# 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

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## Summary

**Background** Transcatheter aortic valve replacement (TAVR) is the preferred treatment option for older patients with symptomatic severe aortic stenosis. Differences in the properties of available TAVR systems can affect clinical outcomes. Among patients undergoing TAVR, we compared the self-expanding ACURATE neo TAVR system with the balloon-expandable SAPIEN 3 TAVR system with regard to early safety and efficacy.

**Methods** In this randomised non-inferiority trial, patients (aged ≥75 years) undergoing transfemoral TAVR for treatment of symptomatic severe aortic stenosis, and who were deemed to be at increased surgical risk, were recruited at 20 tertiary heart valve centres in Germany, the Netherlands, Switzerland, and the UK. Participants were randomly assigned (1:1) to receive treatment with the ACURATE neo or the SAPIEN 3 with a computer-based randomly permuted block scheme, stratified by study centre and Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) category. The primary composite safety and efficacy endpoint comprised all-cause death, any stroke, life-threatening or disabling bleeding, major vascular complications, coronary artery obstruction requiring intervention, acute kidney injury (stage 2 or 3), rehospitalisation for valve-related symptoms or congestive heart failure, valve-related dysfunction requiring repeat procedure, moderate or severe prosthetic valve regurgitation, or prosthetic valve stenosis within 30 days of the procedure. Endpoint assessors were masked to treatment allocation. Non-inferiority of ACURATE neo compared with SAPIEN 3 was assessed in the intention-to-treat population on the basis of a risk-difference margin of 7·7% for the primary composite endpoint, with a one-sided α of 0·05. This trial is registered with ClinicalTrials.gov (number NCT03011346) and is ongoing but not recruiting.

**Findings** Between Feb 8, 2017, and Feb 2, 2019, up to 5132 patients were screened and 739 (mean age 82·8 years [SD 4·1]; median STS-PROM score 3·5% [IQR 2·6–5·0]) were enrolled. 30-day follow-up was available for 367 (99%) of 372 patients allocated to the ACURATE neo group, and 364 (99%) of 367 allocated to the SAPIEN 3 group. Within 30 days, the primary endpoint occurred in 87 (24%) patients in the ACURATE neo and in 60 (16%) in the SAPIEN 3 group; thus, non-inferiority of the ACURATE neo was not met (absolute risk difference 7·1% [upper 95% confidence limit 12·0%], p=0·42). Secondary analysis of the primary endpoint suggested superiority of the SAPIEN 3 device over the ACURATE neo device (95% CI for risk difference –1·3 to –12·9, p=0·0156). The ACURATE neo and SAPIEN 3 groups did not differ in incidence of all-cause death (nine patients [2%] *vs* three [1%]) and stroke (seven [2%] *vs* 11 [3%]); whereas acute kidney injury (11 [3%] *vs* three [1%]) and moderate or severe prosthetic aortic regurgitation (34 [9%] *vs* ten [3%]) were more common in the ACURATE neo group.

**Interpretation** TAVR with the self-expanding ACURATE neo did not meet non-inferiority compared to the balloon-expandable SAPIEN 3 device in terms of early safety and clinical efficacy outcomes. An early composite safety and efficacy endpoint was useful in discriminating the performance of different TAVR systems.

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## Introduction

Transcatheter aortic valve replacement (TAVR) has been developed as an alternative to surgical aortic valve replacement for patients with symptomatic severe aortic stenosis at increased risk for surgery. Accumulating evidence from randomised clinical trials in patients at extreme, high, intermediate, and low risk for surgery catalysed the rapid adoption of TAVR for the treatment of severe aortic stenosis in older patients across the entire risk spectrum.[1–7]

Available TAVR systems differ with respect to mechanism of deployment, size (in terms of vascular access), potential for repositionability, haemodynamic

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See **Online** for appendix

## Research in context

### Evidence before this study

Transcatheter aortic valve replacement (TAVR) with balloon-expandable valves has been associated with favourable clinical outcomes compared with surgical aortic valve replacement in patients with symptomatic severe aortic stenosis across the spectrum of risk. With the anticipated expansion of TAVR into lower-risk patients, transcatheter device-versus-device trials gain increasing relevance in view of periprocedural and long-term outcomes. We searched PubMed and conference abstracts on Aug 5, 2019, with no language restrictions, using the following search terms "transcatheter aortic valve replacement" OR "transcatheter aortic valve implantation" AND "randomized". Our search found three head-to-head randomised comparisons, two of which compared a balloon-expandable valve with a self-expanding valve. The CHOICE trial showed superior device success in patients treated with second-generation balloon-expandable valves (Edwards SAPIEN XT) compared with first-generation self-expanding valves (CoreValve) in 241 patients with aortic stenosis at high-risk for surgery. The SOLVE-TAVI trial showed equivalence of a newer-iteration balloon-expandable device (Edwards SAPIEN 3) compared with a newer-iteration self-expanding device (Evolut R) with regard to a composite of all-cause death, stroke, moderate-to-severe aortic regurgitation, or permanent pacemaker implantation at 30 days in 447 patients with severe symptomatic aortic stenosis. The ACURATE neo system is a novel, self-expanding transcatheter heart valve that has been associated with similar clinical outcomes, lower transvalvular gradients, and lower rates of permanent pacemaker implantation compared with balloon-expandable valves in a propensity score-matched analysis of 1121 patients. Conversely, rates of paravalvular leakage were higher in patients treated with the ACURATE neo valve compared with those treated with the balloon-expandable SAPIEN 3 prosthesis. No evidence from randomised controlled trials comparing ACURATE neo with the benchmark balloon-expandable SAPIEN 3 system is available.

### Added value of this study

The SCOPE I trial is the first randomised trial to compare the self-expanding ACURATE neo valve with the balloon-expandable SAPIEN 3 prosthesis in patients with severe symptomatic aortic stenosis. The study hypothesis of non-inferiority of the ACURATE neo compared with the SAPIEN 3 with regard to a primary safety and efficacy composite endpoint assessed at 30 days was not met. In a secondary analysis, the balloon-expandable SAPIEN 3 device was superior to the self-expanding ACURATE neo device with respect to the primary composite endpoint. The difference was largely driven by valve-related dysfunction due to paravalvular aortic regurgitation as assessed by an independent echocardiographic core laboratory. Most of the individual clinical components of the primary endpoint were similar between groups. The composite safety and efficacy endpoint used in this trial was able to adequately discriminate the performance of individual TAVR devices at short-term follow-up.

### Implications of all the available evidence

Conceptual differences between available devices for TAVR affect safety and efficacy endpoints and challenge the generalisability of landmark strategy trials (TAVR *vs* surgical aortic valve replacement) to all available devices. TAVR with the ACURATE neo device is associated with higher incidence of paravalvular leakage than that of the SAPIEN 3 prosthesis, while rates of death, stroke, and myocardial infarction are similar. An early composite safety and efficacy endpoint could be useful in discriminating the performance of future iterations of TAVR systems.

performance, and risk of atrioventricular conductance disturbances. Thus, although landmark clinical trials have established TAVR as the preferred treatment option in older patients with severe aortic stenosis, the generalised applicability of these findings to the entire range of available TAVR systems is challenged by the variety among these systems. Evidence from strategy trials[1–7] signals the need for randomised comparisons between available transcatheter valves to identify an appropriate endpoint to critically assess device-specific performance during short-term and long-term follow-up. Only two previously published randomised controlled trials have compared TAVR devices: the CHOICE trial[8] compared a first-generation balloon-expandable device to a first-generation self-expanding device with regard to device success based on the Valve Academic Research Consortium (VARC) definition; and the REPRISE III trial[9] compared a mechanically expanding device to a self-expanding device with respect to a 30-day composite safety endpoint and a 1-year composite efficacy endpoint.

Multiple versions of the balloon-expandable SAPIEN TAVR system (Edwards Lifesciences, Irvine, CA, USA) have been investigated in several randomised trials and prospective registries, and have shown excellent safety and efficacy outcomes.[1,4,6,10,11] The ACURATE neo (Boston Scientific, Marlborough, MA, USA) transcatheter heart valve is a novel, self-expanding TAVR prosthesis associated with favourable outcomes in non-randomised studies.[12–15] The current randomised trial (SCOPE I) is the first study to compare the safety and efficacy of the ACURATE neo with the SAPIEN 3 TAVR prosthesis in patients with severe, symptomatic aortic stenosis undergoing transfemoral TAVR.

## Methods

### Study design and participants

The SCOPE I trial is an investigator-initiated, multicentre, assessor-masked, randomised controlled trial conducted at 20 tertiary, high-volume heart valve centres in Germany, the Netherlands, Switzerland, and

the UK. The trial was designed to compare the safety and efficacy of two TAVR systems: the ACURATE neo bioprosthesis, which combines a self-expanding nitinol frame with three porcine pericardial leaflets, and a stent body with an outer and inner pericardial skirt;[16] and the SAPIEN 3 prosthesis, consisting of a balloon-expandable cobalt-chromium frame accommodating a tri-leaflet valve manufactured from bovine pericardial tissue, and featuring an outer sealing cuff and an internal skirt to mitigate paravalvular regurgitation[17] (appendix p 22). Experience with both TAVR systems under investigation was required, with a minimum of 30 implantations per centre of each of the two valves before inclusion of the first patient at each site.

Patients aged 75 years or older with symptomatic, severe aortic stenosis who were deemed to be at increased surgical risk by the heart team constituted the target population and were screened for eligibility. Severe aortic stenosis was defined by an aortic valve area less than 1·0 $cm^2$ or less than 0·6 $cm^2/m^2$ if indexed to body surface area. Anatomical characteristics of the aortic annulus and access vessels were assessed by multislice CT at each site, and had to be able to accommodate either TAVR device in accordance with the manufacturers' instructions for use. Major exclusion criteria were congenital anomalies of the aortic valve, pre-existing left-sided prosthetic valves, need for emergency procedures, severely reduced left ventricular ejection fraction (<20%), any concomitant procedure except for a percutaneous coronary intervention, stroke or myocardial infarction in the 30 days before valve implantation, and any planned non-cardiac surgery within 30 days after implantation. A complete list of the inclusion and exclusion criteria is provided in the appendix (p 6). Eligible patients were informed about the study purpose and risks, and all participating patients provided written informed consent.

Approval from an appropriately constituted competent ethics committee was sought at each site, and study conduct complied with the Declaration of Helsinki. Detailed information on participating investigators, sites, and the administrative structure of the trial is provided in the appendix (pp 3–5).

## Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio to undergo TAVR with either the ACURATE neo or the SAPIEN 3 system. Randomisation was done by means of a computer-based randomly permuted block randomisation scheme, with block sizes of 4, 6, or 8, stratified by study centre and Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM; strata <3%, ≥3 to <8%, and ≥8%). Patients and treating physicians were aware of group allocations, whereas outcome assessors were masked to the allocated TAVR system. Trial statisticians conducted all study analyses. The primary statistician potentially had access to unmasked data, and an independent statistician who was masked to treatment allocation corroborated the primary endpoint analyses.

## Procedures

Required preparatory evaluations such as medical history, electrocardiography, echocardiography, laboratory tests, assessment of coronary status, and multislice CT are part of routine clinical practice before TAVR. Study-specific pre-evaluations were the Kansas City Cardiomyopathy

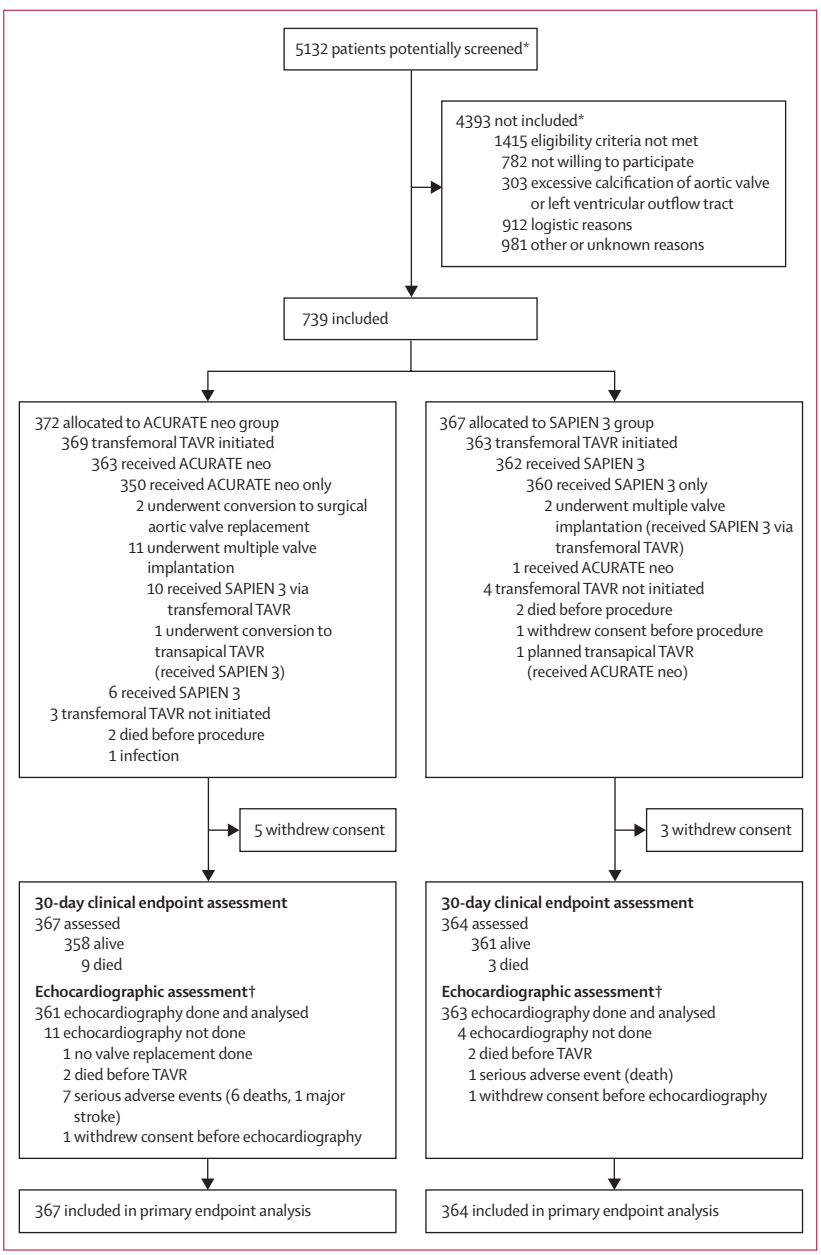



***Figure 1:*** **Trial profile**
TAVR=transcatheter aortic valve replacement. *Because some sites reported the total number of patients undergoing transfemoral TAVR instead of screened patients only, the total number of patients reported here represents the upper limit of potentially screened patients. †Numbers refer to the total number of patients at randomisation.

Questionnaire-12 (KCCQ-12) and baseline stroke scores (National Institutes of Health Stroke Scale and modified Rankin Scale).

The mode of anaesthesia was selected according to local standard practice. Pre-dilatation was mandatory in the ACURATE neo group; post-dilatation for both valves was done at the operator's discretion. Access site closure was done according to local practice. Post-procedural monitoring of heart rhythm was recommended for at least 12 h, and minimally required laboratory analyses included haemoglobin, creatinine, and high-sensitivity troponin values, with repeat measurements required in case of suspected significant bleeding, acute kidney injury, or periprocedural myocardial infarction. After successful TAVR, dual antiplatelet therapy with aspirin and clopidogrel was recommended for at least 3 months in patients with normal sinus rhythm, followed by lifelong 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 I are illustrated in the appendix (pp 7, 23).

| | ACURATE neo (N=372) | SAPIEN 3 (N=367) |
|---|---|---|
| Age, years | 82·6 (4·3) | 83·0 (3·9) |
| Sex | | |
| Female | 218 (59%) | 202 (55%) |
| Male | 154 (41%) | 165 (45%) |
| Body-mass index, kg/m² | 27·3 (4·4) | 27·9 (4·7) |
| Symptoms | | |
| NYHA classification III or IV | 287 (77%) | 268 (73%) |
| CCS grade III or IV | 21 (6%), N=372 | 23 (6%), N=365 |
| Syncope | 37 (10%) | 44 (12%) |
| Predicted risk of mortality (STS-PROM score)* | | |
| Median % (IQR) | 3·7% (2·5–4·9) | 3·4% (2·6–5·2) |
| Low score (<3%) | 134 (36%) | 136 (37%) |
| Intermediate score (≥3–<8%) | 207 (56%) | 203 (55%) |
| High score (≥8%) | 31 (8%) | 28 (8%) |
| Medical conditions and medical history | | |
| Diabetes | 108 (29%) | 116 (32%) |
| Hypercholesterolaemia | 211 (57%) | 216 (59%) |
| Hypertension | 341 (92%) | 333 (91%) |
| Current smoker | 9 (2%) | 11 (3%) |
| Coronary artery disease | 218 (59%) | 219 (60%) |
| Chronic obstructive pulmonary disease | 33 (9%) | 44 (12%) |
| Extracardiac arteriopathy† | 46 (12%) | 40 (11%) |
| Creatinine concentration >2 mg/dL | 15 (4%) | 17 (5%) |
| History of atrial fibrillation or flutter | 133 (36%) | 136 (37%) |
| Permanent pacemaker | 43 (12%) | 36 (10%) |
| Previous myocardial infarction | 39 (10%) | 47 (13%) |
| Previous percutaneous coronary intervention | 117 (31%) | 126 (34%) |
| Previous coronary artery bypass grafting | 31 (8%) | 30 (8%) |
| Previous aortic valvuloplasty | 5 (1%) | 3 (1%) |
| Previous stroke or transient ischaemic attack | 47 (13%) | 47 (13%) |
| Echocardiography findings | | |
| Aortic valve mean gradient, mm Hg | 42·9 (17·2), N=371 | 41·5 (15·1), N=367 |
| Aortic valve area, cm² | 0·7 (0·2), N=368 | 0·7 (0·2), N=364 |
| Left ventricular ejection fraction, % | 56·4 (11·1) | 57·1 (10·7) |
| CT findings | | |
| Aortic annulus perimeter, mm | 75·7 (5·2) | 75·9 (5·1) |
| Aortic annulus area, mm² | 439·1 (59·6) | 442·9 (60·3) |

Data are n (%), mean (SD), or median (IQR). NYHA=New York Heart Association. CCS=Canadian Cardiovascular Society. *Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score at 30 days in patients undergoing surgical aortic valve replacement. †One or more of the following: claudication; carotid occlusion or >50% stenosis; amputation for arterial disease; or previous or planned intervention on the abdominal aorta, limb arteries, or carotids.

***Table 1:*** **Baseline clinical characteristics in the intention-to-treat population**

## Outcomes

The primary endpoint was a combination of two VARC-2-derived endpoints (early safety and clinical efficacy) at 30 days, as follows: all-cause death, any stroke, life-threatening or disabling bleeding, major vascular complications, coronary artery obstruction requiring intervention, acute kidney injury (stage 2 or higher), rehospitalisation for valve-related symptoms or congestive heart failure, valve-related dysfunction requiring repeat procedure, and valve-related dysfunction determined by echocardiography (mean aortic valve gradient ≥20 mm Hg and either effective orifice area ≤0·9–1·1 cm² [depending on body surface area] or Doppler velocity index <0·35; or moderate or severe prosthetic valve regurgitation as defined by VARC-2).[18] Details of the clinical and echocardiographic components of the primary composite endpoint are presented in the appendix (p 8).

Secondary endpoints assessed at 30 days encompassed all individual components of the primary endpoint, procedural complications, clinical safety endpoints (spontaneous myocardial infarction, endocarditis, valve thrombosis, new-onset atrial fibrillation or flutter, any tachyarrhythmia resulting in haemodynamic instability or requiring therapy, and new pacemaker implantation), composite endpoints as defined by VARC-2,[18] New York Heart Association (NYHA) functional class, KCCQ-12 summary scores, and bioprosthesis function as assessed by echocardiography.

An independent clinical events committee (Cardiovascular European Research Center, Massy, France) masked to treatment allocation adjudicated all primary endpoint-related adverse events. All follow-up echocardiograms were assessed by an independent core laboratory (Medical Research Development, Hospital La Zarzuela, Madrid). Further prespecified follow-up visits and analyses will be done after 1 year and 3 years.

## Statistical analysis

A sample size of 730 patients was calculated to provide 80% power to show non-inferiority of the ACURATE neo to the SAPIEN 3 regarding the primary endpoint at 30 days, assuming (on the basis of registry data) that the primary endpoint would occur in 22% of patients in each treatment group, at a non-inferiority margin of

7·7% and a one-tailed α=0·05, anticipating a low attrition rate.[13]

Estimates of the risk differences between the two treatment groups regarding the primary endpoint were pooled over the predefined STS-PROM strata by means of the Cochran-Mantel-Haenszel method and Wald-type confidence limits calculated using the Sato variance estimator.[19] The non-inferiority assumption was tested at a one-sided significance level with α set to 0·05. Non-inferiority would be met if the upper limit of the one-sided 95% CI of the risk difference did not cross the prespecified non-inferiority margin. The analysis of the primary composite endpoint was done according to the intention-to-treat principle in a complete case analysis. Prespecified sensitivity analyses were done in the per-protocol population (including patients in whom the procedure was initiated and the allocated device used and implanted, and who had no protocol violations regarding eligibility or the implantation procedure) in view of potential bias towards non-inferiority of the intention-to-treat analysis if treatment crossovers and protocol violations were frequent.

Secondary analyses of the primary endpoint included an overall superiority analysis and predefined subgroup analyses at a two-tailed α=0·05 for superiority and treatment-by-subgroup interaction tests. Further exploratory secondary analyses investigated between group differences in relation to procedural complications, secondary clinical safety endpoints, and echocardiographic findings. A post-hoc sensitivity analysis of haemodynamic valve function as assessed by echocardiography was done, restricted to patients in whom the assigned valve was successfully implanted and functional at the time of echocardiographic assessment.

Depending on the distribution, continuous variables are presented as mean (SD) and compared by Student's *t* test, or median (IQR) and compared by Wilcoxon rank sum test. Categorical variables are presented as proportions and compared by Fisher's exact test or risk difference using the Cochran-Mantel-Haenszel method and the Sato variance estimator. Time-to-event analyses were done using Kaplan-Meier estimates and compared with the log-rank test. All statistical analyses were done with Stata software (version 15.1).

The study is registered at ClinicalTrials.gov (NCT03011346).

### 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 report. The first author (JL), senior author (TP), and trial statistician (DH) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

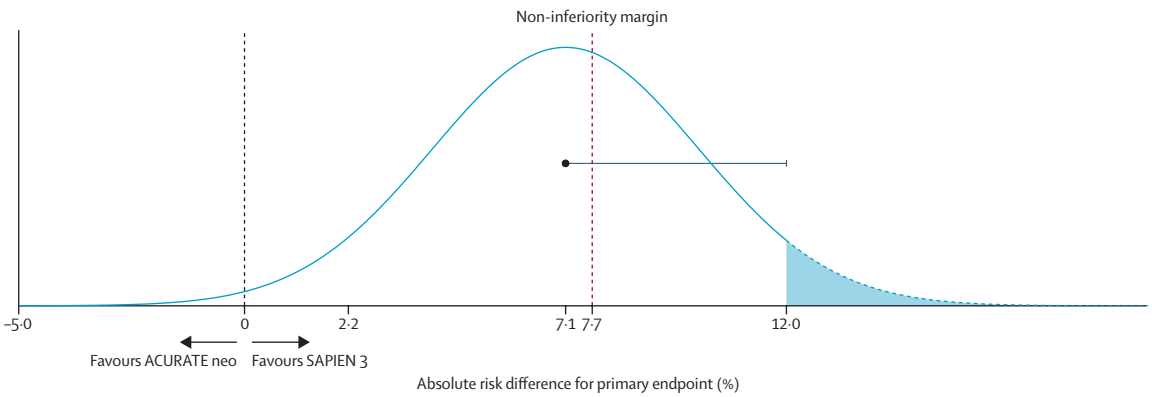
Between Feb 8, 2017, and Feb 2, 2019, up to 5132 patients were screened and 739 (14%) patients were included at 20 European sites (full screening and inclusion numbers are presented in the appendix [pp 9–10]). 372 patients were allocated to the ACURATE neo and 367 to the SAPIEN 3 TAVR system. Eight (1%) patients withdrew consent before 30-day follow-up, none of whom had an adverse event relevant to the primary endpoint up to the time of withdrawal. None of the remaining patients were lost to follow-up with regard to the 30-day clinical primary endpoint assessment; thus, clinical follow-up information for the primary endpoint was available for 731 (99%) patients (figure 1). Echocardiographic assessment of valve-related dysfunction was available for

| | ACURATE neo (N=372) | SAPIEN 3 (N=367) | p value |
|---|---|---|---|
| Transfemoral TAVR not initiated | 3 (1%) | 4 (1%) | 1·00 |
| Death before procedure | 2 (1%) | 2 (1%) | .. |
| Withdrawal | 0 | 1 (<1%) | .. |
| Other medical reason* | 1 (<1%) | 1 (<1%) | .. |
| Transfemoral TAVR initiated† | 369 (99%) | 363 (99%) | 0·72 |
| Procedure time, min | 53·2 (26·5), N=368 | 46·0 (25·9), N=363 | 0·0002 |
| Total contrast volume, mL | 136 (55·6), N=367 | 110 (45·9), N=362 | <0·0001 |
| General anaesthesia | 94 (25%) | 84 (23%) | 0·49 |
| Pre-dilatation | 325 (88%) | 83 (23%) | <0·0001 |
| Cerebral protection device | 9 (2%) | 7 (2%) | 0·80 |
| Transfemoral access mode | .. | .. | 0·37 |
| Percutaneous | 368 (>99%) | 360 (99%) | .. |
| Surgical cut-down | 1 (<1%) | 3 (1%) | .. |
| TAVR valve implanted | 369 (100%) | 363 (100%) | 1·00 |
| Surgical aortic valve replacement | 2 (1%) | 0 | 0·50 |
| Access closure device | 369 (100%) | 362 (>99%) | 0·50 |
| Post dilatation | .. | .. | <0·0001 |
| None | 176 (48%) | 315 (87%) | .. |
| One | 164 (44%) | 44 (12%) | .. |
| Two or more | 29 (8%) | 4 (1%) | .. |
| Procedural complications‡ | | | |
| Valve malpositioning | 5 (1%) | 2 (1%) | 0·26 |
| Coronary artery obstruction requiring intervention | 0 | 0 | 1·00 |
| Periprocedural myocardial infarction | 1 (<1%) | 1 (<1%) | 0·96 |
| Implantation of multiple valves | 11 (3%) | 2 (1%) | 0·0119 |
| Cardiac tamponade | 4 (1%) | 5 (1%) | 0·72 |
| Annular rupture | 2 (1%) | 1 (<1%) | 0·57 |
| Left ventricular perforation | 1 (<1%) | 0 | 0·32 |
| Conversion to open heart surgery | 3 (1%) | 0 | 0·08 |
| Immediate procedural death | 3 (1%) | 1 (<1%) | 0·32 |

p values are derived from Fisher's exact tests for categorical variables and Student's *t* tests for continuous variables unless stated otherwise. TAVR=transcatheter aortic valve replacement. *One patient (ACURATE neo group) never underwent valve replacement because of an infection, and one patient (SAPIEN 3 group) underwent planned transapical TAVR. †The procedure was deemed initiated if the patient was given sedation or anaesthesia in the procedure room with the intent to perform transfemoral TAVR; the percentages reported below were calculated on the number of patients in whom TAVR was initiated. ‡All procedural complications were adjudicated by an independent clinical event committee; percentages were calculated on the number of patients in whom TAVR was initiated; p values were inferred from significance testing of the risk difference obtained by means of the Cochran-Mantel-Haenszel method to pool estimates across the predefined Society of Thoracic Surgeons Predicted Risk of Mortality score categories using the Sato variance estimator.

***Table 2:*** **Procedural characteristics and outcomes in the intention-to-treat population**

A




B

| | Events, n/N (%) | | Risk difference, % (95% CI)* | p value |
|---|---|---|---|---|
| | ACURATE neo group | SAPIEN 3 group | | |
| **Primary analysis** | | | | |
| Primary endpoint (non-inferiority analysis) | 87/367 (24%) | 60/364 (16%) | 7·1% (NA to 12·0) | 0·42 |
| **Secondary analyses** | | | | |
| Primary endpoint (superiority analysis) | 87/367 (24%) | 60/364 (16%) | 7·1% (1·3 to 12·9) | 0·0156 |
| **Individual components of primary endpoint** | | | | |
| All-cause death | 9/367 (2%) | 3/364 (1%) | 1·6% (−0·2 to 3·4) | 0·09 |
| Stroke (any) | 7/367 (2%) | 11/364 (3%) | −1·1% (−3·3 to 1·1) | 0·33 |
| Life-threatening or disabling bleeding | 14/367 (4%) | 9/364 (2%) | 1·3% (−1·2 to 3·9) | 0·30 |
| Major vascular complications | 29/367 (8%) | 20/364 (5%) | 2·3% (−1·3 to 5·9) | 0·21 |
| Coronary artery obstruction requiring intervention | 0/367 (0%) | 0/364 (0%) | NA | NA |
| Acute kidney injury, stage 2 or 3 | 11/367 (3%) | 3/364 (1%) | 2·1% (0·2 to 4·1) | 0·0340 |
| Rehospitalisation for valve-related dysfunction or congestive heart failure | 4/367 (1%) | 5/364 (1%) | −0·3% (−1·9 to 1·3) | 0·72 |
| Valve-related dysfunction requiring repeat procedure | 3/367 (1%) | 1/364 (<1%) | 0·5% (−0·5 to 1·6) | 0·32 |
| Valve-related dysfunction (echocardiography)† | 35/361 (10%) | 17/363 (5%) | 5·0% (1·3 to 8·8) | 0·0084 |



***Figure 2:*** **Primary endpoint**
(A) Probability distribution (with point estimate and one-sided 95% CI) of the risk difference for frequency of the primary endpoint between the two groups. (B) Primary and secondary analyses of the primary endpoint and its components in the intention-to-treat population. The red line indicates the non-inferiority margin (prespecified at 7·7%). All 95% CIs and p values are two-sided except those of the primary, non-inferiority analysis (one-sided). STS-PROM=Society of Thoracic Surgeons Predicted Risk of Mortality. NA=not applicable. VARC-2=Valve Academic Research Consortium 2. *95% CIs are pooled across the predefined STS-PROM score categories by means of the Cochran-Mantel-Haenszel method and calculated using the Sato variance estimator. †Comprises mean aortic valve gradient ≥20 mm Hg and either effective orifice area ≤0·9–1·1 cm² (depending on body surface area) or Doppler velocity index <0·35; or moderate or severe prosthetic valve regurgitation as defined by VARC-2; patients for whom follow-up echocardiography was not available (owing to a primary endpoint-related clinical event) were included in the primary endpoint analyses, but not in the individual echocardiographic component.

724 (98%) of 739 patients and was missing only for patients who died before TAVR (four [1%]), never underwent a valve replacement (one [<1%]), withdrew consent (two [<1%]), or died (seven [1%]) or had a major stroke (one [<1%]) shortly after TAVR. The study flow chart for the per-protocol cohort is provided in the appendix (p 24).

Baseline demographic and clinical characteristics are presented in table 1. The mean age of the study population was 82·8 years (SD 4·1) and 420 (57%) patients were female. The median STS-PROM score in the study population was 3·5% (IQR 2·6–5·0). Aortic valve mean gradient was 42·2 mm Hg (16·2), mean aortic valve area was 0·7 cm² (0·2), and mean left ventricular ejection fraction was 56·7% (10·9) at baseline. Baseline imaging findings and medication use are detailed in the appendix (pp 11–13).

Table 2 summarises the procedural characteristics and complications. Two (1%) patients in the ACURATE neo group required conversion to surgical aortic valve replacement and one (<1%) patient was converted to transapical TAVR. Implantation of multiple valves was more frequent in the ACURATE neo group (11 [3%] patients) than in the SAPIEN 3 group (two [1%]). Implanted valve sizes are listed in the appendix (p 14).

At 30 days, the primary composite endpoint occurred in 87 (24%) patients in the ACURATE neo group and in 60 (16%) patients in the SAPIEN 3 group, with an absolute risk difference of 7·1% and a one-sided upper 95% confidence limit of 12·0% (figure 2). Thus, non-inferiority of the ACURATE neo was not established for the primary endpoint.

Secondary analysis showed a significantly increased incidence of the primary endpoint at 30 days in the ACURATE neo group compared with the SAPIEN 3 group (risk difference 7·1% [95% CI 1·3–12·9], p=0·0156; figure 2). The proportions of patients with stage 2 or 3 acute kidney injury or valve-related dysfunction (based on echocardiographic findings) within 30 days were significantly greater in the ACURATE neo group than the SAPIEN 3 group; however, no significant differences were observed with regard to any other components of the primary endpoint, including all-cause mortality (nine [2%] patients with ACURATE neo *vs* three [1%] with SAPIEN 3) and stroke (seven [2%] *vs* 11 [3%]; figure 2), or any secondary clinical endpoints (table 3).

Predefined subgroup analyses showed no significant interactions between device type and STS-PROM category, sex, left ventricular ejection fraction, or eccentricity index of the annulus (appendix p 25). Sensitivity analyses of the primary endpoint in the per-protocol cohort showed robust findings for both non-inferiority (risk difference 6·8% [upper 95% confidence limit 12·1%], p=0·39) and superiority (risk difference 6·8% [95% CI 0·6–13·1], p=0·0325) analyses of the ACURATE neo compared with the SAPIEN 3 (appendix p 26).

All individual causes of death and cases of selected procedural complications are shown in the appendix (pp 15–17). The proportions of patients who required new pacemaker implantation were similar between the ACURATE neo group (37 patients [10%]) and the SAPIEN 3 group (34 [9%]). VARC-2 composite endpoints are presented in the appendix (p 18). There were no between-group differences with regard to functional NYHA class or KCCQ-12 summary score at 30-day follow-up (appendix pp 29–30).

With regard to the echocardiographic findings, moderate or severe paravalvular aortic regurgitation at follow-up was documented in 34 (9%) patients in the ACURATE neo group and in ten (3%) patients in the SAPIEN 3 group (figure 3). Median mean transprosthetic gradient was lower and median effective orifice area larger in patients treated with the ACURATE neo than those treated with the SAPIEN 3 device (figure 3). These findings were consistent in post-hoc sensitivity analyses restricted to patients in whom the assigned valve was successfully implanted and functional at the time of echocardiographic assessment (appendix p 31).

| | ACURATE neo (N=367) | SAPIEN 3 (N=364) | p value |
|---|---|---|---|
| All-cause death or disabling stroke | 12 (3%) | 7 (2%) | 0·26 |
| All-cause death | 9 (2%) | 3 (1%) | 0·09 |
| Cardiovascular death | 8 (2%) | 3 (1%) | 0·13 |
| Cerebrovascular event | 10 (3%) | 12 (3%) | 0·66 |
| Stroke | 7 (2%) | 11 (3%) | 0·33 |
| Disabling stroke | 4 (1%) | 4 (1%) | 0·99 |
| Non-disabling stroke | 3 (1%) | 7 (2%) | 0·21 |
| Transient ischaemic attack | 3 (1%) | 1 (<1%) | 0·31 |
| Bleeding (VARC-2) | 97 (26%) | 77 (21%) | 0·10 |
| Life-threatening or disabling bleeding | 14 (4%) | 9 (2%) | 0·30 |
| Major | 41 (11%) | 33 (9%) | 0·21 |
| Minor | 43 (12%) | 38 (10%) | 0·10 |
| Vascular complication (VARC-2) | 59 (16%) | 64 (18%) | 0·55 |
| Major | 29 (8%) | 20 (5%) | 0·37 |
| Minor | 31 (8%) | 44 (12%) | 0·60 |
| Acute kidney injury | 31 (8%) | 25 (7%) | 0·46 |
| AKIN stage 2 | 7 (2%) | 2 (1%) | 0·10 |
| AKIN stage 3 | 4 (1%) | 1 (<1%) | 0·20 |
| Renal replacement therapy | 3 (1%) | 1 (<1%) | 0·35 |
| Repeat intervention for valve-related dysfunction | 3 (1%) | 1 (<1%) | 0·32 |
| Balloon aortic valvuloplasty | 1 (<1%) | 1 (<1%) | 1·00 |
| Transcatheter aortic valve replacement | 1 (<1%) | 0 | 0·32 |
| Surgical aortic valve replacement | 1 (<1%) | 0 | 0·32 |
| Spontaneous myocardial infarction | 2 (1%) | 0 | 0·16 |
| ST-elevation* | 0 | 0 | NA |
| Non-ST-elevation* | 2 (1%) | 0 | 0·16 |
| Prosthetic valve endocarditis | 2 (1%) | 1 (<1%) | 0·59 |
| Prosthetic valve thrombosis | 0 | 1 (<1%) | 0·30 |
| New atrial fibrillation or flutter | 11 (3%)† | 12 (3%) | 0·83 |
| Any tachyarrhythmia resulting in haemodynamic instability or requiring therapy | 26 (7%)† | 25 (7%) | 0·90 |
| New pacemaker implantation | 37 (10%)† | 34 (9%) | 0·76 |

Data are n (%). p values were inferred from significance testing of the risk difference obtained by means of the Cochran-Mantel-Haenszel method to pool estimates across the predefined Society of Thoracic Surgeons Predicted Risk of Mortality score categories and using the Sato variance estimator. VARC-2=Valve Academic Research Consortium 2. AKIN=Acute Kidney Injury Network. NA=not applicable. Unless specified otherwise, endpoints were adjudicated by the independent clinical event committee. *Site-reported only, not adjudicated by independent clinical event committee. †N=368 (in one patient, the corresponding events occurred before patient withdrawal).

***Table 3:*** **Selected secondary clinical endpoints at 30 days in the intention-to-treat population**

## Discussion

In this multicentre, randomised non-inferiority trial of older patients with symptomatic severe aortic stenosis at increased surgical risk, TAVR with the self-expanding ACURATE neo prosthesis was not non-inferior to the balloon-expandable SAPIEN 3 prosthesis with respect to a composite safety and clinical efficacy endpoint at 30 days. Secondary analyses revealed superiority of the SAPIEN 3 compared with the ACURATE neo TAVR system with respect to the primary endpoint at 30 days, with lower incidence of acute kidney injury and moderate or severe paravalvular regurgitation in the SAPIEN 3 group. Conversely, the median mean transvalvular gradient was lower and the median mean aortic valve area larger in the ACURATE neo compared to the SAPIEN 3 group at follow-up echocardiography.

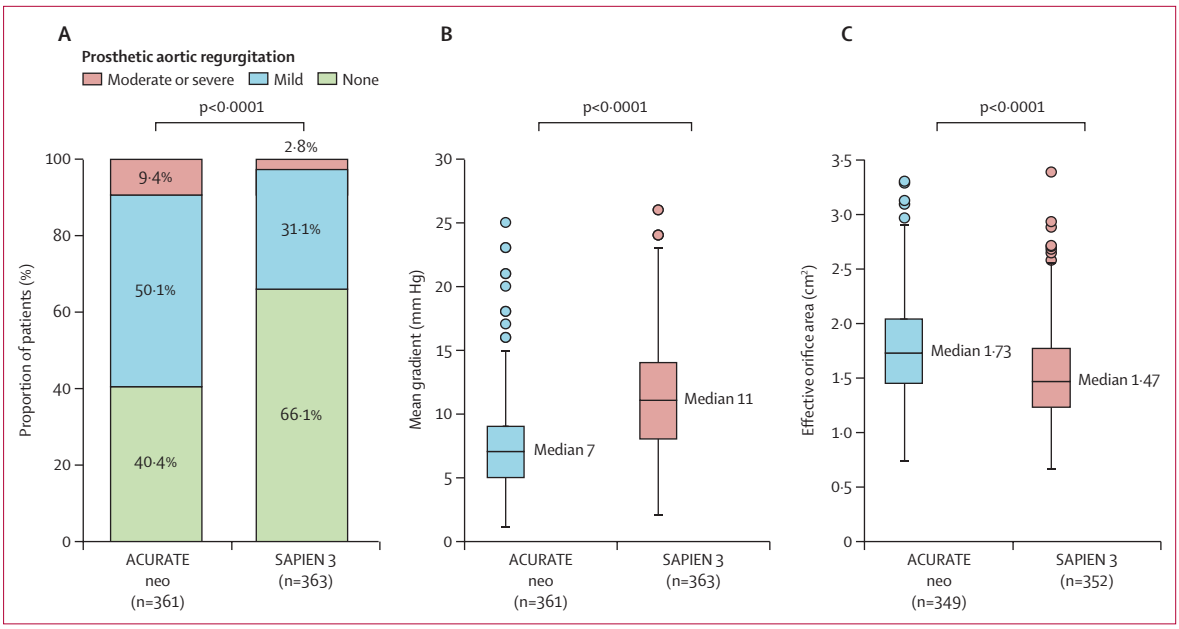



***Figure 3:*** **Echocardiographic valve performance at 30 days**
(A) Proportions of patients with none, mild, or moderate or severe prosthetic aortic valve regurgitation in each group at 30-day follow-up in the intention-to-treat population (p value is from Fisher's exact test). Transprosthetic mean gradient (B) and effective orifice area (C) in the two groups. Boxes represent median and IQR, and whiskers represent the range, excluding outliers. Outliers (individual data points) were defined as values more than 1·5 IQRs above the upper quartile or below the lower quartile. p values are from Wilcoxon rank sum tests. All measures were assessed at an independent echocardiographic core laboratory.

Exploratory analyses indicated no difference between the two treatment groups with regard to all-cause and cardiovascular deaths, stroke, or frequency of new pacemaker implantation at 30 days.

The increased incidence of the primary endpoint in the ACURATE neo group was robust in per-protocol sensitivity analyses, and was primarily driven by the increased proportion of patients with moderate or severe paravalvular prosthetic aortic regurgitation, as assessed by an independent echocardiographic core laboratory. Paravalvular aortic regurgitation of moderate or greater severity has previously been associated with impaired prognosis.[4,20] Potential factors contributing to the greater paravalvular regurgitation in the ACURATE neo compared to the SAPIEN 3 group include differences in the structure of the sealing skirt and a lower radial force of the ACURATE neo device, in conjunction with the anatomical characteristics of the device landing zone (particularly calcium distribution).[16,17,21,22] An iteration of the ACURATE neo valve featuring an advanced sealing skirt could further mitigate the risk of paravalvular regurgitation, and requires further evaluation.[23] The clinical relevance of the lower residual transvalvular gradients and greater effective orifice areas observed with the supra-annular ACURATE neo compared to the intra-annular SAPIEN 3 valve remains to be elucidated. Acute kidney injury was more frequent in the ACURATE neo than in the SAPIEN 3 group, which could be due to the significantly longer mean procedure time, the higher frequencies of pre-dilatation and post-dilatation (and associated periods of hypotension), and the higher mean contrast volume used with the ACURATE neo. The low frequency of new pacemaker implantation with both TAVR systems is notable when considering the rates reported for other devices.[9]

The major strengths of the SCOPE I trial are the high rates of 30-day clinical and echocardiographic follow-up, the independent assessor-masked adjudication of clinical events, and the independent assessment of follow-up echocardiographies. In addition, the observed frequencies of events were close to those assumed for sample size calculation, which is especially important in the setting of a non-inferiority margin for risk difference with respect to retaining the estimated power for the primary endpoint analysis.

Our findings need to be interpreted in the light of several limitations. First, the primary endpoint was a composite of heterogeneous individual components, including clinical and echocardiographic parameters. Nevertheless, this endpoint identified significant differences between the two valves, with the principal driver being paravalvular regurgitation. Second, the trial was not powered to show differences with regard to individual clinical endpoints. Third, the early (30-day) primary endpoint of the trial precludes meaningful evaluations of differences in long-term clinical outcomes and valve durability, which are key considerations for the use of TAVR in younger patients. However, early endpoint assessment mitigates the dilution of procedure-related events by a high baseline risk of adverse events in older

patients and provides high specificity for device-related outcomes. Fourth, CIs and p values derived from secondary superiority analyses did not account for multiple testing. However, the two-sided p value of 0·0156 for superiority found in the analysis of the primary endpoint would continue to be statistically significant at a two-sided alpha of 0·025 (0·5/2) after a Bonferroni correction to control the overall type I error rate in the presence of simultaneous non-inferiority and superiority testing of the primary outcome. Fifth, assessment of CT scans was not done by a central core laboratory, and CT measurements can be prone to inter-site and inter-rater variability. Sixth, even though the study was designed to include a TAVR population with minimal exclusion criteria, selection bias of enrolled patients might have affected our findings. Finally, the echocardiographic core laboratory was not masked to treatment allocation because of the visible differences in the stent frame.

As TAVR emerges as a valid treatment option for patients with severe, symptomatic aortic stenosis across all risk categories, high-quality studies comparing different TAVR devices are needed to provide sound evidence of the strengths and limitations of these devices, with the aim of optimising device selection for individual patients. The SCOPE I trial is one of the first studies to fill this important gap by reporting an early composite safety and efficacy endpoint to differentiate between devices.

In conclusion, TAVR with the ACURATE neo did not meet non-inferiority compared with the SAPIEN 3 device with respect to a composite safety and efficacy endpoint at 30 days. Differences in favour of the SAPIEN 3 TAVR system were driven by differences in the severity of paravalvular regurgitation and the frequency of stage 2 or 3 acute kidney injury.

#### Contributors

TP, JL, and SW conceived and designed the study. JL, TP, DH, and SW were responsible for the acquisition of data. W-KK recruited the highest number of patients. DH performed the analyses and interpreted the results in collaboration with all other authors. JL, TP, and SW wrote the first draft of the report. All authors critically revised the report for important intellectual content and approved the final version.

#### Declaration of interests

W-KK is a proctor for Boston Scientific and Abbott, and has received speaker fees from Boston Scientific, Abbott, and Edwards Lifesciences. HM has received speaker fees from or is a proctor for Abbott, Biotronik, Boston Scientific, and Edwards Lifesciences. AL is a consultant to Medtronic, Edwards, Boston Scientific, Abbott, Transverse Medical, AstraZeneca, and Claret Medical; owns stock options from Emboline and Transverse Medical; and has received speaker honoraria from Edwards, Boston Scientific, Medtronic, Abbott, AstraZeneca, Bayer, and Novartis. BP has received unrestricted research grants and speaker fees from Edwards Lifesciences. LaC reports personal fees from Boston Scientific, Medtronic, and Edwards Lifesciences. LeC is a proctor for Boston Scientific and has received travel support and speaker fees from Boston Scientific. SS reports grants from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott; and personal fees from BTG, Teleflex, and Boston Scientific. PJ served as an unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St Jude Medical, and The Medicines Company; has received research grants to the institution from AstraZeneca, Biotronik, Biosensors International, Eli Lilly, and The Medicines Company; and has received honoraria to their institution for participation in advisory boards from Amgen, but has not received personal payments by any pharmaceutical company or device manufacturer. SW has received institutional grants from Abbott, Amgen, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, Medicines Company, and St Jude, as well as speaker fees from AstraZeneca, Eli Lilly, Abbott, Biotronik, Boston Scientific, Bayer, and Biosensors. TP has received institutional research grants from Biotronik, Boston Scientific, and Edwards Lifesciences, speaker fees from Biotronik and Boston Scientific, and is a consultant for HighLife SAS. All other authors declare no competing interests.

#### Data sharing

The SCOPE I trial is an investigator-initiated trial with multiple pre-defined sub-studies. Internal investigators who actively participated in the study and who provide a methodologically sound study proposal will be granted priority access to the study data for a period of 24 months. After 24 months, data used in this Article plus relevant documentation will be made available to external investigators (those not affiliated to the trial) whose proposed use of the data has been approved by an independent review committee identified by the steering committee for this purpose. Data will be deposited at https://boris.unibe.ch/132668/, where study proposals can also be filed.

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