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Routine Cerebral Embolic Protection during Transcatheter Aortic-Valve Implantation

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ABSTRACT

BACKGROUND

Transcatheter aortic-valve implantation (TAVI) is associated with procedure-related stroke. Cerebral embolic protection (CEP) devices may reduce embolization to the cerebral circulation and hence the incidence of stroke.

METHODS

We conducted a randomized, controlled trial across 33 centers in the United Kingdom. We randomly assigned 7635 participants with aortic stenosis in a 1:1 ratio to undergo TAVI with a CEP device (CEP group) or TAVI without a CEP device (control group). The primary outcome was stroke within 72 hours after TAVI or before discharge from the hospital (if discharge occurred sooner).

RESULTS

A total of 3815 participants were assigned to the CEP group and 3820 to the control group. A primary-outcome event occurred in 81 of 3795 participants (2.1%) in the CEP group and in 82 of 3799 participants (2.2%) in the control group (difference, −0.02 percentage points; 95% confidence interval, −0.68 to 0.63; P=0.94). Disabling stroke occurred in 47 participants (1.2%) in the CEP group and in 53 (1.4%) in the control group. Death occurred in 29 participants (0.8%) in the CEP group and in 26 (0.7%) in the control group. Overall access-site complications appeared to be similar in the two groups (8.1% in the CEP group and 7.7% in the control group). A total of 24 serious adverse events occurred in 22 of 3798 participants (0.6%) in the CEP group, and 13 serious adverse events occurred in 13 of 3803 participants (0.3%) in the control group.

CONCLUSIONS

Among participants undergoing TAVI, routine use of CEP did not decrease the incidence of stroke within 72 hours. (Funded by the British Heart Foundation and Boston Scientific; BHF PROTECT-TAVI ISRCTN Registry number, ISRCTN16665769.)

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Transcatheter aortic-valve implantation (TAVI) is an effective and widely used treatment for patients with severe aortic stenosis. Procedure-related stroke remains an unpredictable complication that increases the risk of death and reduces the chance of returning to functional independence.[1,2] Stroke that is related to the TAVI procedure can be caused by embolism, hemorrhage, or cardiovascular collapse with cerebral hypoperfusion.

Cerebral embolic protection (CEP) devices are designed to prevent debris released during the TAVI procedure from reaching the brain, thereby reducing the risk of embolic stroke.[3] The Sentinel CEP device (Boston Scientific) is the only CEP device currently approved for clinical use in the United States and Europe. The PROTECTED TAVR trial investigated the use of CEP to prevent stroke related to transcatheter aortic-valve replacement (TAVR).[4] The trial included 51 sites from North America, Europe, and Australia. It concluded recruitment after enrolling 3000 patients according to prespecified stopping rules, but the incidence of stroke was lower than expected. The incidence of stroke within 72 hours did not differ significantly between the CEP group and the control group, but disabling stroke occurred in fewer patients assigned to the CEP group. Hence, the potential effect of CEP on stroke warranted further evaluation.[5,6] We conducted the British Heart Foundation Randomized Trial of Routine Cerebral Embolic Protection in Transcatheter Aortic Valve Implantation (BHF PROTECT-TAVI) to evaluate whether the routine use of CEP in TAVI procedures would reduce the incidence of clinical stroke.

Methods

Trial Design and Oversight

BHF PROTECT-TAVI is a prospective, open-label, multicenter, randomized, controlled trial with blinded adjudication of the outcomes. It was conducted in the United Kingdom to evaluate the routine use of a CEP device (Sentinel, Boston Scientific) to prevent stroke in patients with aortic-valve stenosis undergoing TAVI.[7]

The trial protocol (available with the full text of this article at NEJM.org) was designed by a group of 15 academic investigators (listed in the Supplementary Appendix, available at NEJM.org) and was approved by the U.K. Health Research Authority. The British Heart Foundation funded the trial, and Boston Scientific provided support for CEP devices through an investigator-sponsored research grant but was not involved in the design, conduct, or reporting of the trial. The regulatory sponsor of the trial was the University of Oxford; the London School of Hygiene and Tropical Medicine Clinical Trials Unit coordinated the trial, and its trial statisticians performed the statistical analyses.

A total of 32 U.K. National Health Service (NHS) centers and 1 private TAVI center participated in the trial, and 29.6% of all TAVI procedures undertaken across NHS participating sites were enrolled. Independent trial steering and data monitoring committees provided trial oversight. An independent clinical events committee whose members were unaware of the trial-group assignments adjudicated the primary outcome of stroke. Research staff at participating sites gathered the data (see the Supplementary Appendix for additional details). The authors had access to the trial data and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The first author wrote the manuscript, and all the authors contributed to subsequent revisions and approved the submission for publication.

Participants

We enrolled patients with aortic stenosis who were scheduled to undergo TAVI and in the opinion of the treating physician were clinically and anatomically suitable for treatment with the Sentinel CEP device. All the participants were 18 years of age or older and provided written informed consent to join the trial. Full eligibility criteria are described in the Supplementary Appendix.

Randomization

The participants were randomly assigned in a 1:1 ratio to undergo TAVI with CEP (CEP group) or without CEP (control group). Randomization was stratified according to trial site with the use of random permuted blocks.

Trial Procedures

The Sentinel CEP device is usually delivered percutaneously from the right radial artery and deploys filters in the left common carotid artery (distal filter) and right innominate artery (proximal filter). Clinical sites were eligible to enroll in the trial after standardized training in the use

of the device. A total of 13 sites were using Sentinel CEP devices in clinical practice before the trial started. Standard clinical training was performed at sites with no previous experience with the device, with 10 devices provided for training. There was no formal roll-in period. There was no mandated screening of the aortic arch anatomy, and patient eligibility for inclusion in the trial was left to the discretion of the treating physician. Full deployment of the CEP device was defined as correct placement of both filters for the duration of the TAVI procedure.

A participant's stroke-free survival after TAVI was determined with the use of the Questionnaire for Verifying Stroke-Free Status, which was administered daily for the first 72 hours or until hospital discharge.[8] It is a validated structured questionnaire in which a negative answer to all eight questions accurately predicts stroke-free persons; a positive response to any of the questions was used to prompt further assessment for a stroke outcome, as described in the Supplementary Appendix.

TRIAL OUTCOMES

The primary outcome was stroke within 72 hours after the TAVI procedure or before discharge from the hospital (if discharge occurred sooner). Stroke was defined as a new or worsened focal or global neurologic deficit of presumed vascular origin, either ischemic or hemorrhagic, that occurred after randomization and that persisted for more than 24 hours or led to death within 24 hours after symptom onset. Stroke was not defined by imaging alone. Participants who underwent mechanical thrombectomy for acute ischemic stroke within the 72-hour period after TAVI were classified as having had a stroke, regardless of the success of the mechanical thrombectomy procedure. Non–stroke-related deaths within the 72-hour period after TAVI were a secondary outcome.

Secondary outcomes that were evaluated within 72 hours after TAVI or at the time of hospital discharge (if discharge occurred sooner) included death from any cause; a composite of death from any cause or stroke; a composite of death from any cause, stroke, or transient ischemic attack (TIA); and access-site vascular complications according to Valve Academic Research Consortium (VARC-2) criteria.[9] Access-site complications were also evaluated at 6 to 8 weeks after the TAVI procedure.

For participants who had a stroke during the trial, stroke severity was assessed according to the National Institutes of Health Stroke Scale (NIHSS) score at the time of the initial assessment (scores ranged from 0 to 42, with higher scores indicating more severe stroke), and the level of disability after the stroke was assessed with the use of the modified Rankin scale at 6 to 8 weeks after the TAVI procedure (scores range from 0 to 6, with higher scores indicating greater disability). Severe stroke was defined by an NIHSS score of 10 or higher.[10] Disabling stroke was defined by a modified Rankin scale score of 2 or higher and an increase from the preprocedure baseline score of at least 1 point.[11-13] Participants with a neurologic deficit of less than 24 hours in duration were included in the secondary outcome analysis as having had a TIA.

STATISTICAL ANALYSIS

We estimated that a sample of 7730 participants would provide the trial with 80% power at a two-sided 5% significance level to show the superiority of CEP if the incidence of stroke was 3% in the control group and 2% in the CEP group, with allowance for a 1% loss to follow-up. An independent data monitoring committee was established and met regularly, with formal interim analyses planned at 50% and 70% enrollment to assess efficacy and futility. The Haybittle–Peto approach with a P value of less than 0.001 was used as a guideline to consider stopping early for benefit at each analysis.

The data monitoring committee reviewed the second interim analysis on February 5, 2024, when 5411 participants had been enrolled. The trial steering committee reviewed blinded data on the incidence of stroke at this time. Given an incidence of 2.0%, the sample-size calculation was revised to 9712 participants to have the power to show the superiority of CEP if the incidence of stroke was 2.4% in the control group and 1.6% in the CEP group. The trial protocol was amended accordingly.

The data monitoring committee met for an additional interim analysis when 134 stroke events had accrued. The data monitoring committee recommended to the trial steering committee that the trial discontinue enrollment because the lower limit of the 99% confidence interval excluded a 40% relative risk reduction for the primary outcome and the prespecified futility criterion had

therefore been met. Enrollment was discontinued on October 9, 2024.

The statistical analysis plan (available with the protocol) was finalized before the trial-group assignments were unblinded. The primary and secondary outcome measures were assessed in the modified intention-to-treat population. Risk ratios and risk differences were calculated for the primary and other binary outcomes together with 95% confidence intervals with the use of generalized linear models for binomial outcomes. The two-sided P value for the primary outcome was based on these models.

The modified intention-to-treat analysis included all randomly assigned participants whose TAVI procedure was started, according to the group to which they were assigned, irrespective of whether they received the intervention as allocated, but excluded participants who did not undergo TAVI, who withdrew consent, or who underwent randomization in error. The TAVI procedure was considered to have started once the first arterial puncture was performed.

Complier average causal effect (CACE) analysis was undertaken to address nonadherenece to allocated treatment.[14,15] The CACE was estimated with the use of two-stage least-squares instrumental variable regression, in which the first stage regressed treatment received on randomly assigned treatment and the second stage regressed the primary outcome on the predicted probabilities of receipt of CEP that were obtained from the first stage.

Prespecified subgroup analyses were performed for the primary outcome by fitting an interaction between the subgroup and randomized treatment with the use of a generalized linear model. A prespecified secondary analysis for the primary outcome adjusted the modified intention-to-treat population and CACE analyses for age and sex. Given that the primary outcome does not account for the competing risk of non–stroke-related death, a prespecified unmatched win ratio analysis was also conducted to estimate the effect of CEP on a hierarchical outcome of death from any cause, disabling stroke, or nondisabling stroke within 72 hours after TAVI or before hospital discharge (if discharge occurred sooner).

Data are presented as mean values with standard deviations or median values with interquartile ranges or counts and percentages, as appropriate. Results are reported as point estimates with 95% confidence intervals. The confidence intervals for secondary outcomes were not adjusted for multiplicity and therefore should not be used to infer treatment effects. Complete-case analyses were conducted for all outcomes except for disabling stroke, in which missing modified Rankin scale scores at 6 to 8 weeks were imputed with the use of the last-observation-carried-forward approach. Post hoc analyses involving multiple imputation and best-case and worst-case approaches were also used. All analyses were conducted with the use of Stata software, version 17.0 (StataCorp).

RESULTS

PARTICIPANTS AND ENROLLMENT

Between October 29, 2020, and October 9, 2024, a total of 7635 participants underwent randomization, with 3815 assigned to the CEP group and 3820 assigned to the control group (Fig. 1 and Table S1 in the Supplementary Appendix). A total of 17 participants were withdrawn from each group; thus, 3798 participants in the CEP group and 3803 in the control group were eligible for inclusion in the modified intention-to-treat population. The baseline demographic and clinical characteristics of the participants and procedural details are shown in Table 1 and Table S2 and appeared to be balanced between the groups. The mean (±SD) age of the participants was 81.2±6.5 years, and 38.7% were women. Overall, the trial cohort was representative of the U.K. population of patients undergoing TAVI (Table S3).

Both filters of the CEP device were fully and correctly deployed for the duration of the procedure in 3058 of 3768 participants (81.2%) assigned to the CEP group (Table S4). At least one filter (either proximal or distal) of the CEP device was fully and correctly deployed for the duration of the procedure in 87.5% of the participants assigned to the CEP group.

OUTCOMES

Stroke within 72 hours after TAVI or before hospital discharge (primary outcome) occurred in 81 of 3795 participants (2.1%) assigned to the CEP group and in 82 of 3799 participants (2.2%) assigned to the control group (difference, −0.02 percentage points; 95% confidence interval [CI], −0.68 to 0.63; P=0.94). Severe stroke occurred in

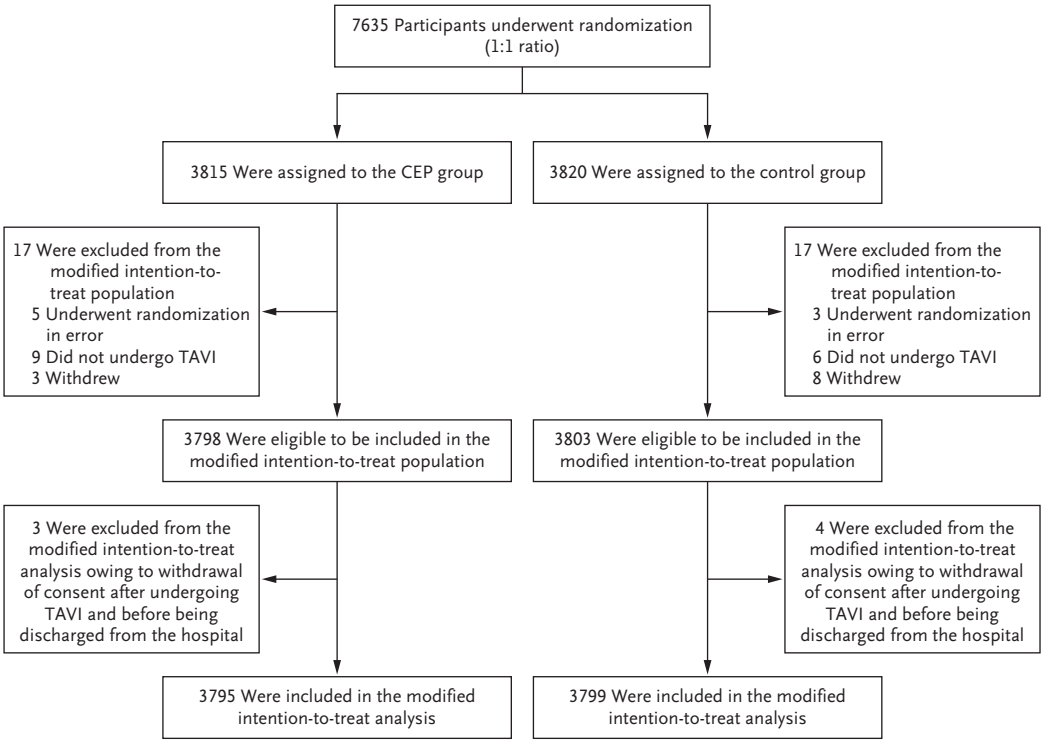

Figure 1. Randomization and Treatment.

CEP denotes cerebral embolic protection, and TAVI transcatheter aortic-valve implantation.

18 of 3795 participants (0.5%) in the CEP group and in 19 of 3799 participants (0.5%) in the control group (difference, 0.0 percentage points; 95% CI, −0.3 to 0.3). Most strokes occurred within 24 hours after the TAVI procedure (Fig. S1). Disabling stroke within 6 to 8 weeks after the TAVI procedure occurred in 47 of 3795 participants in the CEP group (1.2%) and in 53 of 3799 participants (1.4%) in the control group (difference, −0.2 percentage points; 95% CI, −0.7 to 0.4) (Table 2 and the Supplementary Appendix). Death from any cause within 72 hours after the TAVI procedure or before hospital discharge occurred in 29 of 3795 participants (0.8%) in the CEP group and in 26 of 3799 participants (0.7%) in the control group (difference, 0.1 percentage points; 95% CI, −0.3 to 0.5). Death within 8 weeks after the TAVI procedure occurred in 81 of 3793 participants (2.1%) in the CEP group and in 72 of 3798 participants (1.9%) in the control group. Additional clinical outcomes are shown in Table 2 and Tables S5 and S6.

After CACE analysis, the incidence of both stroke and disabling stroke was similar in the CEP and control groups (between-group difference, −0.2 percentage points [95% CI, −1.0 to 0.6] for stroke and −0.2 percentage points [95% CI, −0.9 to 0.4] for disabling stroke) (Table S7); these findings are consistent with those in the modified intention-to-treat analysis. The results of the prespecified age- and sex-adjusted analyses of the modified intention-to-treat population and CACE analyses are shown in Figure S2. The incidence of stroke within 72 hours after TAVI or before hospital discharge in prespecified subgroups is shown in Figure 2.

ADVERSE EVENTS

Clinical complications and adverse events appeared to be similar in the CEP and control groups (Tables S8 and S9). A total of 24 serious adverse events occurred in 22 of 3798 participants (0.6%) in the CEP group, and 13 serious adverse events occurred in 13 of 3803 participants (0.3%) in the control group.

Access-site complications before hospital dis-

Table 1. Demographic and Clinical Characteristics of the Participants.*

Characteristic	CEP Group (N=3798)	Control Group (N=3803)
Demographic		
Age — yr	81.2±6.5	81.3±6.5
Female sex — no. (%)	1484 (39.1)	1461 (38.4)
Race or ethnic group — no. (%)†		
White	3547 (93.4)	3543 (93.2)
Asian, Black, mixed, or other	60 (1.6)	61 (1.6)
Not known	191 (5.0)	199 (5.2)
Clinical		
Hypercholesterolemia treated with drugs — no./total no. (%)	2358/3722 (63.4)	2259/3737 (60.4)
Hypertension treated with drugs — no./total no. (%)	2558/3738 (68.4)	2528/3753 (67.4)
Medically treated diabetes — no./total no. (%)	793/3793 (20.9)	767/3798 (20.2)
Previous TIA — no./total no. (%)	319/3762 (8.5)	291/3754 (7.8)
Previous stroke — no./total no. (%)	217/3763 (5.8)	235/3754 (6.3)
Known dementia or cognitive impairment — no./total no. (%)	31/3762 (0.8)	38/3747 (1.0)
Other neurologic disease — no./total no. (%)	112/3764 (3.0)	122/3751 (3.3)
Coronary artery disease — no./total no. (%)	1234/3565 (34.6)	1168/3550 (32.9)
History of congestive heart failure — no./total no. (%)	531/3758 (14.1)	482/3765 (12.8)
Previous TAVI — no./total no. (%)	15/3798 (0.4)	17/3801 (0.4)
History of atrial fibrillation or flutter — no./total no. (%)	1256/3751 (33.5)	1269/3753 (33.8)
History of peripheral vascular disease — no./total no. (%)	262/3424 (7.7)	255/3397 (7.5)
Bovine, or other, head and neck vessel anatomy — no./total no. (%)	491/3684 (13.3)	463/3662 (12.6)
Bicuspid valve anatomy — no./total no. (%)	322/3713 (8.7)	305/3727 (8.2)
EuroSCORE II‡		
No. of participants evaluated	2896	2921
Median (IQR)	2.4 (1.6–4.1)	2.4 (1.6–4.0)
Mean aortic-valve gradient		
No. of participants evaluated	3589	3592
Median (IQR) — mm Hg	43 (35–53)	43 (35–52)
Left ventricular function — no./total no. (%)		
Good: LVEF ≥50%	2803/3679 (76.2)	2835/3688 (76.9)
Fair: LVEF 30–49%	671/3679 (18.2)	662/3688 (18.0)
Poor: LVEF <30%	205/3679 (5.6)	191/3688 (5.2)
Aortic-valve calcification — no./total no. (%)		
Not severe	1946/3734 (52.1)	1911/3720 (51.4)
Severe	1788/3734 (47.9)	1809/3720 (48.6)
LVOT calcification — no./total no. (%)		
Not severe	3565/3709 (96.1)	3574/3710 (96.3)
Severe	144/3709 (3.9)	136/3710 (3.7)

* Plus–minus values are means ±SD. CEP denotes cerebral embolic protection, IQR interquartile range, LVEF left ventricular ejection fraction, LVOT left ventricular outflow tract, TAVI transcatheter aortic-valve implantation, and TIA transient ischemic attack.

† Race or ethnic group was reported by the participant. The categories were Asian or Asian British (Indian, Pakistani, Bangladeshi, and any other Asian background), Black or Black British (African, Caribbean, and any other Black background), White (British, Irish, and any other White background), mixed (White and Asian, White and Black African, White and Black Caribbean, and any other mixed background), other ethnic group (Chinese and any other ethnic group), and missing (not stated or unknown).

‡ Values for the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) range from 0 to 100%, with higher values indicating a greater risk of death.

Table 2. Primary and Secondary Outcomes.*

Outcome	CEP Group (N=3798)	Control Group (N=3803)	Treatment Effect	
			Risk Difference (95% CI)†	Risk Ratio (95% CI)†
	no./total no. (%)		*percentage points*	
Primary outcome				
Stroke within 72 hr after TAVI or before discharge, if sooner	81/3795 (2.1)	82/3799 (2.2)	−0.02 (−0.68 to 0.63)‡	0.99 (0.73 to 1.34)‡
Ischemic stroke	80/3795 (2.1)	82/3799 (2.2)		
Hemorrhagic stroke	1/3795 (<0.1)	0/3799		
Secondary outcomes				
Disabling stroke within 6 to 8 wk after TAVI§¶	47/3795 (1.2)	53/3799 (1.4)	−0.2 (−0.7 to 0.4)	0.89 (0.60 to 1.31)
Ischemic stroke	47/3795 (1.2)	53/3799 (1.4)		
Hemorrhagic stroke	0/3795	0/3799		
Severe stroke within 72 hr after TAVI or before discharge, if sooner‖	18/3795 (0.5)	19/3799 (0.5)	0.0 (−0.3 to 0.3)	0.95 (0.50 to 1.80)
Ischemic stroke	18/3795 (0.5)	19/3799 (0.5)		
Hemorrhagic stroke	0/3795	0/3799		
Death within 72 hr after TAVI or before discharge, if sooner	29/3795 (0.8)	26/3799 (0.7)	0.1 (−0.3 to 0.5)	1.12 (0.66 to 1.89)
Death or stroke within 72 hr after TAVI or before discharge, if sooner	108/3795 (2.8)	104/3799 (2.7)	0.1 (−0.6 to 0.8)	1.04 (0.80 to 1.36)
Death	29/3795 (0.8)	26/3799 (0.7)		
Nonfatal stroke	79/3795 (2.1)	78/3799 (2.1)		
Death, stroke, or TIA within 72 hr after TAVI or before discharge, if sooner	126/3795 (3.3)	117/3799 (3.1)	0.2 (−0.6 to 1.0)	1.08 (0.84 to 1.38)
Death	29/3795 (0.8)	26/3799 (0.7)		
Nonfatal stroke	79/3795 (2.1)	78/3799 (2.1)		
TIA	18/3795 (0.5)	13/3799 (0.3)		

* A total of three participants in the CEP group and four participants in the control group withdrew consent before discharge from the hospital and are excluded. CI denotes confidence interval.
† The confidence intervals for the secondary outcomes are not adjusted for multiplicity and should not be used to infer treatment effect.
‡ P=0.94.
§ Disabling stroke was defined by a score on the modified Rankin scale of 2 or higher (on a scale from 0 to 6, with higher scores indicating greater disability) and an increase of at least 1 point from the preprocedure baseline modified Rankin scale score.
¶ The last observation was carried forward for four participants in the CEP group and one participant in the control group.
‖ Severe stroke was defined by a National Institutes of Health Stroke Scale score of 10 or higher (on a scale from 0 to 42, with higher scores indicating more severe stroke).

charge occurred in 304 of 3772 participants (8.1%) in the CEP group and in 290 of 3776 participants (7.7%) in the control group (difference, 0.4 percentage points; 95% CI, −0.8 to 1.6). Access-site complications at the site of arterial access for the aortogram were reported between discharge and 6 to 8 weeks after the TAVI procedure in 27 of 3347 participants (0.8%) in the CEP group and in 13 of 3378 participants (0.4%) in the control group (difference, 0.4 percentage points; 95% CI, 0.1 to 0.8); there were 25 minor access-site complications in the CEP group and 12 in the control group (Table S10).

DISCUSSION

In BHF PROTECT-TAVI, we tested the effect of routine CEP use on the incidence of stroke among

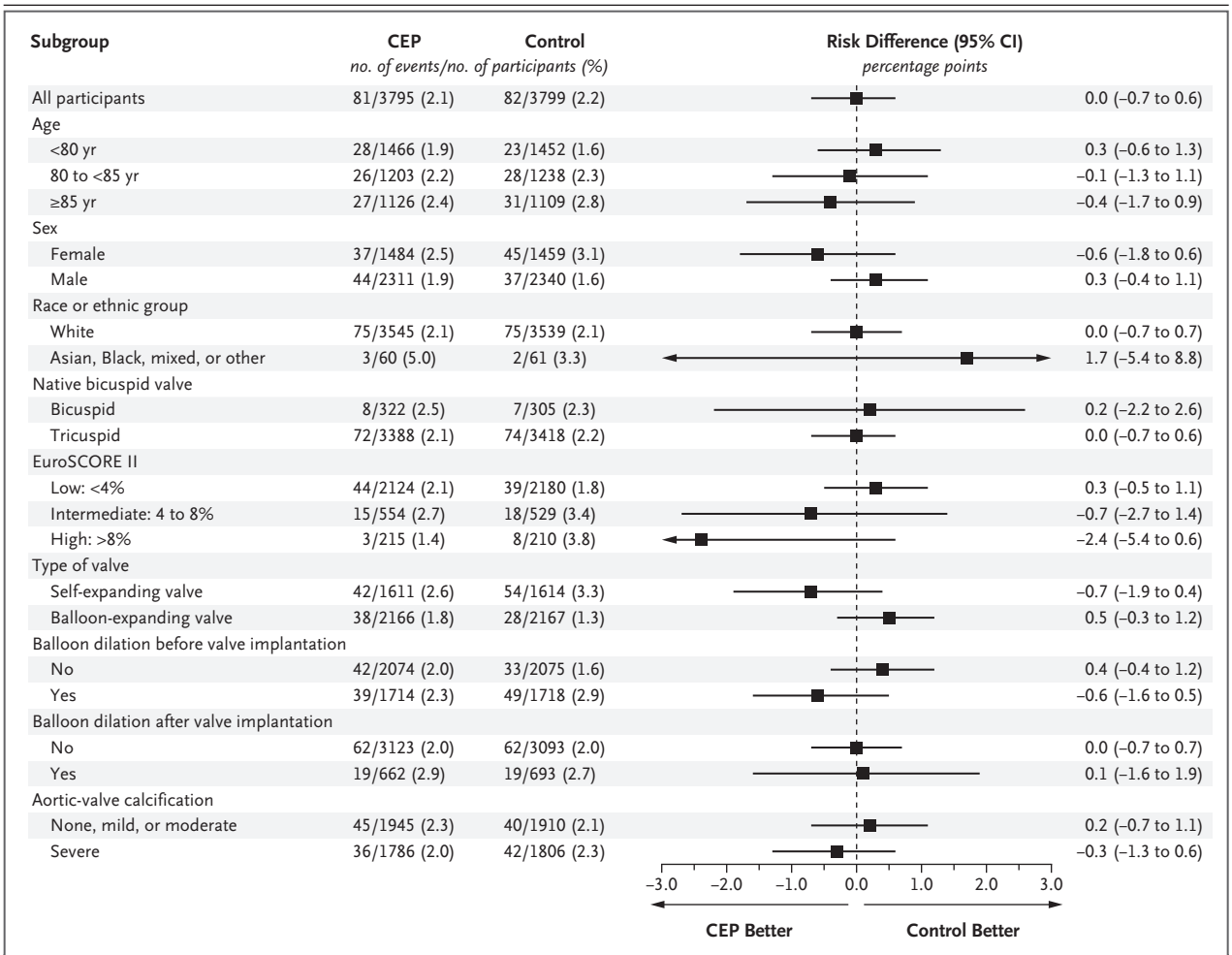

Figure 2. Incidence of Stroke within 72 Hours after TAVI or before Hospital Discharge (If Discharge Occurred Sooner) According to Subgroup.

The confidence intervals are not adjusted for multiplicity and should not be used to infer treatment effect. Race or ethnic group was reported by the participant. Values for the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) range from 0 to 100%, with higher values indicating a greater risk of death.

participants undergoing TAVI. The overall incidence of stroke within 72 hours or before hospital discharge (if discharge occurred sooner) was 2.1% among participants assigned to the CEP group and 2.2% among those assigned to the control group. There were no substantial between-group differences with respect to severe stroke, disabling stroke, or death.

The results of BHF PROTECT-TAVI are consistent with the reported results of the PROTECTED TAVR trial, which also showed no evidence of a treatment effect with CEP for the primary outcome of stroke. We saw no apparent decrease in the incidence of disabling stroke with CEP. Our reported incidence of stroke was lower than that in the PROTECTED TAVR trial, in which the overall incidence was 2.6%.[4] In our trial, the incidence of stroke in the control group was 2.2%, which is higher than the incidence of in-hospital stroke reported in the national U.K. TAVI registry (2021–2022, 1.9%; 2022–2023, 1.4%; and 2023–2024, 1.6%),[16,17] which suggests that stroke events were not underreported in our trial population. In addition, we used a clinical definition of stroke (symptom duration >24 hours), rather than one that incorporates imaging with a shorter dura-

tion of symptoms. This discrepancy between definitions may explain the difference in stroke incidence and the number of outcome events categorized as TIAs between the two trials: 3 in the PROTECTED TAVR trial and 31 in BHF PROTECT-TAVI.

Unlike in the PROTECTED TAVR trial, our definition of adherence to CEP device deployment required both device filters to be fully deployed for the duration of the procedure. The eligibility criteria for enrollment in our trial were less restrictive than those in the PROTECTED TAVR trial. Thus, a larger proportion of patients undergoing TAVI at our centers were enrolled in the trial, and enrolled participants may have included those with complex access or aortic arch anatomy who would have been ineligible for enrollment in the PROTECTED TAVR trial. These factors may explain some of the differences in the incidence of device deployment reported in the two trials.

At the start of our trial, one third of participating centers were experienced with Sentinel CEP implantation. We compared the success of device deployment according to our trial criteria for the first 100 cases at each site with subsequent cases and found that they appeared to be similar, as did the incidence of stroke (Table S11). We also analyzed the incidence of successful device deployment across quartiles of the recruitment period at each site and found that they were similar (Table S12), which suggests that the CEP technology was adopted successfully by the centers. There was no indication that any potential learning effect at centers influenced the results.

Instrumental variable regression is an established and increasingly used method to adjust for nonadherence to treatment allocation by estimating the CACE.[14,15] In BHF PROTECT-TAVI, the CACE analysis did not show any difference in outcome according to trial group.

Our trial has other limitations. Although consecutive enrollment of participants was encouraged, the trial was conducted during the coronavirus disease 2019 pandemic, which affected clinical research activity in the United Kingdom. Despite our efforts to recruit a diverse population, the majority of participants in our trial were White, and participants from minority racial or ethnic groups (Asian, Black, mixed, or other) were underrepresented in the trial.

In this trial involving participants undergoing TAVI, routine use of CEP did not decrease the incidence of stroke within 72 hours.

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