The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 6, 2022 VOL. 387 NO. 14

Cerebral Embolic Protection during Transcatheter Aortic-Valve Replacement

Samir R. Kapadia, M.D., Raj Makkar, M.D., Martin Leon, M.D., Mohamed Abdel-Wahab, M.D., Thomas Waggoner, D.O., Steffen Massberg, M.D., Wolfgang Rottbauer, M.D., Ph.D., Samuel Horr, M.D., Lars Sondergaard, M.D., Juhana Karha, M.D., Robert Gooley, M.B., B.S., Ph.D., Lowell Satler, M.D., Robert C. Stoler, M.D., Steven R. Messé, M.D., Suzanne J. Baron, M.D., Julia Seeger, M.D., Susheel Kodali, M.D., Amar Krishnaswamy, M.D., Vinod H. Thourani, M.D., Katherine Harrington, M.D., Stuart Pocock, Ph.D., Rodrigo Modolo, M.D., Ph.D., Dominic J. Allocco, M.D., Ian T. Meredith, M.D., Ph.D., and Axel Linke, M.D., for the PROTECTED TAVR Investigators*

ABSTRACT

BACKGROUND

Transcatheter aortic-valve replacement (TAVR) for the treatment of aortic stenosis can lead to embolization of debris. Capture of debris by devices that provide cerebral embolic protection (CEP) may reduce the risk of stroke.

METHODS

We randomly assigned patients with aortic stenosis in a 1:1 ratio to undergo transfemoral TAVR with CEP (CEP group) or without CEP (control group). The primary end point was stroke within 72 hours after TAVR or before discharge (whichever came first) in the intention-to-treat population. Disabling stroke, death, transient ischemic attack, delirium, major or minor vascular complications at the CEP access site, and acute kidney injury were also assessed. A neurology professional examined all the patients at baseline and after TAVR.

RESULTS

A total of 3000 patients across North America, Europe, and Australia underwent randomization; 1501 were assigned to the CEP group and 1499 to the control group. A CEP device was successfully deployed in 1406 of the 1489 patients (94.4%) in whom an attempt was made. The incidence of stroke within 72 hours after TAVR or before discharge did not differ significantly between the CEP group and the control group (2.3% vs. 2.9%; difference, −0.6 percentage points; 95% confidence interval, −1.7 to 0.5; P=0.30). Disabling stroke occurred in 0.5% of the patients in the CEP group and in 1.3% of those in the control group. There were no substantial differences between the CEP group and the control group in the percentage of patients who died (0.5% vs. 0.3%); had a stroke, a transient ischemic attack, or delirium (3.1% vs. 3.7%); or had acute kidney injury (0.5% vs. 0.5%). One patient (0.1%) had a vascular complication at the CEP access site.

CONCLUSIONS

Among patients with aortic stenosis undergoing transfemoral TAVR, the use of CEP did not have a significant effect on the incidence of periprocedural stroke, but on the basis of the 95% confidence interval around this outcome, the results may not rule out a benefit of CEP during TAVR. (Funded by Boston Scientific; PROTECTED TAVR ClinicalTrials.gov number, NCT04149535.)

The authors' affiliations are listed in the Appendix. Dr. Kapadia can be contacted at kapadis@ccf.org or at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., J2-3, Cleveland, OH 44195.

*A full list of the PROTECTED TAVR investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 17, 2022, at NEJM.org.

N Engl J Med 2022;387:1253-63.
DOI: 10.1056/NEJMoa2204961

A Quick Take is available at NEJM.org

Transcatheter aortic-valve replacement (TAVR) is an established treatment for patients with aortic stenosis across the spectrum of surgical risk.[1-9] Embolization of debris from the valve or the vasculature can cause periprocedural stroke,[10,11] leading to increased morbidity and mortality.[12-15] Even in the absence of clinical symptoms, the majority of patients (68 to 93%) have defects identified on diffusion-weighted perfusion imaging after TAVR.[10,16,17] Although the risk of stroke with TAVR is decreasing with newer-generation devices and is similar to that after surgical aortic-valve replacement,[5,6,18-20] it remains an important and troubling complication of the procedure.[21,22]

The Sentinel cerebral embolic protection (CEP) device (Boston Scientific) was approved by the Food and Drug Administration (FDA) for the capture and removal of embolic material during TAVR to reduce the risk of periprocedural ischemic injury to the brain.[17,23,24] The pivotal randomized trial of the Sentinel device that was completed for FDA approval had a primary end point of cerebral lesion volume in protected brain territories, as measured by magnetic resonance imaging.[24] In that trial, the Sentinel device was shown to be safe and captured debris in 99% of patients, but the reduction in new cerebral lesion volume was not significant and the trial was not powered to assess stroke.

An analysis by the Society of Thoracic Surgeons–American College of Cardiology Transcatheter Valve Therapy Registry showed that after commercial approval of the CEP device, approximately 13% of TAVR procedures included the use of such a device.[25] A larger randomized trial of CEP during TAVR that includes clinical stroke as an end point would be relevant to health care providers and patients. The PROTECTED TAVR trial was conducted to investigate whether CEP reduces the risk of periprocedural stroke with TAVR.

Methods

Trial Design and Oversight

This prospective, postmarket, multicenter, randomized, controlled trial evaluated the Sentinel CEP device in patients with aortic stenosis undergoing transfemoral TAVR (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The patients were randomly assigned in a 1:1 ratio to undergo TAVR with CEP (CEP group) or without CEP (control group). Randomization was stratified according to center, operative risk (low risk or intermediate or higher risk), and intended TAVR valve type (balloon-expandable or nonballoon-expandable device).

The trial protocol, available at NEJM.org, was developed by the principal investigators (the first and last authors) and the trial sponsor (Boston Scientific) with input from the steering committee (Tables S1 and S2) and was approved by all the institutional review boards of the participating institutions. Major clinical events were adjudicated by an independent clinical events committee. An independent data and safety monitoring board provided trial oversight. Analyses of the primary and other clinical end points were performed by the sponsor; independent statistical validation of the results was provided by IQVIA, a contract research organization. The principal investigators had unrestricted access to the data and wrote the first draft of the manuscript, and all the authors provided critical review. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. There were no data confidentiality restrictions between the sponsor and authors or their institutions; findings were to be published regardless of the results.

Patients

A full list of the inclusion and exclusion criteria is provided in Table S3. Patients were eligible if they had aortic stenosis and were scheduled to undergo TAVR with transfemoral placement of a commercially available device. Patients were excluded if either the left common carotid or the brachiocephalic artery had greater than 70% diameter stenosis or if the anatomical structure was otherwise incompatible with the placement of the CEP device. All the patients provided written informed consent.

Trial Device and Procedure

The Sentinel Cerebral Protection System has two filters within a single 6-French delivery catheter (2 mm in diameter); the filters are placed percutaneously from the right radial or brachial artery in the brachiocephalic artery (proximal filter)

and the left common carotid artery (distal filter) before TAVR (Fig. S2). All the investigators were experienced in deploying the Sentinel CEP device and had performed at least 20 procedures involving its use.

TRIAL END POINTS AND SUBGROUP ANALYSES

The primary end point was clinical stroke within 72 hours after TAVR or before discharge (whichever came first). Stroke was defined as an acute episode of a focal or global neurologic dysfunction caused by vascular injury to the brain, spinal cord, or retina resulting from hemorrhage or infarction.[26] For the purposes of the trial, "discharge" referred to discharge from the treating facility; transfer to another institution was not considered to be part of the initial hospitalization. A neurology professional (board-certified or board-eligible neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner) performed neurologic examinations at baseline (after randomization) and after TAVR. In patients in whom stroke was suspected, neuroimaging was performed according to the standard of care at each site at the discretion of the treating physician. Routine neuroimaging was not performed to identify covert (asymptomatic) brain infarction. An independent clinical events committee adjudicated all stroke events, with stroke subtype characterized according to definitions of the Neurologic Academic Research Consortium (NeuroARC): type 1.a to 1.d and type 2.b events were considered to be strokes (Table S4).[26]

Additional prespecified end points included stroke severity, which was assessed with the use of the modified Rankin scale (range, 0 to 6, with a score of 0 indicating no symptoms and 6 indicating death) at 30 days (within a window of ±7 days), with nondisabling stroke defined as a score of <2 (or as a score of ≥2 if the score had not increased from the prestroke baseline score) and disabling stroke defined as a score of ≥2 and an increase of at least 1 point from the prestroke baseline score; death from any cause; a composite end point of stroke, transient ischemic attack, or delirium; acute kidney injury; and vascular complications at the CEP access site. Neurologic assessments at baseline and before discharge included the modified Rankin scale, the National Institutes of Health Stroke Scale, the Montreal Cognitive Assessment, and the Confusion Assessment Method for Intensive Care Unit Patients (further details on these instruments are provided in the Supplementary Appendix).

Prespecified subgroup analyses were performed according to sex and operative risk. Additional patient subgroups of interest were identified before unmasking of the trial-group assignments.

STATISTICAL ANALYSIS

This trial used an adaptive group-sequential design with an initial planned enrollment of 3000 patients and a scheduled interim analysis when enrollment reached 70% (2100 patients). The design allowed for early stoppage of the trial if a significant difference in favor of the CEP group was observed or a reestimation of sample size was indicated (additional details are provided in the Statistical Methods section in the Supplementary Appendix). On the basis of contemporary published reports of the incidence of stroke among patients undergoing TAVR,[23,25,27-29] we estimated that the planned enrollment of 3000 patients would provide the trial with greater than 90% power to show the superiority of CEP if the incidence of stroke was 4% in the control group and 2% in the CEP group.

The analysis of the primary end point was performed in the intention-to-treat population, which included all patients enrolled in the trial regardless of whether the assigned treatment was received. Continuous variables were summarized with the use of descriptive statistics and were compared with the use of a Student's t-test; discrete variables were reported as counts and percentages. The trial groups were compared with the use of the chi-square test or Fisher's exact test; with respect to the primary end point, the chi-square test was used to assess the superiority of CEP use over nonuse during TAVR. Univariate and multivariate analyses were performed to assess predictors of the primary end point and other outcomes. Because there was no plan for adjustment for multiple comparisons of secondary end points, between-group differences are presented as point estimates with 95% confidence intervals that were not adjusted for multiplicity and thus should not be used to infer definitive treatment effects. Statistical analyses

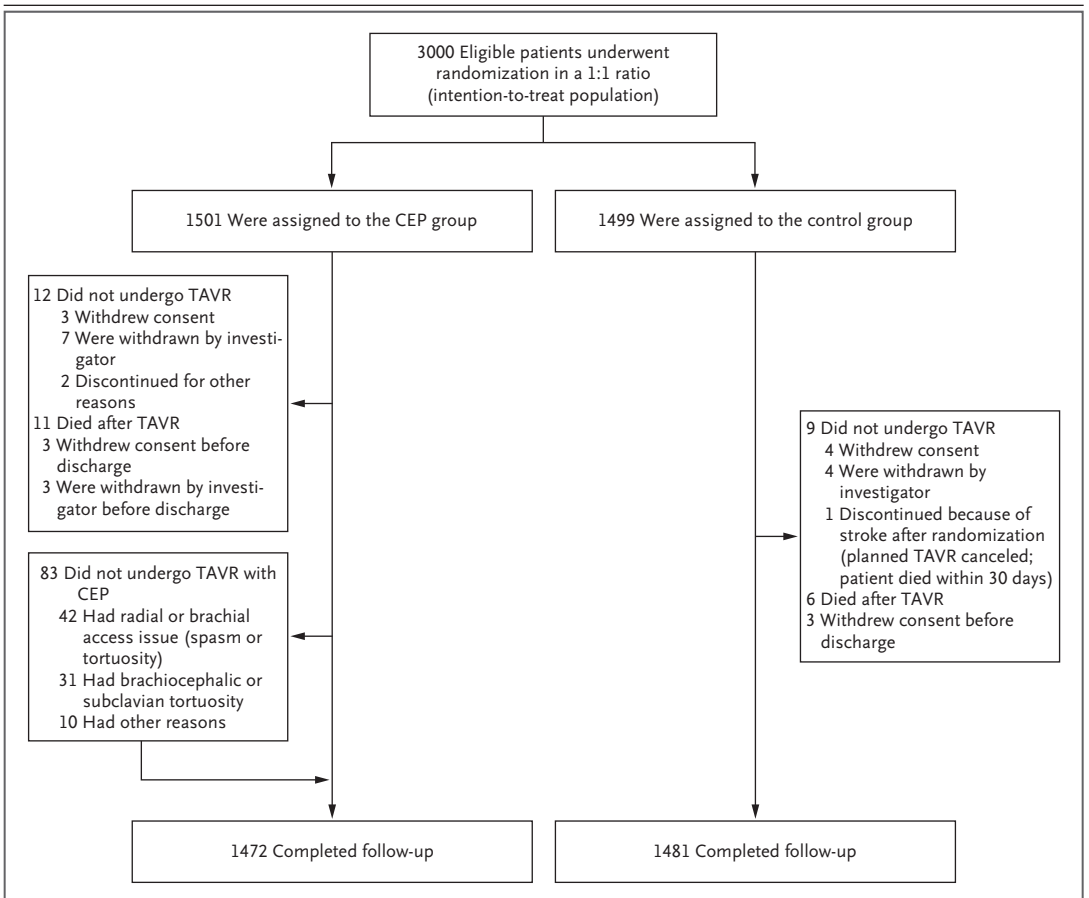

Figure 1. Randomization, Treatment, and Follow-up.

Patients eligible for transcatheter aortic-valve replacement (TAVR) were randomly assigned to the cerebral embolic protection (CEP) group (TAVR with CEP) or the control group (TAVR only). Data on all patients were collected for 72 hours after TAVR or up to the time of hospital discharge (whichever came first). In the patients who received a diagnosis of periprocedural stroke, scoring on the modified Rankin scale was also performed at 30 days (within a window of ±7 days) after stroke.

were performed with SAS software, version 9.4 or later (SAS Institute).

RESULTS

PATIENTS AND ENROLLMENT

A total of 3000 patients at 51 centers across North America, Europe, and Australia were enrolled and underwent randomization from February 2020 through January 2022 (Table S1). In the interim analysis of the first 2100 patients enrolled, stroke had occurred in 23 of 1051 patients (2.2%) in the CEP group and in 25 of 1049 patients (2.4%) in the control group. On the basis of these results and the prespecified sample-size reestimation algorithm, the data and safety monitoring board recommended a final sample size of 3000. The intention-to-treat population included 1501 patients in the CEP group and 1499 patients in the control group (Fig. 1). Among the patients who underwent randomization, 21 did not undergo a TAVR procedure; CEP was successfully deployed in 1406 of the 1489 patients (94.4%) in whom an attempt was made.

The patients in the trial were generally representative of the overall population eligible for TAVR with CEP (Table S5). The mean (±SD) age of the patients was 78.9±7.8 years, and the mean Society of Thoracic Surgeons surgical risk score, which represents the predicted risk of death after surgery, was 3.4±2.7% (scores range from 0 to 100%, with higher values indicating higher

risk). The demographic and clinical characteristics of the patients at baseline and the procedural characteristics were generally similar in the two trial groups (Table 1), with the exception of a higher percentage of female patients in the CEP group than in the control group (42.0% vs. 37.8%). Procedural and discharge details (anesthesia use, CEP deployment, length of hospital stay, and discharge location) are provided in Tables S6 and S8. Details of neurologic assessments performed at baseline are provided in Table S7.

PRIMARY AND ADDITIONAL CLINICAL END POINTS

The incidence of clinical stroke within 72 hours after TAVR or before discharge (primary end point) did not differ significantly between the CEP group and the control group (2.3% [34 of 1501 patients] vs. 2.9% [43 of 1499]; difference, −0.6 percentage points; 95% confidence interval [CI], −1.7 to 0.5; P=0.30) (Fig. 2); however, as reflected by the 95% confidence interval, the results may not rule out a benefit of CEP during TAVR. All the patients who received a diagnosis of stroke underwent neuroimaging. Most stroke events occurred within 24 hours after the TAVR procedure (Fig. S3). Stroke severity and subtype according to the NeuroARC categorization are shown in Figure S4. Disabling stroke occurred in 0.5% of the patients (8 of 1501) in the CEP group and in 1.3% of patients (20 of 1499) in the control group (difference, −0.8 percentage points; 95% CI, −1.5 to −0.1) (Fig. 2). Additional clinical end points within 72 hours after TAVR or before discharge are shown in Table 2. There were no substantial differences between the CEP group and the control group with respect to death from any cause; a composite end point of stroke, transient ischemic attack, or delirium; or acute kidney injury. Vascular complications at the CEP access site were infrequent — 1 patient (0.1%) had a major bleeding event at the radial access site during sheath removal. The CEP device could not be deployed in 83 of the 1501 patients (5.5%) assigned to the CEP group (Fig. 1). A per-protocol analysis involving patients who received the assigned treatment yielded results similar to those in the intention-to-treat population (Table S9).

Among the patients with stroke, there was no apparent difference between the CEP group and the control group with respect to all-cause mortality within 72 hours after TAVR or before discharge (2.9% [1 of 34] vs. 4.7% [2 of 43]) or at the 30-day follow-up (11.8% [4 of 34] vs. 11.6% [5 of 43]). The results of neurologic assessments in the patients with stroke are shown in Table S10, and the 30-day clinical outcomes are shown in Table S11. Additional details on discharge and length of hospital stay are provided in Table S8.

SUBGROUP AND MULTIVARIABLE ANALYSES

The incidences of stroke and disabling stroke within 72 hours after TAVR or before discharge in various subgroups are shown in Fig. 3 and Fig. S5, respectively. Figure S6 shows the results for the primary end point according to geographic region. In a multivariable analysis, female sex was associated with stroke (odds ratio, 1.93; 95% CI, 1.20 to 3.12), and use of a balloon-expandable valve was inversely associated with stroke (odds ratio, 0.46; 95% CI, 0.28 to 0.76) (Table S12). A post hoc multivariable analysis of disabling stroke was also performed (Table S13).

DISCUSSION

In this large, randomized, prospective trial of CEP use during TAVR, the CEP device was successfully deployed in 94.4% of patients in whom an attempt was made and was not associated with an increased risk of complications. The incidence of periprocedural stroke within 72 hours after TAVR or before discharge (primary end point) was lower than expected (2.6% overall) and did not differ significantly between the CEP group and the control group.

In an earlier clinical trial comparing TAVR and surgical aortic-valve replacement, the associated risk of stroke was identified as a major limitation of TAVR.[30] Stroke continues to be an important complication of TAVR, with mortality of 16.7% at 30 days,[13] and remains a major concern among patients.[21,22] Although stroke is largely unpredictable, the risk is primarily procedural, with most stroke events resulting from embolic material being released at the time of the valve implantation procedure.[10-12] Single-center studies, the Transcatheter Valve Therapy Registry, and administrative databases have also evaluated the use of a CEP device during TAVR.[17,23,25,27,28,31] Some propensity-matched analyses have shown that the use of a CEP device during TAVR was

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline and Procedural Characteristics.*

Characteristic	CEP (N=1501)	Control (N=1499)
Demographic		
Age — yr	78.9±8.0	78.9±7.8
Female sex — no. (%)	631 (42.0)	566 (37.8)
Clinical		
STS surgical risk score — %†	3.3±2.7	3.4±2.8
Surgical risk according to heart team — no. (%)		
High or extreme risk	457 (30.4)	456 (30.4)
Intermediate risk	499 (33.2)	512 (34.2)
Low risk	545 (36.3)	531 (35.4)
NIHSS total score‡	0.4±1.0	0.3±0.9
Modified Rankin scale score§		
Mean score	0.6±1.0	0.5±0.9
Score of 0–1 — no./total no. (%)	1253/1501 (83.5)	1287/1497 (86.0)
Score of ≥2 — no./total no. (%)	248/1501 (16.5)	210/1497 (14.0)
EQ-5D index score¶	0.8±0.2	0.8±0.2
EQ visual-analogue scale score‖	67.6±19.7	68.3±18.0
Coexisting condition and medical history — no./total no. (%)		
Diabetes mellitus, medically treated	501/1501 (33.4)	522/1499 (34.8)
Hypertension	1306/1500 (87.1)	1312/1497 (87.6)
Peripheral vascular disease	165/1484 (11.1)	162/1481 (10.9)
Coronary artery disease	850/1493 (56.9)	880/1493 (58.9)
Previous coronary revascularization	495/1495 (33.1)	548/1497 (36.6)
History of atrial fibrillation	511/1498 (34.1)	469/1495 (31.4)
History of cerebrovascular events	114/1496 (7.6)	122/1491 (8.2)
History of transient ischemic attacks	77/1491 (5.2)	81/1487 (5.4)
Procedural		
Native bicuspid valve — no./total no. (%)	131/1500 (8.7)	121/1499 (8.1)
Bioprosthesis: nonnative valve — no./total no. (%)	56/1500 (3.7)	37/1499 (2.5)
Balloon-expandable valve implanted — no./total no. (%)	957/1489 (64.3)	948/1488 (63.7)
Balloon dilation before valve implant — no./total no. (%)	573/1489 (38.5)	624/1490 (41.9)
Balloon dilation after valve implant — no./total no. (%)	390/1489 (26.2)	383/1490 (25.7)

* Plus–minus values are means ±SD. Patients eligible for transcatheter aortic-valve replacement (TAVR) were randomly assigned to the cerebral embolic protection (CEP) group (TAVR with CEP) or the control group (TAVR only).

† The Society of Thoracic Surgeons (STS) surgical risk score is used to assess the 30-day postoperative risk of death after cardiovascular surgery; scores (based on >50 clinical variables) range from 0 to 100%, with higher values indicating higher risk. The score is used by multidisciplinary heart teams to screen patients included in studies of TAVR and stratify them according to risk of death. Scores were available for 1481 patients in the CEP group and for 1482 patients in the control group.

‡ The National Institutes of Health Stroke Scale (NIHSS) total score is used to assess the severity of stroke; scores range from 0 to 42, with higher scores indicating greater impairment. A score of less than 6 indicates a strong probability of a good recovery, whereas a score greater than 16 indicates a strong probability of death. On average, a 1-point increase in the NIHSS score reflects a decrease in the likelihood of a favorable outcome by 17%. Scores were available for 1499 patients in the CEP group and for 1494 patients in the control group.

§ The modified Rankin scale score is used to assess the degree of disability or dependence in the daily activities of patients who have had a stroke or other causes of neurologic disability. Scores range from 0 to 6, with 0 indicating no symptoms, 1 an ability to carry out usual activities despite some symptoms, 2 slight disability, 3 moderate disability,

Table 1. (Continued.)

4 moderately severe disability, 5 severe disability, and 6 death. Scores were available for 1501 patients in the CEP group and for 1497 patients in the control group.

¶ The EuroQol Group 5-Dimension (EQ-5D) index score is based on five questions on mobility, self-care, pain, usual activities, and psychological status and is used to assess quality-of-life health status. Scores range from 0 to 1, with a score of 1 indicating full health and 0 a health status "as bad as death." Scores were available for 1497 patients in the CEP group and for 1495 patients in the control group.

‖ The EQ visual-analogue scale is a self-reported assessment of overall health status; scores range from 0 to 100, with 0 indicating "the worst health you can imagine" and 100 "the best possible health you can imagine." Scores were available for 1498 patients in the CEP group and for 1496 patients in the control group.

associated with lower risks of disabling and nondisabling stroke and a higher incidence of stroke-free survival than when TAVR was performed without such protection.[27,28] An instrumental variable analysis of the data from the Transcatheter Valve Therapy Registry did not show that CEP during TAVR led to a lower risk of stroke than when the procedure was performed without it, but an analysis based on propensity-score matching showed that CEP during TAVR led to a slightly lower overall risk of site-reported stroke (adjusted odds ratio, 0.82; 95% CI, 0.69 to 0.97) and lower 30-day mortality (1.4% vs. 2.2%, P<0.001).[25] A retrospective study of a publicly available administrative claims database (the Nationwide Readmission Database) likewise showed that mortality after stroke was lower among patients who underwent TAVR with CEP than without it (6.6% vs. 11.8%, P=0.02).[31]

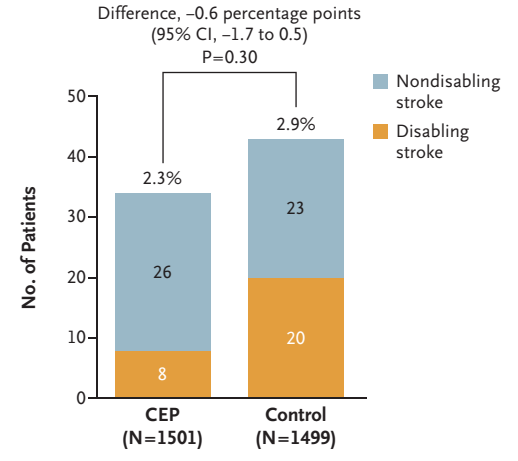

Figure 2. Stroke within 72 Hours after TAVR or before Discharge (Primary End Point) in the Intention-to-Treat Population.

Stroke within 72 hours after TAVR or before discharge (whichever came first) was adjudicated by an independent clinical events committee.

In regard to the lower-than-expected incidence of stroke in the current trial, the expected incidence was estimated on the basis of previous studies,[23,25,27-29] and the evolution of practice and treatment patterns over time may have contributed to differences between the expected and observed incidence of stroke. In addition, the mean Society of Thoracic Surgeons surgical risk score was lower in this trial than in previous studies. Furthermore, although sites were encouraged to enroll consecutive patients, the CEP device used here was commercially available and the possibility of enrollment bias in presumed higher-risk scenarios cannot be excluded. A residual stroke risk of 2.3% remained in the CEP group, which may have been affected by the inability of the CEP device studied here to filter all small debris, owing to either malapposition or embolic material smaller than the pore size and the fact that the CEP device used in the current trial does not cover the left vertebral artery, thereby limiting complete cerebral coverage. Moreover, hemorrhagic strokes cannot be prevented with the use of a CEP device.

Disabling stroke occurred in fewer patients in the CEP group than in the control group, and on the basis of adjudicated NeuroARC definitions, fewer patients in this CEP group had an ischemic stroke. This result is consistent with the mechanism of action of CEP, which would be expected to reduce the risk of embolic stroke but not hemorrhagic or other types of strokes. Six disabling ischemic strokes occurred in the CEP group — one in a patient in whom CEP could not be delivered; one in a patient with an embolized valve who was also resuscitated during the procedure; one in a patient who had clinical symptoms consistent with stroke but in whom lesion localization was uncertain; two in the occipital lobes, which are not fully protected by

Table 2. Clinical and Neurologic Outcomes within 72 Hours after TAVR or before Discharge.*

Outcome	CEP (N=1501)	Control (N=1499)	Difference (95% CI)†
Clinical			
Primary end point: stroke — no. (%)	34 (2.3)	43 (2.9)	–0.6 (–1.7 to 0.5)
Disabling	8 (0.5)	20 (1.3)	–0.8 (–1.5 to –0.1)
Ischemic	6 (0.4)	17 (1.1)	–0.7 (–1.4 to –0.1)
Hemorrhagic	2 (0.1)	3 (0.2)	–0.1 (–0.4 to 0.2)
Nondisabling	26 (1.7)	23 (1.5)	0.2 (–0.7 to 1.1)
Ischemic	26 (1.7)	23 (1.5)	0.2 (–0.7 to 1.1)
Hemorrhagic	0	0	0
Death — no. (%)			
Any cause	8 (0.5)	4 (0.3)	0.3 (–0.2 to 0.7)
Cardiovascular cause	8 (0.5)	4 (0.3)	0.3 (–0.2 to 0.7)
Noncardiovascular cause	0	0	0
Safety composite end point: death from any cause or stroke — no. (%)	41 (2.7)	45 (3.0)	–0.3 (–1.5 to 0.9)
Neurologic composite end point: stroke, transient ischemic attack, or delirium — no. (%)	46 (3.1)	55 (3.7)	–0.6 (–1.9 to 0.7)
Stroke — no. (%)	34 (2.3)	43 (2.9)	–0.6 (–1.7 to 0.5)
Transient ischemic attack — no. (%)	1 (0.1)	2 (0.1)	–0.1 (–0.3 to 0.2)
Delirium — no. (%)	12 (0.8)	11 (0.7)	0.1 (–0.6 to 0.7)
Major or minor vascular complication at the CEP access site — no. (%)	1 (0.1)	0	0.1 (–0.1 to 0.2)
Stage 2 or 3 acute kidney injury ≤72 hours after TAVR — no. (%)	8 (0.5)	7 (0.5)	0.1 (–0.4 to 0.6)
Neurologic			
NIHSS total score‡	0.4±1.8	0.4±1.2	0.1 (–0.1 to 0.2)
Modified Rankin scale score			
Mean score§	0.6±1.1	0.6±1.1	0.0 (–0.1 to 0.1)
Score of 0–1 — no./total no. (%)	1221/1468 (83.2)	1247/1473 (84.7)	–1.5 (–4.1 to 1.2)‡
Score of ≥2 — no./total no. (%)	247/1468 (16.8)	226/1473 (15.3)	1.5 (–1.2 to 4.1)‡

* Plus–minus values are means ±SD. Analyses were performed in the intention-to-treat population.
† Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other end points, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes. For the end points that are reported in percentages, the difference is reported in percentage points
‡ NIHSS scores were available for 1466 patients in the CEP group and for 1469 patients in the control group.
§ Modified Rankin scale scores were available for 1468 patients in the CEP group and for 1473 patients in the control group.

this CEP device; and one in the territory of the middle cerebral artery, which the studied CEP device is designed to protect. On the basis of the incidence of disabling stroke (0.5% in the CEP group and 1.3% in the control group), the number of patients needed to treat to prevent one additional disabling stroke would be 125. Although this trial was not powered to assess disabling stroke and a residual risk of stroke was observed with the use of the CEP device, given patient concerns over disabling stroke,[21,22] the observed difference in the incidence of this outcome between the CEP group and the control

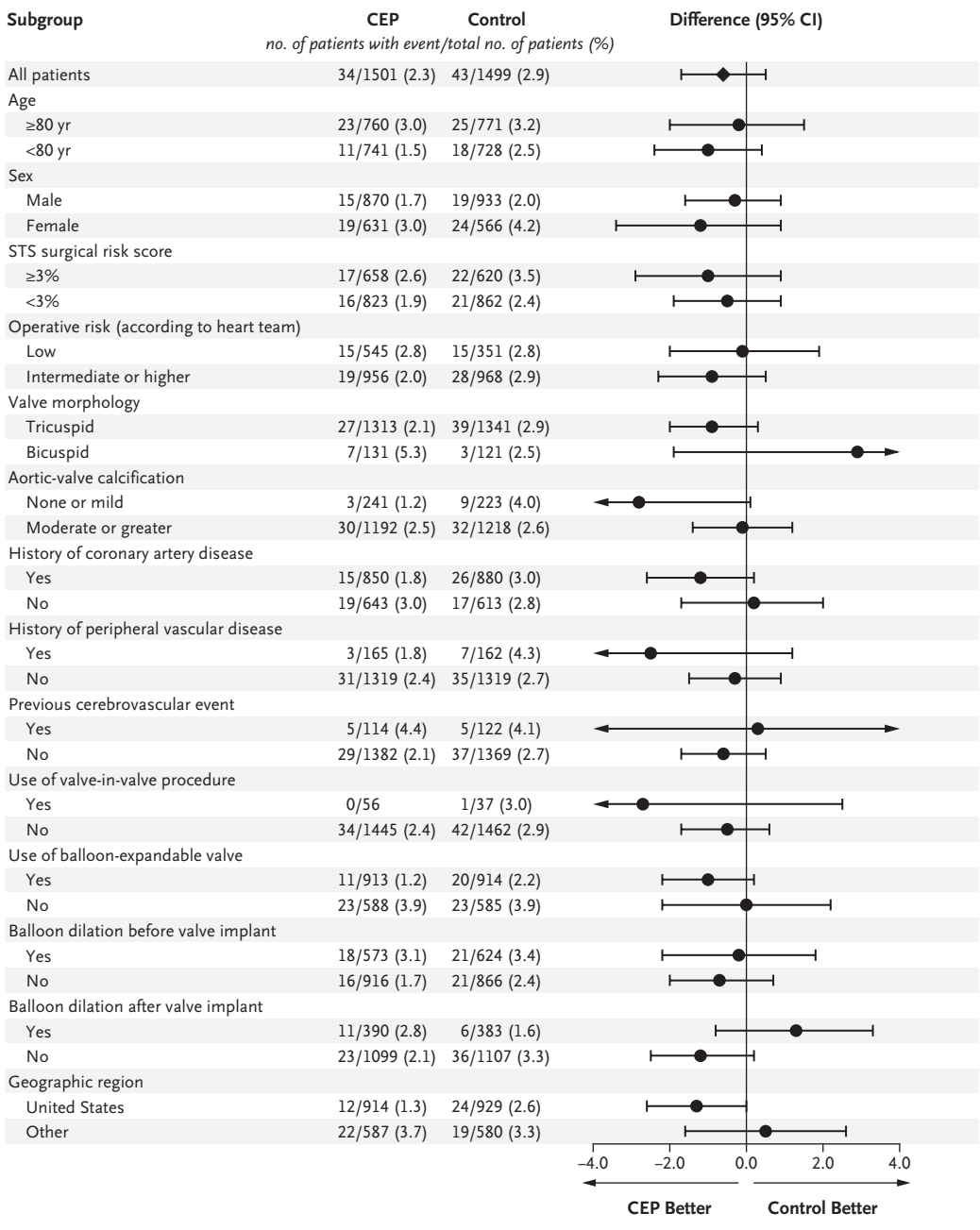

Figure 3. Difference in the Incidence of Stroke within 72 Hours after TAVR or before Discharge according to Major Subgroups of Interest.

Prespecified subgroup analyses were performed according to sex and operative risk (low, intermediate, or high or extreme); other patient subgroups of interest were identified before unmasking of the trial-group assignments. The Society of Thoracic Surgeons (STS) surgical risk score is used to assess the 30-day postoperative risk of death after cardiovascular surgery; scores (based on >50 clinical variables) range from 0 to 100%, with higher values indicating higher risk. The score is used by multidisciplinary heart teams to screen patients included in studies of TAVR and stratify them according to risk of death.

group may be considered to be important by patients and caregivers.

The design of the trial was intended to facilitate enrollment and data collection, while providing a meaningful assessment of the value of CEP during routine TAVR. The methods used in this trial led to several limitations. Granular data on clinical outcomes were restricted to a small number of end points, with only short-term follow-up. Neurologic professionals were not unaware of a patient's clinical course and hospital record, which may also have affected stroke reporting. In addition, despite the large number of patients and the use of randomization, the CEP group included a greater percentage of female patients than the control group; female sex has been reported to be a risk factor for stroke with TAVR[14,32] and was identified as such in the current trial as well. Finally, the trial results apply to the Sentinel CEP device and cannot be generalized to other CEP devices.

The subgroup analyses performed in the trial did not show a specific population that might benefit from selective CEP use or any procedural factors potentially associated with a benefit from CEP use (e.g., type of anesthesia, valve type, and balloon dilation before or after valve implant). Although the trial did not definitively identify a role for CEP in all patients undergoing TAVR, the CEP device was safe and may be a reasonable choice for some patients and physicians. The ultimate decision regarding the use of a CEP device during TAVR should be based on careful discussions between caregivers and patients about the risks and benefits and should incorporate personalized interpretation of the data from this and other trials of CEP, as well as other factors, including device cost. Additional data on the effectiveness of CEP during TAVR are forthcoming from ongoing trials, in particular, the BHF PROTECT-TAVI (British Heart Foundation Randomized Trial of Routine Cerebral Embolic Protection in Transcatheter Aortic Valve Implantation; ISRCTN Registry number, ISRCTN16665769), which features a randomized trial design with the Sentinel CEP device that is similar to that of the current trial and has a projected enrollment of nearly 8000 patients. A patient-level prospective meta-analysis of the combined trial data from the PROTECTED TAVR and BHF PROTECT-TAVI is planned (PROSPERO Registry number, CRD42022324160) and should help clarify unanswered questions.

In this randomized trial involving patients with aortic stenosis undergoing TAVR, the incidence of procedural complications was similar among those who underwent TAVR with or without CEP. The use of a CEP device during TAVR did not lead to a significantly lower incidence of periprocedural stroke, but on the basis of the 95% confidence interval around this outcome, the results may not rule out a benefit of CEP during TAVR.

Supported by Boston Scientific.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' affiliations are as follows: the Department of Cardiovascular Medicine (S.R.K.), Cleveland Clinic Foundation (A.K.), Cleveland; Smidt Heart Institute, Cedars–Sinai Medical Center, Los Angeles (R. Makkar); Columbia Interventional Cardiovascular Care (M.L.), Columbia University Medical Center (S.K.), New York; Leipzig Heart Center, University of Leipzig, Leipzig (M.A.-W.), Medizinische Klinik und Poliklinik I, Klinikum der Universität München and German Center for Cardiovascular Research (DZHK), Munich Heart Alliance, Munich (S.M.), Universitaetsklinikum Ulm, Ulm (W.R.), Medical Campus Lake Constance, Friedrichshafen (J.S.), and the Clinic for Internal Medicine and Cardiology, Technische Universität Dresden, Herzzentrum, Dresden (A.L.) — all in Germany; Pima Heart and Vascular, Tucson Medical Center Healthcare, Tucson, AZ (T.W.); Centennial Medical Center, Nashville (S.H.); Rigshospitalet, Copenhagen University Hospital, Copenhagen (L. Sondergaard); Heart Hospital of Austin, Austin (J.K.), Baylor Heart and Vascular Hospital, Dallas (R.C.S.), and Baylor Scott and White the Heart Hospital–Plano, Plano (K.H.) — all in Texas; Monash Medical Centre, Clayton, VIC, Australia (R.G.); Washington Hospital Center, Washington, DC (L. Satler); the Department of Neurology, University of Pennsylvania, Philadelphia (S.R.M.); Lahey Hospital and Medical Center, Burlington (S.J.B.), and Boston Scientific, Marlborough (R. Modolo, D.J.A., I.T.M.) — both in Massachusetts; Piedmont Heart Institute, Atlanta (V.H.T.); and the London School of Hygiene and Tropical Medicine, London (S.P.).

REFERENCES

1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.
2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.

3. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972-81.
4. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790-8.
5. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609-20.
6. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 2016;387:2218-25.
7. Reardon MJ, Kleiman NS, Adams DH, et al. Outcomes in the randomized CoreValve US Pivotal High Risk Trial in patients with a Society of Thoracic Surgeons risk score of 7% or less. JAMA Cardiol 2016;1:945-9.
8. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380:1695-705.
9. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med 2019;380:1706-15.
10. Fanning JP, Walters DL, Platts DG, Eeles E, Bellapart J, Fraser JF. Characterization of neurological injury in transcatheter aortic valve implantation: how clear is the picture? Circulation 2014;129:504-15.
11. Van Mieghem NM, Schipper MEI, Ladich E, et al. Histopathology of embolic debris captured during transcatheter aortic valve replacement. Circulation 2013;127:2194-201.
12. Vlastra W, Jimenez-Quevedo P, Tchétché D, et al. Predictors, incidence, and outcomes of patients undergoing transfemoral transcatheter aortic valve implantation complicated by stroke. Circ Cardiovasc Interv 2019;12(3):e007546.
13. Huded CP, Tuzcu EM, Krishnaswamy A, et al. Association between transcatheter aortic valve replacement and early postprocedural stroke. JAMA 2019;321:2306-15.
14. Habertheuer A, Gleason TG, Kilic A, et al. Impact of perioperative stroke on midterm outcomes after transcatheter aortic valve replacement. Ann Thorac Surg 2020;110:1294-301.
15. Kapadia SR, Huded CP, Kodali SK, et al. Stroke after surgical versus transfemoral transcatheter aortic valve replacement in the PARTNER trial. J Am Coll Cardiol 2018;72:2415-26.
16. Ghanem A, Müller A, Nähle CP, et al. Risk and fate of cerebral embolism after transfemoral aortic valve implantation: a prospective pilot study with diffusion-weighted magnetic resonance imaging. J Am Coll Cardiol 2010;55:1427-32.
17. Haussig S, Mangner N, Dwyer MG, et al. Effect of a cerebral protection device on brain lesions following transcatheter aortic valve implantation in patients with severe aortic stenosis: the CLEAN-TAVI randomized clinical trial. JAMA 2016;316:592-601.
18. Kapadia S, Agarwal S, Miller DC, et al. Insights into timing, risk factors, and outcomes of stroke and transient ischemic attack after transcatheter aortic valve replacement in the PARTNER trial (Placement of Aortic Transcatheter Valves). Circ Cardiovasc Interv 2016;9(9):e002981.
19. Thyregod HGH, Steinbrüchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. J Am Coll Cardiol 2015;65:2184-94.
20. Winter M-P, Bartko P, Hofer F, et al. Evolution of outcome and complications in TAVR: a meta-analysis of observational and randomized studies. Sci Rep 2020;10:15568.
21. Everett EA, Everett W, Brier MR, White P. Appraisal of health states worse than death in patients with acute stroke. Neurol Clin Pract 2021;11:43-8.
22. Post PN, Stiggelbout AM, Wakker PP. The utility of health states after stroke: a systematic review of the literature. Stroke 2001;32:1425-9.
23. Van Mieghem NM, van Gils L, Ahmad H, et al. Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial. EuroIntervention 2016;12:499-507.
24. Kapadia SR, Kodali S, Makkar R, et al. Protection against cerebral embolism during transcatheter aortic valve replacement. J Am Coll Cardiol 2017;69:367-77.
25. Butala NM, Makkar R, Secemsky EA, et al. Cerebral embolic protection and outcomes of transcatheter aortic valve replacement: results from the transcatheter valve therapy registry. Circulation 2021;143:2229-40.
26. Lansky AJ, Messé SR, Brickman AM, et al. Proposed standardized neurological endpoints for cardiovascular clinical trials: an Academic Research Consortium initiative. J Am Coll Cardiol 2017;69:679-91.
27. Seeger J, Gonska B, Otto M, Rottbauer W, Wöhrle J. Cerebral embolic protection during transcatheter aortic valve replacement significantly reduces death and stroke compared with unprotected procedures. JACC Cardiovasc Interv 2017;10:2297-303.
28. Seeger J, Kapadia SR, Kodali S, et al. Rate of peri-procedural stroke observed with cerebral embolic protection during transcatheter aortic valve replacement: a patient-level propensity-matched analysis. Eur Heart J 2019;40:1334-40.
29. Ndunda PM, Vindhyal MR, Muutu TM, Fanari Z. Clinical outcomes of Sentinel Cerebral Protection System use during transcatheter aortic valve replacement: a systematic review and meta-analysis. Cardiovasc Revasc Med 2020;21:717-22.
30. Schaff HV. Transcatheter aortic-valve implantation — at what price? N Engl J Med 2011;364:2256-8.
31. Isogai T, Bansal A, Vanguru HR, et al. Cerebral embolic protection and stroke-related mortality following transcatheter aortic valve replacement. JACC Cardiovasc Interv 2022;15:569-71.
32. Almarzooq ZI, Kazi DS, Wang Y, et al. Outcomes of stroke events during transcatheter aortic valve implantation. EuroIntervention 2022;18(4):e335-e344.