A Randomized Comparison of the ACURATE neo versus the SAPIEN 3 Transcatheter Heart Valve System in Patients with Symptomatic Severe Aortic Stenosis

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on behalf of the SCOPE I investigators

Disclosure Statement of Financial Interest

I, Jonas Lanz, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Background

- TF TAVR has become an indispensable treatment option for patients with symptomatic severe aortic stenosis across all risk categories
- The generalizability of outcomes observed in landmark trials comparing TAVR with SAVR to other commercial TAVR systems is limited by differences in device properties and the lack of head-to-head device comparisons
- Iterations of the balloon-expandable SAPIEN THV system have been extensively investigated in several large-scale, high-quality RCTs and registries setting the current benchmark in terms of safety and efficacy
- The ACURATE neo is a novel, self-expanding TAVR prosthesis associated with favorable outcomes in non-randomized studies

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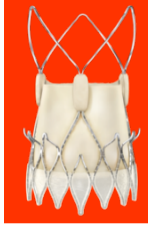
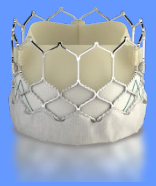
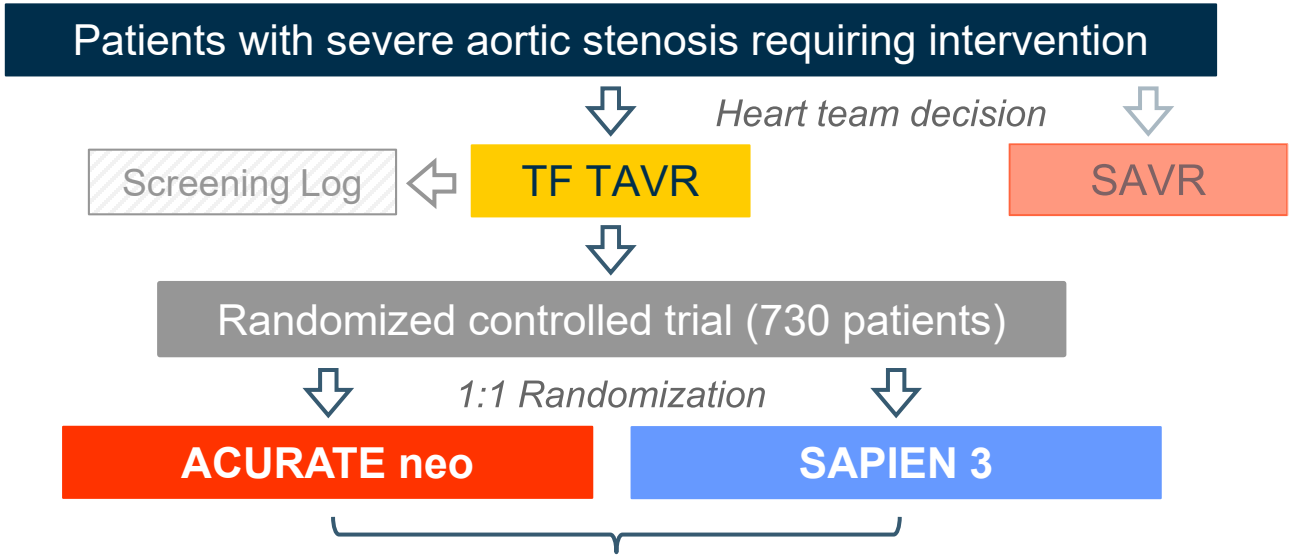
Objective

To compare **early safety** and **efficacy** of the **self-expanding ACURATE neo** to the **balloon-expandable SAPIEN 3** transcatheter heart valve system in patients with symptomatic severe aortic stenosis undergoing **transfemoral TAVR**

Study Devices

	 **ACURATE neo™** Aortic Valve System	 **SAPIEN 3™** Transcatheter Heart Valve System
Frame	Nitinol	Cobalt-chromium
Leaflets	Porcine pericardium, supra-annular	Bovine pericardium, intra-annular
Expansion	Self-expanding (top-down)	Balloon-expandable
Recapturable	No	No
Valve sizes	S (23 mm), M (25 mm), L (27 mm)	23 mm, 26 mm and 29 mm
Sheath inner diameter	18-French	14- and 16-French expandable
Paravalvular leakage reduction	Outer & inner skirt	Outer cuff & inner skirt
CE mark / FDA approval	Sep 2014 / No	Jan 2014 / Jun 2015

Study Design



Follow-up:
at 30-days, 1 and 3 years

Primary endpoint:
Combined early safety & clinical efficacy at 30 days
(VARC-2)

Eligibility Criteria

Major Inclusion Criteria

- Age ≥ 75 years
- Aortic valve area < 1 cm^2
- Clinical symptoms
  (> NYHA I, angina, syncope)
- Inoperable *or* at increased risk for SAVR based on risk scores *and/or* heart team recommendation
- Aortic annulus dimensions and peripheral access suitable for either device

Major Exclusion Criteria

- Congenital anomaly of aortic valve
- Emergency procedures
- LV-EF< 20%
- Left-sided prosthetic valve
- Concomitant planned procedure
  (except for PCI)
- Stroke or myocardial infarction
  (previous 30 days)
- Planned non-cardiac surgery
  (next 30 days)

Primary Endpoint

Safety & clinical efficacy at 30 days based on VARC-2

- All-cause mortality
- All stroke (disabling and non-disabling)
- Life-threatening or disabling bleeding
- Major vascular complication
- Coronary artery obstruction requiring intervention
- Acute kidney injury (stage 2 or 3)
- Re-hospitalization for valve-related symptoms or worsening CHF
- Valve related dysfunction requiring repeat procedure
- Valve-related dysfunction (echocardiography): mean Gradient ≥ 20 mmHg and EOA ≤ 0.9-1.1 cm^2 and/or DVI < 0.35 AND/OR ≥ moderate regurgitation

Statistical Methods

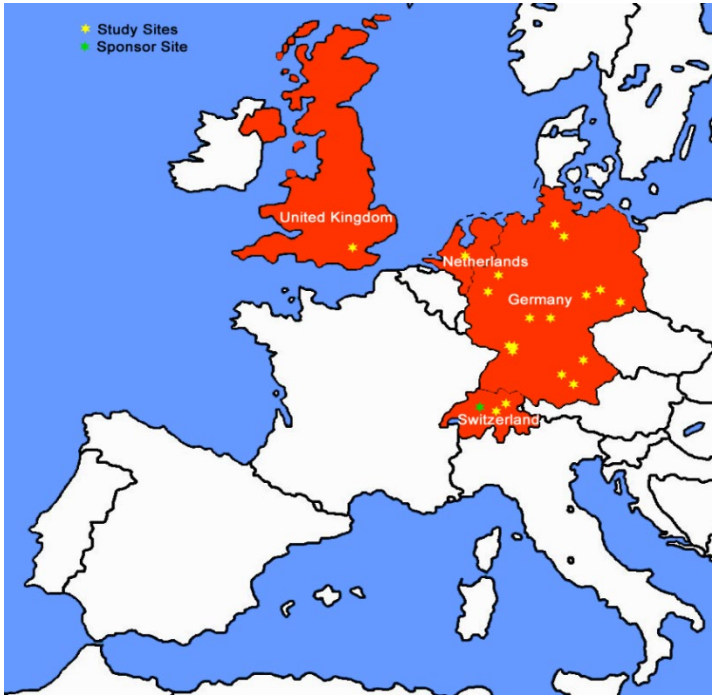
- **Stratified randomization** (by STS-PROM category and site)
- **Non-inferiority design**
  - Assumed primary endpoint event rate: 22%
  - Non-inferiority margin: 7.7% (risk-difference)
  - Power: 80%
  - Type I error (α) = 0.05 (one-sided)
  - 365 patients per group
- **Primary analysis in intention-to-treat cohort**, risk difference pooled over STS strata by Mantel-Haenszel (M-H) method

Trial Organization

- ***Sponsor***
  - Clinical Department of Cardiology, University Hospital Bern, Switzerland
- ***Data management & Monitoring***
  - University Hospital & Clinical Trials Unit, University of Bern, Switzerland
- ***Statistics***
  - Clinical Trials Unit, University of Bern, Switzerland
- ***Clinical Events Committee***
  - Cardiovascular European Research Center (CERC), Massy, France
- ***Echocardiography Core Laboratory***
  - Medical Research Development, Hospital La Zarzuela, Madrid, Spain
- ***Funder***
  - Boston Scientific, Marlborough, Massachusetts, USA

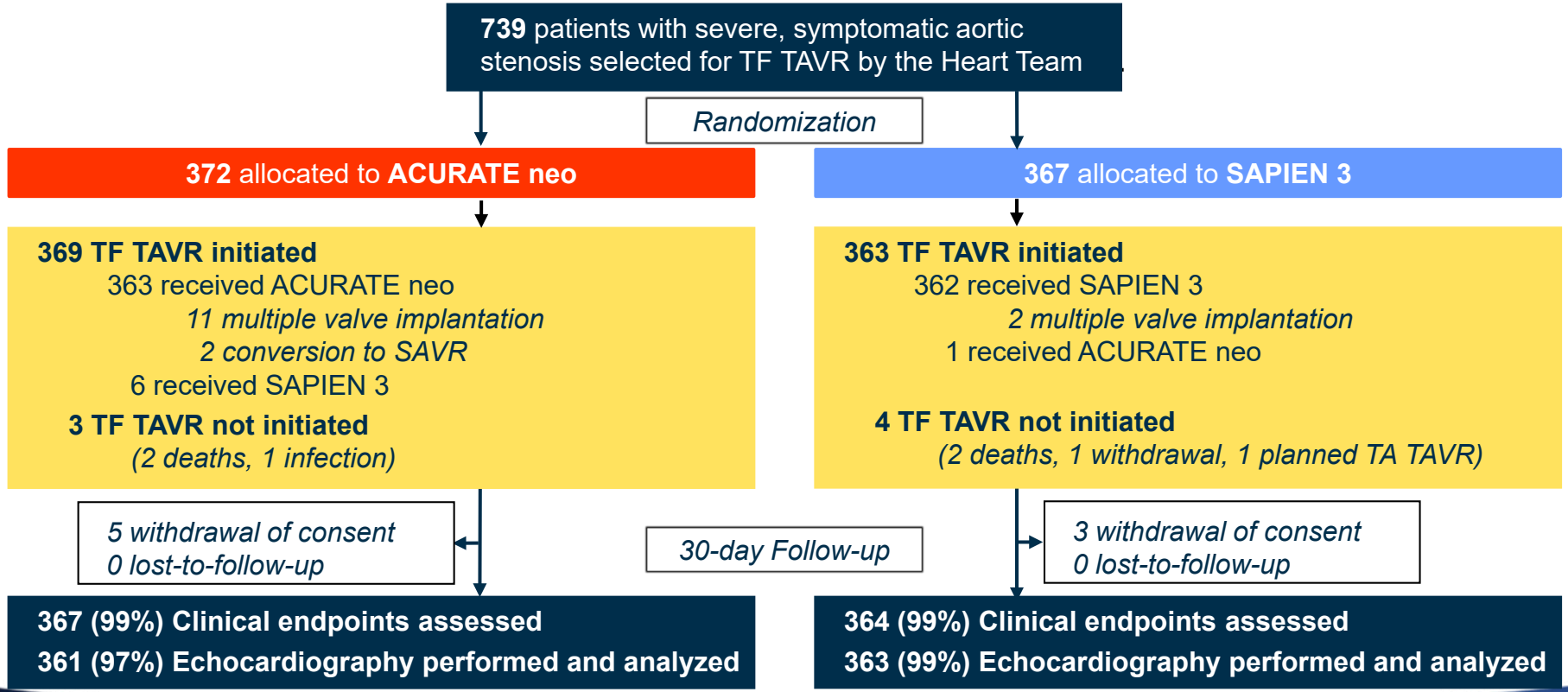
Study Sites

20 European sites, 4 Nations: Switzerland (3), Germany (15), Netherlands (1), UK (1)



Study Site	Local Principal Investigator
Klinikum Augsburg	Christian Thilo, MD
Zentralklinik, Bad Berka	Stefan Richter, MD
Heart and Vascular Center, Bad Bevensen	Christof Burgdorf, MD
Kerckhoff Heart and Thorax Center, Bad Nauheim	Won-Keun Kim, MD Thomas Walther, MD
Cardio-vascular Center Bad Neustadt,	Sebastian Kerber, MD
St.-Johannes-Hospital, Dortmund	Helge Möllmann, MD
Heart Center, Dresden	Axel Linke, MD
Helios Klinik, Karlsruhe	Lars Conzelmann, MD
St. Vincentius-Kliniken, Karlsruhe	Alexander Würth, MD
Städtisches Klinikum, Karslruhe	Gerhard Schymik, MD
University Heart Center, Cologne	Stephan Baldus, MD
Heart Center, Leipzig	Holger Thiele, MD
German Heart Centre, Munich	Michael Joner, MD
University Medical Center, Regensburg	Michael Hilker, MD
University Medical Center, Utrecht	Pieter Stella, MD
St Thomas` Hospital, London	Simon Redwood, MD
Bern University Hospital, Bern	Thomas Pilgrim, MD
Lucerne Cantonal Hospital, Lucerne	Stefan Toggweiler, MD
University Hospital Zurich, Zurich	Maurizio Taramasso, MD

Patient Flow Chart



Baseline Characteristics *(intention-to-treat)*

	ACURATE neo (N = 372)	SAPIEN 3 (N = 367)
Demographics		
Age - *years (mean ± SD)*	82.6 ± 4.3	83.0 ± 3.9
Female sex	218 (59%)	202 (55%)
Symptoms		
NYHA classification III or IV	287 (77%)	268 (73%)
Risk assessment		
STS-PROM score - *median (interquartile range)*	3.7 (2.6, 4.9)	3.4 (2.6, 5.2)
STS-PROM score categories		
low STS-PROM (< 3%)	134 (36%)	136 (37%)
intermediate STS-PROM (≥ 3% and < 8%)	207 (55%)	203 (55%)
high STS-PROM (≥ 8%)	31 (8%)	28 (8%)

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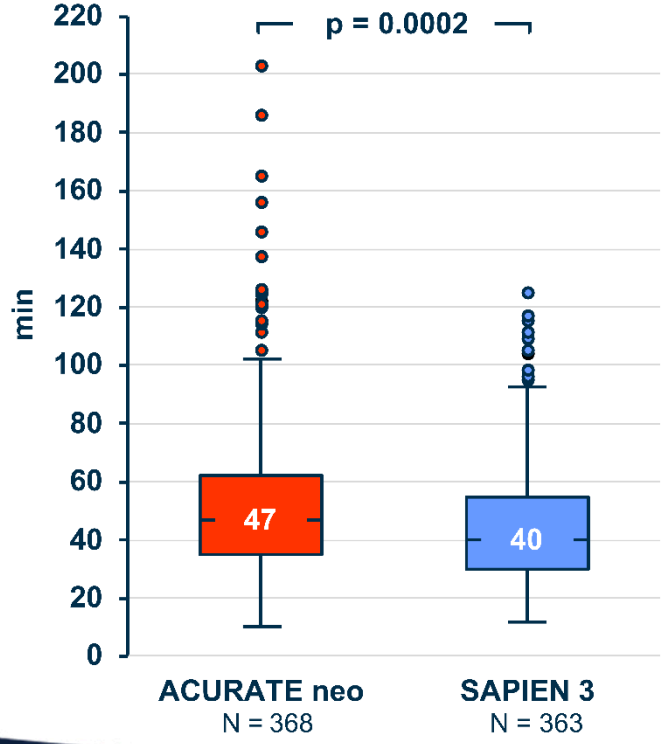
Baseline Imaging Characteristics *(intention-to-treat)*

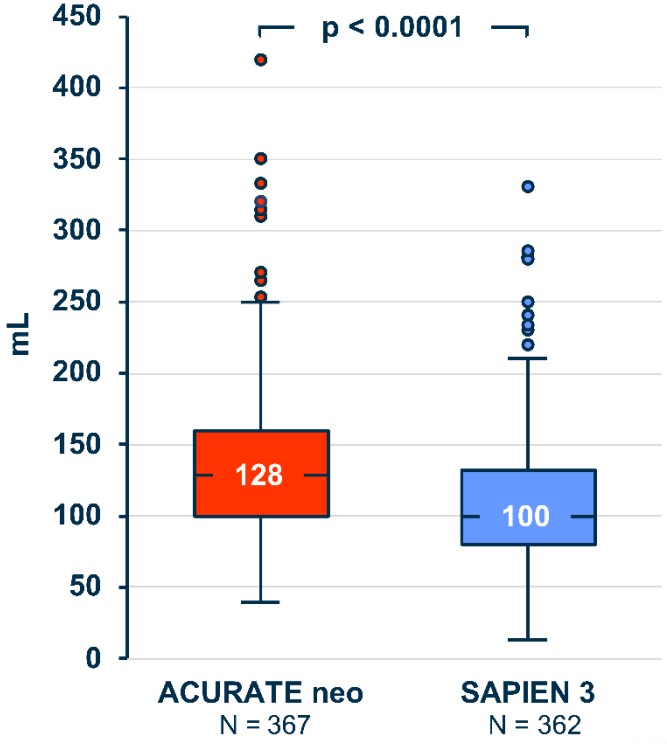
	ACURATE neo (N = 372)	SAPIEN 3 (N = 367)
Echocardiography		
Aortic valve mean gradient - *mmHg (mean ± SD)*	42.9 ± 17.2	41.5 ± 15.1
Aortic valve area - *cm^2 (mean ± SD)*	0.7 ± 0.2	0.7 ± 0.2
Left ventricular ejection fraction - *% (mean ± SD)*	56.4 ± 11.1	57.1 ± 10.7
Computed tomography		
Aortic annulus perimeter - *mm (mean ± SD)*	75.7 ± 5.2	75.9 ± 5.1
Aortic annulus area - *mm^2 (mean ± SD)*	439.1 ± 59.6	442.9 ± 60.3
Aortic valve calcification, moderate or severe	286 (77%)	286 (78%)
LVOT calcification, moderate or severe	94 (25%)	99 (27%)

Procedural Characteristics

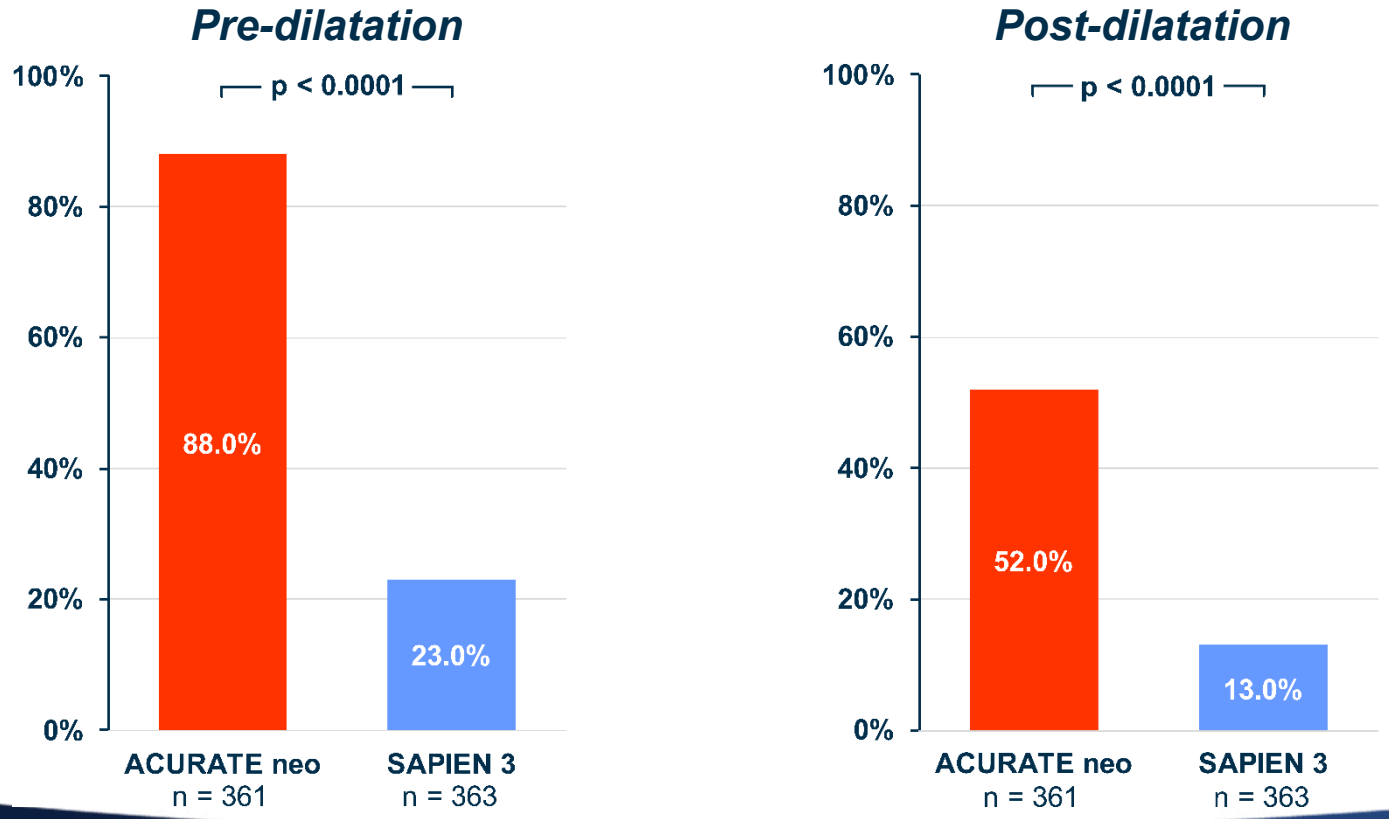
Procedure Time



Contrast Volume



Procedural Characteristics



Procedural Adverse Events *(intention-to-treat)*

	ACURATE neo (N = 369)	SAPIEN 3 (N = 363)	P value
Valve mal-positioning	5 (1%)	2 (1%)	0.26
Implantation of multiple valves	**11 (3%)**	**2 (1%)**	**0.0119**
Coronary artery obstruction requiring intervention	0 (0%)	0 (0%)	1.00
Peri-procedural myocardial infarction	1 (0.3%)	1 (0.3%)	0.96
Cardiac tamponade	4 (1%)	5 (1%)	0.72
Annular rupture	2 (1%)	1 (0.3%)	0.57
Left ventricular perforation	1 (0.3%)	0 (0%)	0.32
Conversion to open heart surgery	3 (1%)	0 (0%)	0.08
SAVR	2 (1%)	0 (0%)	0.50
Immediate procedural death	3 (1%)	1 (0.3%)	0.32

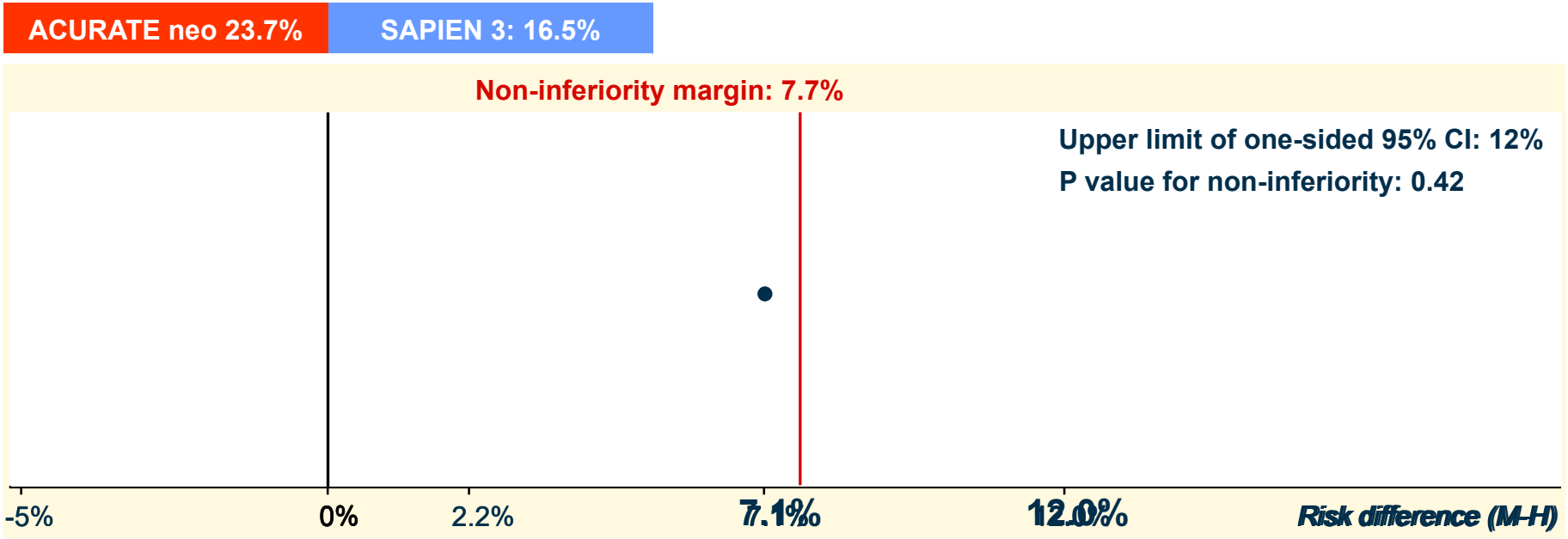
Primary Endpoint Rates at 30 days

Intention-to-treat

ACURATE neo	SAPIEN 3
87/367 (**23.7%**)	60/364 (**16.5%**)

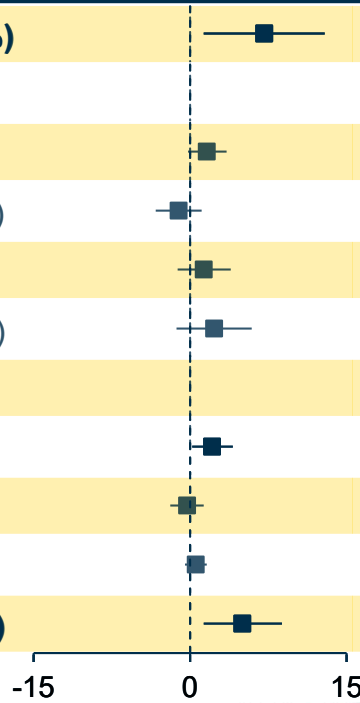
Primary Endpoint

Primary analysis at 30 days (intention-to-treat)



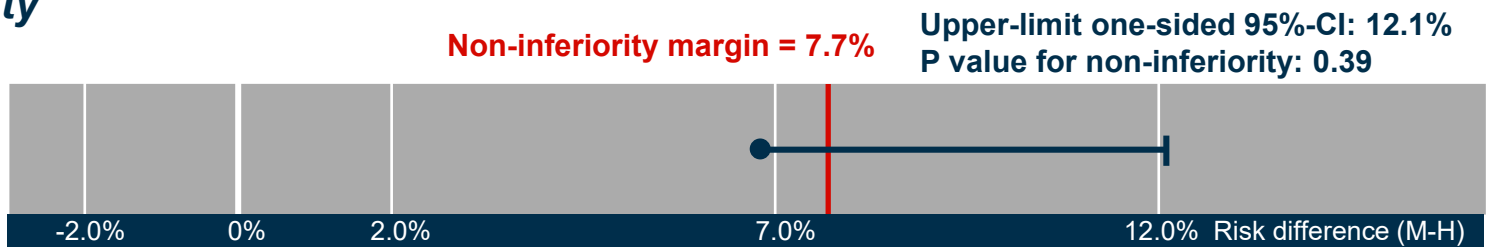
Primary Endpoint - Secondary Analyses at 30 days

	ACURATE neo	SAPIEN 3	Risk difference % (95%-CI)	P value
	No. of events/total no. (%)			
Primary endpoint *(superiority analysis)*	**87/367 (23.7%)**	**60/364 (16.5%)**		**0.0156**
Single components of primary endpoint				
All-cause death	9/367 (2.5%)	3/364 (0.8%)		0.09
Stroke (any)	7/367 (1.9%)	11/364 (3.0%)		0.33
Life-threatening or disabling bleeding	14/367 (3.8%)	9/364 (2.5%)		0.30
Major vascular complications	29/367 (7.9%)	20/364 (5.5%)		0.21
Coronary artery obstruction requiring intervention	0/367 (0%)	0/364 (0%)		n/a
Acute kidney injury, stage 2 or 3	**11/367 (3.0%)**	**3/364 (0.8%)**		**0.0340**
Re-hospitalization for valve-related dysfunction or CHF	4/367 (1.1%)	5/364 (1.4%)		0.72
Valve-related dysfunction requiring repeat procedure	3/367 (0.8%)	1/364 (0.3%)		0.32
Valve-related dysfunction *(echocardiography)*	**35/361 (9.7%)**	**17/363 (4.7%)**		**0.0084**

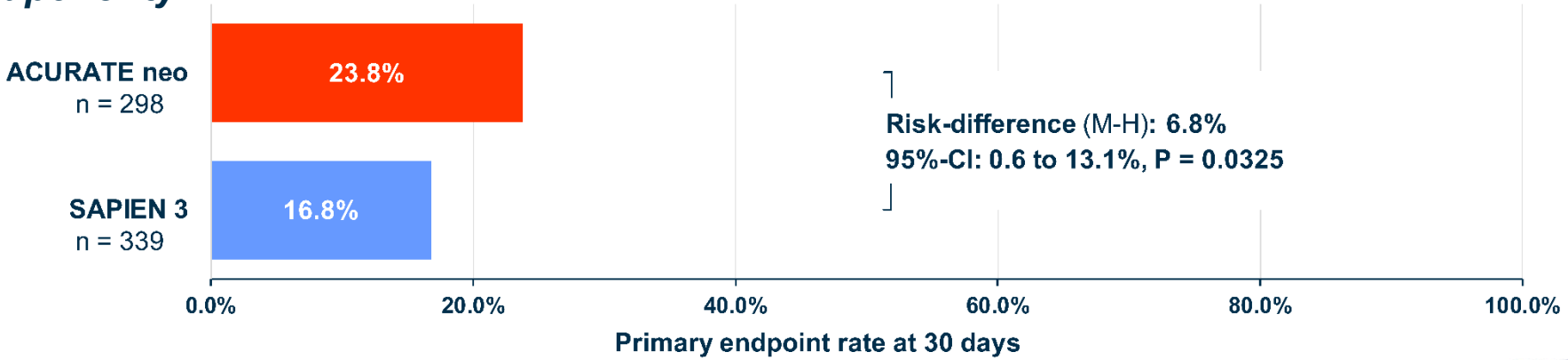


Primary Endpoint - Per Protocol Analyses

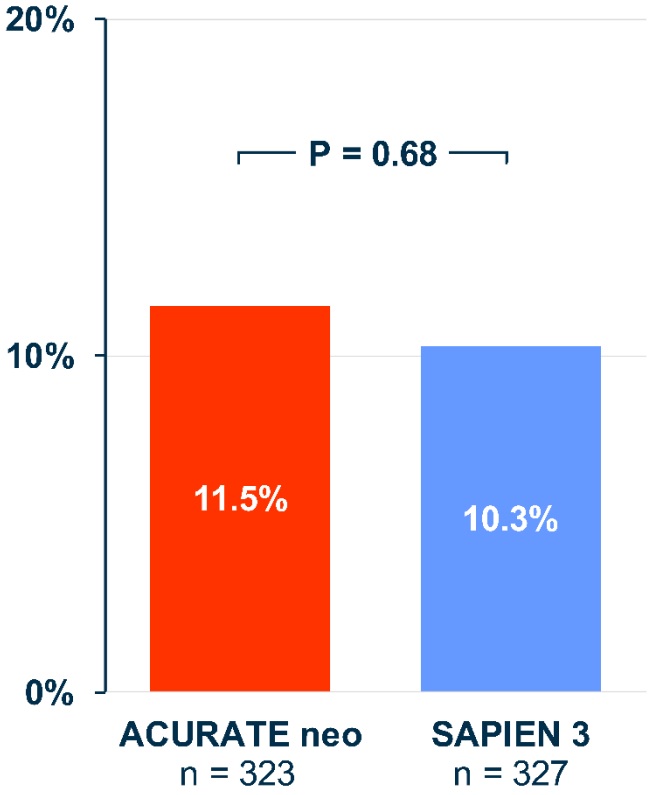
Non-inferiority



Superiority



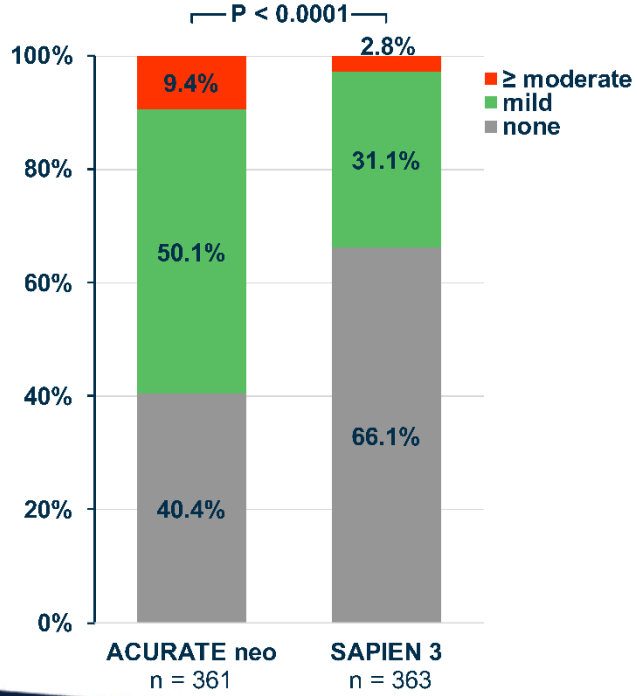
New Pacemaker Implantation



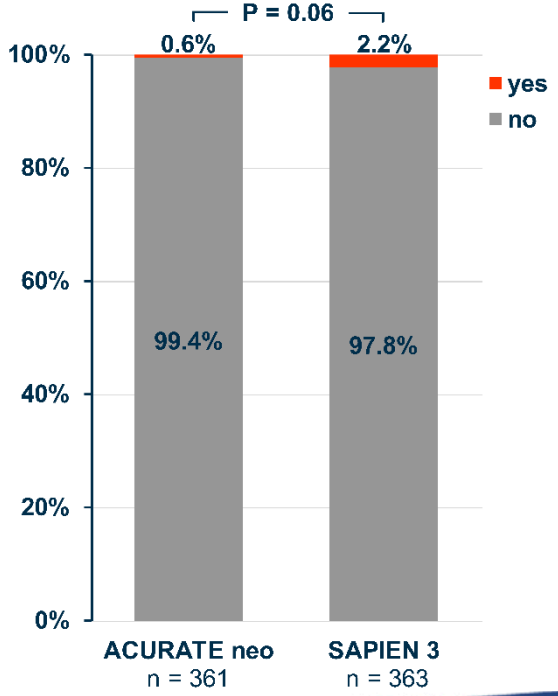
Numbers refer to the cohort at risk
(patients with pacemaker at baseline excluded)

Echocardiographic Valve Performance

Paravalvular Aortic Regurgitation



Mean Gradient ≥20 mmHg AND EOA ≤ 0.9-1.1 cm² and/or DVI < 0.35



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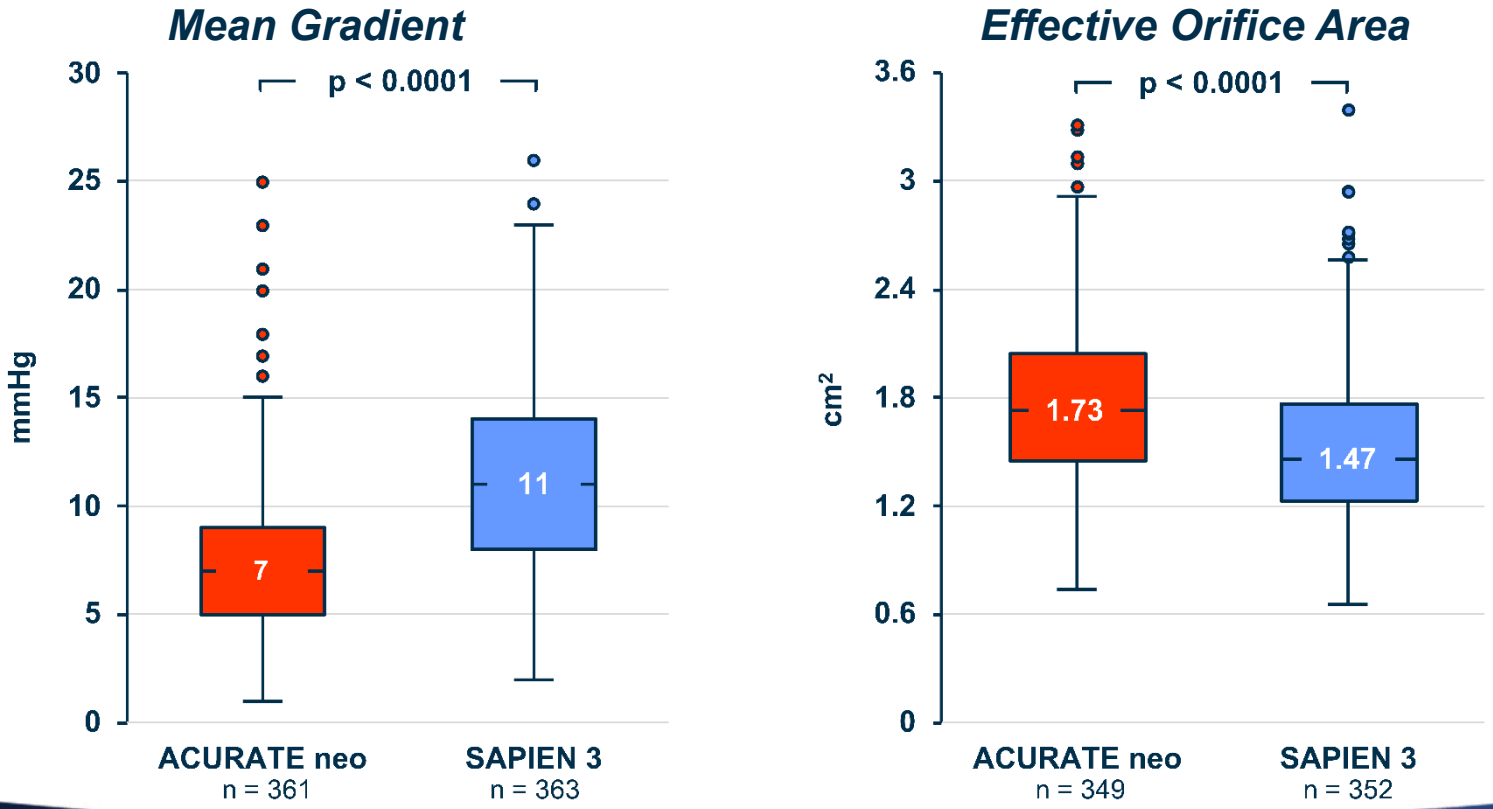

Limitations

- **Not powered for individual clinical endpoints**
- **Early primary endpoint** limits evaluation of device differences in terms of long-term clinical outcomes
- **Single-blinded trial**
  - visible differences in the stent frame precluded blinding of echocardiography core laboratory
- **Lack of** assessment of aortic root **CT** angiographies by a **central core laboratory** at baseline

Summary of Major Results

- **Non-inferiority of ACURATE neo** versus SAPIEN 3 with respect to composite safety and efficacy endpoint at 30 days **not met**
- **Superiority of SAPIEN 3** with regard to composite safety and efficacy endpoint at 30 days in secondary analyses, **driven by** lower rates of **paravalvular regurgitation** and **acute kidney injury (stage 2 or 3)**
- **Higher rates of multiple valve implantation with ACURATE neo**
- **Lower** transvalvular **gradients** and **larger effective orifice area** with **ACURATE neo**
- **Low mortality, stroke** and **pacemaker rates with both** devices

Conclusions

- **ACURATE neo did not meet non-inferiority** compared to the SAPIEN 3 device **regarding the primary composite safety and efficacy endpoint at 30 days**
- **Differences** between the two TAVR devices were **driven by moderate or severe paravalvular regurgitation** and stage 2 or 3 **acute kidney injury in favor of** the **SAPIEN 3** device
- **An early composite** safety and efficacy **endpoint proved useful in discriminating** the performance of different **TAVR systems**

Simultaneous Publication in *The Lancet*

Safety and efficacy of a self-expanding versus a balloon-expandable bioprosthesis for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: a randomised non-inferiority trial

Jonas Lanz, Won-Keun Kim*, Thomas Walther, Christof Burgdorf, Helge Möllmann, Axel Linke, Simon Redwood, Christian Thilo, Michael Hilker, Michael Joner, Holger Thiele, Lars Conzelmann, Lenard Conradi, Sebastian Kerber, Gerhard Schymik, Bernard Prendergast, Oliver Husser, Stefan Stortecky, Dik Heg, Peter Jüni, Stephan Windecker, Thomas Pilgrim, for the SCOPE I investigators†*

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