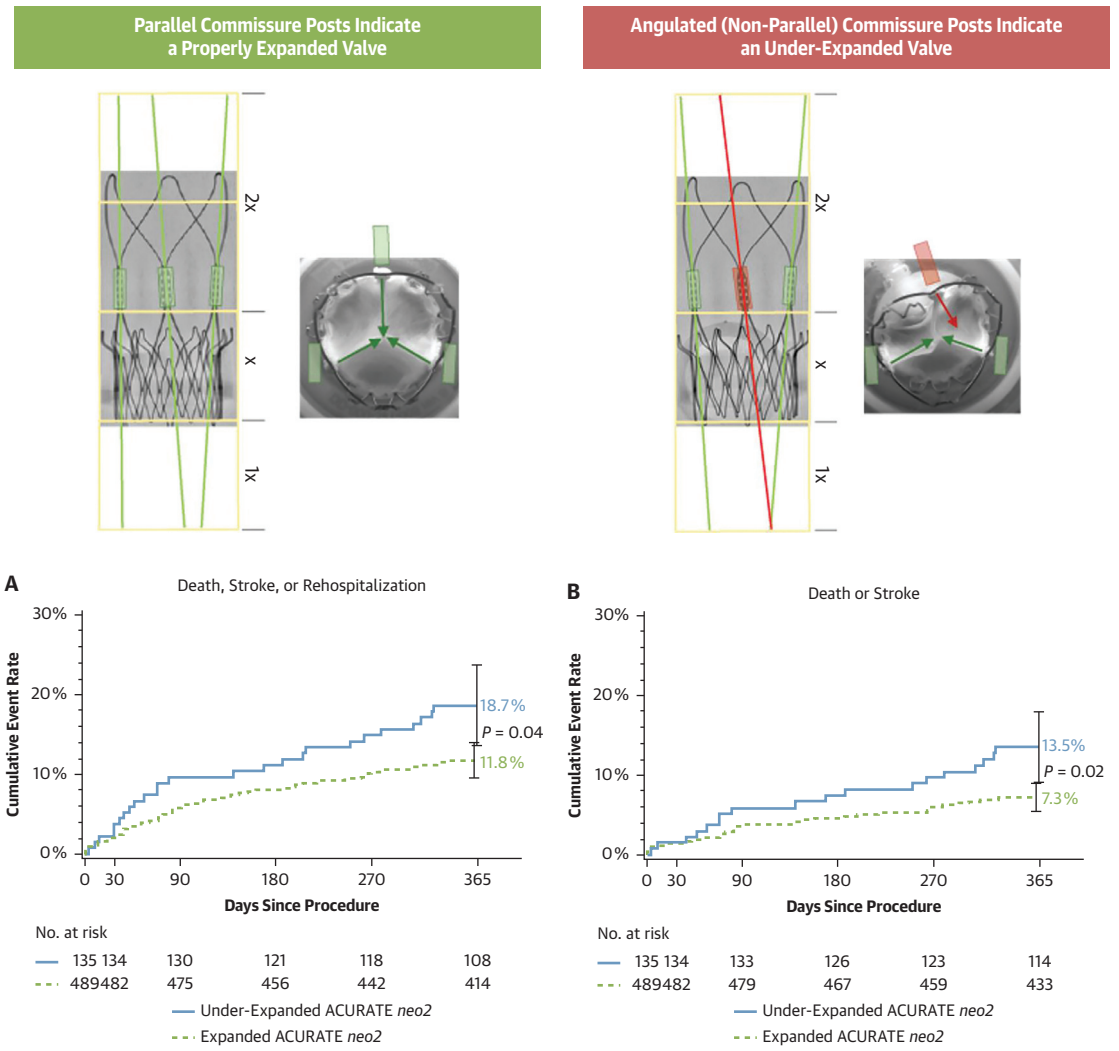


(A) The primary endpoint, a composite of death, stroke, or rehospitalization at 1 year, was assessed in patients treated with underexpanded (blue line; n = 135) and expanded (green dashed line; n = 489) ACURATE neo2 valves. (B) Time to event curves are also shown for death or stroke.

rehospitalization (18.7% vs 11.8%; $P = 0.04$), as well as for the composite of death or stroke (13.5% vs 7.3%; $P = 0.02$). In multivariable analysis, underexpansion of the ACURATE neo2 valve (OR: 1.80; 95% CI: 1.05-3.08; $P = 0.03$) and elevated surgical risk (Society of Thoracic Surgeons score >3%) at baseline (OR: 2.80; 95% CI: 1.72-4.56; $P < 0.001$) were independently associated with a greater risk of the composite endpoint of death, stroke, or rehospitalization at 1 year (Supplemental Table 2).

The incidence of clinical valve thrombosis at 1 year was low and similar in the underexpanded ACURATE

CENTRAL ILLUSTRATION **ACURATE neo2 Valve Frame Underexpansion and Clinical Outcomes**



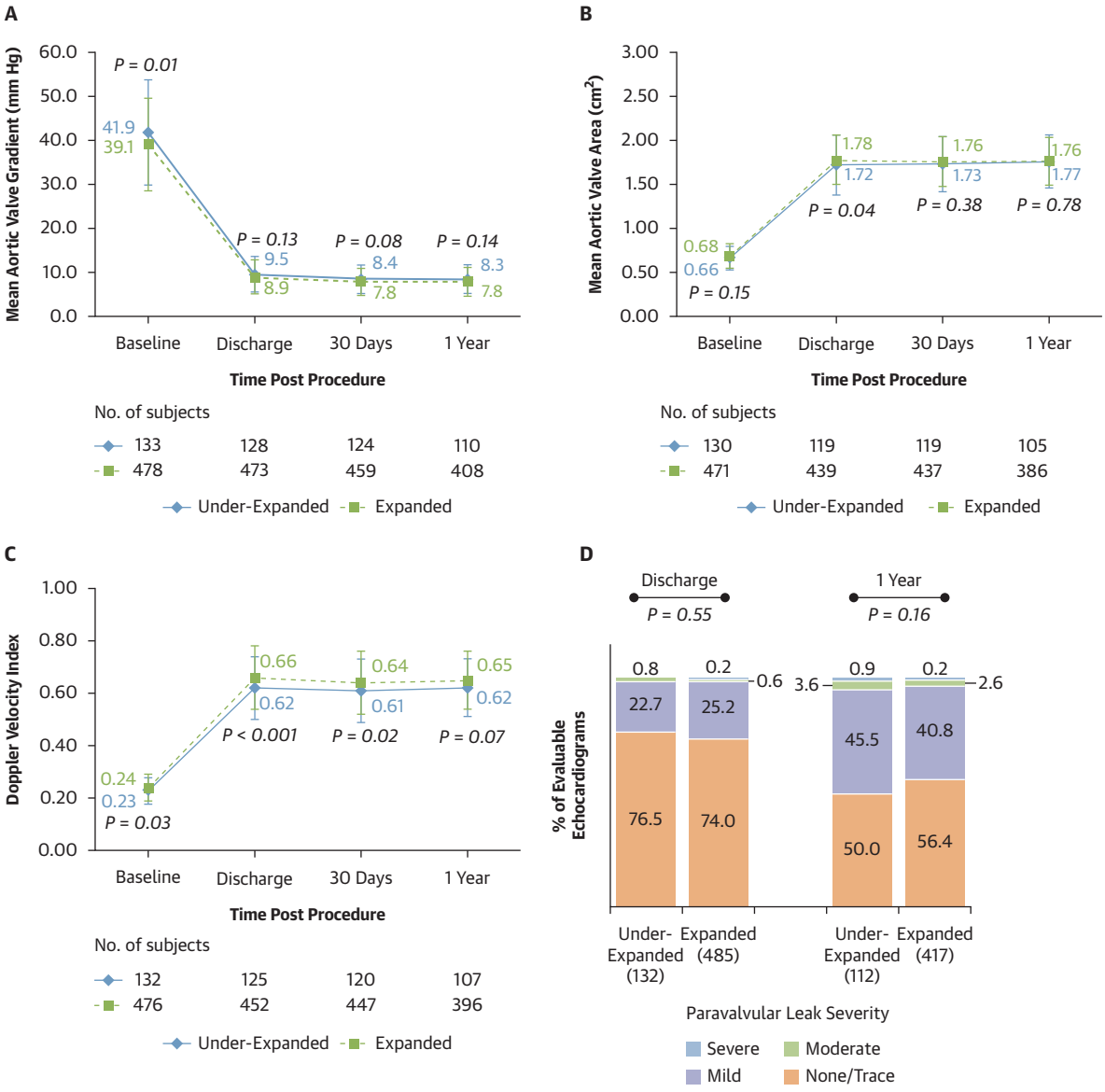
Makkar RR, et al. JACC. 2025;86(4):225–238.

Underexpansion was observed in 21.6% of the ACURATE neo2 valves in the ACURATE IDE study and was associated with higher risk of the composite endpoint of death, stroke, or rehospitalization.

neo2 group compared with the expanded group (2 of 135 [1.5%] vs 2 of 489 [0.4%]; $P = 0.16$) (Table 3). There was no significant difference in the incidence of subclinical leaflet thrombosis in the subset of patients who received a repeat CT image, as assessed by hypoattenuated leaflet thickening, at 30 days (1 of 20 [5.0%] vs 25 of 90 [27.8%]; $P = 0.08$) between the underexpanded and expanded groups.

Echocardiographic outcomes are summarized in Figure 4. There was no significant difference in mean aortic valve gradient between patients with underexpanded and expanded valves at 30 days or 1 year. There was no significant difference in moderate (4.5% vs. 3.8%; $P = 0.78$) or severe (0.9% vs 0.2%; $P = 0.38$) total aortic regurgitation between underexpanded and expanded groups at 1 year. Similarly, there was no significant difference in the incidence of moderate (4.0% vs 3.2% [$P = 0.59$] at 30 days and 3.6% vs 2.6% [$P = 0.54$] at 1 year) or severe (0.0% vs 0.0% [P = NA] at 30 days; 0.9% vs 0.2% [$P = 0.38$] at 1 year)

FIGURE 4 Echocardiographic Outcomes; ACURATE IDE Expansion Analysis Population (N = 624)



Echocardiographic assessments were performed by an independent core laboratory and included mean aortic valve gradient (A), mean aortic valve area (B), Doppler velocity index (C), and the presence and severity of paravalvular aortic regurgitation (D).

paravalvular aortic regurgitation between the underexpanded and expanded valve groups.

IMPACT OF POSTDILATION ON ACURATE NEO2 VALVE EXPANSION. A subset of 137 patients (22%) had evaluable angiograms both before and after valve postdilation. Among these patients, 50 (36.5%) had valve underexpansion identified prior to postdilation. Following postdilation, valve underexpansion improved to the expanded valve category in 27 (54%) of these 50 patients, whereas residual underexpansion persisted in 23 patients (46%).

DEVICE LEARNING CURVE AND ACURATE NEO2 VALVE EXPANSION. There was no significant difference in valve frame underexpansion, when stratified according to terciles of patient enrollment by procedure date (23.2% vs 20.1% vs 21.6%; $P = 0.75$), sites performing less than the median or greater than or equal to the median number of cases (20.0% vs 23.5%;

$P = 0.29$), or sites enrolling <5 or ≥5 patients (19.9% vs 22.4%; $P = 0.48$).

DISCUSSION

This post hoc analysis of the ACURATE IDE trial produced several main findings. First, valve underexpansion was observed in approximately 1 of every 5 patients receiving the ACURATE neo2 valve. Second, greater aortic valvular calcification was associated with underexpansion, likely secondary to lower opening force of this valve. Third, ACURATE neo2 frame underexpansion was associated with an increased risk of the composite endpoint of death, stroke, or rehospitalization at 1 year, as well as death and stroke combined. Finally, the angiographic method introduced in this analysis can be applied intraprocedurally to identify ACURATE neo2 valve frame underexpansion. Importantly, this study underscores the clinical relevance of optimal bioprosthetic valve expansion, if safely achievable, a concept that may extend broadly to other transcatheter valve platforms.

The mechanism for the increased risk of death and/or stroke in patients with underexpanded ACURATE neo2 valves is unclear. Analogous to coronary stenting, in which suboptimal expansion increases the risk of stent thrombosis and subacute and midterm adverse events, the same principles likely apply to transcatheter valve underexpansion, in which full expansion is necessary to ensure adequate hemodynamic function and minimize the risk of microembolic events. Valve underexpansion may contribute to an increased risk of postprocedural adverse outcomes due to compromised leaflet mechanics and impaired valve hemodynamics, particularly through creation of turbulent flow and reduced washout, as well as heightened PVL resulting from incomplete sealing or valve deformation.[18-20,24] Studies of both balloon-expandable and self-expanding valves have suggested that incomplete expansion or prosthesis deformation can restrict leaflet motion, creating areas of low shear stress and low flow that promote thrombus formation[18-20,24]; other studies, including a recent meta-analysis, have suggested a link between subclinical leaflet thrombosis and increased risk of thromboembolic events.[25-27] In the current study, however, rates of clinical and subclinical thrombosis with the ACURATE neo2 valve were overall low and similar between the underexpanded and complete frame expansion groups; the limited sample size precludes definitive conclusions regarding any potential association between valve expansion and leaflet thrombosis, however. Although our findings remain exploratory, valve function seemed marginally worse in the underexpanded valves. It was not statistically significant, but PVL occurred numerically more often in underexpanded valves (mild PVL 46% vs 41%; moderate or greater PVL 4.5% vs 2.8%). Doppler velocity index, a potentially more sensitive and valve size- and flow-independent measure of valve function, was statistically significantly lower (unfavorable) in underexpanded valves; however, no significant differences were observed in aortic valve gradients or valve area. Notably, underexpansion was more frequent in patients with larger aortic annuli, which may have confounded the association between valve expansion and traditional measures such as gradients and valve area.

Our study findings are consistent with a recent retrospective study by Kim et al of data from 604 patients at 2 highly experienced European centers treated with the ACURATE neo2 valve.[28] The study found that underexpansion occurred in 13.9% of patients treated with ACURATE neo2 (compared with 21.6% in the ACURATE IDE study) and was associated with a significant 4-fold increase in the primary endpoint of death, stroke, or rehospitalization at 1 year. In these European patients, the rate of predilation was 86.8%, compared with nearly 100% in the ACURATE IDE trial; 47.7% of predilations in the European cohort were performed with a balloon sized 1 mm smaller than the annulus diameter, compared with 15.7% overall in the ACURATE IDE trial. The European study also evaluated the ability postdilation to resolve initial valve underexpansion; when balloon postdilation was performed using an appropriately sized balloon, underexpansion was mitigated in 89% of cases. In further exploring the relationship between postdilation and valve underexpansion in our own cohort, we analyzed a subset of 137 patients who had evaluable aortograms both before and after postdilation. In this subset, underexpansion resolved in approximately one-half of the cases (54%) after postdilation. Residual underexpansion persisted primarily due to borderline initial underexpansion, inadequate balloon sizing or positioning, and technical balloon preparation factors. It is important to note that postdilation in the ACURATE IDE trial was primarily performed to address PVL and gradients, rather than explicitly targeting valve underexpansion. These findings align closely with the observations by Kim et al, reinforcing postdilation as a critical but not universally effective strategy for fully resolving underexpansion. Given these findings, opportunities remain to further reduce underexpansion through device design

refinement and standardization of procedural techniques, including optimization of balloon sizing and procedural execution. Importantly, despite procedural differences, no association was observed between the device learning curve and valve underexpansion in the current analysis.

Traditionally, the decision to postdilate has been determined solely by the presence of PVL or high residual aortic valve gradients. It is plausible that ACURATE neo2 valve, given its low radial strength, may require more aggressive predilation with larger balloon size and more frequent postdilation to achieve adequate valve frame expansion. It remains to be determined whether more aggressive predilation with larger sized BAV balloons, or postdilation of the ACURATE neo2 valve based on the fluoroscopic assessment to optimize the frame expansion, will affect valve performance, durability, or clinical outcomes. The potential benefit of aggressive predilation and postdilation to achieve complete frame expansion should be carefully weighed against the risk of aortic root injury, stroke, and pacemaker rates. This is particularly relevant given that underexpansion was more frequent in patients with higher burden of total valvular calcium at baseline and may be at higher risk of aortic root injury. In fact, patients with severely calcified anatomies may benefit from cautious predilation and postdilation strategies, diligent intraprocedural imaging assessments to confirm adequate expansion and rule out aortic root injury, and consideration of alternative valve platforms with greater radial strength.

Learnings from the ACURATE IDE trial may have broader implications for understanding valve underexpansion in TAVR, extending beyond the ACURATE neo2 valve to other valve platforms. In the ACURATE IDE trial, most procedures used a single 3-cusp view for aortographic imaging, which may have precluded proper 3-dimensional assessment of valve expansion and led to an inability to assess proper expansion. In the current study, ACURATE neo2 underexpansion was determined by looking at the commissural posts from the 3-cusp view of the valve. Careful imaging guidance during deployment, such as angiographic assessments in multiple planes (eg, 3-cusp and cusp overlap views) or en face views, or echocardiographic modalities such as transesophageal echocardiogram, can further help identify any asymmetrical expansion or underexpansion at the time of implantation even if the initial assessment of valve expansion in a two-dimensional view appears to show a properly expanded stent.

STUDY LIMITATIONS. First, the post hoc nature of the analysis introduces the potential for bias. Evaluable procedural aortograms were not available for all patients due in large part to missing or poor-quality images. Second, data on underexpansion of the control valves were not available. Ideally, the outcomes of ACURATE neo2 expansion group should be compared with the fully expanded valves in the control group. Third, we did not validate underexpansion using post-TAVR CT imaging, which is considered the gold standard for assessing stent frame expansion. Instead, we relied on fluoroscopic criteria and bench testing to define and evaluate underexpansion, which may not capture the full extent of 3-dimensional valve geometry. Although the approach is attractive for potential clinical adoption due to its simplicity, speed, and ease of integration into routine angiographic workflows, its implementation in clinical practice will first require prospective validation to confirm reliability, reproducibility, and predictive utility across diverse operators and institutions. Fourth, although underexpansion was independently associated with worse outcomes, residual confounding due to anatomical, procedural, or operator-related factors cannot be excluded. Fifth, operator experience was limited due to low individual implant volumes, potentially attenuated further by slow enrollment during the COVID-19 pandemic, reducing opportunities for skill refinement. However, no meaningful association between operator experience and clinical outcomes was observed. Sixth, 128 (17%) of 752 patients randomized to the ACURATE neo2 arm were excluded from this analysis due to lack of final angiograms or poor quality of available angiograms. Lastly, given that this is an exploratory analysis, we did not adjust for multiple comparisons, which increases the risk for type I errors.

CONCLUSIONS

Underexpansion of the ACURATE neo2 valve frame in the ACURATE IDE study was frequent and associated with a higher risk of the composite endpoint of death, stroke, or rehospitalization at 1 year. These findings should be considered hypothesis generating, given the post hoc nature of these analyses. Valve design modification to increase the radial strength and careful consideration of predilation and postdilation may improve valve expansion. Whether optimization of ACURATE neo2 valve frame expansion translates into better patient outcomes deserves further investigation.

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APPENDIX For supplemental material, figures, and tables, please see the online version of this paper.