SCOPE II

Comparison of self-expanding bioprostheses for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: the SCOPE II randomised clinical trial

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Disclosure statement of financial interest

I, Corrado Tamburino, I have the following 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.

Disclosure: Speaker fees from Medtronic.

Background

Essential

To establish TAVR as first-line therapy for patients with severe aortic stenosis are demonstration of long-term durability and improvements with regards to a number of adverse procedural outcomes, including paravalvular leakage and the need for new permanent pacemaker implantation.

New TAVR systems

Should undergo head-to-head comparisons and be tested in randomised controlled trials similar to what has been accomplished in the field of coronary stents.

A new generation

Transcatheter valve delivered via transfemoral access is the ACURATE neo (Boston Scientific, Marlborough, MA, USA), which gained CE mark approval in June 2014. In the SCOPE I trial, the ACURATE neo valve proved inferior to the balloon-expandable, intra-annular Sapien 3 valve at 30 days.

Objective

The SCOPE II trial
was designed to compare the early and mid-term performance of the ACURATE neo to the CoreValve Evolut (Medtronic Inc., Minneapolis, MN, USA) self-expanding, supra-annular transcatheter valve.

Study devices

	ACURATE neo	CoreValve Evolut
Frame	Nitinol	Nitinol
Leaflets	Porcine pericardium	Porcine pericardium
Expansion	Self-expanding	Self-expanding
Recapturable	No	Yes
Annular fixation	Yes	Yes
Self-alignment capability	Yes	No
Valve sizes	Small (23 mm), Medium (25 mm), Large (27 mm)	26 mm and 29 mm
Annulus diameter	21–27 mm	18–26 mm
Deliver system diameter	18 and 19 French	14 and 16 French

Study design

Patients with symptomatic severe aortic stenosis undergoing TAVR as established by the Heart Team
N=796

Randomise 1:1

ACURATE neo
N=398

CoreValve Evolut
N=398

Primary endpoint (noninferiority)
All-cause death or stroke at 1 year

Key secondary endpoint (superiority)
New permanent pacemaker implantation at 30 days

Eligibility criteria

Major inclusion criteria

- Age ≥ 75 years
- Severe symptomatic aortic stenosis
- High risk for mortality with conventional SAVR as assessed by the Heart Team *or* risk scores
- Aortic annulus dimensions suitable for both valve types
- Arterial aorto-iliac-femoral axis suitable for transfemoral access

Major exclusion criteria

- Severely reduced LV function
- Prosthetic heart valve in aortic and/or mitral position
- Severe coagulation conditions
- Inability to tolerate anticoagulation therapy
- Active infection
- Congenital or non-calcific acquired aortic stenosis, or unicuspid or bicuspid aortic valve
- Severe eccentricity of calcification
- Anatomy not appropriate for transfemoral implant
- Severe mitral regurgitation

Study endpoints

Primary endpoint (powered for noninferiority)

- All-cause death or any stroke (disabling and non-disabling) at 1 year

Key secondary endpoint (powered for superiority)

- New permanent pacemaker implantation at 30 days

Secondary endpoints

- Components of the primary endpoint at 30 days and 1 year
- Procedural complications
- Clinical safety endpoints (myocardial infarction, hospitalization for valve-related symptoms or worsened congestive heart failure, valve-related dysfunction requiring re-operation, endocarditis, valve thrombosis, new left bundle branch block, new tachyarrhythmias, life-threatening or major bleeding)
- Composite endpoints as defined by VARC-2
- Bioprosthesis function as assessed by echocardiography

Statistical hypothesis for the trial

Noninferiority analysis (primary endpoint)

- 1-year incidence rate: 12%
- Noninferiority margin: 6%
- Power: 80%
- 95% confidence interval (one-sided)

Superiority analysis (key secondary endpoint)

- Predicted rate in the control group: 15%
- Absolute difference: 7%
- Type I error rate: 5% (two-sided)

Rate of loss to follow-up: up to 5%

Required sample size: 764 patients

Intention-to-treat population: all patients randomised, analysed according to the intention-to-treat principle.

Per-protocol population: patients who died before the procedure was initiated or in whom the procedure was initiated and the allocated device used and implanted, and who had no protocol violations regarding eligibility of the implantation procedure.

Noninferiority of the ACURATE neo valve was claimed only if both analyses in the intention-to-treat and per-protocol populations showed non-inferiority.

If noninferiority was shown, the primary endpoint would **then be tested for superiority** using a two-sided type I error rate of 5%.

Trial organization

Cardiovascular European Research Center

Clinical Events Committee

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CEC Chairman

Data and Safety Monitoring Board

Kristian Thygesen
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Hervé Le Breton
Philippe Menasché

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Kris Bogaerts

Trial Management CERC

Murielle Bierlein, PL
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Sponsor

Ceric
Center for European Research Initiatives in Cardiovascular Medicine

Grant Giver

SYMETIS

Study sites

23 European sites, 6 Countries: Denmark (1), France (4), Germany (11), Italy (4), Spain (1), UK (2)

Study site	Inclusion numbers	Local principal investigator
Herzzentrum Leipzig GmbH and Leipzig Heart Institute GmbH	114	Holger Thiele
Herz- und Diabeteszentrum NRW Bad Oeynhausen	77	Smita Sholtz & René Schramm
Brighton and Sussex University Hospital NHS Trust	77	David Hildick-Smith
Istituto Clinico Humanitas Milano	76	Paolo Pagnotta
Elisabeth-Krankenhaus Essen	65	Alexander Wolf
Leeds Teaching Hospitals NHS Trust	51	Michael Cunnington
Clinique Pasteur Toulouse	44	Didier Tchétché
CHRU de Lille, Hôpital Cardiologique	44	Eric Van Belle
IRCCS Policlinico San Donato, Milano	44	Francesco Bedogni
Ospedale San Raffaele, Milano	39	Alaide Chieffo
Azienda Ospedaliero Universitaria Policlinico, Catania	28	Corrado Tamburino
ICPS Massy	24	Philippe Garot

Study site	Inclusion numbers	Local principal investigator
CHRU Brest, Hôpital de la Cavale Blanche	21	Martine Gilard
Heart Center, Rigshospitalet, University of Copenhagen	17	Lars Søndergaard
Universitätsklinikum der J.W. Goethe – Universität Frankfürt	17	Mariuca Vasa-Nicotera
Complejo Hospitalario Universitario de Santiago de Compostela	13	Ramiro Trillo-Nouche
Herzzentrum Dresden	12	Axel Linke
Herzzentrum Brandenburg Bernau	10	Christian Butter
Klinik an der Technischen Universität München	7	Oliver Deutsch
Deutsches Herzzentrum Berlin	6	Jörg Kempfert
Universitätsklinikum der RWTH Aachen	6	Shahram Lotfi
St. Johannes Hospital Dortmund	2	Helge Möllmann
Klinik für Herz- und Kreislauferkrankungen Munich	1	Michael Joner

Patient flow chart

796 Patients Randomised

398 allocated to ACURATE neo		398 allocated to CoreValve	
386 transfemoral TAVR initiated 377 received ACURATE neo 5 received CoreValve 4 received other valve	**12 TAVR were not initiated** **3 intraprocedural deaths** **5 procedural deaths**	**388 TAVR initiated** 366 received CoreValve 26 or 29 4 received ACURATE neo 18 received other valve	**10 TAVR were not initiated** **0 intraprocedural deaths** **1 procedural deaths**
→ 7 exited study		→ 12 exited study	
362 30-days clinical endpoint assessment **282** 30-days echocardiographic endpoint assessment **Status at 30-days: 369 alive, 11 died, 5 exited study**		**360** 30-days clinical endpoint assessment **296** 30-days echocardiographic endpoint assessment **Status at 30-days: 370 alive, 5 died, 13 exited study**	
→ 13 exited study		→ 13 exited study	
318 1-year clinical endpoint assessment **236** 1-year clinical echocardiographic endpoint assessment **Status at 1-year: 317 alive, 43 died, 26 exited study**		**326** 1-year clinical endpoint assessment **242** 1-year clinical echocardiographic endpoint assessment **Status at 1-year: 327 alive, 32 died, 29 exited study**	

Clinical follow-up information was available for 98% patients

Baseline characteristics (intention-to-treat)

	ACURATE neo (N = 398)	**CoreValve Evolut** (N = 398)
Demographics		
Age – years (SD)	83.4 (4.2)	82.9 (4.3)
Female sex, n (%)	263 (66%)	275 (69%)
Symptoms		
NYHA classification III or IV, n (%)	262 (66%), N=397	250 (63%), N=394
CCS class 3 or 4, n (%)	18 (5%), N=397	22 (6%), N=394
Syncope, n (%)	35 (9%), N=397	56 (14%), N=394
Risk assessment		
STS-PROM score, n (SD)	4.6 (3.0)	4.5 (2.7)

Procedural characteristics (intention-to-treat)

	ACURATE neo (N=398)	**CoreValve Evolut** (N=398)	**P value**
Transfemoral TAVR performed	386 (97%)	388 (97%)	0.83
Procedure time, min (SD)	72 (32), N=380	75 (39), N=384	0.37
Total contrast volume, mL (SD)	133 (47), N=378	132 (65), N=384	0.70
General anesthesia, n (%)	52 (13%)	52 (13%)	0.98
Transfemoral access mode			
Percutaneous, n (%)	385 (100%), N=385	385 (99%)	0.08
Surgical cut-down, n (%)	0 (0%), N=385	3 (1%)	
Access closure device, n (%)	382 (99%), N=385	385 (99%)	1.00
Pre-dilation, n (%)	306 (79%)	160 (41%)	**<0.0001**
Device size (waist), mm (SD)	25 (2)	28 (2)	**<0.0001**
Post-dilatation, n (%)	177 (46%)	139 (36%)	**0.005**

Percentages were calculated on the number of patients in whom TAVR was initiated.

Procedural complications (intention-to-treat)

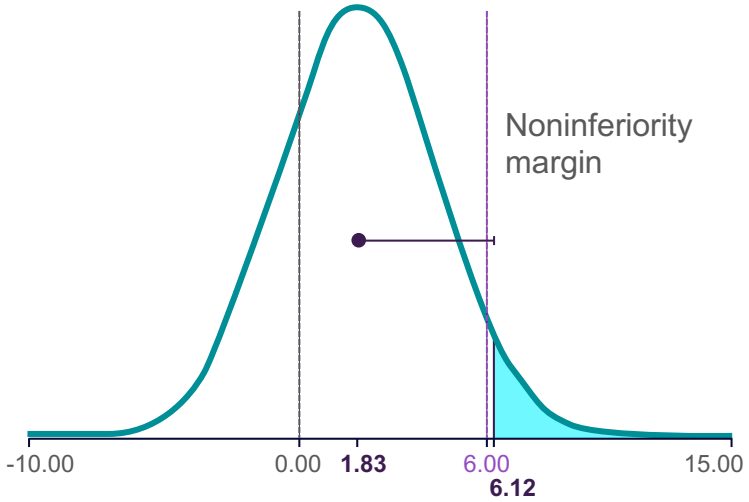
	ACURATE neo (N=398)	CoreValve Evolut (N=398)	P value
Valve malpositioning, n (%)	2 (<1%)	9 (2%)	0.06
Coronary artery obstruction, n (%)	2 (1%)	0	0.25
Hemodynamic instability, n (%)	6 (2%)	3 (1%)	0.34
Cardiac tamponade, n (%)	4 (1%)	4 (1%)	1.00
Annular rupture, n (%)	1 (<1%)	1 (<1%)	1.00
Conversion to open heart surgery, n (%)	0	2 (1%)	0.50
Access site complication, n (%)	33 (9%)	24 (6%)	0.22
Bleeding, n (%)	8 (2%)	9 (2%)	1.00
Intra-procedural death, n (%)	3 (1%)	0	0.12

Percentages were calculated on the number of patients in whom TAVR was initiated.

Primary endpoint

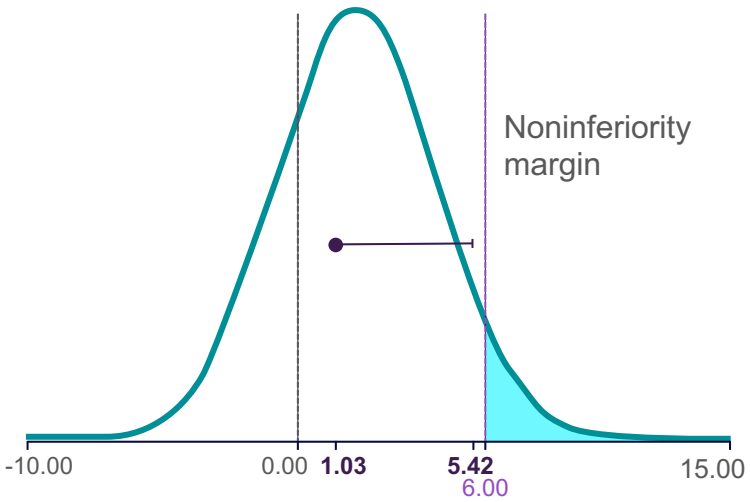
Death or stroke at 1 year (intention-to-treat)

ACURATE neo: 15.8% | **CoreValve Evolut: 13.9%**



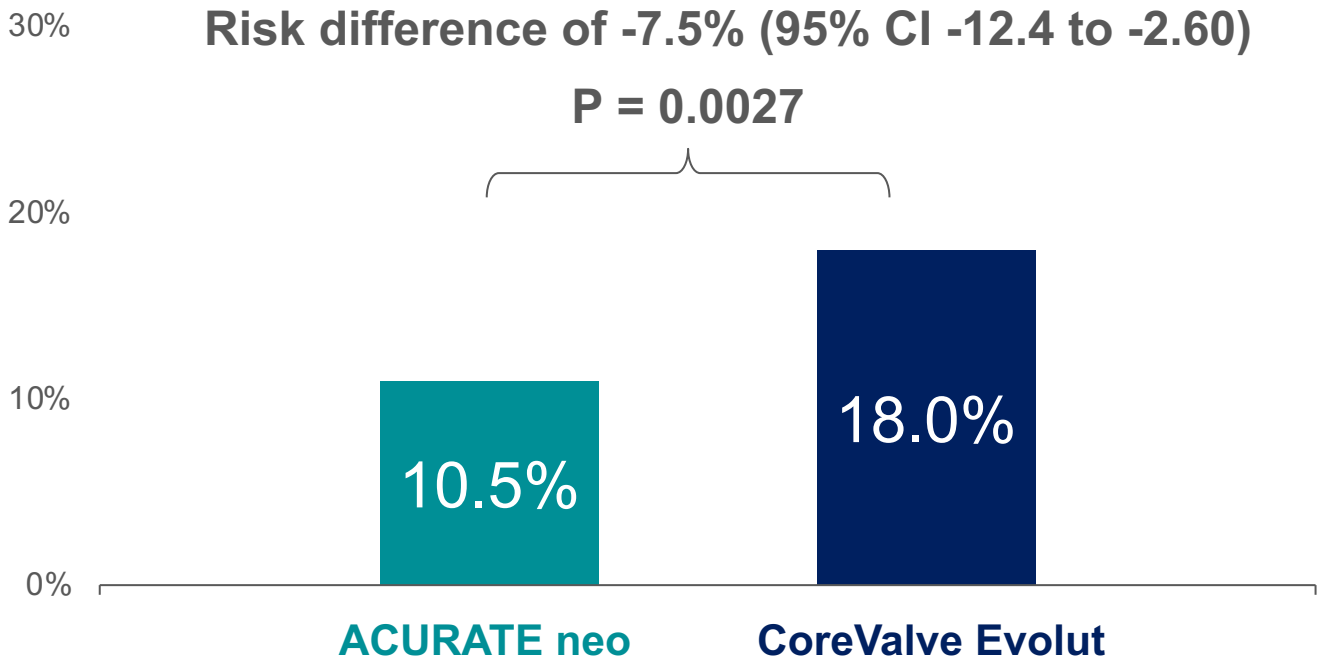
Death or stroke at 1 year (per-protocol)

ACURATE neo: 15.3% | **CoreValve Evolut: 14.3%**



Because the results of the intention-to-treat and per-protocol analyses were inconsistent, noninferiority of the ACURATE neo was not established for the primary endpoint

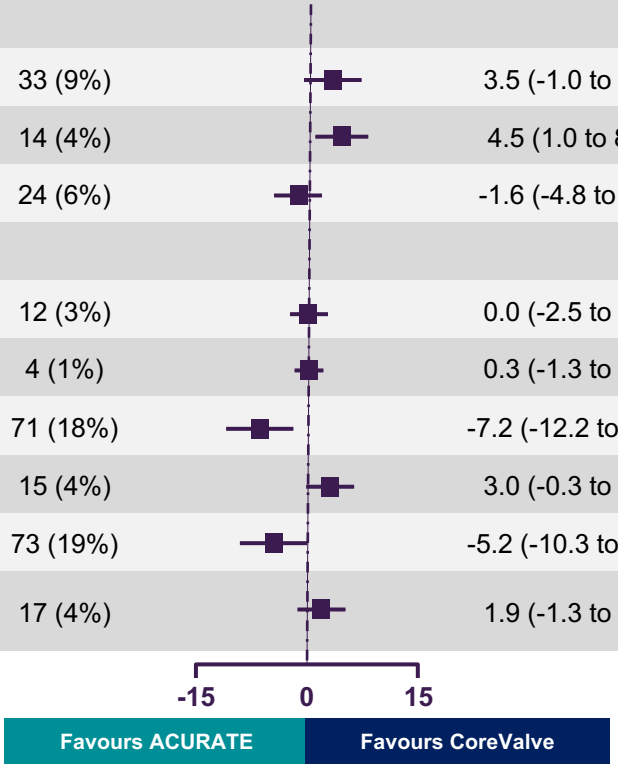
New pacemaker implantation at 30 days (intention-to-treat)



Secondary endpoints at 1 year (intention-to-treat)

Events, n (%)

	ACURATE neo (N=398)	CoreValve (N=398)	Risk difference (95% CI)	p value
Components of primary endpoint				
All-cause death	46 (13%)	33 (9%)	3.5 (-1.0 to 8.0)	0.13
Cardiac death	31 (8%)	14 (4%)	4.5 (1.0 to 8.0)	**0.01**
Stroke	18 (5%)	24 (6%)	-1.6 (-4.8 to 1.6)	0.33
Other secondary endpoints				
Life threatening or major bleeding	12 (3%)	12 (3%)	0.0 (-2.5 to 2.5)	1.00
Myocardial infarction	5 (1%)	4 (1%)	0.3 (-1.3 to 1.8)	0.76
New pacemaker implantation	43 (11%)	71 (18%)	-7.2 (-12.2 to -2.3)	**0.0043**
Hospitalisation for cardiac reasons	26 (7%)	15 (4%)	3.0 (-0.3 to 6.3)	0.079
New left bundle branch block	53 (14%)	73 (19%)	-5.2 (-10.3 to -0.0)	**0.048**
Any tachyarrhythmia resulting in haemodynamic instability or requiring therapy	24 (6%)	17 (4%)	1.9 (-1.3 to 5.2)	0.24

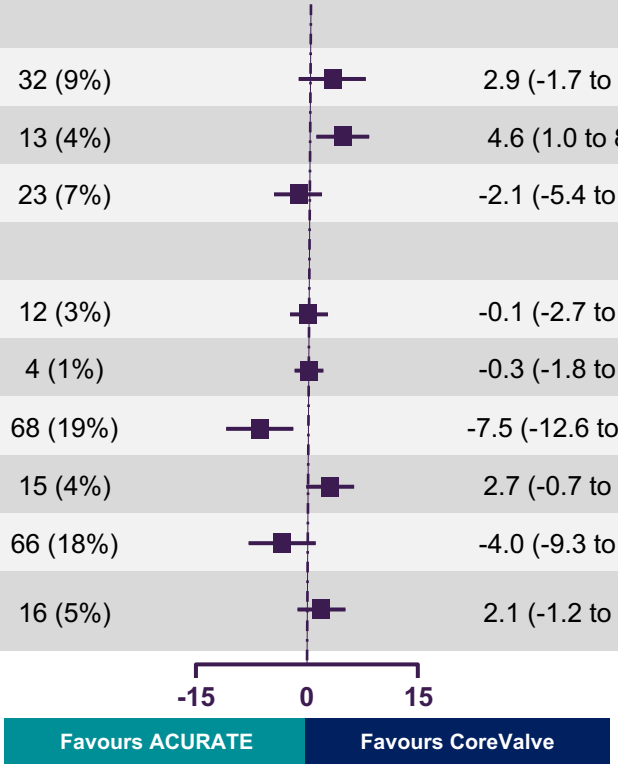


Percentages are Kaplan-Meier estimates or cumulative incidence estimates taking mortality as a competing risk into account

Secondary endpoints at 1 year (per-protocol)

Events, n (%)

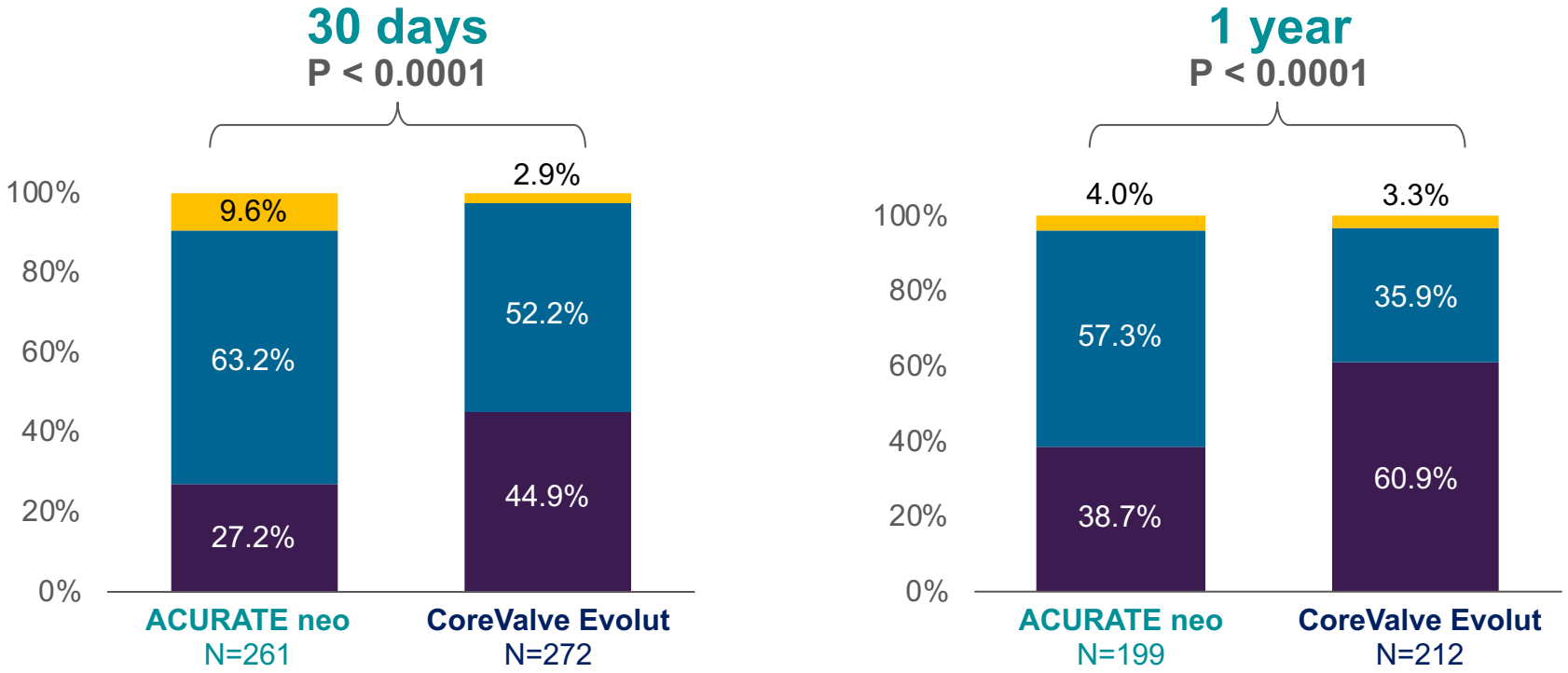
	ACURATE neo (N=375)	CoreValve (N=366)	Risk difference (95% CI)	p value
Components of primary endpoint				
All-cause death	43 (12%)	32 (9%)	2.9 (-1.7 to 7.5)	0.22
Cardiac death	39 (8%)	13 (4%)	4.6 (1.0 to 8.0)	**0.01**
Stroke	16 (4%)	23 (7%)	-2.1 (-5.4 to 1.2)	0.21
Other secondary endpoints				
Life threatening or major bleeding	12 (3%)	12 (3%)	-0.1 (-2.7 to 2.5)	0.95
Myocardial infarction	3 (1%)	4 (1%)	-0.3 (-1.8 to 1.1)	0.67
New pacemaker implantation	42 (11%)	68 (19%)	-7.5 (-12.6 to -2.4)	**0.0043**
Hospitalisation for cardiac reasons	25 (7%)	15 (4%)	2.7 (-0.7 to 6.1)	0.12
New left bundle branch block	53 (14%)	66 (18%)	-4.0 (-9.3 to 1.4)	0.14
Any tachyarrhythmia resulting in haemodynamic instability or requiring therapy	24 (7%)	16 (5%)	2.1 (-1.2 to 5.5)	0.21



Percentages are Kaplan-Meier estimates or cumulative incidence estimates taking mortality as a competing risk into account

Aortic regurgitation

Core lab assessment



Study limitations

The trial was not powered to show differences with regard to individual clinical endpoints, with the exception of new permanent pacemaker implantation at 30 days.

Follow-up is limited at 1 year, which precludes meaningful evaluations of differences in long-term clinical outcomes and valve durability.

Follow-up echocardiography was available only for a proportion of the initial population.

Summary of major results (intention-to-treat)

Among 796 randomized patients, clinical follow-up information was available for 778 (98%) patients

	ACURATE neo	CoreValve Evolut
Within 1 year		
Primary endpoint	15.8%	13.9%
(absolute risk difference 1.8%, upper one-sided 95% confidence limit 6.1%, p=0.0549 for noninferiority)		
Within 30 days		
New permanent pacemaker implantation	10.5%	18.0%
(absolute risk difference -7.5%, 95% confidence interval -12.4 to -2.60, p=0.0027 for superiority)		

Conclusions

TAVR with the ACURATE neo valve did not meet noninferiority compared with the CoreValve Evolut bioprosthesis **with respect to a composite of death or stroke at 1 year.**

In a secondary analysis with limited statistical power, **cardiac death was increased at 1 year in patients who received the ACURATE neo valve.**

The **two bioprostheses differed** with respect to technical characteristics such as **degree of aortic regurgitation and need for new permanent pacemaker implantation.**

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