Circulation

ORIGINAL RESEARCH ARTICLE

Comparison of Self-Expanding Bioprostheses for Transcatheter Aortic Valve Replacement in Patients With Symptomatic Severe Aortic Stenosis

SCOPE 2 Randomized Clinical Trial

BACKGROUND: Few randomized trials have compared bioprostheses for transcatheter aortic valve replacement, and no trials have compared bioprostheses with supra-annular design. The SCOPE 2 trial (Safety and Efficacy Comparison of Two TAVI Systems in a Prospective Randomized Evaluation 2) was designed to compare the clinical outcomes of the ACURATE neo and CoreValve Evolut bioprostheses for transcatheter aortic valve replacement.

METHODS: SCOPE 2 was a randomized trial performed at 23 centers in 6 countries between April 2017 and April 2019. Patients ≥75 years old with an indication for transfemoral transcatheter aortic valve replacement as agreed by the heart team were randomly assigned to receive treatment with either the ACURATE neo (n=398) or the CoreValve Evolut bioprostheses (n=398). The primary end point, powered for noninferiority of the ACURATE neo bioprosthesis, was all-cause death or stroke at 1 year. The key secondary end point, powered for superiority of the ACURATE neo bioprosthesis, was new permanent pacemaker implantation at 30 days.

RESULTS: Among 796 randomized patients (mean age, 83.2±4.3 years; mean Society of Thoracic Surgeons Predicted Risk of Mortality score, 4.6±2.9%), clinical follow-up information was available for 778 (98%) patients. Within 1 year, the primary end point occurred in 15.8% of patients in the ACURATE neo group and in 13.9% of patients in the CoreValve Evolut group (absolute risk difference, 1.8%, upper 1-sided 95% confidence limit, 6.1%; *P*=0.0549 for noninferiority). The 30-day rates of new permanent pacemaker implantation were 10.5% in the ACURATE neo group and 18.0% in the CoreValve Evolut group (absolute risk difference, –7.5% [95% CI, –12.4 to –2.60]; *P*=0.0027). No significant differences were observed in the components of the primary end point. Cardiac death at 30 days (2.8% versus 0.8%; *P*=0.03) and 1 year (8.4% versus 3.9%; *P*=0.01), and moderate or severe aortic regurgitation at 30 days (10% versus 3%; *P*=0.002) were significantly increased in the ACURATE neo group.

CONCLUSIONS: Transfemoral transcatheter aortic valve replacement with the self-expanding ACURATE neo did not meet noninferiority compared with the self-expanding CoreValve Evolut in terms of all-cause death or stroke at 1 year, and it was associated with a lower incidence of new permanent pacemaker implantation. In secondary analyses, the ACURATE neo was associated with more moderate or severe aortic regurgitation at 30 days and cardiac death at 30 days and 1 year.

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Key Words: ACURATE neo ■ bioprosthesis ■ CoreValve Evolut ■ randomized clinical trial ■ supra-annular ■ TAVI ■ TAVR

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Clinical Perspective

What Is New?

- In a randomized trial of 796 patients undergoing transcatheter aortic valve replacement, death or stroke at 1 year occurred in 15.8% of patients who received the ACURATE neo valve and in 13.9% of those who received the CoreValve Evolut valve (*P*=0.0549 for noninferiority).
- New permanent pacemaker implantation at 30 days was less common in the ACURATE neo group (10.5% versus 18.0%; *P*=0.0027).
- Cardiac death (at 30 days and 1 year) and moderate or severe aortic regurgitation (at 30 days) were more frequent in patients randomized to the ACURATE neo valve.

What Are the Clinical Implications?

- Head-to-head randomized comparisons of transcatheter aortic valve replacement valves using clinical end points are instrumental to detect potential differences in outcomes and inform physicians at the time of valve selection.
- Design ameliorations are necessary to mitigate the risk of paravalvular regurgitation with the ACURATE neo valve and improve clinical outcomes at the early term and midterm.

Transcatheter aortic valve replacement (TAVR) is an established treatment option for patients with symptomatic severe aortic stenosis.[1,2] Comparative studies of self-expanding and balloon-expandable bioprostheses for TAVR in patients across the spectrum of surgical risk have shown safety and efficacy outcomes at 1 year that are at least similar to those of surgical aortic valve replacement.[3–9] However, essential for the establishment of TAVR as first-line therapy for patients who are younger or those who are at lower surgical risk are demonstration of long-term durability and improvements with regards to many adverse procedural outcomes, including vascular complications, paravalvular leakage, and the need for new permanent pacemaker implantation.[10] The rates of pacemaker implantation differ considerably between TAVR devices and are generally higher with self-expanding bioprostheses.[11]

Procedural and midterm outcomes of TAVR have improved over the years with modifications of valve designs and development of lower-profile devices.[12] However, comparisons of TAVR devices in randomized controlled trials are scant,[13–17] in particular for newer-generation valves,[14,15] and limited to comparisons of bioprostheses with supra-annular versus intra-annular design. In contrast, no randomized controlled trials have specifically compared different self-expanding bioprostheses with supra-annular design. In view of the worldwide growing number of TAVR procedures and technological refinements going along with development of new devices, new TAVR systems should undergo head-to-head comparisons and be tested in randomized controlled trials similar to what has been accomplished in the field of coronary stents. A new-generation transcatheter valve delivered through transfemoral access is the ACURATE neo (Boston Scientific, Marlborough, MA), which gained Conformite Europeenne mark approval in June 2014.[18] In the SCOPE (Safety and Efficacy Comparison of Two TAVI Systems in a Prospective Randomized Evaluation) 1 trial, the self-expanding ACURATE neo valve was compared with the balloon-expandable, intra-annular Sapien 3 valve (Edwards Lifesciences, Irvine, CA).[15] The SCOPE 2 trial was designed to compare the early term and midterm performance of the ACURATE neo to the CoreValve Evolut (Medtronic Inc, Minneapolis) self-expanding, supra-annular transcatheter valve.

METHODS

The authors declare that all supporting data are available within the article and its Data Supplement.

Study Design

The SCOPE 2 trial is a multicenter, randomized, parallel-design, noninferiority, open-label trial conducted at 23 tertiary, high-volume heart valve centers in Denmark, France, Italy, Germany, Spain, and the United Kingdom. The trial was designed to compare the safety and efficacy of 2 TAVR systems: ACURATE neo and CoreValve Evolut. The ACURATE neo bioprosthesis consists of 3 porcine pericardial leaflets mounted on a self-expanding nitinol frame with an upper crown that provides supra-annular anchoring and caps the native leaflets, a waist that conforms to the native annulus, and a lower crown protruding few millimeters into the left ventricular outflow tract; an inner and outer porcine pericardium fabric skirt covers the inflow tract of the nitinol stent. The CoreValve Evolut R system, which is recapturable and repositionable, also consists of 3 porcine pericardial leaflets mounted on a self-expanding nitinol frame and features a skirt made from a single layer of porcine pericardium. Use of subsequently marketed iterations of the CoreValve system that were not available at the time of trial design (eg, Evolut PRO) was allowed by the study protocol. The Evolut PRO system features the same platform and valve design of Evolut R, with the addition of an outer pericardial wrap at the bottom of the bioprosthesis. Features of the study valves are schematized in Figure I in the Data Supplement.

Approval from an appropriately constituted competent ethics committee was sought at each site, and the study conduct complied with the Declaration of Helsinki. Detailed information on participating investigators, sites, and the administrative structure of the trial is provided in Tables I and II and Figure II in the Data Supplement.

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Patients

Patients aged ≥75 years with symptomatic severe aortic stenosis were included if they were deemed to be at increased risk for mortality with conventional surgical aortic valve replacement as assessed by the heart team. Anatomic characteristics of the aortic annulus and access vessels were assessed by multislice computed tomographic measurements at each site and had to be able to accommodate either TAVR device in compliance with the manufacturers' instructions for use. In particular, patients were included if they had aortic annulus diameters ranging between 21 and 26 mm and perimeters between 66 and 81.7 mm, corresponding to the ranges covered by the small, intermediate, and large sizes of the ACURATE neo valve and the 26 and 29 sizes of the CoreValve Evolut valve. Patients were excluded if they had a severely reduced left ventricular ejection fraction (<20%), preexisting prosthetic valves in the aortic or mitral positions, bicuspid or unicuspid valves, severe mitral regurgitation, or peripheral anatomy inappropriate for transfemoral implant because of size, disease, and degree of calcification or tortuosity of the aorta or iliofemoral arteries. A complete list of the inclusion and exclusion criteria is provided in Table III in the Data Supplement. Eligible patients were informed about the study purpose and risks, and all participating patients provided written informed consent.

Randomization and Masking

Eligible patients were randomly assigned in a 1:1 ratio to undergo TAVR with either the ACURATE neo or the CoreValve Evolut system. Randomization was done by means of a computer-based randomly permuted block randomization scheme, with block sizes of 4, 6, or 8. Patients and treating physicians were not blinded to group allocations.

Procedures

Preparatory evaluations including medical history, electrocardiography, echocardiography, laboratory tests, assessment of coronary status, and multislice computed tomography were obtained as part of routine clinical practice before TAVR. The choice of prosthesis size was based on multislice computed tomography measurements but also took into account other anatomic features, such as the distribution and severity of the calcification and eccentricity of the aortic annulus. Three-dimensional echocardiography, aortic angiography, and balloon sizing during the implantation procedure could provide additional information with regard to proper sizing of the annulus. The final decision on the chosen valve size was left to the discretion of the team performing the procedure. The mode of anesthesia was selected according to local standard practice. Pre- and postdilatation procedures were performed at the operator's discretion. The manufacturer recommends predilatation of the ACURATE neo valve. Access site closure was done according to local practice. Minimally required laboratory analyses included hemoglobin, creatinine, and high-sensitivity troponin values. Dual antiplatelet therapy (preferably with aspirin and clopidogrel) was recommended for at least 3 months, followed by single antiplatelet therapy. In patients with an indication for oral anticoagulation or who had undergone recent coronary stent implantation, combination regimens and their duration were given at the discretion of the operator. The study schedule and design of SCOPE 2 are illustrated in Table IV and Figure III in the Data Supplement.

Study End Points

The primary end point was the composite of all-cause death or any stroke (disabling and nondisabling) at 1 year. The prespecified key secondary end point was new permanent pacemaker implantation at 30 days. Additional secondary end points included the components of the primary end point at 30 days and 1 year, procedural complications, clinical safety end points (myocardial infarction, hospitalization for valve-related symptoms or worsened congestive heart failure, valve-related dysfunction requiring reoperation, endocarditis, valve thrombosis, new left bundle-branch block, new tachyarrhythmias, life-threatening or major bleeding), composite end points as defined by the VARC (Valve Academic Research Consortium) 2,[19] and bioprosthesis function as assessed by echocardiography.

An independent clinical events committee (Cardiovascular European Research Center, Massy, France) adjudicated all end point–related adverse events. All follow-up echocardiograms were assessed by an independent core laboratory (Cardiovascular European Research Center).

Statistical Analysis

The primary end point was evaluated using a noninferiority analysis. We predicted a 1-year incidence of 12% for this end point in the CoreValve Evolut group and assumed the same rate in the ACURATE neo group. Noninferiority of the ACURATE neo valve was met if the upper limit of the 1-sided 95% CI of the difference in event rates between the 2 groups at 1 year did not cross the prespecified absolute noninferiority margin of 6%. After allowing for a rate of loss to follow-up of up to 5%, we determined that a sample size of 764 patients in total would provide 80% power to detect noninferiority. For the key secondary end point of new permanent pacemaker implantation, tested for superiority of the ACURATE neo valve, we predicted an event rate of 15% at 30 days in the CoreValve Evolut group. Using a 2-sided type I error rate of 5% and allowing for a rate of loss to follow-up of up to 5%, we determined that 680 patients in total would provide 80% power to detect an absolute difference of 7% in the rate of new permanent pacemaker implantation between study groups.

Two populations were defined for the analysis. The intention-to-treat population contains all patients randomized and is analyzed according to the intention-to-treat principle. The per-protocol population comprises patients who died before the procedure was initiated or in whom the procedure was initiated and the allocated device used and implanted and patients who had no protocol violations on 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 noninferiority. If noninferiority were shown, the primary end point would then be tested for superiority using a 2-sided type I error rate of 5%.

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The estimates at 1 year for the primary end point were obtained from a Kaplan-Meier curve and compared between treatment groups by means of a *Z*-test. In addition, a stratified analysis over Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) categories (≤4%, 5% to 8%, >8%) using Mantel-Haenszel weights was performed as a sensitivity analysis.[20] Further secondary analyses encompassed analyses in the intention-to-treat and per-protocol cohorts of secondary clinical and echocardiographic end points at 30 days and 1 year, and prespecified subgroup analyses with interaction tests for sex, STS-PROM categories (≤4%, 5% to 8%, >8%), left ventricular ejection fraction (<50% versus ≥50%), coronary artery disease status, and aortic annulus valve eccentricity index (≤0.25 versus >0.25).

Depending on the distribution, continuous variables are presented as mean (SD) and compared by Student *t* test, or median (interquartile range), and compared by unpaired *t* tests or Wilcoxon rank-sum tests. Categorical variables are presented as proportions and compared by Fisher exact tests or an exact trend test for ordinal variables. Time-to-event end points were analyzed using Kaplan-Meier estimates if mortality was part of the end point or using cumulative incidence functions with the delta method for the estimation of the standard error, taking mortality as competing risk into account otherwise.[21] The day of the procedure was taken as day 0. For patients without a procedure, the day of randomization was taken as day 0. With the exception of the primary noninferiority analysis, all *P* values and 95% CIs were 2-sided. All statistical analyses were done with SAS software version 9.4 (SAS/STAT version 15.1).

The study is registered at ClinicalTrials.gov (Unique identifier: NCT03192813).

Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the article. The first author (C.T.), the corresponding author (D.C.), and the trial statistician (K.B.) had full access to all the data in the study and had final responsibility for the decision to submit the article for publication.

RESULTS

Between April 2017 and April 2019, 796 patients were randomized at 23 European sites. Of them, 398 patients were allocated to the ACURATE neo valve and 398 patients to the CoreValve Evolut valve, representing the intention-to-treat population (Figure 1). Patients analyzed in the per-protocol population were 375 and 366 in the ACURATE neo and CoreValve Evolut groups, respectively (Figure IV in the Data Supplement). Clinical follow-up information for the primary end point was available for 778 (98%) patients of the intention-to-treat population. Echocardiographic assessment of valve-related dysfunction was available for 565 (71%) patients at 1 to 7 days, 459 (58%) patients at 30 days, and 368 (46%) patients at 1 year in the intention-to-treat population.

Baseline demographic and clinical characteristics of the intention-to-treat population are presented in Table 1. The mean age was 83.2 years (SD, 4.3), and 538 (68%) patients were female. The mean STS-PROM score in the study population was 4.6% (SD, 2.9). Frailty assessment is summarized in Table V in the Data Supplement. Baseline demographic and clinical characteristics of the per-protocol population are provided in Table VI in the Data Supplement.

Table 2 summarizes the procedural characteristics and complications in the intention-to-treat population. Predilatation and postdilatation were more common in the ACURATE neo group. The device size at annular contact was smaller in the ACURATE neo group (see Table VII in the Data Supplement for a list of implanted valve sizes). Procedural complications were similar between groups. Procedural characteristics and complications of the per-protocol population are provided in Tables VIII and IX in the Data Supplement.

At 1 year, in the analysis of the intention-to-treat population, the primary composite end point occurred in 59 (15.8%) patients in the ACURATE neo group and in 52 (13.9%) patients in the CoreValve Evolut group, with an absolute risk difference of 1.8% and a 1-sided upper 95% confidence limit of 6.1% (*P*=0.0549 for noninferiority; Figure 2; Figure V in the Data Supplement). In the sensitivity analysis of the primary end point stratified over STS-PROM score using Mantel-Haenszel weights, the *P* value for noninferiority was 0.0689. In the analysis of the per-protocol cohort, the primary composite end point occurred in 55 (15.3%) patients in the ACURATE neo group and in 50 (14.3%) patients in the CoreValve Evolut group, with an absolute risk difference of 1.0% and a 1-sided upper 95% confidence limit of 5.4% (*P*=0.0314 for noninferiority and *P*=0.70 for superiority; Figures VI and VII in the Data Supplement). Thus, 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 end point.

In the intention-to-treat analysis, the key secondary end point of new permanent pacemaker implantation at 30 days occurred in 41 (10.5%) patients in the ACURATE neo group and in 70 (18.0%) patients in the CoreValve Evolut group, with an absolute risk difference of –7.5% (95% CI, –12.4 to –2.60; *P*=0.0027) (Table 3). At 1 year, the proportions of patients with new pacemaker implantation and new left bundle-branch block were significantly lower in the ACURATE neo group than in the CoreValve Evolut group. No statistically significant differences were observed with regard to all-cause death (Figure VIII in the Data Supplement) and stroke (either disabling or nondisabling) at 30 days and 1 year. There was a statistically significant increased incidence of cardiac death in the ACURATE neo group both at 30 days (2.8% versus 0.8%; *P*=0.03) and 1 year (8.4% versus 3.9%; *P*=0.01). Details of cardiac death events for

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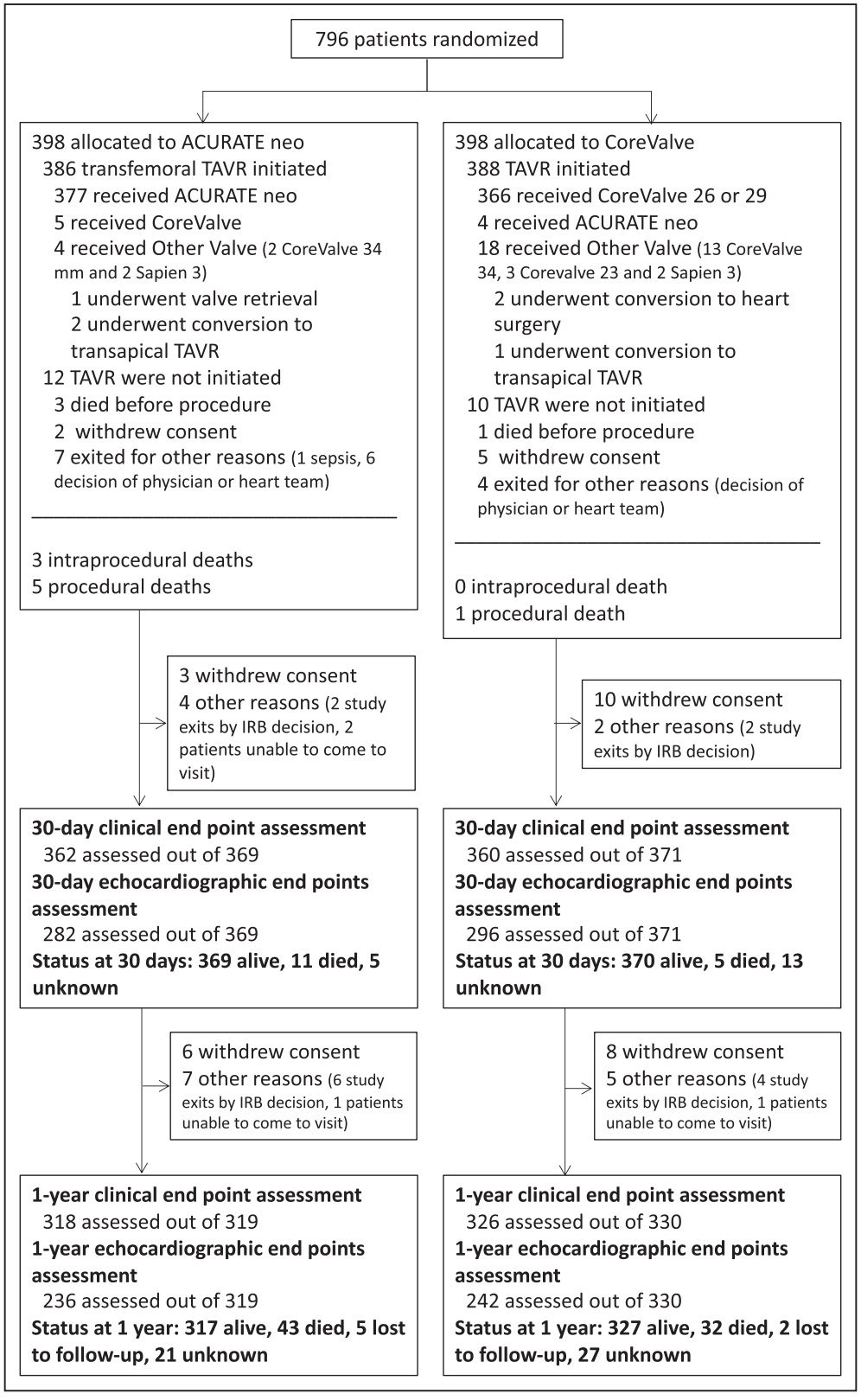

Figure 1. Trial profile.
Patient disposition in the ACURATE neo and CoreValve Evolut groups. IRB indicates institutional review board; and TAVR, transcatheter aortic valve replacement.

patients who were randomized to the ACURATE neo valve and those who were randomized to the CoreValve Evolut valve are provided in Table X and Figure IX in the Data Supplement. Secondary clinical end points in the intention-to-treat and per-protocol analyses are provided in Tables XI and XII in the Data Supplement.

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Table 1. Baseline Clinical Characteristics of the Intention-to-Treat Population

Variable	ACURATE neo (N=398)	CoreValve Evolut (N=398)
Age, y, mean (SD)	83.4 (4.2)	82.9 (4.3)
Sex, n (%)		
Female	263 (66)	275 (69)
Male	135 (34)	123 (31)
Body mass index, kg/m^2, mean (SD)	27.2 (5.0)	27.3 (4.9)
Symptoms, n (%)	N=397	N=394
New York Heart Association class III or IV	262 (66)	250 (63)
Canadian Cardiovascular Society class 3 or 4	18 (5)	22 (6)
Syncope	35 (9)	56 (14)
Predicted risk of mortality (Society of Thoracic Surgeons Predicted Risk of Mortality score),* %	4.6 (3.0)	4.5 (2.7)
Medical conditions and medical history, n (%)	N=397	N=394
Diabetes	108 (27)	113 (29)
Dyslipidemia	212 (53)	192 (49)
Hypertension	350 (88)	328 (83)
Current smoker	15 (4)	12 (3)
Coronary artery disease	171 (43)	149 (38)
Chronic obstructive pulmonary disease	37 (9)	55 (14)
Extracranial cerebral artery disease	21 (5)	19 (5)
Peripheral artery disease	30 (8)	41 (10)
Dialysis	3 (1)	2 (1)
History of atrial fibrillation	138 (35)	126 (32)
Previous permanent pacemaker implantation	35 (9)	40 (10)
Previous myocardial infarction	36 (9)	31 (8)
Previous percutaneous coronary intervention	107 (27)	96 (24)
Previous cardiac surgery	28 (7)	16 (4)
Previous aortic valvuloplasty	5 (1)	7 (2)
Previous stroke or transient ischemic attack	43 (11)	56 (14)
Computed tomography findings		
Aortic annulus perimeter, mean (SD), mm	74 (5), N=371	73 (5), N=363
Aortic annulus area, mean (SD), mm^2	429 (54), N=380	416 (56), N=376
Area derived diameter, median (interquartile range), mm	23 (22, 24), N=313	23 (22, 24), N=315

*Society of Thoracic Surgeons Predicted Risk of Mortality score at 30 days in patients undergoing surgical aortic valve replacement.

Table 2. Procedural Characteristics and Outcomes in the Intention-to-Treat Population

Variable	ACURATE neo (N=398)	CoreValve Evolut (N=398)	*P* value
Transfemoral transcatheter aortic valve replacement performed	386 (97%)	388 (97%)	0.83
Procedure time, min	72 (32), N=380	75 (39), N=384	0.37
Total contrast volume, mL	133 (47), N=378	132 (65), N=384	0.70
General anesthesia	52 (13%)	52 (13%)	0.98
Transfemoral access mode			
Percutaneous	385 (100%), N=385	385 (99%)	0.08
Surgical cutdown	0 (0%), N=385	3 (1%)	
Access closure device	382 (99%), N=385	385 (99%)	1.00
Predilatation	306 (79%)	160 (41%)	<0.0001
Device size (waist), mm	25 (2)	28 (2)	<0.0001
Postdilatation	177 (46%)	139 (36%)	0.005
Procedural complications (Valve Academic Research Consortium 2)			
Valve malpositioning	2 (<1%)	9 (2%)	0.06
Coronary artery obstruction	2 (1%)	0	0.25
Hemodynamic instability	6 (2%)	3 (1%)	0.34
Cardiac tamponade	4 (1%)	4 (1%)	1.00
Annular rupture	1 (<1%)	1 (<1%)	1.00
Conversion to open heart surgery	0	2 (1%)	0.50
Access site complication	33 (9%)	24 (6%)	0.22
Bleeding	8 (2%)	9 (2%)	1.00
Intraprocedural death	3 (1%)	0	0.12

Data are n (%) or mean (SD). Percentages were calculated on the number of patients in whom transcatheter aortic valve replacement was initiated. *P* values are derived from Fisher exact tests for categorical variables and Student *t* tests or Wilcoxon rank-sum tests for continuous variables.

Structural valve deterioration and valve-related dysfunction according to VARC-2 definitions were more frequent at 30 days in the ACURATE neo group (Table XIII in the Data Supplement). Moderate or severe aortic regurgitation was the most frequent cause of valve-related dysfunction with the ACURATE neo valve (Figure 3). Aortic regurgitation was paravalvular in 96% of cases, and paravalvular regurgitation was higher in the ACURATE neo group in both the intention-to-treat and per-protocol populations (Tables XIV through XVI in the Data Supplement). At 1 year, there were no differences in structural valve deterioration and valve-related dysfunction between groups. The degree of aortic regurgitation was significantly different between groups, but no differences were observed in moderate or severe regurgitation. There were no differences between valves with respect to measurements of aortic

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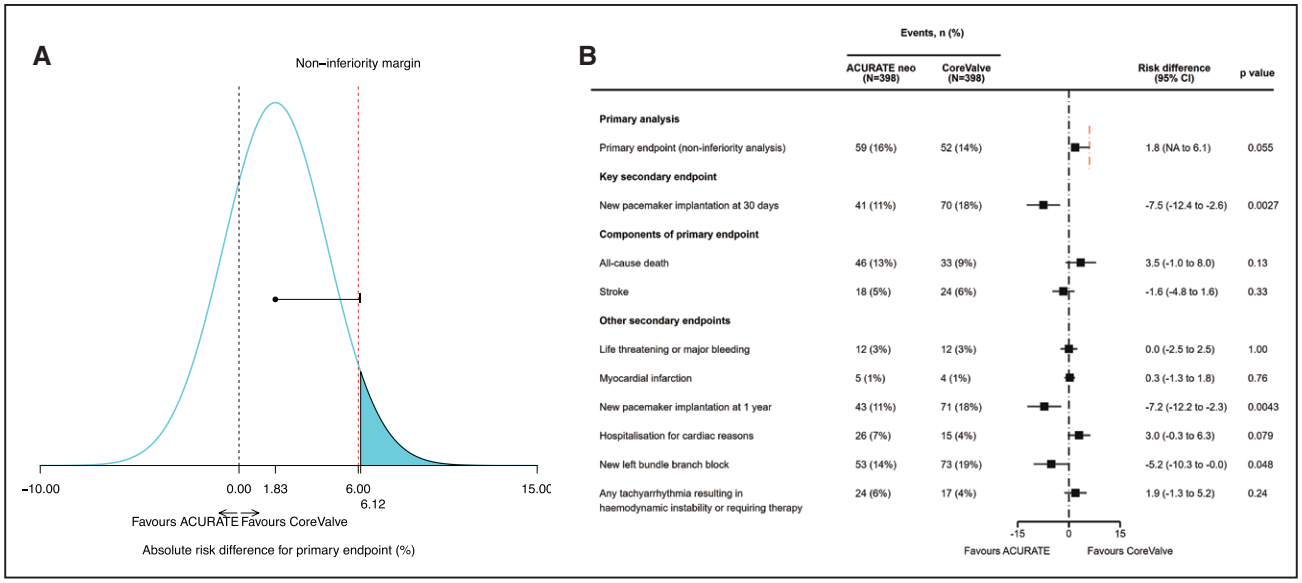

Figure 2. Primary end point and selected secondary clinical end points.
A, Probability distribution (with point estimate and 1-sided 95% CI) of the risk difference for frequency of the primary end point (all-cause death or stroke at 1 year) between the 2 groups in the intention-to-treat population. The red line indicates the noninferiority margin (prespecified at 6%). **B**, Primary and secondary analyses of selected end points in the intention-to-treat population. Outcomes are reported at 1 year if not otherwise specified. Percentages are Kaplan-Meier estimates for the end points including mortality or cumulative incidence considering death as a competing risk for the other end points. All 95% CIs and *P* values are 2-sided except those of the primary, noninferiority analysis (1-sided). NA indicates not applicable.

stenosis and severe patient-prosthesis mismatch both at 30 days and 1 year.

Predefined subgroup analyses of the primary end point showed a significant interaction between device type and STS-PROM category (Figure X in the Data Supplement), with the 1-sided upper 95% confidence limit exceeding the margin of noninferiority in patients with STS-PROM 5% to 8% or >8% but not in patients with STS-PROM ≤4%. Kaplan-Meier curves for cardiac death by device type and STS-PROM category are shown in Figure XI in the Data Supplement.

DISCUSSION

In this multicenter, randomized comparison of self-expanding, supra-annular bioprostheses for patients with symptomatic severe aortic stenosis, transfemoral TAVR with the ACURATE neo valve was not established to be noninferior to the CoreValve Evolut bioprosthesis with respect to the composite of death or stroke at 1 year. Secondary analyses revealed a significant reduction in new permanent pacemaker implantation, an early increase in moderate or severe aortic regurgitation (mostly paravalvular), and significant increases in cardiac death at 30 days and 1 year with the ACURATE neo valve.

Before SCOPE 2, 5 trials compared TAVR devices in a randomized fashion. In the CHOICE trial (Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve versus Edwards SAPIEN XT; N=241), the primary end point of device success occurred more frequently with the intra-annular Sapien XT (Edwards Lifesciences, Irvine, CA) bioprosthesis than with the supra-annular CoreValve bioprosthesis,[13] and the clinical outcomes were not statistically significantly different at 5 years.[22] In the SOLVE-TAVI trial (Comparison of second-generation seLf-expandable versus balloon-expandable valves and general versus local anaesthesia in transcatheter aortic valve implantation; N=447), the second-generation Sapien and CoreValve bioprostheses were equivalent with respect to a composite efficacy end point at 30 days.[14] In the SCOPE 1 trial (Comparison of second-generation seLf-expandable versus balloon-expandable valves and general versus local anaesthesia in transcatheter aortic valve implantation; N=739), the ACURATE neo valve was inferior to the Sapien 3 valve with respect to a composite of safety and clinical efficacy outcomes at 30 days.[15] In the REPRISE 3 trial (Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System–Randomized Clinical Evaluation 3; N=912), the first-generation mechanically expandable and fully recapturable Lotus (Boston Scientific, Marlborough, MA) bioprosthesis was noninferior to the CoreValve bioprosthesis (either first- or second-generation) with respect to a primary safety composite end point at 30 days and a primary efficacy composite end point at 1 year.[16] In the PORTICO IDE trial (Portico Re-sheathable Transcatheter Aortic Valve System US Investigational Device Exemption trial; N=750), the first-generation self-expanding Portico (Abbott Vascular, Santa Clara, CA) bioprosthesis was associated with similar rates of death or disabling stroke at 2 years compared with

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Table 3. Selected Secondary Clinical End Points in the Intention-to-Treat Population

Variable	ACURATE neo (N=398)	CoreValve Evolut (N=398)	Risk difference (95% CI)	*P* value
30 d				
All-cause death	13 (3%)	6 (2%)	1.77 (–0.41 to 3.95)	0.11
Cardiac death	11 (3%)	3 (1%)	2.05 (0.17 to 3.94)	0.03
Noncardiac death	2 (1%)	3 (1%)	–0.28 (–1.41 to 0.86)	0.63
Stroke	13 (3%)	17 (4%)	–1.04 (–3.74 to 1.66)	0.45
Disabling	6 (2%)	10 (3%)	–1.03 (–3.01 to 0.96)	0.31
Nondisabling	7 (2%)	7 (2%)	–0.01 (–1.88 to 1.86)	0.99
All–cause death or disabling stroke	17 (4%)	15 (4%)	0.49 (–2.31 to 3.29)	0.73
Hospitalization for valve-related symptoms or worsened congestive heart failure	9 (2%)	5 (1%)	1.00 (–0.89 to 2.90)	0.30
Life-threatening or major bleeding (Bleeding Academic Research Consortium 3b or more)	8 (2%)	9 (2%)	–0.26 (–2.29 to 1.77)	0.80
Myocardial infarction	1 (<1%)	1 (<1%)	0.00 (–0.70 to 0.70)	1.00
Valve-related dysfunction requiring repeat procedure	1 (<1%)	1 (<1%)	0.01 (–0.70 to 0.71)	0.99
Implantation of multiple valves	1 (<1%)	4 (1%)	–0.83 (–2.01 to 0.36)	0.18
Prosthetic valve endocarditis	0	0	0.00 (NC to NC)	…
Prosthetic valve thrombosis	0	0	0.00 (NC to NC)	…
New left bundle-branch block	52 (13%)	70 (18%)	–4.54 (–9.59 to 0.51)	0.08
Any tachyarrhythmia resulting in hemodynamic instability or requiring therapy	20 (5%)	13 (3%)	1.81 (–1.01 to 4.63)	0.21
New pacemaker implantation	41 (11%)	70 (18%)	–7.48 (–12.4 to –2.60)	0.0027
1 y				
All-cause death	46 (13%)	33 (9%)	3.47 (–1.01 to 7.95)	0.13
Cardiac death	31 (8%)	14 (4%)	4.49 (1.03 to 7.96)	0.01
Noncardiac death	15 (5%)	19 (5%)	–0.86 (–4.09 to 2.37)	0.60
Stroke	18 (5%)	24 (6%)	–1.61 (–4.85 to 1.62)	0.33
Disabling	7 (2%)	14 (4%)	–1.86 (–4.17 to 0.45)	0.11
Nondisabling	11 (3%)	10 (3%)	0.25 (–2.08 to 2.58)	0.83
All-cause death or disabling stroke	51 (14%)	42 (11%)	2.43 (–2.34 to 7.21)	0.32
Hospitalization for valve-related symptoms or worsened congestive heart failure	26 (7%)	15 (4%)	2.97 (–0.34 to 6.27)	0.08
Life-threatening or major bleeding (Bleeding Academic Research Consortium 3b or more)	12 (3%)	12 (3%)	0.00 (–2.45 to 2.46)	1.00
Myocardial infarction	5 (1%)	4 (1%)	0.25 (–1.31 to 1.81)	0.76
Valve-related dysfunction requiring repeat procedure	1 (<1%)	3 (1%)	–0.55 (–1.59 to 0.49)	0.30
Prosthetic valve endocarditis	2 (1%)	2 (1%)	–0.01 (–1.08 to 1.07)	0.99
Prosthetic valve thrombosis	0	0	0.00 (NC to NC)	…
New left bundle-branch block	53 (14%)	73 (19%)	–5.19 (–10.3 to –0.04)	0.048
Any tachyarrhythmia resulting in hemodynamic instability or requiring therapy	24 (6%)	17 (4%)	1.93 (–1.30 to 5.16)	0.24
New pacemaker implantation	43 (11%)	71 (18%)	–7.21 (–12.2 to –2.26)	0.0043

Percentages are Kaplan-Meier estimates or cumulative incidence estimates taking mortality as a competing risk into account. *P* values were inferred from significance testing of the risk difference. End points were adjudicated by an independent clinical event committee. NC indicates not computed.

a range of commercial balloon-expandable or self-expanding valves, but it was associated with higher rates of the primary composite safety end point at 30 days.[17] None of these trials specifically compared 2 self-expanding bioprostheses with supra-annular design.

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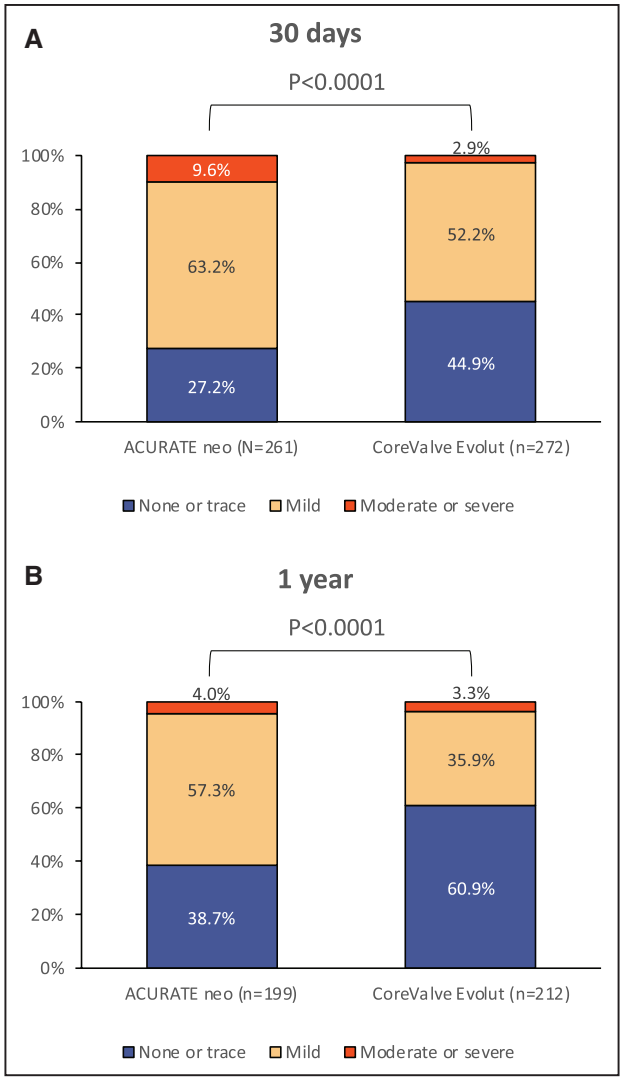

Figure 3. Aortic regurgitation.
Rates of aortic regurgitation in the ACURATE neo and CoreValve Evolut groups are shown at 30 days (**A**) and 1 year (**B**). Aortic regurgitation was paravalvular in 96% of cases.

In randomized trials, the intention-to-treat analysis is intended to maintain the prognostic balance generated from the original random treatment allocation, hence providing a conservative estimate of the treatment effect. However, in noninferiority trials, an intention-to-treat analysis can potentially increase the risk of wrongly claiming noninferiority in case of differential dropouts, crossover, or protocol violations between groups. Therefore, reporting of a per-protocol analysis is also recommended, given that this analysis aims to better isolate the effect of the intervention.[23] Although in SCOPE 2 noninferiority was met in the per-protocol analysis, the prespecified statistical plan did not allow claiming for noninferiority because the result of the intention-to-treat analysis was inconsistent, due to the upper boundary of the CI for the risk difference in the primary end point crossing the noninferiority margin of 6%. The nominal risk difference in the primary end point was 1.8% in the intention-to-treat population and 1.0% in the per-protocol population (where the *P* value for a subsequent superiority test was 0.70). There were no statistically significant differences in the components of the primary end point (all-cause death and stroke) in both the analyses, but the trial was not powered for these outcomes.

All-cause death occurred at 1 year in 13% of patients in the ACURATE neo group and 9% of patients in the CoreValve Evolut group. These rates are similar to those reported in PARTNER (Placement of Aortic Transcatheter Valve Trial) 2 but higher than those reported in SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation), 2 trials that enrolled a similar population of patients at intermediate surgical risk.[6,7] However, in SURTAVI, patients were on average 3.4 years younger than in SCOPE 2. Compared with the CoreValve Evolut valve, cardiac mortality was increased with the ACURATE neo valve at 30 days and at 1 year in the intention-to-treat population, a finding that was consistent at 1 year but not at 30 days in the per-protocol population. Because the trial was also not powered for cardiac death and because adjudication of cardiac death is vulnerable to misclassification in the absence of autopsy, a cautious interpretation is necessary. Events adjudicated as cardiac death by the clinical event committee were 11 and 3 in the ACURATE neo and CoreValve Evolut arms at 30 days (10 and 3 in the per-protocol cohort), respectively (Table X in the Data Supplement). Of them, 3 and 1, respectively, occurred after randomization but before the TAVR procedure. Intraprocedural death occurred in 3 patients randomized to the ACURATE neo valve (1 actually received the CoreValve Evolut valve) and no patients randomized to the CoreValve Evolut valve. At 1 year, events adjudicated as cardiac deaths by the clinical event committee were 31 and 14 in the ACURATE neo and CoreValve Evolut arms (30 and 13 in the per protocol cohort), respectively. Heart failure was adjudicated as the cause underlying most of these events (Table X in the Data Supplement).

It is of note that the ACURATE neo valve was associated with a significant early increase in aortic regurgitation, including moderate or severe regurgitation, which has a known link with increased mortality at 1 year in the TAVR literature.[24] Moderate or severe regurgitation occurred in 10% of patients treated with the ACURATE neo valve at 30 days, which is similar to the rate reported at the same follow-up in the SCOPE 1 trial.[15] Moderate or severe regurgitation at 1 year was 4%, a decrease that may be partly explained by survival bias. Moderate or severe aortic regurgitation early postprocedure was infrequent in patients who died from adjudicated cardiac causes (Table X in the Data Supplement). Because echocardiographic follow-up was missing in a sizeable proportion of patients both at 30 days and 1 year, the link between aortic

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regurgitation and cardiac mortality cannot be conclusively inferred from our data.

In SCOPE 2, patients with aortic annuli larger than 26 mm were intentionally not randomized because, based on the chart sizes of the manufacturers, such diameters can be addressed by available sizes of the CoreValve bioprosthesis but not by a corresponding available size of the ACURATE neo valve, lacking the premise of equipoise. Although annulus sizes were similar at preprocedural computed tomography, the valves implanted in the ACURATE neo group had smaller average diameters. This may contribute to explain the higher incidence of paravalvular aortic regurgitation in the ACURATE neo group despite more frequent postdilatation compared with the CoreValve Evolut group. We found evidence of a significant statistical interaction between the result of the trial in the intention-to-treat population and the STS-PROM category, which raises the hypothesis that patients at lower surgical risk could be more likely to reach noninferiority in a dedicated trial than those at higher surgical risk. It may be hypothesized that patients at higher surgical risk present with anatomic conditions that challenge the performance of the ACURATE neo valve, for example by lowering the contact area between the prosthesis and the aorta, and thus resulting in increased paravalvular leakage. This hypothesis needs to be proven in dedicated studies with computed tomography imaging, evaluation of annulus calcification, and assessment of procedural oversizing.

SCOPE 2 was powered to detect a difference in the key secondary end point of new permanent pacemaker implantation at 30 days. In that respect, the ACURATE neo valve was found superior, with an absolute difference of 7.5% in the intention-to-treat population and 7.8% in the per-protocol population compared with the CoreValve Evolut bioprosthesis. Because the operators could not be blinded to treatment assignment because of the different designs of the bioprostheses, caution is needed in interpreting this end point, especially in the context of a noninferiority trial that did not meet its primary objective. However, this result is plausible as it can be explained by the relatively low radial force exerted on the aortic annulus and the lower protrusion in the left ventricle of the ACURATE neo system, which features stabilizing arches to facilitate correct positioning. In addition, the rates of new permanent pacemaker implantation in the ACURATE neo and CoreValve Evolut groups are in line with the rates reported in recent literature of the 2 bioprostheses.[25,26]

The SCOPE 2 trial illustrates the characteristics of 2 contemporary valves with supra-annular design. A strength of the trial is the independent core-laboratory assessment of follow-up echocardiographies. The observed frequencies of events were close to those assumed for sample size calculation, and the results are provided in intention-to-treat and per-protocol analyses, which is especially important in the setting of noninferiority testing to avoid an unintentionally biased interpretation. Our findings need also to be interpreted in the light of several limitations. First, the trial was not powered to show differences with regard to individual clinical end points, with the exception of new permanent pacemaker implantation. Second, the trial included a range of centers from countries with a possibly different level of experience in the implantation of the study valve. For example, in some countries (eg, Germany, Italy), the study valve was available and used by the participating centers before the study was initiated. In contrast, in France, the valve was not distributed before the study was initiated. Data to analyze the effect of a learning curve with the investigated device, if any, were not collected. Third, the CoreValve Evolut Pro device became available at the end of the study period, but the actual proportion of patients who received it was not collected. Fourth, follow-up is limited at 1 year, which precludes meaningful evaluations of differences in long-term clinical outcomes and valve durability. Fifth, follow-up echocardiography was available only for a proportion of the initial population.

TAVR is expanding worldwide as a treatment option for patients with symptomatic severe aortic stenosis. Head-to-head comparisons of commercially available valves are important to fully appreciate their strengths and limitations, and meaningfully inform the operators at the time of valve selection. The ACURATE neo valve has proven inferior to the Sapien 3 valve at 30 days in SCOPE 1 and did not show noninferiority to the CoreValve Evolut valve in SCOPE 2. It should be noted that the ACURATE neo valve used in these trials is the first iteration of the device, which was compared versus current iterations of the Sapien and CoreValve bioprostheses. Design improvements, such as the availability of larger sizes and the addition of a skirt for advanced sealing, are necessary to mitigate the risk of paravalvular regurgitation and improve clinical outcomes at early term and midterm. A new iteration of the study device, named ACURATE neo2, incorporates an annular sealing technology intended to reduce the incidence of paravalvular regurgitation.[18]

In conclusion, 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 secondary analyses with limited statistical power, cardiac death was increased at 30 days and 1 year in patients who received the ACURATE neo valve. The 2 bioprostheses differed with respect to technical characteristics such as degree of paravalvular regurgitation and need for new permanent pacemaker implantation.

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Supplemental Materials

Data Supplement Tables I–XVI
Data Supplement Figures I–XI

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