One-year Outcomes of ACURATE *neo2* vs Approved TAVR Devices in All-risk Patients with Severe AS: **the ACURATE IDE Trial**

Michael Reardon, MD

Houston Methodist DeBakey Heart & Vascular Center

Houston, TX

On behalf of the ACURATE IDE Investigators

CRF®

TCT® TRANSCATHETER CARDIOVASCULAR THERAPEUTICS®

Disclosure of Relevant Financial Relationships

Within the prior 24 months, I have had a relevant financial relationship with a company producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

Nature of Financial Relationship	**Ineligible Company**
Consultant Fees/Honoraria	Boston Scientific, Medtronic, Abbott, Gore Medical, Anteris, J Valve

All relevant financial relationships have been mitigated.
Faculty disclosure information can be found on the app

Background Clinical Experience

ACURATE *neo2* Aortic Valve System is commercially available in 60+ countries (outside US) with 80,000+ patients treated with the ACURATE Platform globally

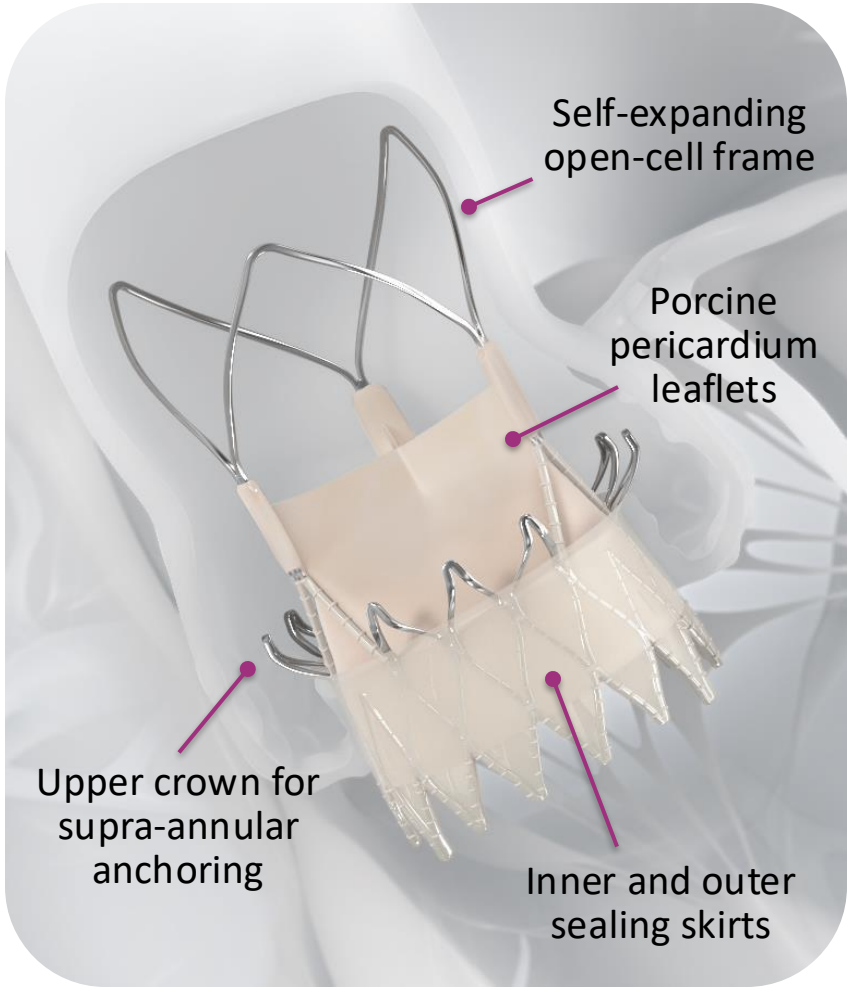
Post-market study/registry :	ACURATE *neo2* PMCF N=250		Early neo2 Registry[3] N=554	PROVE Registry[4] N=1044
	30 days[1]	1 year[2]	30 Days	30 Days
All-cause Mortality	0.8%	5.1%	1.3%	1.4%
All Stroke	0.8%	3.0%	2.7%	2.2%
Rehospitalization	0%	1.7%	3.0%	--
New Pacemaker*	6.5%	8.3%	6.2%	9.3%
AV Gradient	8.6 mmHg	7.6 mmHg	7.6 mmHg	6.8 mmHg (at discharge)
PVL ≥ Moderate	1.9%	0.6%	2.8%	3.4%

*Among patients without a pacemaker at baseline

The ACURATE IDE trial evaluates ACURATE *neo2* vs select commercially available balloon-expandable (SAPIEN 3 or newer) or self-expanding (Evolut or newer) devices

[1]Kim WK, et al. *EuroIntervention* 2023;19:83-92. [2]Kim WK, et al. *EuroIntervention* 2024;20:85-94. [3]Ruck A, et al. *J Am Heart Assoc*. 2023;12:e029464. [4]Thiele H. Presented at EuroPCR May 2024.

ACURATE *neo2* Valve Design



Unique frame design

- Self-expanding Nitinol frame with top-down deployment
- Open-cell design with axial stabilization arches
- Supports unrestricted coronary access[1] & predictable commissure alignment[2]

Supra-annular leaflet positioning

- Designed to provide large EOAs and low gradients[3]

Inner and outer sealing skirts

- Dynamic sealing to mitigate PVL[4]

Technical Specs

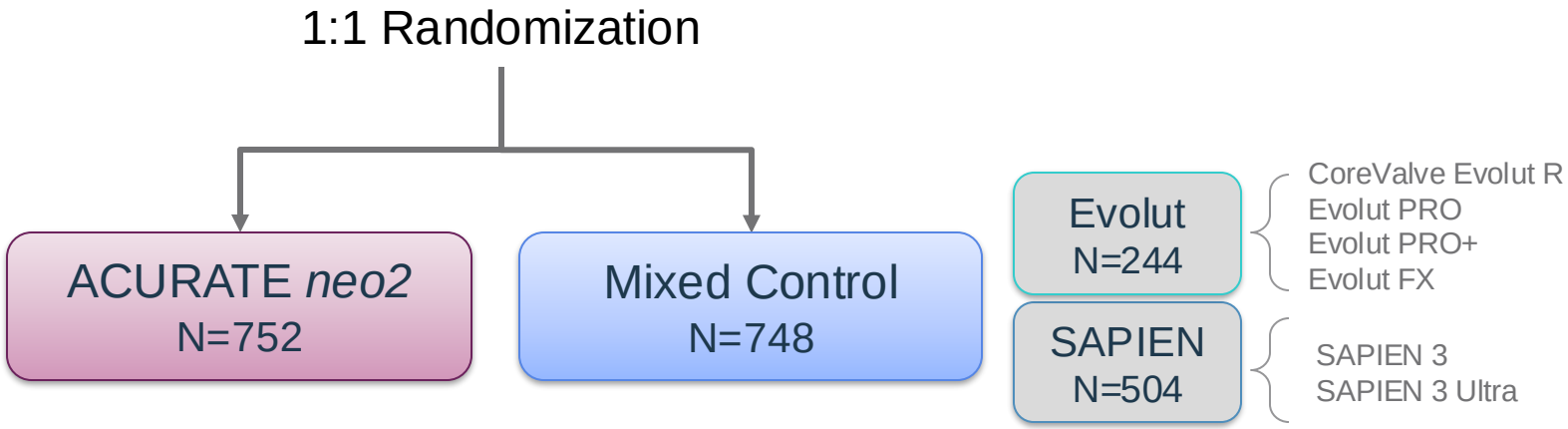
- **Available sizes:** 23 mm (S), 25 mm (M), 27 mm (L)
- **Pre-dilation required:** recommended balloon size is 1 mm smaller than perimeter-derived annular diameter

[1]Barbanti M, et al. *JACC Cardiovasc Interv*. 2020;13(21):2542-2555. [2]Bieliauskas G, et al. *JACC Cardiovasc Interv*. 2021;14(19):2097–2108. [3]Möllmann H, et al. *Clin Res Cardiol*. 2021;110(12):1912-1920. [4]Kim WK, et al. *EuroIntervention*. 2023;19(1):83-92.

ACURATE IDE Trial Design

Prospective, multicenter, randomized study
N=1500 patients with symptomatic severe native aortic stenosis indicated for TAVR

Operators pre-specify valve type to be used if randomized to Control



- **Primary Endpoint: Composite of all-cause mortality, stroke or rehospitalization† at 1 year**
- Follow-Up: Discharge/7d post-procedure, 30d, 6mo, 1-10y post-procedure

† Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); per VARC-2 definition

ACURATE IDE Trial Administration

Principal Investigators

Michael Reardon, MD **Raj Makkar, MD**

Core Laboratories

Angiography & CT: Baim Institute for Clinical Research
Director: C. Michael Gibson, MD

Echocardiography: Cardialysis
Director: Claire B. Ren, MD, PhD

4D CT: University of British Columbia
Directors: Philipp Blanke, MD; Jonathon Leipsic, MD

Data Monitoring Committee

W. Douglas Weaver, MD <*Chair*>
Steven Bailey, MD
Mark Gorman, MD
Frederick Grover, MD
F.W.A. Verheugt, MD
Jan Tijssen, PhD

Clinical Events Committee

Andreas Baumbach, MD <*Chair*>
Jean-Marie Annoni, MD
Evald Christiansen, MD
Stéphane Cook, MD
Enrico Ferrari, MD
Norbert Frey, MD
Oliver Guttmann, MD
Raban Jeger, MD
Nikolaus Löffelhardt, MD
Felix Mahfoud, MD
Friedrich Medlin, MD
Thierry Royer, MD
José Ramón Rumoroso, MD
Bernard Valeix, MD
Roberto Violini, MD

Top Enrolling Sites

Enrollment rank	Investigator(s)	Clinical Site
1	**Raj R Makkar**	Cedars-Sinai Medical Center
2	**Eric Gnall** **Basel Ramlawi**	Lankenau Medical Center
3	**Ravi Ramana**	Advocate Christ Medical Center
4	**Pantelis Diamantouros**	London Health Sciences Center
5	**Srinivasa Potluri**	Baylor Scott and White Heart Hospital
6	**Sanjay Samy**	Albany Medical Center
6	**Neal Kleiman** **Michael Reardon**	Houston Methodist Hospital
8	**Andrew Rassi**	Kaiser Permanente San Francisco Medical Center
9	**Vivek Rajagopal** **Vinod Thourani**	Piedmont Heart Institute
10	**Steven J Yakubov**	OhioHealth Riverside Methodist Hospital
11	**Apurva Badheka**	Providence Regional Medical Center Everett
11	**Paul Sorajja**	Abbott Northwestern Hospital
13	**Santiago Garcia**	Lindner Center for Research and Education
14	**John Wang**	Medstar Union Memorial Hospital
15	**Michael J Rinaldi**	Sanger Heart and Vascular Institute

Key Inclusion Criteria

Severe Symptomatic Aortic Stenosis

- AVA ≤ 1.0 cm^2 *or* AVA index ≤ 0.6 cm^2/m^2
- *AND* mean gradient ≥ 40 mmHg *or* max AV velocity ≥ 4.0 m/s *or* Doppler velocity index ≤0.25
- NYHA Functional Class ≥ II
- Heart Team agreement that subject is indicated for TAVR

Documented aortic annulus size of ≥21 mm and ≤27 mm

- Based on the center assessment of pre-procedure diagnostic imaging and confirmed by the Case Review Committee

Key Exclusion Criteria

Anatomic

- Unicuspid or bicuspid valve
- Pre-existing prosthetic aortic or mitral valve
- Severe (4+) aortic, tricuspid, or mitral regurgitation
- Moderate or severe mitral stenosis (mitral valve area ≤1.5 cm^2 and diastolic pressure half-time ≥150 ms, Stage C or D[4])
- Severe LV dysfunction (LVEF < 20%)
- Severe/eccentric calcification of aortic annulus
- Hypertrophic cardiomyopathy
- Severe vascular disease or vascular anatomy not suitable for safe arterial access

Clinical

- Acute MI within 1 month
- Stroke or TIA within 6 months
- Renal insufficiency (eGFR < 20 ml/min) and/or renal replacement therapy
- History of endocarditis within 6 months or active systemic infection or sepsis
- Hemodynamic or respiratory instability
- Untreated coronary artery disease
- Untreated conduction system disorder
- Life expectancy <12 months due to non-cardiac, comorbid conditions

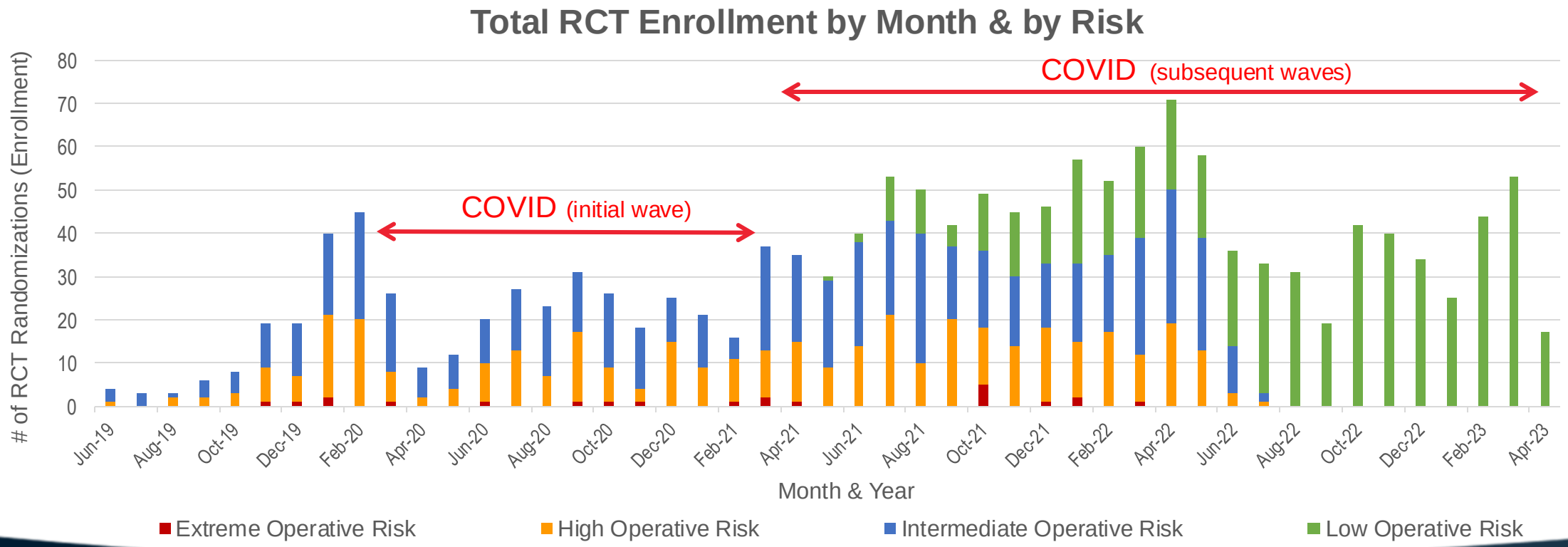
Statistical Methods

Primary hypothesis	**Non-inferiority of ACURATE *neo2* vs Control for the primary endpoint of all-cause mortality, stroke or rehospitalization† at 1y**
	• *Non-inferiority test performed using Bayesian method; ITT population*
Expected rate	22.3% for both arms
	• *Based on a weighted average of historical TAVR data**
Non-inferiority margin (Δ)	8%
	• *36% relative to expected rate*
One-sided alpha (α)	0.025
Power	>90%
Sample size	1,500 subjects (750 per arm)
	• *Assumes 5% attrition*

* Historical studies include: CoreValve Extreme-Risk & High-Risk, Evolut Low-Risk, SURTAVI, PARTNER (I, II, 2A, 3), LRT (all devices)
† Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); per VARC-2 definition

Trial Enrollment Timeline

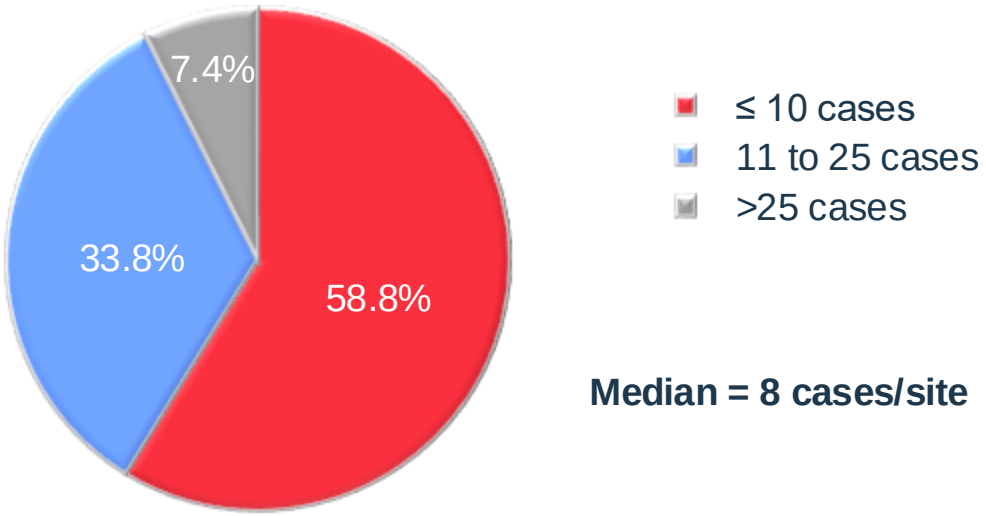
- 1500 RCT subjects enrolled at 70 centers in United States and Canada
- Enrollment occurred over a 47-month period, with higher risk patients enrolled earlier in the trial



ACURATE *neo2* Implant Metrics

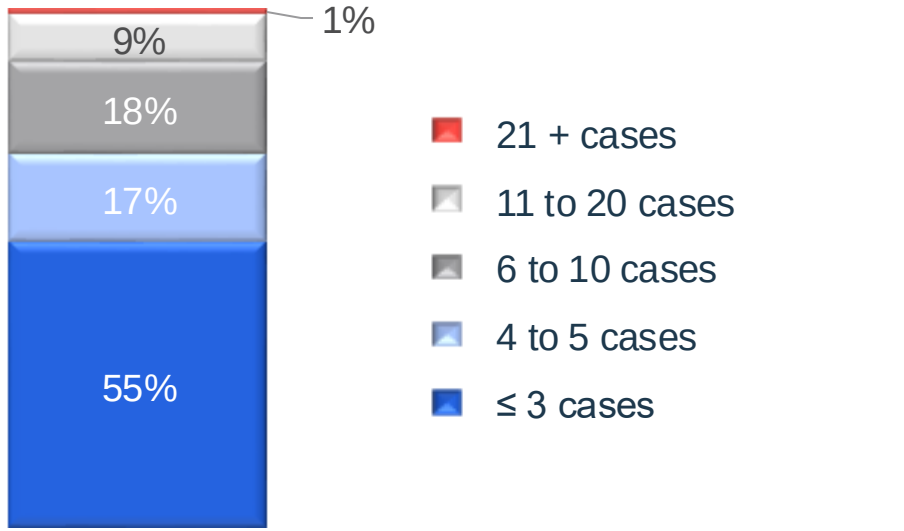
- Sites averaged 2.9 months between ACURATE *neo2* implants
- Total site volume of ACURATE *neo2* cases was low
  - 72% of physicians had 5 or fewer cases over the course of the trial
  - Only 10% of implanters did more than 10 cases

ACURATE *neo2* Cases per Site

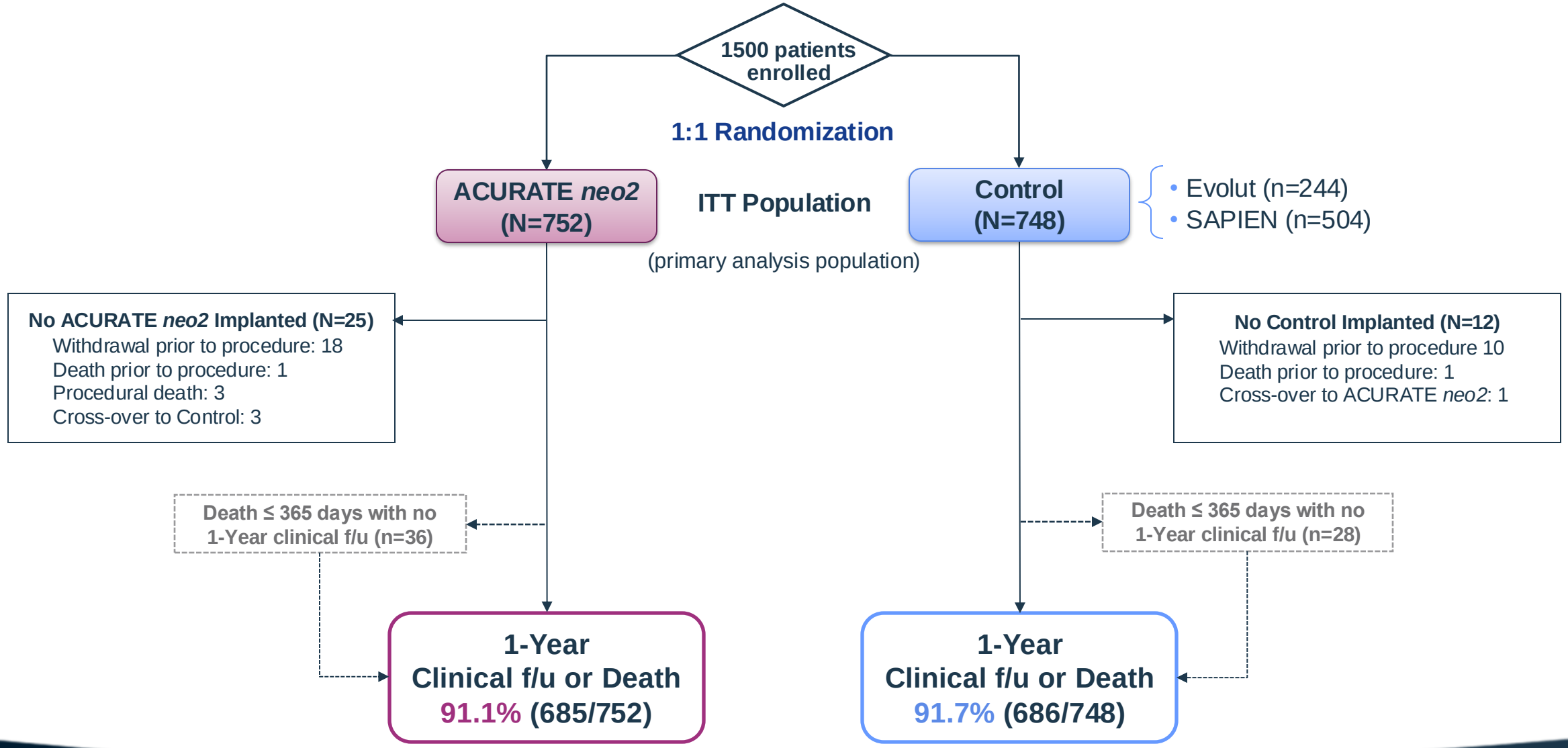


Median = 8 cases/site

ACURATE *neo2* Cases per Implanting Physician



Subject Disposition



Note: Control devices include CoreValve Evolut R, Evolut PRO, Evolut PRO+, and Evolut FX and SAPIEN 3, SAPIEN 3 Ultra

Baseline Characteristics and Medical History

	ACURATE *neo2* (N=752)	Control (N=748)	Evolut (N=244)	SAPIEN (N=504)
Age (yrs)	78.0±6.9 (752)	79.0±6.5 (748)	78.8±6.0 (244)	79.1±6.8 (504)
Female (%)	52.5% (395/752)	51.2% (383/748)	57.8% (141/244)	48.0% (242/504)
STS Score (%)	2.7±1.8 (752)	2.8±1.9 (748)	2.9±2.1 (244)	2.8±1.8 (504)
Operative Risk Group (Site assessed, CEC-confirmed)				
High/Extreme Operative Risk	25.5% (192/752)	28.6% (214/748)	27.5% (67/244)	29.2% (147/504)
Intermediate Operative Risk	38.6% (290/752)	36.9% (276/748)	38.9% (95/244)	35.9% (181/504)
Low Operative Risk	35.9% (270/752)	34.5% (258/748)	33.6% (82/244)	34.9% (176/504)
Medical History				
Diabetes mellitus (medically treated)	31.6% (238/752)	29.4% (220/748)	33.2% (81/244)	27.6% (139/504)
History of hypertension	89.4% (672/752)	88.0% (658/748)	89.8% (219/244)	87.1% (439/504)
History of AKI	0.3% (2/752)	0.0% (0/748)	0.0% (0/244)	0.0% (0/504)
History of atrial fibrillation	23.0% (173/752)	22.2% (166/748)	22.5% (55/244)	22.0% (111/504)
Prior pacemaker implant	6.4% (48/752)	7.0% (52/748)	7.4% (18/244)	6.7% (34/504)
Prior Stroke	6.9% (52/752)	6.0% (45/748)	7.8% (19/244)	5.2% (26/504)
Pre-procedure Echocardiography (Site-reported)				
Aortic valve area (cm^2)	0.77±0.17 (750)	0.76±0.18 (746)	0.76±0.22 (242)	0.76±0.16 (504)
Mean aortic gradient (mmHg)	44.7±10.8 (746)	44.3±10.4 (744)	44.6±9.8 (242)	44.2±10.8 (502)

Note: Control devices include CoreValve Evolut R, Evolut PRO, Evolut PRO+, and Evolut FX and SAPIEN 3, SAPIEN 3 Ultra

Procedural Characteristics

	ACURATE *neo2* (N=752)	Control (N=748)	P-value	Evolut (N=244)	SAPIEN (N=504)
Correct positioning of a single valve into the proper anatomical location	98.4% (721/733)	99.1% (730/737)	0.243	97.5% (235/241)	99.8% (495/496)
Prosthetic aortic valve malpositioning*	1.2% (9/752)	0.9% (7/748)	0.623	2.5% (6/244)	0.2% (1/504)
Valve migration	0.1% (1/752)	0.3% (2/748)	0.624	0.8% (2/244)	0.0% (0/504)
Valve embolization	0.9% (7/752)	0.7% (5/748)	0.568	1.6% (4/244)	0.2% (1/504)
Ectopic valve deployment	0.1% (1/752)	0.7% (5/748)	0.123	2.0% (5/244)	0.0% (0/504)
Conversion to open-heart surgery	0.8% (6/733)	0.3% (2/737)	0.178	0.8% (2/241)	0.0% (0/496)
TAV-in-TAV*	0.7% (5/752)	0.1% (1/748)	0.218	0.0% (0/244)	0.2% (1/504)
Embolic protection device	30.6% (217/710)	26.8% (187/697)	0.122	25.3% (56/221)	27.5% (131/476)
Pre-dilation during index procedure	99.6% (730/733)	33.0% (243/737)	<0.001	48.1% (116/241)	25.6% (127/496)
Post-dilation balloon performed	26.1% (191/733)	11.3% (83/737)	<0.001	14.5% (35/241)	9.7% (48/496)

Note: Control devices include CoreValve Evolut R, Evolut PRO, Evolut PRO+, and Evolut FX and SAPIEN 3, SAPIEN 3 Ultra
*CEC-adjudicated; all other data in table is site-reported

Primary Endpoint – Bayesian Analysis

Hypothesis Test in ITT population

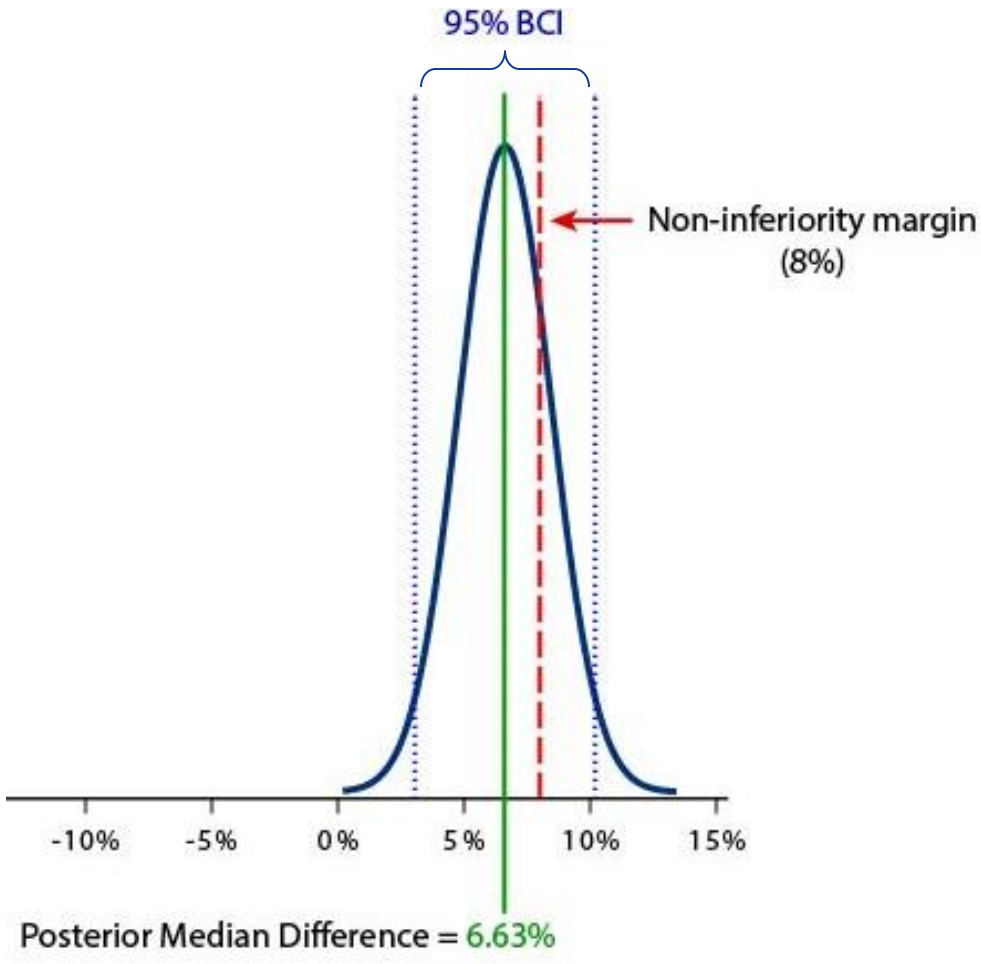
$$PE_{\_ACURATE} - PE_{\_Control} < \Delta_{non\text{-}inferiority}$$

For the primary endpoint of all-cause mortality, stroke or rehospitalization† at 1 year

Posterior Median and 95% BCI		Non-Inferiority Test*	
ACURATE *neo2*	Control	Posterior Median Difference and 95% BCI	Non-inferiority Margin
16.16% [13.38%,19.07%]	9.53% [7.47%,11.89%]	**6.63%** [3.04%,10.20%]	**8.0%**

Upper bound of 95% BCI exceeds prespecified non-inferiority margin

Non-inferiority of ACURATE *neo2* vs Control for the primary endpoint was not met

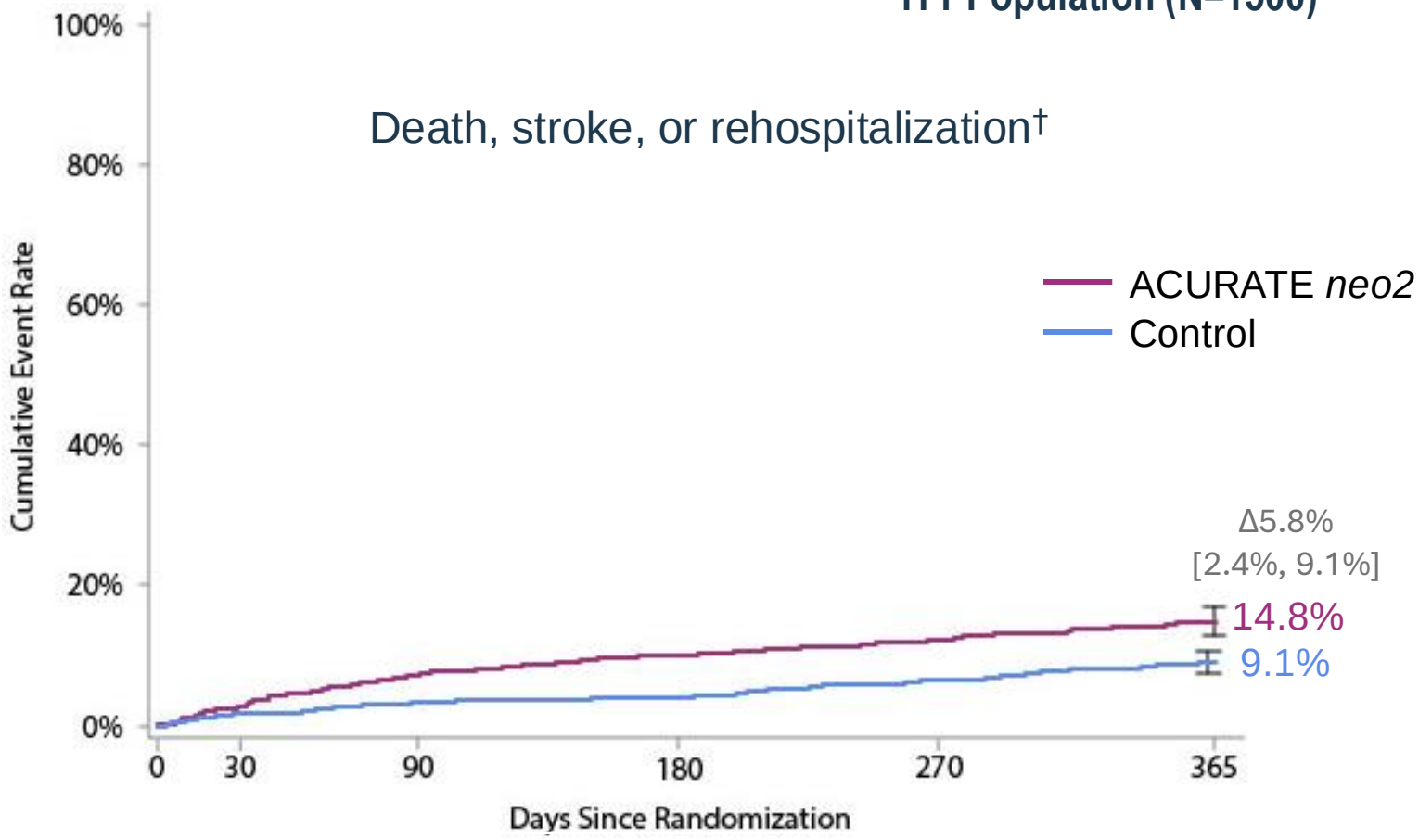


Note: Control devices include CoreValve Evolut R, Evolut PRO, Evolut PRO+, and Evolut FX and SAPIEN 3, SAPIEN 3 Ultra
† Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); per VARC-2 definition
* Posterior probability for non-inferiority was 77.9%, which is lower than the non-inferiority test threshold of 97.5%

Kaplan-Meier Analysis through 1 Year

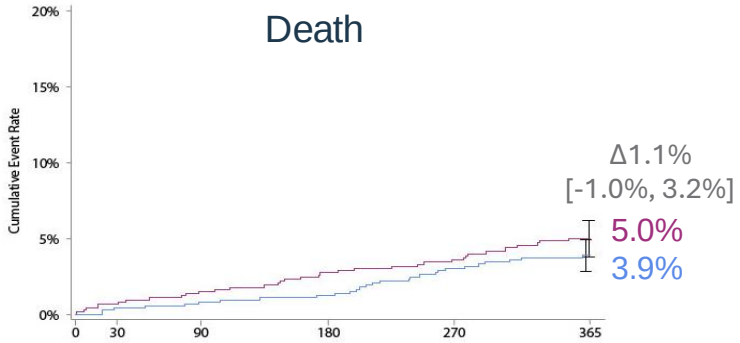
ITT Population (N=1500)

Death, stroke, or rehospitalization†

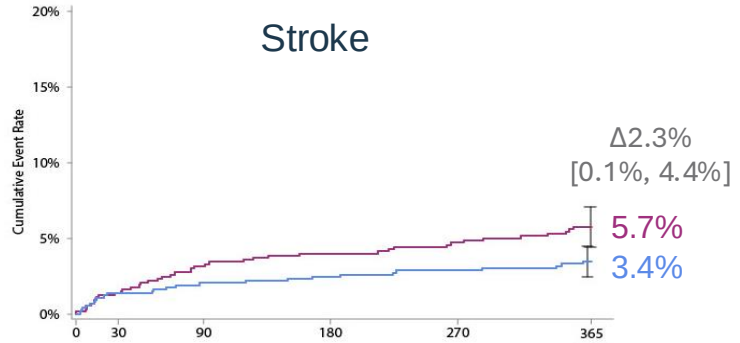


No. at risk						
ACURATE *neo2* (N=752)	752	733	711	676	651	617
Control (N=748)	748	737	723	706	695	654

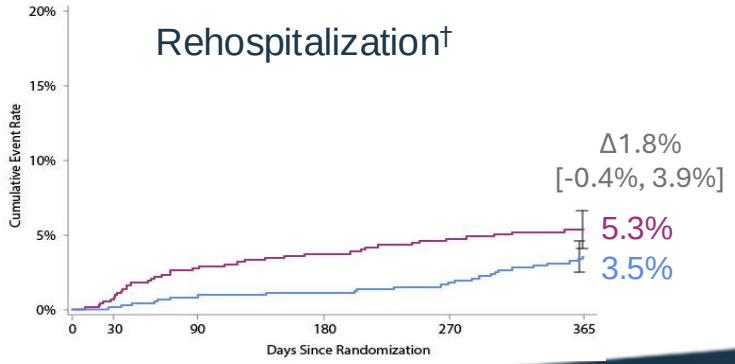
Death



Stroke



Rehospitalization†



CRF® TCT®

Note: Control devices include CoreValve Evolut R, Evolut PRO, Evolut PRO+, and Evolut FX and SAPIEN 3, SAPIEN 3 Ultra

† Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); per VARC-2 definition

Additional Safety Outcomes

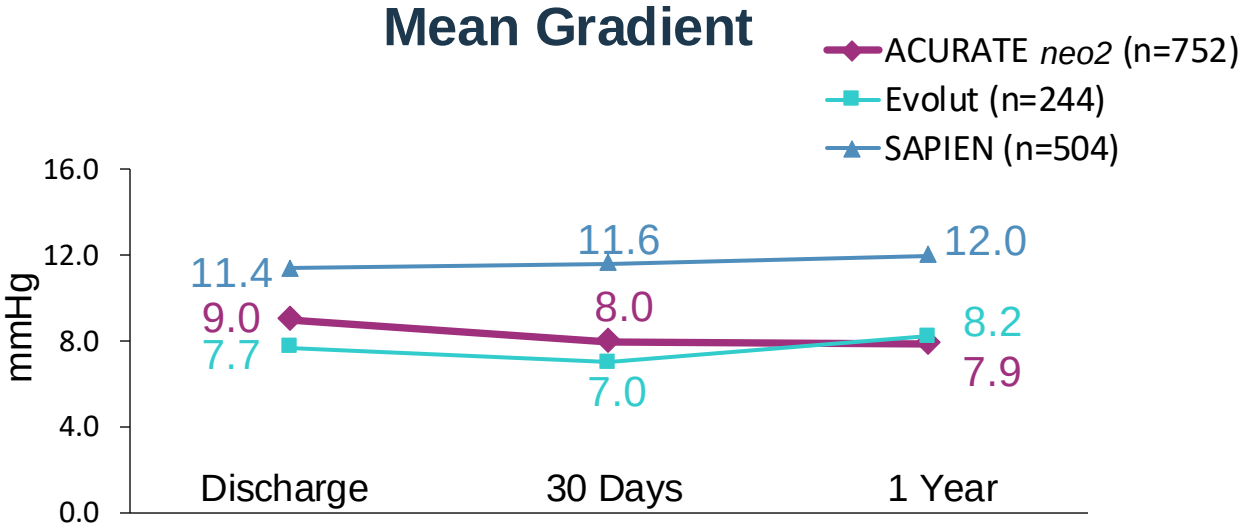
Time-to-Event Analysis through 1 Year Post-Procedure, ITT Population (N=1500)

	ACURATE *neo2* (N=752)	Control (N=748)	Hazard Ratio [95% CI]	Evolut (N=244)	SAPIEN (N=504)
Death	5.0% (36)	3.9% (28)	1.30 [0.80, 2.14]	3.4% (8)	4.1% (20)
Cardiovascular death	3.7% (27)	1.8% (13)	2.10 [1.09, 4.08]	2.5% (6)	1.5% (7)
Stroke	5.7% (41)	3.4% (25)	1.68 [1.02, 2.75]	5.8% (14)	2.3% (11)
Disabling stroke	2.0% (14)	1.2% (9)	1.57 [0.68, 3.64]	2.9% (7)	0.4% (2)
Bleeding	6.2% (45)	6.0% (44)	1.03 [0.68, 1.56]	4.6% (11)	6.8% (33)
Life-threatening or disabling bleeding	3.6% (26)	3.3% (24)	1.09 [0.63, 1.90]	2.1% (5)	3.9% (19)
Acute kidney injury (Stage 2/3)	0.0% (0)	0.0% (0)	NA	0.0% (0)	0.0% (0)
Major vascular complication	3.1% (23)	2.0% (15)	1.55 [0.81, 2.96]	2.5% (6)	1.8% (9)
Access site related	2.6% (19)	1.5% (11)	1.74 [0.83, 3.66]	2.1% (5)	1.2% (6)
Myocardial infarction	2.4% (17)	0.7% (5)	3.47 [1.28, 9.39]	0.9% (2)	0.6% (3)
Periprocedural (≤72 h post index procedure)	0.4% (3)	0.0% (0)	NA	0.0% (0)	0.0% (0)
Spontaneous (>72 h post index procedure)	2.0% (14)	0.7% (5)	2.85 [1.03, 7.91]	0.9% (2)	0.6% (3)
Prosthetic aortic valve thrombosis*	0.7% (5)	2.6% (19)	0.26 [0.10, 0.71]	1.3% (3)	3.3% (16)
New permanent pacemaker implantation	11.2% (82)	12.0% (88)	0.93 [0.69, 1.26]	14.1% (34)	10.9% (54)
New PPI in PM-naïve patients	12.0% (82)	12.8% (88)	0.93 [0.69, 1.26]	15.3% (34)	11.7% (54)
New onset of Atrial fibrillation	2.3% (17)	2.3% (17)	1.01 [0.51, 1.97]	2.9% (7)	2.0% (10)

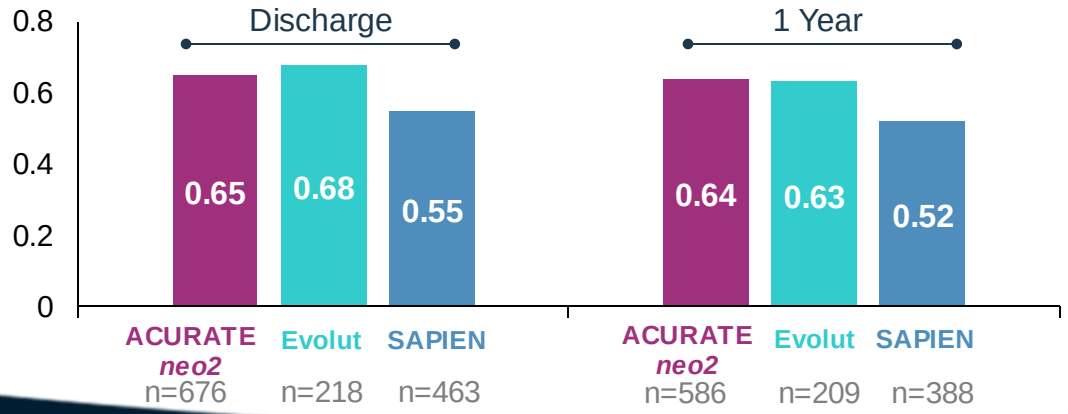
Note: Control devices include CoreValve Evolut R, Evolut PRO, Evolut PRO+, and Evolut FX and SAPIEN 3, SAPIEN 3 Ultra
*Clinically evident leaflet thrombosis

Echocardiography Outcomes

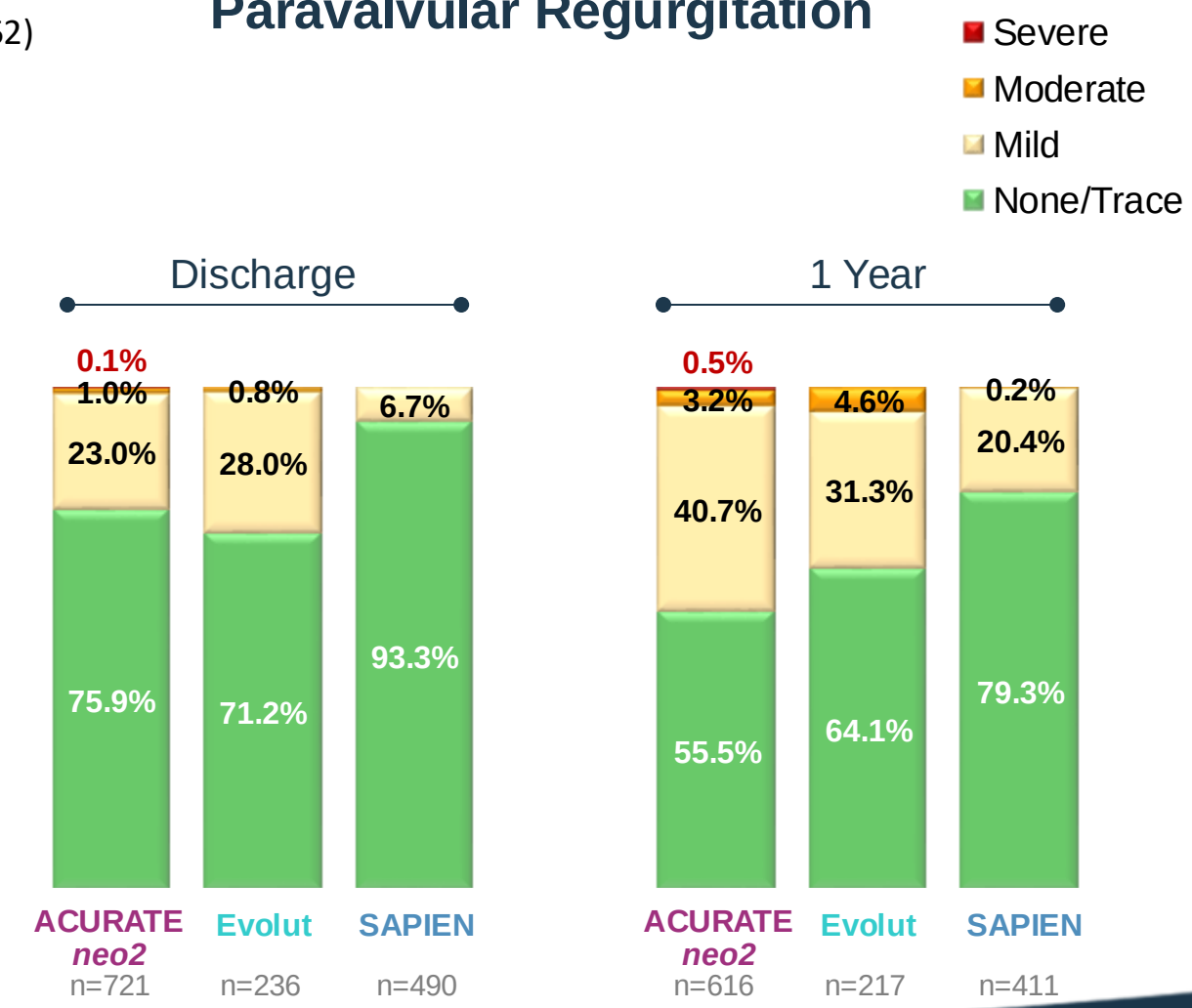
Mean Gradient



Doppler Velocity Index (DVI)



Paravalvular Regurgitation



Note: Control devices include CoreValve Evolut R, Evolut PRO, Evolut PRO+, and Evolut FX and SAPIEN 3, SAPIEN 3 Ultra

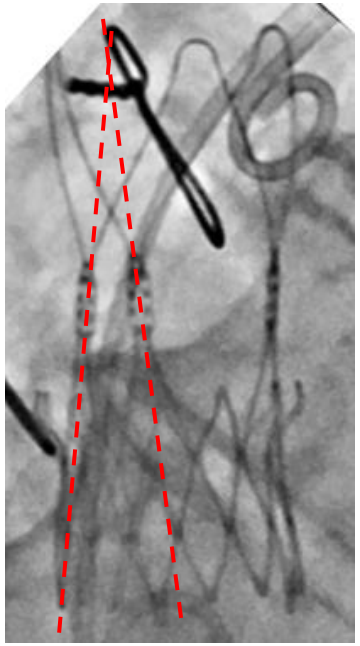
Review of ACURATE *neo2* Performance

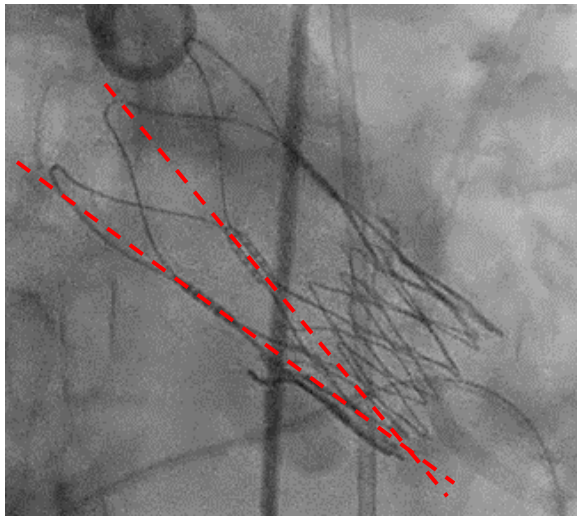
- Despite limited operator experience with ACURATE *neo2*, early outcomes were encouraging
  - Periprocedural outcomes were favorable and comparable to Control
  - Echo parameters (gradient and leak) were as expected
  - No acute safety signals
- COVID-related factors impacted implanter experience with ACURATE *neo2*
  - Extended trial enrollment/length, de-prioritization of investigational cases, and limits on supplies and staffing (both hospital staff & sponsor support)

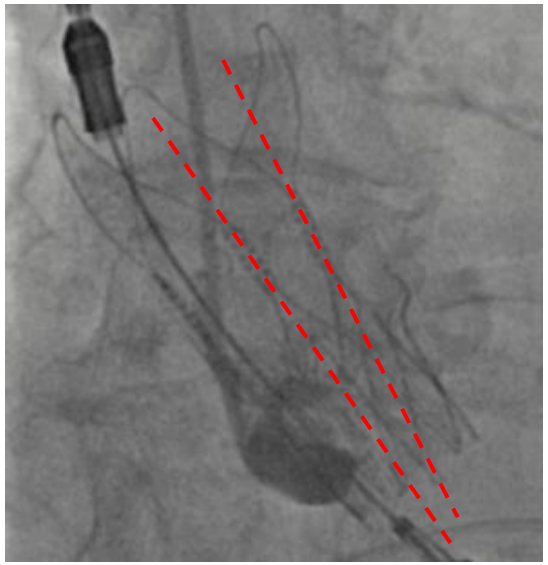
Are there other factors that affected 1-year outcomes?

Retrospective Review

- A post-hoc case review of ACURATE *neo2* implantation evaluated proper valve frame expansion per angiographic imaging
  - Under-expansion can be identified by non-parallel commissure posts



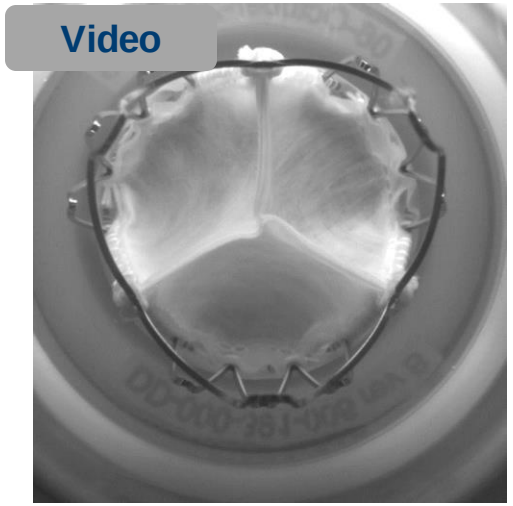




Valve frame under-expansion was present in ~20% of ACURATE *neo2* cases

Bench Testing: Impact of Valve Frame Under-Expansion

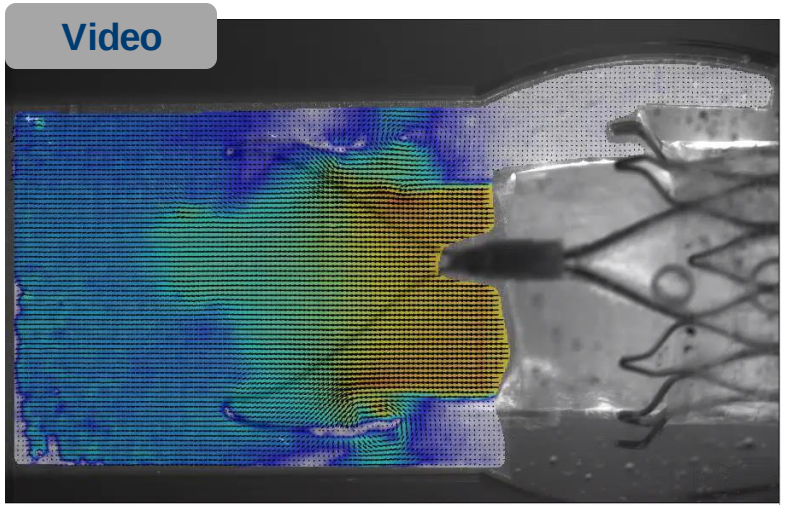
Video



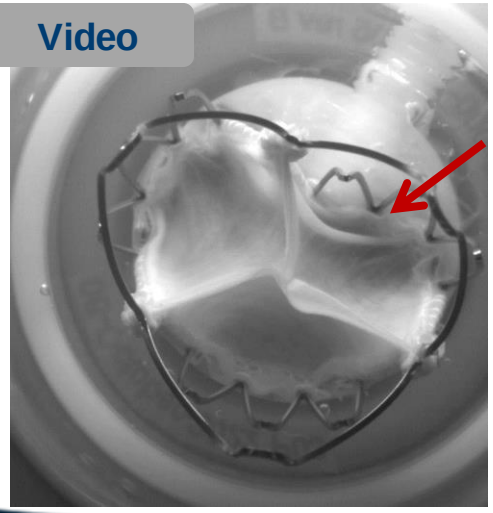
Expanded ACURATE *neo2*
Max Velocity 1.6 m/s

- Laminar flow
- Adequate washout

Video



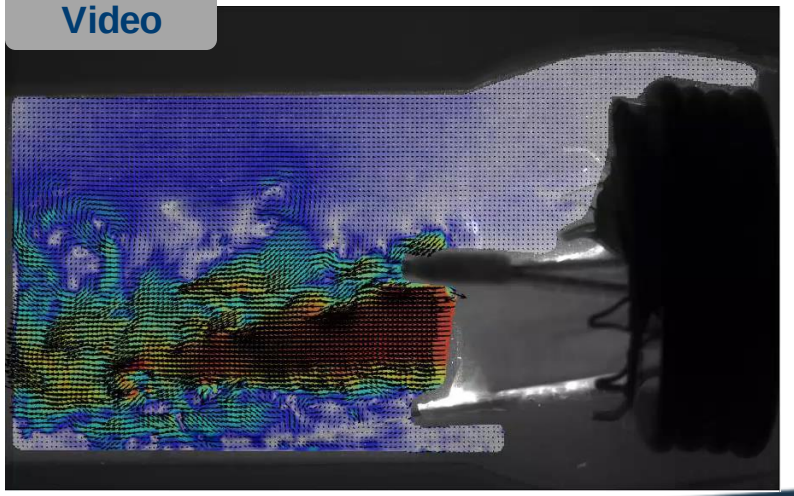
Video



Under-Expanded ACURATE *neo2*
Max Velocity 3.1 m/s

- Turbulent flow
- Reduced washout

Video



Post-Hoc Clinical Analysis: Valve Frame Expansion

Time-to-Event Analysis through 1 Year Post-Procedure (N=703)

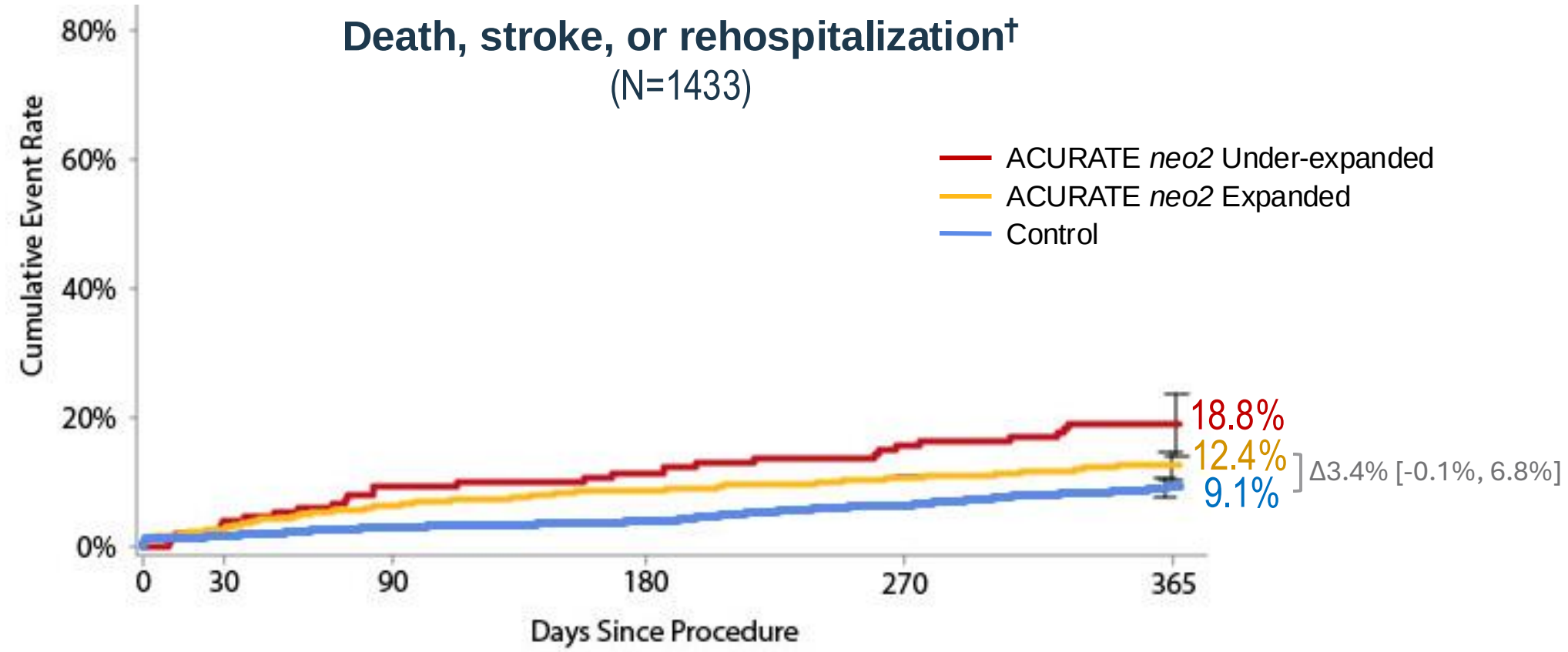
- Patients with under-expanded valves had increased rates of death (2-fold) and stroke (3-fold) compared to those with well-expanded valves

ACURATE *neo2*

	Expanded Valve Frame (N=553)	Under-Expanded Valve Frame (N=150)	P-value
Primary Endpoint: Death, stroke, or rehospitalization†	**12.4% (68)**	**18.8% (28)**	0.050
Individual components			
Death	**3.7% (20)**	**7.4% (11)**	0.054
Stroke	**3.5% (19)**	**11.0% (16)**	<0.001
Rehospitalization†	**5.9% (32)**	**2.7% (4)**	0.131

† Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); per VARC-2 definition

Post-Hoc Clinical Analysis: Valve Frame Expansion

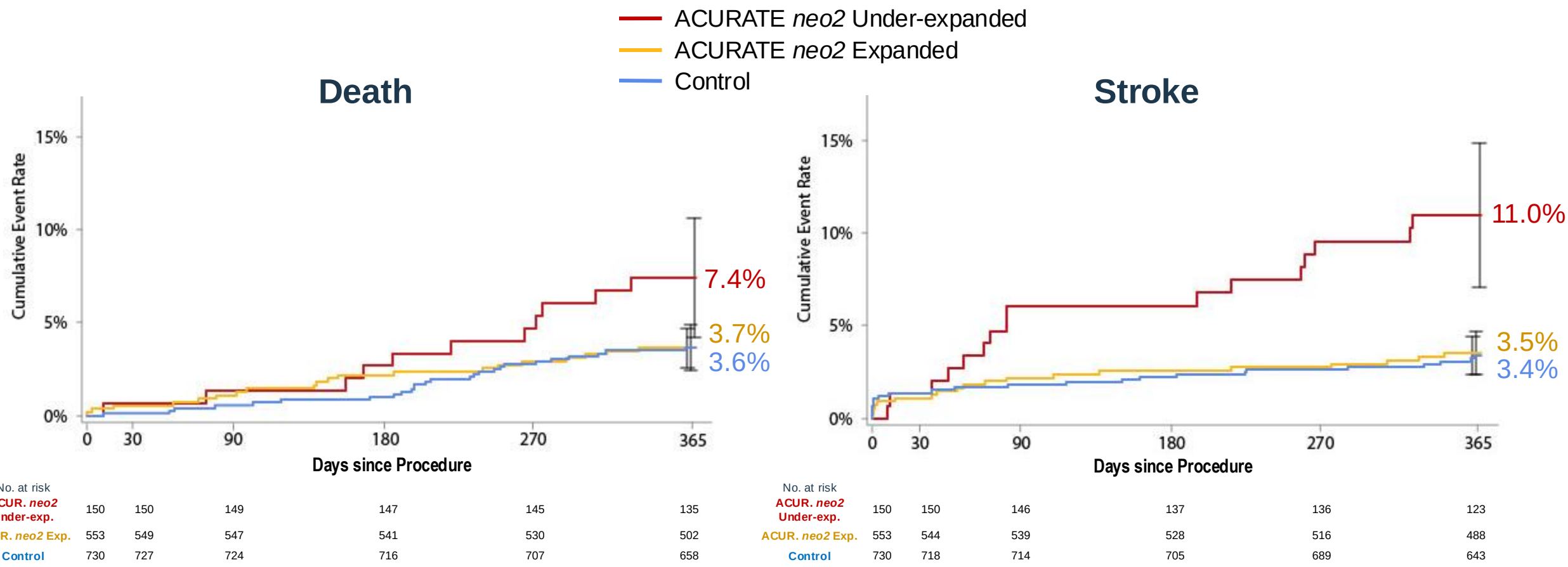


No. at risk						
ACUR. *neo2* Under-exp. (N=150)	150	150	144	135	132	121
ACUR. *neo2* Expanded (N=553)	553	543	535	514	497	465
Control (N=730)	730	718	713	699	689	635

CRF® TCT®

Note: Control devices include CoreValve Evolut R, CoreValve Evolut PRO, Evolut PRO+, and Evolut FX and SAPIEN 3, SAPIEN 3 Ultra
† Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); per VARC-2 definition

Post-Hoc Clinical Analysis: Valve Frame Expansion



No. at risk						
ACUR. *neo2* Under-exp.	150	150	149	147	145	135
ACUR. *neo2* Exp.	553	549	547	541	530	502
Control	730	727	724	716	707	658

No. at risk						
ACUR. *neo2* Under-exp.	150	150	146	137	136	123
ACUR. *neo2* Exp.	553	544	539	528	516	488
Control	730	718	714	705	689	643

Death and stroke at 1 year are comparable for ACURATE *neo2* Expanded and Control

ACURATE *neo2* Under-Expansion: Potential Associations

- Valve under-expansion has the potential to impact later clinical outcomes
- Procedural technique may play a role
  - Pre- and post-dilation was inconsistent with commercial practice due to use of smaller-than-recommended balloons, which has an impact on valve expansion

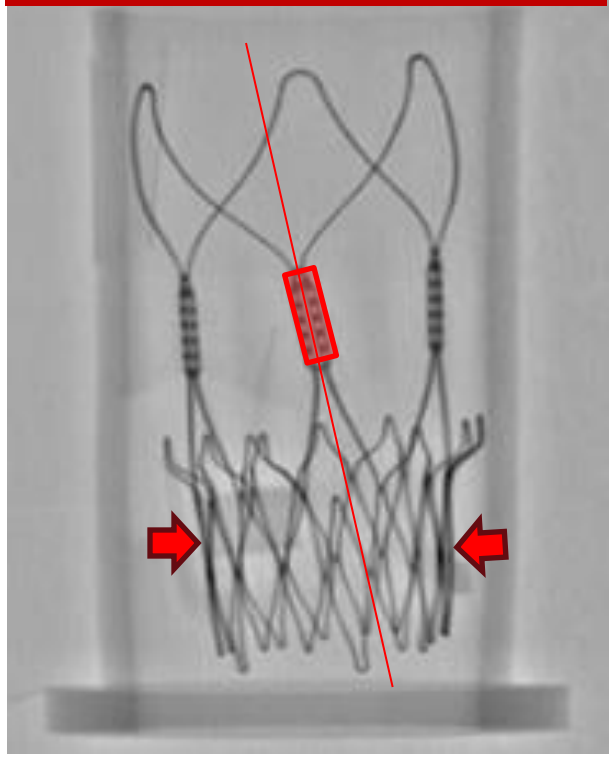
- Optimization of valve expansion is a combination of:
  - Effective pre-dilation
    - Balloon diameter 1 mm smaller than perimeter-derived annular diameter*
  - Recognition of under expansion after valve implantation
    - Angulated posts & 2nd view
  - Improvement of valve expansion by performing post-dilation

* Exception for unfavorable anatomy (ie, adverse root features)

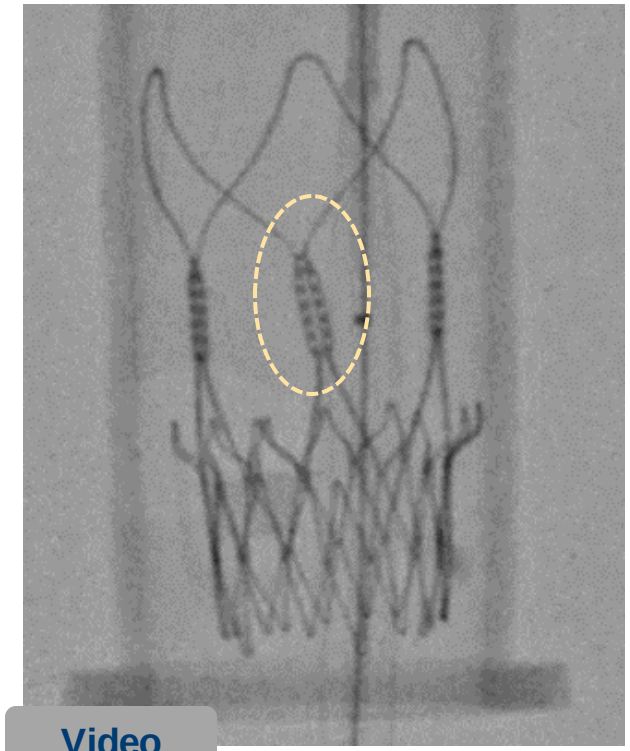
Importance of Post-Dilation: Proof of Concept

ACURATE *neo2* under-expansion can be easily recognized and is improved by post-dilation

Valve under expanded with angulated post evident

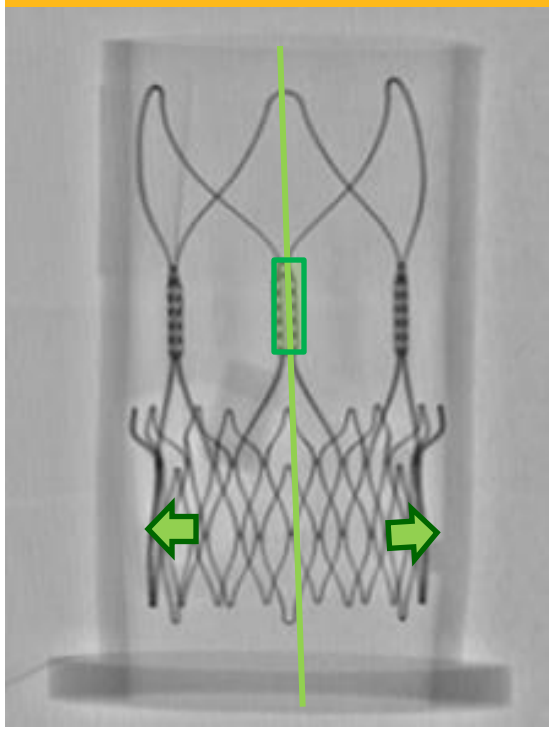


Post-dil resolves under-expansion & angulation of commissural post



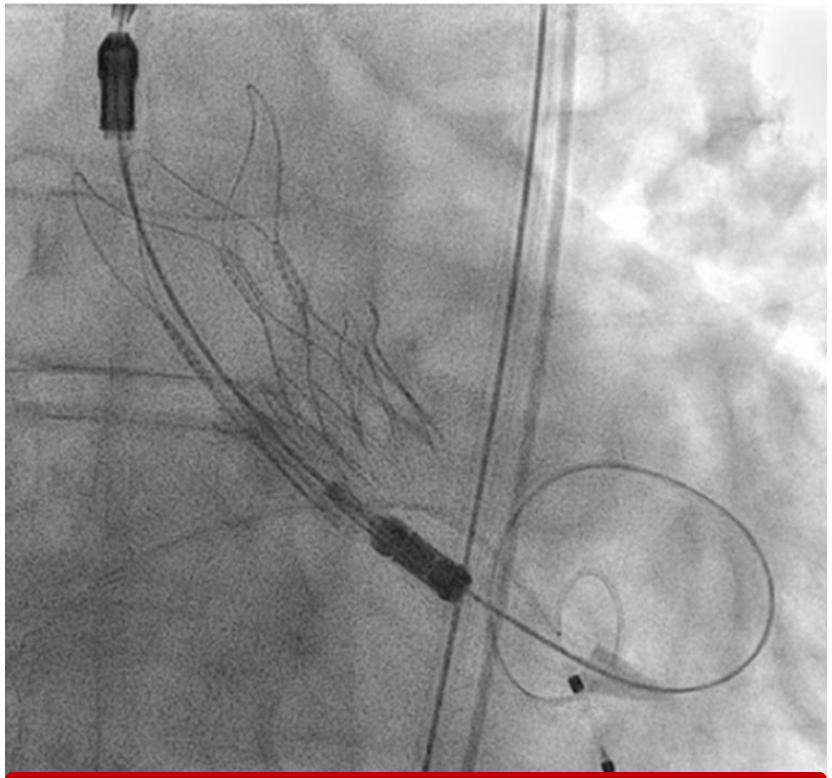
Video

Expanded valve with no angulated post evident



Importance of Post-Dilation: Case Example

Under-expansion is easy to identify and correct during the procedure

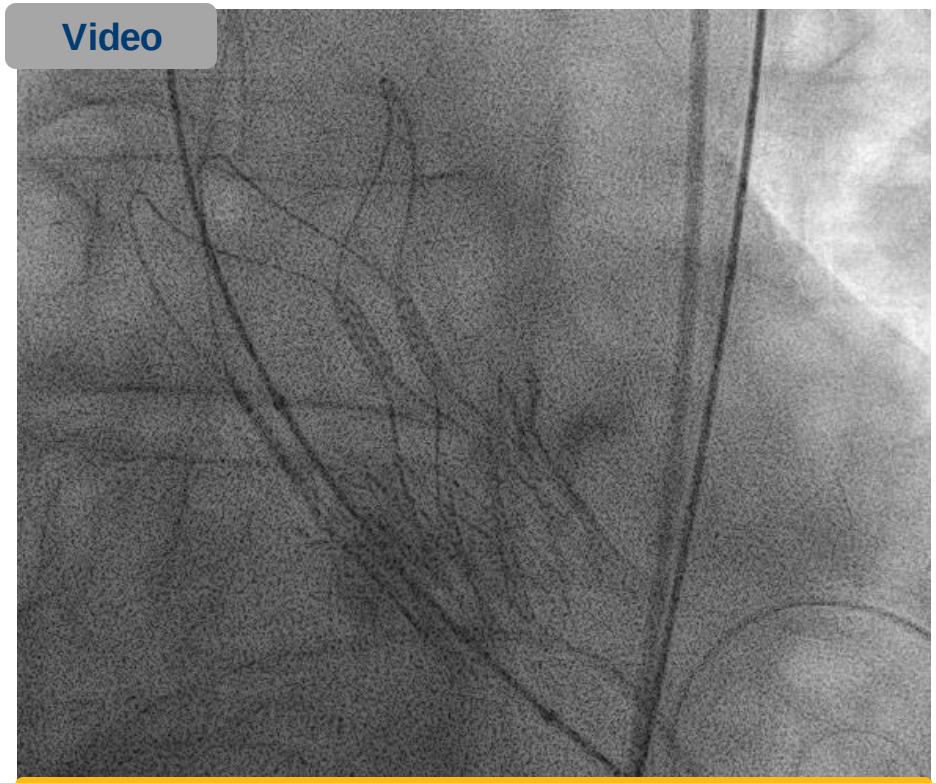


ACURATE *neo2* 27mm with ineffective pre-dil
(implanted in perimeter-derived diameter of 24.5mm)

When is post dilation recommended?

- Gradient ≥10mmHg ✓
- ≥ mild PVL ✓
- Valve under expansion New
  - Identified by diameter or non-parallel posts (2nd view)
  - Easy to visualize on ACURATE *neo2* frame

Video



Post-dilation eliminates under expansion

Study Limitations

- Trial-related factors
  - First RCT experience with ACURATE *neo2* enrolled patients of all risks
  - Control arm included two comparator devices, with operator selection of preferred Control at time of randomization

- Enrollment factors
  - COVID – impact on staffing resources (hospital & sponsor support); supply constraints; investigational cases deprioritized relative to commercial cases
  - Operators less experienced with ACURATE *neo2* compared to Control devices

ACURATE IDE Trial Key Take-Aways

- The ACURATE IDE Trial is the largest head-to-head trial to evaluate TAVR with ACURATE *neo2*
  - Ability to compare ACURATE *neo2* with commercially available devices was complicated by a challenging trial environment (trial-related and enrollment factors)
- Post-hoc analyses identified ACURATE *neo2* valve under-expansion as a potential factor contributing to clinical outcomes
  - Adverse impact of under-expansion was not evident when evaluating early clinical outcomes, but became apparent at 1 year
  - Patients with well-expanded ACURATE *neo2* valves are comparable to Control for death and stroke at 1 year
  - Recognition of ACURATE *neo2* valve frame under-expansion during procedure allows for post-dilation to optimize valve function

Deep-dive session on the ACURATE IDE study

- Date/Time: Wednesday, October 30th 12:15-1:30 pm
- Location: Presentation Theater #5 (FDA Theater)
  - Moderator: Michael Joseph Rinaldi
  - Faculty
    - Michael J. Reardon – A Closer Look at the ACURATE IDE Study
    - Ole de Backer – ACURATE IDE Insights: Optimizing Clinical Implants
    - Janarthanan Sathananthan – Summary and Next Steps