JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 69, NO. 4, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.10.023

ORIGINAL INVESTIGATIONS

Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement

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ABSTRACT

BACKGROUND Neurological complications after transcatheter aortic valve replacement (TAVR) may be reduced with transcatheter cerebral embolic protection (TCEP).

OBJECTIVES This study evaluated the safety and efficacy of TCEP during TAVR.

METHODS Nineteen centers randomized 363 patients undergoing TAVR to a safety arm (n = 123), device imaging (n = 121), and control imaging (n = 119). The primary safety endpoint consisted of major adverse cardiac and cerebrovascular events (MACCE) at 30 days, and the primary efficacy endpoint was reduction in new lesion volume in protected brain territories on magnetic resonance imaging scans at 2 to 7 days. Patients underwent neurocognitive assessments, and the debris captured was analyzed.

RESULTS The rate of MACCE (7.3%) was noninferior to the performance goal (18.3%, $p_{noninferior} < 0.001$) and not statistically different from that of the control group (9.9%; p = 0.41). New lesion volume was 178.0 mm^3 in control subjects and 102.8 mm^3 in the device arm (p = 0.33). A post hoc multivariable analysis identified pre-existing lesion volume and valve type as predictors of new lesion volume. Strokes at 30 days were 9.1% in control subjects and 5.6% in patients with devices (p = 0.25) Neurocognitive function was similar in control subjects and patients with devices, but there was a correlation between lesion volume and neurocognitive decline (p = 0.0022). Debris found within filters in 99% of patients included thrombus, calcification, valve tissue, artery wall, and foreign material.

CONCLUSIONS TCEP was safe, captured embolic debris in 99% of patients, and did not change neurocognitive function. Reduction in new lesion volume on magnetic resonance scans was not statistically significant. (Cerebral Protection in Transcatheter Aortic Valve Replacement [SENTINEL]; NCT02214277) (J Am Coll Cardiol 2017;69:367–77)

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ABBREVIATIONS AND ACRONYMS

FLAIR = fluid-attenuated inversion recovery

MACCE = major adverse cardiac and cerebral events

MRI = magnetic resonance imaging

TAVR = transcatheter aortic valve replacement

TCEP = transcatheter cerebral embolic protection

Transcatheter aortic valve replacement (TAVR) is an important therapy for high-risk and intermediate-risk patients with severe aortic stenosis (1-8). However, stroke remains a concerning complication and is associated with increased mortality and morbidity (1,2,4,9-13). Additionally, clinically "silent" brain infarctions seen on magnetic resonance imaging (MRI) are associated with neurocognitive function changes (14-17), and these infarctions occur in as many of 80% of patients after TAVR (18-21). Although the etiology of strokes and MRI perfusion abnormalities is multifactorial, most are the result of embolization of debris during the procedure (22,23). Previous exploratory studies attempted to minimize procedural embolization by using either transcatheter filters or deflection devices (24-30). This randomized trial was designed to assess the safety of transcatheter cerebral embolic protection (TCEP) during TAVR and the efficacy of TCEP in reducing the effects of cerebral embolization.

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METHODS

PATIENTS. The study included 363 patients with severe symptomatic aortic stenosis and planned TAVR who were at high surgical risk from 17 centers in the United States and 2 centers in Germany. All patients had multislice computed tomography scans that were analyzed by a core laboratory and reviewed by a committee to determine treatment eligibility for the Sentinel TCEP device (Claret Medical, Santa Rosa, California). Other exclusion criteria were known contraindications for right radial or brachial artery access and inability to undergo MRI brain evaluation for any reason.

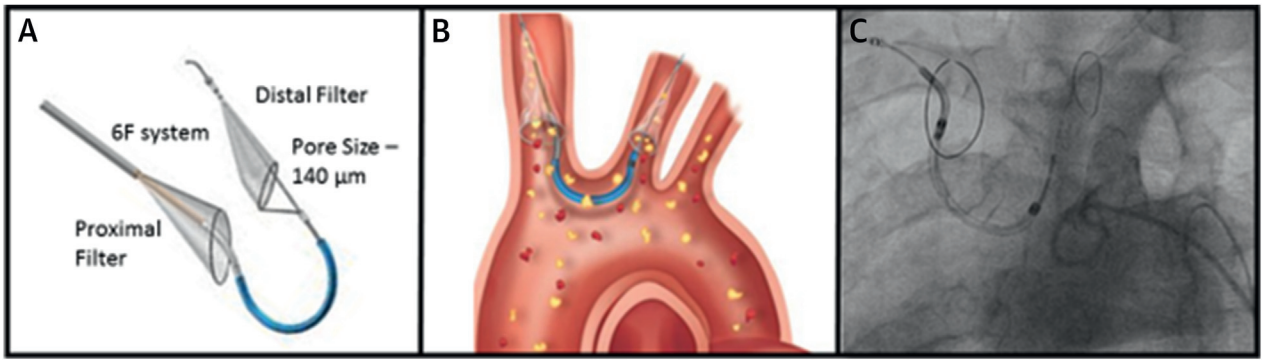
STUDY DEVICE AND PROCEDURE. The Sentinel TCEP device consists of 2 filters within a single 6-F delivery catheter percutaneously placed from the right radial (preferred) or brachial artery over a 0.014-inch guidewire (**Figure 1**). The filters are positioned in the brachiocephalic and the left common carotid arteries before TAVR and are withdrawn into the catheter and removed after TAVR as previously described (26,31).

STUDY DESIGN. Patients undergoing TAVR were prospectively randomized 1:1:1 into a safety arm (TCEP only) and 2 imaging cohorts, in which patients were randomly treated with TCEP (device arm) or without TCEP (control arm) (**Figure 2**). TCEP safety was assessed in the safety and device arms of the study (device safety cohort). The safety arm was included to assess safety without increasing cost of the trial by eliminating MRI cost. Patients were blinded to treatment assignment. Blinded diffusion-weighted MRI and neurocognitive function

The SENTINEL trial was funded by Claret Medical. Dr. Kodali is a consultant for Edwards Lifesciences. Dr. Makkar has received research support from Edwards Lifesciences and St. Jude Medical; is a consultant for Abbott Vascular, Cordis, and Medtronic; and holds equity in Entourage Medical. Dr. Mehran has received research grant support from Eli Lilly/DSI, Bristol-Myers Squibb, AstraZeneca, The Medicines Company, OrbusNeich, Bayer, and CSL Behring; is a consultant for Janssen Pharmaceuticals, Osprey Medical, Watermark Research Partners, and Medscape; is a member of the scientific advisory board of Abbott Laboratories; and holds equity or stock options in Claret Medical and Elixir Medical. Dr. Lazar is on the advisory board of Claret Medical; and holds stock options in Claret Medical. Dr. Zivadinov is a consultant for Teva Pharmaceuticals, Biogen Idec, EMD Serono, Genzyme-Sanofi, Claret Medical, IMS Health, and Novartis; has been on the speakers bureau of Genzyme-Sanofi and Novartis; has received research grants from Teva Pharmaceuticals, Genzyme-Sanofi, Novartis, Claret Medical, InteKrin-Coherus, Biogen, and IMS Health; serves on the editorial board of the *Journal of Alzheimer's Disease, BMC Medicine, BMC Neurology, Veins and Lymphatics,* and *Clinical CNS Drugs*; and is Executive Director and Treasurer of the International Society for Neurovascular Disease. Dr. Dwyer has received consulting fees from Claret Medical; has received research grant support from Novartis; and has served on an advisory board for Novartis. Dr. Jilaihawi is a consultant for Edwards Lifesciences, St. Jude Medical, and Venus MedTech. Dr. Virmani is a consultant for 480 Biomedical, Abbott Vascular, Medtronic, and W. L. Gore; has speaking engagements with Merck; receives honoraria from Abbott Vascular, Boston Scientific, Lutonix, Medtronic, and Terumo; and has received institutional research support from Abbott Vascular, BioSensors International, Biotronik, Boston Scientific, Medtronic, MicroPort Medical, OrbusNeich Medical, SINO Medical Technology, and Terumo. Dr. Anwaruddin is a speaker, consultant, and proctor for Edwards Lifesciences and Medtronic; is a consultant for the American College of Radiology; and has received institutional research support from Claret Medical. Dr. Thourani is a consultant for Edwards Lifesciences, Sorin Medical, St. Jude Medical, and Direct Flow Medical. Drs. Nazif, Nakamura, McCabe, and Zajarias are consultants for Edwards Lifesciences. Dr. Szeto is a consultant for MicroInterventional Devices, Edwards Lifesciences, and Medtronic. Dr. Svensson holds equity in Cardiosolutions and ValvXchange; and has intellectual property rights for Posthorax. Ms. Alu is a consultant for Claret Medical. Ms. White is a consultant for Claret Medical through Duke Clinical Research Institute. Ms. Kraemer is a consultant for Claret Medical. Dr. Parhizgar is an employee of Claret Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Kapadia and Kodali contributed equally to this work. Deepak L. Bhatt, MD, MPH, served as Guest Editor-in-Chief for this paper.

Manuscript received October 1, 2016; revised manuscript received October 21, 2016, accepted October 22, 2016.

FIGURE 1 The Dual-Filter Embolism Protection Device

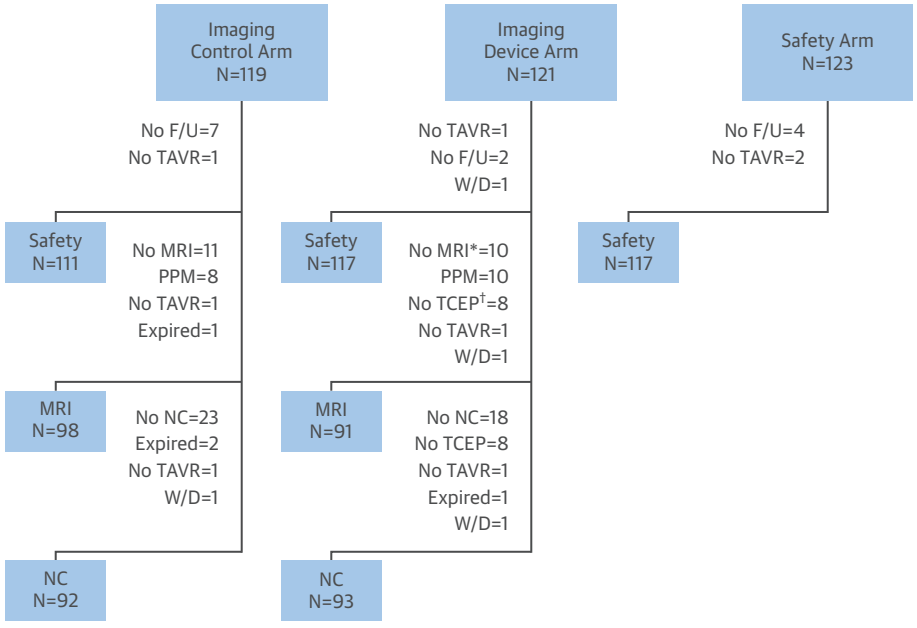


(A) The device. **(B)** The proximal filter is placed in the innominate artery and the distal filter placed in the left carotid artery. The pore size of the filters is 140 μm. **(C)** A fluoroscopic image of the device.

assessments were performed in the device and control arms. Particulate debris from the extracted filters was studied in the device arm. All patients underwent rigorous neurological evaluations post-TAVR at 30 and 90 days.

BRAIN MRI STUDIES. Brain MRI using a 3-T scanner was performed in both imaging arms (device and control) at baseline and post-TAVR at 2 to 7 days and at 30 days. All MRI studies were analyzed by a core laboratory in a blinded manner. Online Appendix 1

FIGURE 2 Study Flow



The study randomized patients in 3 arms including an imaging control arm, an imaging device arm, or a safety arm with 1:1:1 randomization. Patients in the safety arm were followed for clinical events without magnetic resonance imaging (MRI) or neurocognitive (NC) testing. The figure shows the patients and reasons for not having either type of testing. *No MRI patients included 4 due to patient unavailability, 4 patient refusals, 1 scan completed but not of sufficient quality to be read by the core laboratory, and 1 unknown. †No TCEP patients included 4 with unsuitable anatomy, 1 radial/brachial access failure, 1 Allen's test failure, 1 patient who could not fit in the MRI, and 1 device removed before TAVR due to difficulty moving over the wire. F/U = follow-up; PPM = permanent pacemaker; TAVR = transcatheter aortic valve replacement; TCEP = transcatheter embolic protection; W/D = study withdrawal.

describes the methodology for MRI acquisition and analysis. Post-TAVR studies were matched with baseline scans, and subtraction analyses were performed to identify new lesions. Protected territories were defined as brain territories entirely perfused by vessels protected by TCEP, and the term "all territories" refers to the entire brain.

NEUROCOGNITIVE FUNCTION. Device and control arm subjects underwent neurocognitive assessment evaluating 7 domains of neurocognitive function: bihemispheral and hemisphere-specific attention, executive function, processing speed, working memory, visual memory, mental status, and depression (Online Appendix 2). Trained and certified test administrators and neurocognitive core laboratory personnel were blinded to randomization.

HISTOPATHOLOGIC ASSESSMENT OF DEBRIS. All filters from the device arm were stored in formalin and analyzed in a histopathology core laboratory. Extracted debris was stained, examined with light microscopy, sized, and catalogued as thrombus, calcium, valve tissue, or catheter fragments.

STUDY ENDPOINTS. The primary safety endpoint was occurrence of major adverse cardiac and cerebrovascular events (MACCE) at 30 days compared with a historical performance goal. MACCE was defined as follows: all death; all strokes (disabling and nondisabling, VARC-2 [Valve Academic Research Consortium-2]); and acute kidney injury (stage 3, VARC-2) (32). Stroke occurrence was assessed by neurologist-administered National Institutes of Health stroke score and modified Rankin score at baseline (<14 days pre-procedure), discharge, and 30 days. For patients experiencing a stroke within 30 days, 90-day National Institutes of Health stroke score and modified Rankin score were also administered by a neurologist to determine stroke severity.

The primary efficacy endpoint was reduction in median total new lesion volume in protected territories between the device and control arms, as assessed by diffusion-weighted MRI at 2 to 7 days after TAVR. Minimum treatment effect of 30% reduction in median total new lesion volume in protected territories was a pre-specified success criterion. Total new lesion volume was defined as the sum of all diffusion-positive new cerebral lesion volumes in post-procedural scans relative to the pre-TAVR scans.

Other pre-specified secondary endpoints included device success, vascular complications, new lesion number in protected and all territories, and the correlation of lesion volume with neurocognitive function changes and histopathological evaluations.

STATISTICAL ANALYSIS. The Fisher exact test was used to compare categorical variables. Continuous variables, presented as mean ± SD or medians with interquartile ranges as appropriate, were compared with the use of analysis of variance, nonparametric analysis of variance, or the Wilcoxon rank sum test. The point estimate for the historical performance goal for the primary safety endpoint at 30 days post-TAVR was derived from a review of published reports of 30-day TAVR outcomes (1,2,4). The boundary was selected by first weighting the published MACCE rates by the expected proportion of transfemoral and transapical cases by using the following formula: weighted MACCE rate = [20.2% × 20% (TA) + 12.0% × 80% (TF)] × 2/3 + [12.62] × 1/3 = 13.3%. The performance goal of 18.3% was derived by adding a conservative noninferiority margin of 5% to the weighted published report rate of 13.3%. Sample size estimates for comparing the total new lesion volume from the protected territories between the 2 randomized imaging arms were made on the basis of a Wilcoxon-Mann-Whitney test, assuming data with a log-normal distribution and the following means: raw: test 474.2 ± 813.6 versus control 1,029.7 ± 2,424.12; log-normal: test 5.4 ± 1.2 versus control 6.0 ± 1.3. Accordingly, 72 subjects per arm were required, with an 80% power and an alpha of 0.05 (2-sided). With an estimated loss allowance of 35%, 120 subjects were planned for randomization to each imaging arm to achieve 75 evaluable subjects. The primary efficacy endpoint, consisting of new median lesion volume differences in the test and control arms, was compared using the Wilcoxon rank sum test.

A *z*-score for each neurocognitive function domain was calculated on the basis of normative mean ± SD for each neurocognitive test. Change scores were calculated by subtracting baseline scores from the 30- or 90-day post-TAVR scores. Comparison of the change in composite neurocognitive *z*-scores was performed to control for Mini-Mental State Examination, education, and depression scores.

Multivariable analysis was undertaken to determine covariates of new lesion volumes, by starting with all baseline univariate predictors with a p value of <0.10. Stepwise linear regression was performed to identify independent predictors. Adjustment models to account for the effect of multivariable predictors on new lesion volume are described in Online Appendix 3.

Statistical analyses were performed on the intention-to-treat population using SAS version 9.3 software (SAS Institute, Cary, North Carolina).

TABLE 1 Baseline Characteristics and Procedural Details

	Control Arm (n = 119)	Device Arm (n = 121)	Safety Arm (n = 123)	Total Randomized (n = 363)	p Value*
Age, yrs	85.0 (78.4–89.4)	83.1 (77.2–87.2)	82.5 (76.4–87.5)	83.4 (78.0–88.2)	0.1371
Male	51.3 (61/119)	47.9 (58/121)	44.7 (55/123)	47.9 (174/363)	0.6062
BMI, kg/m^2	27.0 (23.8–30.5)	27.0 (23.7–32.1)	26.2 (22.7–30.4)	26.7 (23.4–30.8)	0.3103
STS PROM Score	6.6 (4.5–8.6)	5.6 (3.9–8.0)	5.8 (3.9–8.0)	6.0 (4.2–8.1)	0.0860
History of atrial fibrillation	30.3 (36/119)	34.7 (42/121)	30.1 (37/123)	31.7 (115/363)	0.6932
History of PVD	15.1 (18/119)	14.0 (17/121)	16.3 (20/123)	15.2 (55/363)	0.9003
History of CAD	55.5 (66/119)	50.4 (61/121)	53.7 (66/123)	53.2 (193/363)	0.7341
Previous CABG	21.0 (25/119)	18.2 (22/121)	14.6 (18/123)	17.9 (65/363)	0.4289
Previous PCI	16.8 (20/119)	17.4 (21/121)	15.4 (19/123)	16.5 (60/363)	0.9367
History of diabetes	37.8 (45/119)	40.5 (49/121)	26.8 (33/123)	35.0 (127/363)	0.0577
Previous stroke†	5.0 (6/119)	4.1 (5/121)	8.1 (10/123)	5.8 (21/363)	0.4376
Previous TIA	6.7 (8/119)	7.4 (9/121)	8.1 (10/123)	7.4 (27/363)	0.9678
Heavily calcified aorta	2.5 (3/119)	1.7 (2/121)	3.3 (4/123)	2.5 (9/363)	0.7791
NYHA functional class III/IV	82.8 (96/116)	84.9 (101/119)	81.7 (98/120)	83.1 (295/355)	0.8077
Lesion volume as calculated on FLAIR, mm^3	7,916.7 (3,865.4–17,315.3)	7,377.5 (2,562.9–19,181.5)	N/A	7,847.9 (3,243.2–17,854.5)	0.4306‡
Echocardiographic findings					
Valve area, cm^2	0.7 ± 0.20 (118)	0.7 ± 0.17 (119)	0.7 ± 0.18 (122)	0.7 ± 0.18 (359)	0.6603
Mean aortic valve gradient, mm Hg	41.0 (33.0–47.0)	42.7 (33.6–52.0)	41.0 (31.9–49.0)	41.0 (33.0–49.0)	0.3334
Procedural details					
Sentinel device access					0.4918
Radial	NA	91.2 (104/112)	95.0 (114/119)	93.2 (218/231)	
Brachial	NA	7.0 (8/112)	4.2 (5/119)	5.6 (13/231)	
Both filters deployed	NA	92.0 (103/112)	96.6 (115/119)	94.4 (218/231)	0.1570
At least 1 filter deployed	NA	99.1 (111/112)	100.0 (119/119)	99.6 (230/231)	0.4848
Procedure time§	68.0 (41.0–96.0)	83.5 (54.0–118.0)	78.0 (52.0–101.0)	74.0 (52.0–106.0)	0.0050
Fluoroscopy time	15.0 (9.0–20.0)	18.0 (12.0–29.0)	14.0 (10.0–27.0)	15.0 (10.0–26.0)	0.0402
TAVR device used					0.7176
SAPIEN XT	16.9 (20/118)	17.5 (21/120)	19.0 (23/121)	17.8 (64/359)	
SAPIEN 3	53.4 (63/118)	55.8 (67/120)	47.9 (58/121)	52.4 (188/359)	
CoreValve	5.9 (7/118)	2.5 (3/120)	3.3 (4/121)	3.9 (14/359)	
CoreValve Evolut R	23.7 (28/118)	24.2 (29/120)	29.8 (36/121)	25.9 (93/359)	

Values are median (interquartile range), % (n/N), or mean ± SD (n). *p values are testing for statistical differences across randomized arms; continuous data are compared using ANOVA for mean, nonparametric ANOVA for median; categorical data are compared using the Fisher exact test. †Defined as neurological deficit lasting >24 h confirmed by imaging. ‡The basis is the 2-sided Wilcoxon test. §Defined as time from first vascular access puncture to achievement of hemostasis at the TAVR access site.

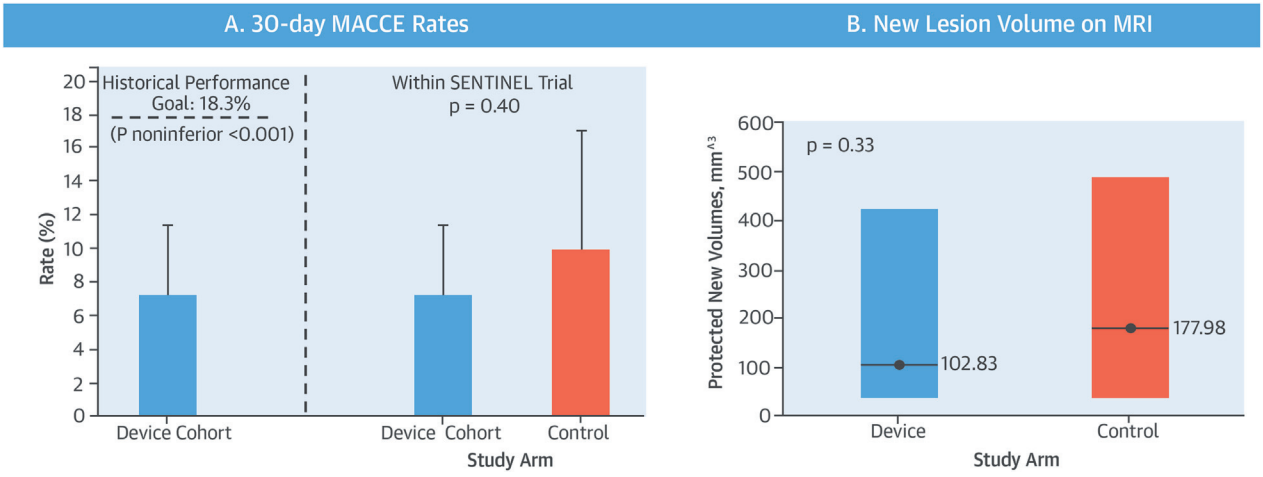
ANOVA = analysis of variance; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; FLAIR = fluid-attenuated inversion recovery; NA = not applicable; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; STS PROM = Society of Thoracic Surgeons predicted risk of operative mortality; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

RESULTS

STUDY CHARACTERISTICS. A total of 240 patients were randomized to the imaging cohort (119 control, 121 device), and 123 patients were randomized to the safety arm (Figure 2). Within the imaging cohort, MRI studies at baseline and 2 to 7 days post-TAVR were performed in 189 (78.8%) patients, and neurocognitive assessments were completed at baseline and 30 days in 185 (77.1%) patients. Baseline characteristics of the safety cohort and of participants with and without paired MRI studies (primary efficacy cohorts) are presented in Online Tables 1 and 2. There were no significant differences between groups in the primary safety cohort. The only baseline characteristics that differed between those with and without paired MRI were history of previous coronary artery bypass graft and mean gradient.

The study population was older (median age 83.4 years), the majority (52.1%) consisted of female patients, the median Society of Thoracic Surgeons score was 6.0%, and frequent comorbidities included atrial fibrillation (31.7%) and previous strokes (5.8%). Baseline characteristics were well balanced for the entire population (Table 1) and for the paired MRI and paired neurocognitive function cohorts (Online Tables 3 and 4). Because of timing of U.S. Food and Drug Administration approval and operator choice, 4 different TAVR devices were used in this trial: SAPIEN XT (17.8%) and SAPIEN 3 (52.4%) (Edwards Lifesciences, Irvine, California) and CoreValve (3.9%) and Evolut R (25.9%)

CENTRAL ILLUSTRATION **Primary Safety and Efficacy Endpoints**



Kapadia, S.R. et al. J Am Coll Cardiol. 2017;69(4):367-77.

(A) The rate of major adverse cardiac and cerebrovascular events (MACCE) in the device and safety arms was 7.3%, and the upper bound of the 95% confidence interval (11.4%) was less than the 18.3% performance goal ($p < 0.001$ for noninferiority). The rate of these adverse events in the control arm (9.9%) was not statistically different compared with the device and safety arms ($p = 0.405$). **(B)** The median total new lesion volume in protected territories in control and device arms. The median total new lesion volume in protected territories was 42% lower, thus meeting the 30% pre-specified treatment effect success criteria, but it was not significantly different in device versus control arms (102.8 mm^3 vs. 178.0 mm^3; $p = 0.33$). This is a box plot with a **central line** representing the median and a **box** representing the interquartile range (25th to 75th percentile).

(Medtronic, Minneapolis, Minnesota). TAVR systems were used with similar distribution across all 3 randomized treatment groups.

PROCEDURAL DETAILS AND CLINICAL OUTCOMES. TAVR was performed through the femoral artery in 94.7% of cases, and TCEP was delivered from the radial and brachial arteries in 93.2% and 5.6% of cases, respectively. Delivery and retrieval of both filters were successful in 94.4% of patients. In the device arm versus the control arm, there was an increase in total procedure time ($p = 0.01$) and fluoroscopy time ($p = 0.007$) (Table 1).

The rate of MACCE in the device and safety arms was 7.3%. The upper bound of the 95% confidence interval (CI) (11.4%) was less than the 18.3% performance goal ($p < 0.001$ for noninferiority) (Central Illustration, Table 2). The MACCE rate in the control arm (9.9%) was not statistically different from that of the device and safety arms ($p = 0.405$). Stroke rates were not significantly different in the device and safety arms versus the control arm (5.6% vs. 9.1%; $p = 0.25$). There were no differences in other important endpoints including acute kidney injury or vascular complications (Table 2).

MRI EFFICACY PRIMARY OUTCOMES. The median total new lesion volume in protected territories was 42% lower, thereby meeting the 30% pre-specified success criteria, but it was not significantly different in device versus control arms (102.8 mm^3 vs. 178.0 mm^3; $p = 0.33$) (Figure 2). Total new lesion volume in all territories was also not statistically different in device versus control arms (294 mm^3 vs. 309.8 mm^3; $p = 0.81$). New lesion number in device versus control arms in both protected and all territories was unchanged (Table 3). When analyzed by valve type, new

TABLE 2 Clinical Outcomes

30-Day Clinical Outcomes	Control Arm	Safety + Device Arm	p Value
Any MACCE*	9.9 (11/111)	7.3 (17/234)	0.40
Death (all cause)	1.8 (2/111)	1.3 (3/234)	0.65
Stroke	9.1 (10/110)	5.6 (13/231)	0.25
Disabling	0.9 (1/109)	0.9 (2/231)	1.00
Nondisabling	8.2 (9/110)	4.8 (11/231)	0.22
AKI (stage 3)	0.0	0.4 (1/231)	1.00
TIA	0.0	0.4 (1/231)	1.00
Major vascular complication	5.9 (7/119)	8.6 (21/244)	0.53
Radial/brachial	NA	0.4 (1/244)	
Femoral	5.9 (119)	8.2 (20/244)	

Values are % (n/N). *MACCE defined as death (any cause), stroke (any), AKI (stage 3).

AKI = acute kidney injury; MACCE = major adverse cardiac and cerebrovascular events; other abbreviations as in Table 1.

TABLE 3 Median Total New Lesion Volume and Number of New Lesions (Unadjusted Analysis, Day 2 to 7)

	Control Arm (n = 98)	Device Arm (n = 91)	Hodges-Lehmann Estimate of Location Shift (95% CI)	p Value
Median total new lesion volume in protected territories, mm^3	178.0 (34.3–482.5)	102.8 (36.9–423.2)	−21.1 (−94.9 to 21.8)	0.3345*
Median total new lesion volume in all territories, mm^3	309.8 (105.5–859.6)	294.0 (69.2–786.4)	−8.6 (−110.7 to 68.6)	0.8076*
Median number of new lesions in protected territories	3 (1–6)	2 (1–6)	0 (−1 to 0)	0.8979†
Median number of new lesions in all territories	5 (2–10)	3 (2–10)	−1 (−2 to 1)	0.7667†

Values are median (interquartile range). *On the basis of the Wilcoxon test. †On the basis of the negative binomial regression model.
CI = confidence interval.

lesion volume and number in both protected and all territories had significant differences (Online Table 5). The median total new lesion volume at 30 days was 0 for both protected and all territories in the device and control arms (Online Table 6).

POST HOC MULTIVARIABLE ANALYSIS. Univariate and multivariable analyses indicated that baseline T_2/fluid-attenuated inversion recovery (FLAIR) lesion volume on MRI (a marker of previous injury and gliosis) was the strongest predictor of new lesion volume after TAVR (Online Table 7). After adjusting for valve type, baseline T_2/FLAIR lesion volume, and an interaction between valve type and treatment arm, there were significant reductions in new lesion volume in both protected and all territories in the device versus control arms ($p = 0.025$ and $p = 0.050$ for protected and all territories, respectively) (Online Table 8). After similar adjustments for baseline T_2/FLAIR lesion volume, there were variable responses with specific valve types (Online Table 9).

NEUROCOGNITIVE FUNCTION AND HISTOPATHOLOGICAL FINDINGS. Neurocognitive testing showed no difference in overall composite scores at baseline, 30 days, or 90 days between device and control arms (**Table 4**). The change in neurocognitive scores from baseline to 30-day follow-up correlated with median new lesion volume in protected territories ($r = -0.20275$; $R^2 = 4.1$; $p = 0.0109$) and all territories ($r = -0.23562$; $R^2 = 5.6$; $p = 0.003$) (Online Figure 1).

Debris was found in filters in 99% of patients (**Figure 3**). Debris components included acute thrombus with tissue elements, artery wall, calcification, valve tissue, and foreign materials. More than 80% of debris was 150 to 500 μm in maximum diameter; <5% was >1,000 μm (**Figure 3**).

DISCUSSION

We found the following: 1) transcatheter placement of a dual-filter device was successful and safe in most patients; 2) the endpoint of reduction in median new lesion volume on MRI at 2 to 7 days in protected territories was not met; however, after adjusting for valve type and baseline T_2/FLAIR lesion volume in a post hoc analysis, there were significant differences in new lesion volumes favoring embolic protection; 3) neurocognitive function was not significantly improved, but there was correlation between new lesion volume and number and neurocognition at 30 days; and 4) particulate debris was found in almost all patients, including diverse biological and foreign materials.

As in previous, smaller studies (26,31), the dual-filter device was easily delivered and was compatible with standard TAVR workflow. Total procedure time was increased by approximately 13 min, and fluoroscopy time was increased by 3 min. Clinical safety outcomes were lower than the prespecified performance goal, and MACCE point estimates were lower in the device arms compared with the control arm. The largest difference was in minor strokes, but it has been shown that all strokes and even transient ischemic attacks confer an increased mortality risk among patients undergoing TAVR (9).

Historically, demonstration of clinical efficacy with embolic protection to reduce deleterious target organ effects has been problematic. The proposed or accepted use of embolic protection devices for the brain, heart, kidneys, and legs was established on the basis of observational studies indicating device safety combined with surrogate clinical efficacy endpoints (18,19,33–36). Early TAVR trials showing increased periprocedural stroke frequency (1–3) and MRI examinations revealing concordant ischemic deficits (18,19,21) heightened the need for brain-sparing therapies and encouraged the use of quantitative MRI analyses as surrogate endpoints. In our study, TCEP was associated with a 38% reduction in all strokes at 30 days that was nevertheless nonsignificant. There was a 42% reduction in MRI median new

TABLE 4 Neurocognitive Assessments

	Control Arm		Device Arm		
		Change From Baseline		Change From Baseline	p Value*
Attention					
Baseline	−0.17 ± 0.88 (117)	NA	−0.14 ± 0.96 (117)	NA	NA
2–7 days post-TAVR	−0.28 ± 1.10 (65)	−0.01 ± 0.59 (65)	−0.50 ± 1.02 (65)	−0.32 ± 0.70 (65)	0.0334
30-day follow-up	0.03 ± 0.88 (92)	0.14 ± 0.51 (92)	−0.14 ± 0.93 (93)	0.03 ± 0.55 (93)	0.1778
90-day follow-up	0.11 ± 0.87 (76)	0.23 ± 0.55 (76)	0.06 ± 0.87 (77)	0.20 ± 0.49 (77)	0.6103
Executive function					
Baseline	−1.36 ± 1.36 (117)	NA	−1.28 ± 1.3 (117)	NA	NA
2–7 days post-TAVR	−1.36 ± 1.36 (63)	0 ± 1 (63)	−1.70 ± 1.55 (65)	−0.36 ± 1.19 (65)	0.0865
30-day follow-up	−0.99 ± 1.34 (91)	0.25 ± 0.86 (91)	−1.20 ± 1.40 (93)	0.14 ± 0.86 (93)	0.4692
90-day follow-up	−0.79 ± 1.21 (76)	0.39 ± 0.86 (76)	−0.94 ± 1.16 (77)	0.32 ± 0.79 (77)	0.4585
Processing speed					
Baseline	−0.23 ± 0.95 (117)	NA	−0.24 ± 0.91 (117)	NA	NA
2–7 days post-TAVR	−0.47 ± 0.87 (63)	−0.05 ± 0.38 (63)	−0.51 ± 0.94 (65)	−0.06 ± 0.5 (65)	0.9698
30-day follow-up	−0.01 ± 0.86 (90)	0.12 ± 0.39 (90)	−0.11 ± 1.00 (92)	0.14 ± 0.43 (92)	0.5470
90-day follow-up	0.14 ± 0.81 (76)	0.27 ± 0.43 (76)	−0.05 ± 0.86 (77)	0.21 ± 0.46 (77)	0.7272
Verbal memory					
Baseline	−0.64 ± 1.07 (117)	NA	−0.85 ± 0.94 (117)	NA	NA
2–7 days post-TAVR	−1.06 ± 1.06 (66)	−0.63 ± 0.79 (66)	−1.34 ± 1.3 (66)	−0.70 ± 1.03 (66)	0.8534
30-day follow-up	−0.88 ± 1.18 (91)	−0.32 ± 0.80 (91)	−1.09 ± 1.13 (93)	−0.28 ± 0.85 (93)	0.4644
90-day follow-up	−0.61 ± 1.11 (76)	−0.13 ± 0.78 (76)	−0.86 ± 1.05 (77)	−0.02 ± 0.78 (77)	0.2933
Visual memory					
Baseline	−0.72 ± 0.96 (117)	NA	−0.83 ± 0.85 (115)	NA	NA
2–7 days post-TAVR	−0.70 ± 1.01 (65)	0.06 ± 0.86 (65)	−0.87 ± 0.94 (66)	−0.19 ± 0.96 (65)	0.1340
30-day follow-up	−1.02 ± 1.03 (92)	−0.36 ± 0.79 (92)	−1.28 ± 0.94 (93)	−0.46 ± 0.91 (92)	0.4282
90-day follow-up	−0.53 ± 0.98 (76)	0.12 ± 0.81 (76)	−0.58 ± 0.98 (77)	0.17 ± 0.86 (77)	0.6942
Mental status†					
Baseline	26.07 ± 3.32 (116)	NA	26.12 ± 2.95 (114)	NA	NA
2–7 days post-TAVR	26.02 ± 2.81 (62)	−0.25 ± 2.47 (61)	25.41 ± 3.58 (64)	−0.73 ± 2.95 (63)	NA
30-day follow-up	26.82 ± 2.74 (89)	0.52 ± 2.55 (89)	26.24 ± 2.84 (92)	0.41 ± 2.67 (91)	NA
90-day follow-up	27.24 ± 2.47 (76)	0.96 ± 2.42 (76)	26.56 ± 2.60 (77)	0.30 ± 2.76 (76)	NA
Depression					
Baseline	2.70 ± 2.28 (116)	NA	3.33 ± 2.62 (114)	NA	NA
2–7 days post-TAVR	2.26 ± 2.53 (62)	−0.48 ± 1.41 (61)	2.77 ± 2.83 (64)	−0.57 ± 2.12 (63)	NA
30-day follow-up	2.07 ± 2.14 (89)	−0.73 ± 1.57 (89)	2.38 ± 2.43 (91)	−0.68 ± 2.02 (90)	NA
90-day follow-up	2.37 ± 2.75 (76)	−0.49 ± 2.16 (76)	2.53 ± 2.66 (77)	−0.75 ± 2.22 (76)	NA
Overall composite score					
Baseline	−0.63 ± 0.79 (117)	NA	−0.66 ± 0.75 (117)	NA	NA
2–7 days post-TAVR	−0.81 ± 0.93 (66)	−0.16 ± 0.58 (66)	−1.00 ± 0.95 (66)	−0.33 ± 0.65 (66)	0.1894
30-day follow-up	0.59 ± 0.79 (92)	−0.03 ± 0.37 (92)	−0.77 ± 0.82 (93)	−0.09 ± 0.44 (93)	0.4207
90-day follow-up	−0.34 ± 0.72 (76)	0.18 ± 0.35 (76)	−0.47 ± 0.76 (77)	0.18 ± 0.38 (77)	0.9409

Values are mean ± SD (n). *p values calculated on the basis of a model adjusted for education, baseline Geriatric Depression Score, and baseline Mini-Mental State Examination score. †Raw score provided for mental state and depression.

Abbreviations as in Table 1.

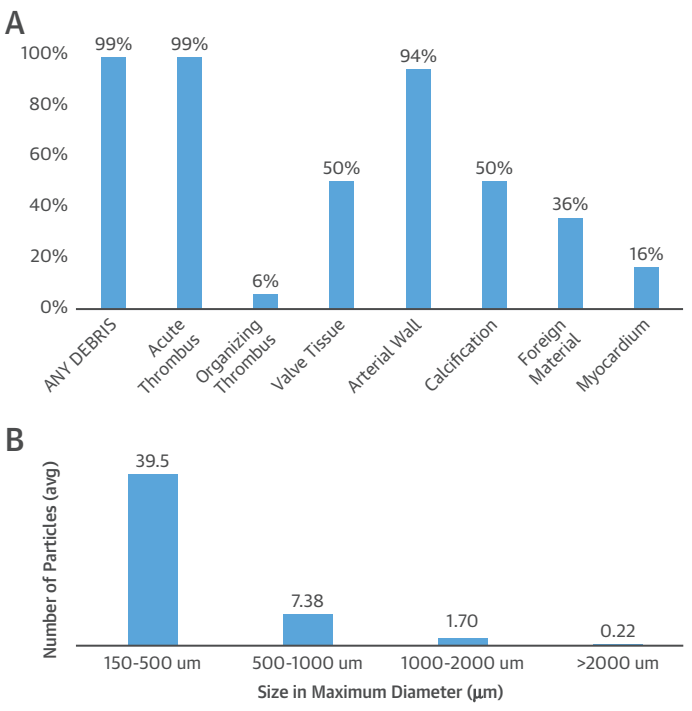
lesion volume at 2 to 7 days in the device arm compared with control subjects, a reduction that was also nonsignificant.

Several study limitations likely contributed to the lack of statistical significance despite the 42% reduction in new lesion volume in protected territories. First, despite the use of 3-T MRI scanners to improve the accuracy of characterizing new lesions, and subtraction imaging methodology to provide unbiased quantitative analyses, there was considerable variance in MRI post-procedure results. This finding was partly caused by rapidly changing new lesion volumes and numbers during the broad 2- to 7-day follow-up. In addition, 3-T MRI is more prone to scanner signal (B0 and B1) inhomogeneity across the brain, although this effect is offset by increased sensitivity and by software correction using the N3 algorithm. Second, there are few benchmark MRI data on which to base control arm assumption, and the observed new lesion volume and number were less

than predicted from the recent CLEAN-TAVI (CLaret embolic protection ANd TAVI) trial (25). This may be the result of using the CoreValve exclusively in CLEAN-TAVI, whereas the use of self-expanding valves was ~20% in the SENTINEL (Cerebral Protection in Transcatheter Aortic Valve Replacement) trial. Third, the impact of baseline T_2/FLAIR lesion volume on new lesion volume was not accounted for in the trial design. Previous studies demonstrated that baseline disease burden is a predictor of clinical events after interventions (37–39). Fourth, at the time of study design, only 1 TAVR device was available in the United States. Different TAVR devices subsequently became available and were included in this trial, but randomization had not been stratified according to valve category. Both the control arm MRI results and the response to embolic protection appeared to differ with varying TAVR systems.

Risk factors for stroke were incompletely understood at the time of study design. When evaluation of univariate predictors of new lesion volume revealed that device type and baseline T_2/FLAIR lesion volume were potentially important confounders of the relationship between TCEP and new lesion volume, we performed multivariable analysis to adjust for the unanticipated baseline differences in brain infarction volume and valve type. After adjusting for these variables, there was a significant difference in new lesion volume favoring neuroprotection in both protected territories ($p = 0.025$) and all territories ($p = 0.050$). The study provides a very interesting observation regarding differences in MRI findings resulting from implanted valve type. In the control group of patients, the volume of new MRI lesions was lower with SAPIEN 3 compared with Evolut R or SAPIEN XT. The overall treatment effect, after adjustment for TAVR device and the interaction between TAVR and treatment, is a 49% reduction in post-procedure new lesion volume in protected areas. However, SAPIEN 3 generated the lowest post-procedure new lesion volume (30% to 50% lower than the other TAVR devices) (Online Table 6). Therefore, SAPIEN 3 derived the least benefit from TCEP, resulting in little to no difference between the treatment arms. The treatment effect of the Sentinel device was significant in non-SAPIEN 3 valves. The reasons for these differences are not clear, and this is an important question for future clinical trials. Other factors may explain these differences, such as the use of pre-dilation or post-dilation, operator experience, or patient selection for different valves. Although these variables did not reach statistical significance in multivariate modeling, the limited power of the study and the possible interaction with valve types do not allow us to rule out their contribution to observed differences among valve types. First-generation balloon-expandable and self-expanding valves have reported similar stroke rates. The clinical stroke rate reported from SAPIEN 3 has been very low, but it has not been directly compared with newer-generation self-expanding valves.

FIGURE 3 Histopathologic Particulate Debris Analysis



This study analyzed the particulate debris from filters. **(A)** The rate of debris capture by type. **(B)** The average number of particles captured by size in maximum diameter.

The neurocognitive function test domains we used were rigorously obtained by trained examiners and customized to optimize the sensitivity of identifying changes associated with diffuse cerebral embolization. Although there was no difference in neurocognition at 30 days between the TCEP and control arms, there was an important relationship linking cumulative neurocognition scores with new lesion volumes and numbers.

As noted in other trials of TCEP during TAVR (22,23), there was a striking consistency of retrieved materials in almost all patients. The observation of frequent thrombus, artery wall, valve tissue, and calcification suggests that aggressive device manipulation within the aortic valvular complex should be avoided whenever possible.

STUDY LIMITATIONS. The dual-filter device appears safe and feasible, but the embolic protection afforded

excludes the territory of the left vertebral artery. The observation that residual new lesions are still present in protected territories after neuroprotection indicates that either the current transcatheter devices are suboptimal in debris capture or that post-procedure particulate embolization is ongoing and occurs after filter removal. It is possible that some of the retrieved material in the filters was not directly related to TAVR, but rather was the result of placement of TCEP. Follow-up MRI studies were not obtained in 25% of patients from the imaging cohort because of patient noncompliance and the need for new pacemakers post-TAVR. Despite being a large randomized trial examining neuroprotection during TAVR, the sample size was too small to assess clinical outcomes and, in retrospect, was also too small to evaluate follow-up MRI findings or neurocognitive outcomes. Finally, the analyses of valve type differences and multivariable analysis to account for confounders should be viewed as hypothesis generating and nondefinitive.

CONCLUSIONS

Several important lessons from this trial should affect future research. The use of quantitative MRI analysis as a surrogate endpoint must be further clarified, including stricter time windows for follow-up studies and larger sample sizes. The requirement of baseline MRI studies to account for previous lesion volume and the need to adjust for differences in valve type (e.g., stratification of valve types during randomization) cannot be overemphasized.

In conclusion, we found reassuring evidence of the safety of dual-filter neuroprotection therapy, and confirmed the high-frequency of embolic debris capture.

ACKNOWLEDGMENT The authors thank Matthew T. Finn, MD (Columbia University Medical Center) for assistance with manuscript preparation.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The dual-filter embolism protection device was safely deployed and effective in collecting particulate embolic debris from patients undergoing TAVR, but reduction in cerebral ischemic lesion volume as assessed by MRI was not statistically significant.

TRANSLATIONAL OUTLOOK: While awaiting further progress in the development of embolism protection devices, the selection of a neuroprotective strategy for patients undergoing TAVR should consider the risk of stroke, safety, and efficacy of available therapies and resource costs.

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KEY WORDS cerebral embolic protection, neuroimaging, stroke, transcatheter aortic valve replacement

APPENDIX For supplemental text, tables, and figures, please see the online version of this article.