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Cerebral embolic protection and severity of stroke following transcatheter aortic valve replacement

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Abstract

Background: The cerebral embolic protection (CEP) device captures embolic debris during transcatheter aortic valve replacement (TAVR). However, the impact of CEP on stroke severity following TAVR remains unclear. Therefore, we aimed to examine whether CEP was associated with reduced severity of stroke following TAVR.

Methods: This was a retrospective cohort study of 2839 consecutive patients (mean age: 79.2 ± 9.5 years, females: 41.5%) who underwent transfemoral TAVR at our institution between 2013 and 2020. We categorized patients into Sentinel CEP users and nonusers. Neuroimaging data were reviewed and the final diagnosis of a cerebrovascular event was adjudicated by a neurologist blinded to the CEP use or nonuse. We compared the incidence and severity (assessed by the National Institutes of Health Stroke Scale [NIHSS]) of stroke through 72 h post-TAVR or discharge between the two groups using stabilized inverse probability of treatment weighting (IPTW) of propensity scores.

Results: Of the eligible patients, 1802 (63.5%) received CEP during TAVR and 1037 (36.5%) did not. After adjustment for patient characteristics by stabilized IPTW, the rate of overall stroke was numerically lower in CEP users than in CEP nonusers, but the difference did not reach statistical significance (0.49% vs. 1.18%, $p = 0.064$). However, CEP users had significantly lower rates of moderate-or-severe stroke (NIHSS ≥ 6: 0.11% vs. 0.69%, $p = 0.013$) and severe stroke (NIHSS ≥ 15: 0% vs. 0.29%, $p = 0.046$). Stroke following CEP use ($n = 8$), compared with stroke following CEP nonuse ($n = 15$), tended to carry a lower NIHSS (median [IQR], 4.0 [2.0–7.0] vs.

Abbreviations: CEP, cerebral embolic protection; IPTW, inverse probability of treatment weighting; NeuroARC, Neurologic Academic Research Consortium; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR, transcatheter aortic valve replacement; TF, transfemoral.

7.0 [4.5–19.0], $p = 0.087$). Four (26.7%) out of 15 patients with stroke following CEP nonuse died within 30 days, with no death after stroke following CEP use.
Conclusions: CEP use may be associated with attenuated severity of stroke despite no significant difference in overall stroke incidence compared with CEP nonuse. This finding is considered hypothesis-generating and needs to be confirmed in large prospective studies.

KEYWORDS
cerebral embolic protection devices, stroke, transcatheter aortic valve replacement

1 | INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an established standard treatment for patients with severe aortic stenosis.[1] Despite a remarkable decrease in most procedural complications following TAVR, the incidence of procedural stroke has remained relatively stable at ~2% over the recent years[2–4] and is a major concern due to its impact on morbidity and mortality.[4–7] The expanding indication of TAVR toward younger patients with a low-risk profile reinforces the importance of minimizing procedural stroke.

Cerebral embolic protection (CEP) is a preventive measure for procedural stroke in TAVR.[8] The Sentinel CEP system (Boston Scientific Corporation) is currently the only commercially available CEP device approved by the US Food and Drug Administration (FDA). However, the pivotal Sentinel trial, the largest randomized trial (n= 363) reported thus far, was not powered to assess the clinical efficacy of Sentinel CEP on reducing the incidence of procedural stroke.[9] Recent large-scale observational studies demonstrated an insignificant or modest inverse association between CEP use and stroke incidence following TAVR.[10–12] However, it should be noted that those observational studies lack data on the severity of stroke assessed by neurologists.

Given the effect of CEP on capture of embolic debris in most cases,[9,13,14] CEP may reduce the severity of stroke following TAVR. However, no existing study has examined the impact of CEP on the severity of stroke. The objective of our study was to examine the association of Sentinel CEP use with the incidence and severity of procedural stroke following transfemoral (TF) approach TAVR.

2 | METHODS

2.1 | Study design and data collection

The present study is a retrospective cohort study using data on TAVR recipients at the Cleveland Clinic. Data on baseline patient characteristics, imaging, procedural characteristics, follow-up, and outcomes were extracted from our prospectively collected institutional registries or were manually extracted from electronic medical records. The present study was approved by the institutional review board of the Cleveland Clinic without any requirement of informed consent due to the retrospective nature of this study. The present study complies with the Declaration of Helsinki. The authors have full access to all the data in the present study and take responsibility for its integrity and the data analysis.

2.2 | Selection of study patients

The present study included consecutive patients aged ≥18 years who underwent TAVR for either severe aortic stenosis or bioprosthetic valve dysfunction at our institution between January 2013 and November 2020. We excluded (i) patients who underwent non-TF TAVR, (ii) those who received a mechanically expandable valve (all of whom received CEP), (iii) those who received CEP via the left radial artery (covering the left subclavian and left carotid arteries; used in TF-TAVR patients due to the aberrant right subclavian artery), (iv) those who received TriGuard HDH (Keystone Heart), and (v) those who underwent conversion to open surgery. Eligible patients were divided according to Sentinel CEP use or not during TF-TAVR. In our institution, the use of Sentinel CEP began in 2015 during the pivotal trial, included some commercially treated patients after FDA approval of the device in June 2017, and was applied routinely since January 2018.

2.3 | Neurological assessment for stroke post-TAVR

In our institution, if an acute cerebrovascular event was clinically suspected, our neurology team was rapidly consulted. All patients with an acute cerebrovascular event underwent a thorough neurological assessment and were treated per standard of care by neurologists. Computed tomography (CT) scan was immediately performed to rule out hemorrhagic stroke, frequently coupled with CT angiography to rule out large vessel occlusion. Cerebral magnetic resonance imaging (MRI) or/and magnetic resonance angiography was typically performed on a nonurgent basis to characterize the distribution and volume of infarcts in selected patients at the discretion of neurologists. These comprehensive neurological

assessments for suspected stoke have been standardized practice at our institution over the whole study years from 2013 to 2020.

2.4 | Imaging analysis for the present study

Stroke was defined according to the Neurologic Academic Research Consortium (NeuroARC) definitions.[15] For this retrospective analysis, neuroimaging data of CT or/and MRI were reviewed and the final diagnosis of a cerebrovascular event was adjudicated by a neurologist blinded to the CEP use or nonuse. Stroke-involved vascular territories were determined by the CT or/and MRI findings and were used to categorize stroke as follows: stroke in proximal filter-protected territories (perfused by the right internal carotid artery or right vertebral artery), stroke in distal filter-protected territories (perfused by the left internal carotid artery), stroke in partially protected territories (perfused by basilar artery and its branches—bilateral posterior cerebral arteries, bilateral superior cerebellar arteries, and bilateral anterior inferior cerebellar arteries, where stroke can occur through either protected or unprotected arteries), and stroke in unprotected territories (perfused by the left vertebral artery). Impaired cerebral circulation was categorized according to imaging findings as well as symptoms: anterior circulation, posterior circulation, both anterior and posterior circulations, and undetermined (defined as the case without any abnormality in CT images when MRI was not available for accurate localization of infarct). Infarct volume was calculated using the ABC/2 formula using diffusion-weighted MRI images (or CT images if diffusion-weighted MRI was not done).[16–18]

2.5 | Outcomes

The primary outcomes were strokes (overall stroke, moderate or severe stroke, and severe stroke) through 72 h post-TAVR or discharge (whichever comes first). The time frame of stroke was consistent with the ongoing PROTECTED TAVR trial (NCT0414 9535). Neurological severity of stroke was assessed by the National Institutes of Health Stroke Scale (NIHSS) at the time of diagnosis and was used to define severe stroke (NIHSS ≥ 15), moderate stroke (NIHSS 6–14), and mild stroke (NIHSS 1–5) as per the NeuroARC definitions.[15] The secondary outcomes were stroke or transient ischemic attack (TIA), in-hospital death, and a composite of in-hospital death or severe stroke. The modified Rankin Scale at discharge and discharge disposition were also assessed in patients who developed stroke. All patients were followed up for 30 days following TAVR, and 30-day mortality after stroke was examined.

2.6 | Statistical analysis

Categorical variables were presented as numbers and percentages and were compared using Fisher's exact test or χ^2 test. Continuous variables were presented as mean ± SD or median (interquartile range [IQR]) and were compared using the unpaired *t*-test or Mann–Whitney *U* test. No patient had missing data on baseline characteristics and outcomes. When we compared the outcomes between the CEP users and nonusers, we conducted a stabilized inverse probability of treatment weighting (IPTW) of propensity scores to adjust for potential confounders.[19] Propensity scores for predicting CEP use were estimated using a nonparsimonious multivariable logistic regression model that included all baseline and procedural characteristics (39 variables) listed in Table 1 as covariates. The model's discrimination of CEP use or nonuse was assessed by calculating the *C*-statistic of the propensity scores. The CEP users were weighted by stabilized IPTW (i.e., average treatment effect weight), which was calculated as $p(N)/PS$ where $p(N)$ was the proportion of the CEP users in the unadjusted cohort and PS was the individual's propensity score for CEP use; the CEP nonusers were weighted by $(1-p(N))/(1-PS)$.[19] We checked the balance of the patient and procedural characteristics between the groups using absolute standardized difference, of which >10% was considered a meaningful difference.[20] The stabilized IPTW analysis examined the population-level average treatment effect of CEP use and provided a more accurate interval estimate of the variance of the main effect and controls for Type I error compared with the non-stabilized IPTW analysis.[21] Subgroup analyses were also performed for overall stroke and moderate or severe stroke in the stabilized IPTW cohort stratified by age (< vs. ≥80 years), sex, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM: ≤ vs. >5% [median value]), estimated glomerular filtration rate (≥ vs. <60 ml/min/1.73 m^2), baseline rhythm, left ventricular ejection fraction (≥ vs. <50%), aortic valve mean gradient (< vs. ≥40 mmHg), valve type (balloon-expandable vs. self-expanding), valve size (≤26 mm vs. ≥29 mm), pre-dilation, or postdilation. The interactions were examined using the Breslow–Day test.

A two-sided *p* value of <0.05 is considered significant in all hypothesis tests. All statistical analyses were conducted using IBM SPSS Statistics, version 28 (IBM Corp.) and Stata 15.0 (StataCorp).

3 | RESULTS

3.1 | Study patients

A total of 2839 eligible patients (mean age: 79.2 ± 9.5 years, females: 41.5%, median STS-PROM: 5.0% [IQR: 3.3–7.8%]) underwent TF-TAVR at our institution (Figure 1). Overall, Sentinel CEP was used in 1802 (63.5%) patients and stroke occurred in 23 (0.81%) patients. The proportion of CEP use increased from 0%–7.9% in 2016 or earlier to 37.8% in 2017 and reached plateaus (>90%) between 2018 and 2020. The stroke rate decreased from ~2.00% in 2015 or earlier to 0.97% in 2016 and remained relatively stable (0.30%–0.86%) between 2017 and 2020 (Supporting Information: Figure S1).

In the unadjusted cohort, the CEP users, as compared with the CEP nonusers, had a lower STS-PROM corresponding to younger age and a lower prevalence of some comorbidities, with higher hemoglobin level and platelets count, and better renal function at

TABLE 1 Comparison of patient and procedural characteristics between TAVR with or without CEP

	Before stabilized IPTW			After stabilized IPTW		
	TAVR without CEP (*n* = 1037)	TAVR with CEP (*n* = 1802)	ASD, %	TAVR without CEP (*n* = 1037)	TAVR with CEP (*n* = 1802)	ASD, %
Baseline patient characteristics						
Age, years	80.2 ± 9.5	78.6 ± 9.4	17.3	79.4 ± 9.7	79.0 ± 9.5	3.8
Female	456 (44.0)	721 (40.0)	8.0	449 (44.1)	773 (42.3)	3.6
Body mass index, kg/m^2	27.6 (24.3–32.4)	28.0 (24.5–32.6)	0.9	27.5 (24.5–32.2)	28.0 (24.5–32.9)	3.3
STS-PROM, %	6.0 (4.2–8.6)	4.5 (2.9–7.0)	34.9	5.3 (3.8–7.9)	4.9 (3.2–8.0)	0.1
Prior PPM/ICD implantation	178 (17.2)	244 (13.5)	10.1	147 (14.4)	250 (13.7)	2.2
Prior PCI	301 (29.0)	549 (30.5)	3.2	296 (29.0)	543 (29.7)	1.4
Prior CABG	346 (33.4)	448 (24.9)	18.8	292 (28.7)	513 (28.1)	1.3
Prior myocardial infarction	256 (24.7)	377 (20.9)	9.0	225 (22.1)	405 (22.2)	0.2
Prior stroke	127 (12.2)	218 (12.1)	0.5	125 (12.3)	230 (12.6)	1.0
Prior TIA	111 (10.7)	167 (9.3)	4.8	102 (10.0)	194 (10.6)	2.0
History of atrial fibrillation/flutter	482 (46.5)	777 (43.1)	6.8	461 (45.2)	813 (44.5)	1.5
Carotid artery disease	274 (26.4)	344 (19.1)	17.6	217 (21.3)	396 (21.7)	0.9
Hypertension	948 (91.4)	1611 (89.4)	6.9	905 (88.8)	1651 (90.3)	4.9
Diabetes mellitus	379 (36.5)	678 (37.6)	2.2	372 (36.5)	668 (36.5)	0.1
Current or recent (<1 year) smoker	49 (4.7)	73 (4.1)	3.3	52 (5.1)	99 (5.4)	1.4
ESRD on dialysis	43 (4.1)	45 (2.5)	9.2	32 (3.1)	65 (3.6)	2.3
NYHA functional class III or IV	900 (86.8)	1294 (71.8)	37.6	804 (78.9)	1429 (78.2)	1.8
Porcelain aorta	22 (2.1)	20 (1.1)	8.0	13 (1.3)	20 (1.1)	1.7
Baseline laboratory findings						
Hemoglobin level, g/dl	11.8 ± 1.8	12.6 ± 1.8	39.2	12.3 ± 1.9	12.3 ± 1.9	1.0
Platelet count,/μl	195517 ± 65916	209465 ± 73907	19.9	203057 ± 67896	203692 ± 71099	0.9
eGFR, ml/min/1.73 m^2	53.9 (39.8–68.7)	59.4 (46.5–74.1)	21.0	57.4 (42.9–70.2)	57.5 (43.3–72.5)	0.6
Baseline electrocardiographic findings						
Atrial fibrillation	170 (16.4)	215 (11.9)	12.8	138 (13.5)	251 (13.7)	0.5
First-degree atrioventricular block	232 (22.4)	366 (20.3)	5.0	220 (21.6)	393 (21.5)	0.2
Right bundle branch block	142 (13.7)	229 (12.7)	2.9	131 (12.9)	226 (12.4)	1.5
Left bundle branch block	69 (6.7)	117 (6.5)	0.6	69 (6.8)	118 (6.5)	1.3
Valve and echocardiographic findings						
Left ventricular ejection fraction, %	54.1 ± 13.2	56.5 ± 11.9	19.4	55.9 ± 13.0	55.7 ± 12.1	2.0
Aortic valve mean gradient, mmHg	43.7 ± 15.4	40.7 ± 14.5	19.8	42.3 ± 14.9	42.4 ± 15.6	0.4
Bicuspid aortic valve	39 (3.8)	104 (5.8)	9.4	50 (4.9)	89 (4.9)	0.2

(Continues)

TABLE 1 (Continued)

	Before stabilized IPTW			After stabilized IPTW		
	TAVR without CEP (*n* = 1037)	TAVR with CEP (*n* = 1802)	ASD, %	TAVR without CEP (*n* = 1037)	TAVR with CEP (*n* = 1802)	ASD, %
Failed bioprosthetic valve	89 (8.6)	176 (9.8)	4.1	102 (10.0)	190 (10.4)	1.3
Aortic regurgitation ≥2+	234 (22.6)	364 (20.2)	5.8	215 (21.1)	403 (22.0)	2.3
Mitral regurgitation ≥2+	317 (30.6)	399 (22.1)	19.2	264 (25.9)	455 (24.9)	2.3
Procedural characteristics						
Nonelective procedure	71 (6.8)	157 (8.7)	7.0	91 (8.9)	152 (8.3)	2.2
Valve type						
Balloon-expandable[a]	920 (88.7)	1682 (93.3)	16.2	921 (90.4)	1648 (90.2)	0.8
Self-expanding[b]	117 (11.3)	120 (6.7)	16.2	98 (9.6)	180 (9.8)	0.8
Valve size (mm)						
≤23	353 (34.0)	670 (37.2)	6.6	380 (37.3)	653 (35.7)	3.3
26	393 (37.9)	676 (37.5)	0.8	374 (36.7)	663 (36.3)	0.8
≥29	291 (28.1)	456 (25.3)	6.2	265 (26.0)	511 (28.0)	4.4
Predilation	556 (53.6)	237 (13.2)	95.0	289 (28.4)	525 (28.7)	0.8
Postdilation	411 (39.6)	776 (43.1)	7.0	453 (44.5)	782 (42.8)	3.4
2nd valve deployment	37 (3.6)	17 (0.9)	17.7	19 (1.9)	36 (2.0)	0.8
Concomitant PCI	19 (1.8)	25 (1.4)	3.5	13 (1.3)	29 (1.6)	2.6
Concomitant vascular intervention	73 (7.0)	135 (7.5)	1.7	62 (6.1)	133 (7.3)	4.8

Note: Values are *n* (%), mean ± SD, or median (interquartile range).

Abbreviations: ASD, absolute standardized difference; CABG, coronary artery bypass grafting; CEP, cerebral embolic protection; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ICD, implantable cardioverter defibrillator; IPTW, inverse probability of treatment weighting; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TIA, transient ischemic attack; TAVR, transcatheter aortic valve replacement.

[a]Includes Sapien valve, Sapien XT, Sapien 3, Sapien 3 Ultra (Edwards Lifesciences).

[b]Includes CoreValve, Evolut R, Evolut PRO, and Evolut PRO+ (Medtronic).

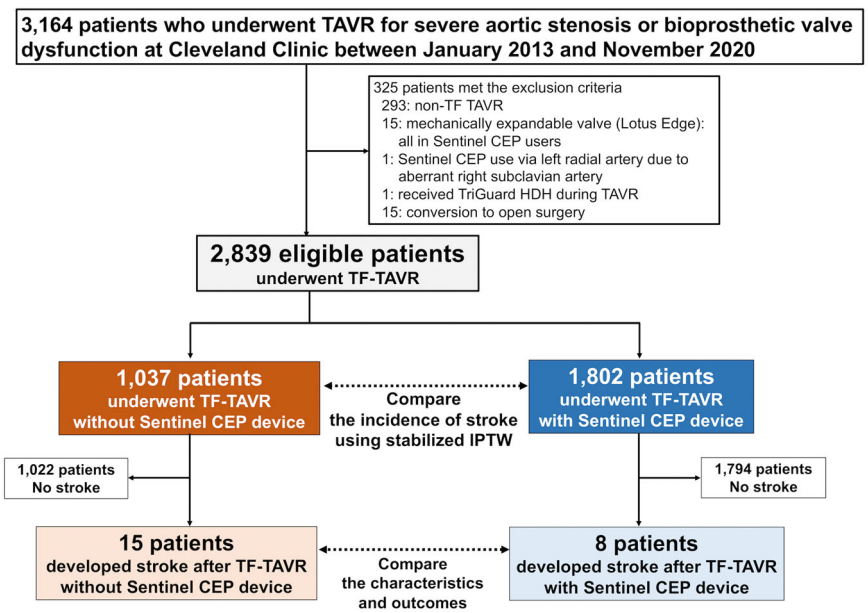

FIGURE 1 Patient selection and overview of the present analyses. CEP, crebral embolic protection; IPTW, inverse probability of treatment weighting; TAVR, transcatheter aortic valve replacement; TF, transfemoral.

baseline (Table 1). After the stabilized IPTW, all patient and procedural characteristics were well-balanced between the two groups. The *C*-statistic of the propensity scores was 0.80. The rates of in-hospital cardiovascular complications other than stroke were similar between the CEP users and nonusers, except for a lower rate of permanent pacemaker/implantable cardioverter defibrillator (ICD) implantation in the CEP users, which is attributable to our high deployment technique that had been applied to reduce the risk of PPM/ICD implantation for all TAVR procedures during the period (2018–2020) in which CEP started to be used routinely (Supporting Information: Table S1).[22]

3.2 | Incidence of stroke following TAVR with or without CEP

In the unadjusted analysis, the CEP users had significantly lower rates of overall stroke, moderate or severe stroke, and severe stroke than the CEP nonusers. Also, the CEP users had significantly lower rates of stroke or TIA, in-hospital death, and a composite of death or severe stroke. After adjustment for patient and procedural characteristics by stabilized IPTW, the rate of overall stroke was numerically lower in CEP users than in CEP nonusers, but the difference did not reach statistical significance (0.49% vs. 1.18%, $p = 0.064$). However, the CEP users had significantly lower rates of moderate or severe stroke (0.11% vs. 0.69%, $p = 0.013$) and severe stroke (0% vs. 0.29%, $p = 0.046$; Table 2). The numbers needed to treat (NNTs) for overall stroke and moderate or severe stroke were 146 and 173, respectively. The subgroup analyses for overall stroke and moderate or severe stroke demonstrated consistent results without significant interactions (Supporting Information: Table S2).

3.3 | Characteristics of stroke following TAVR with or without CEP use

Patients who developed stroke after TAVR with CEP ($n = 8$) were compared to those without CEP ($n = 15$) (Table 3 and Supporting Information: Table S3). Although there was no statistically significant difference in stroke characteristics between the two post-TAVR stroke groups, several substantial differences were observed. The NIHSS tended to be lower in patients with stroke after TAVR with than without CEP (median [IQR], 4.0 [2.0–7.0] vs. 7.0 [4.5–19.0], $p = 0.087$; Figure 2A). The proportions of moderate or severe stroke (25.0% vs. 66.7%) and severe stroke (0.0% vs. 33.3%) tended to be less in patients with stroke after TAVR with CEP. There was no significant difference in the modified Rankin Scale at discharge between the groups (Figure 2B); however, no patient with stroke after TAVR with CEP died within 30 days post-TAVR, whereas 4 (26.7%) out of 15 patients with stroke after TAVR without CEP died within 30 days (3 in-hospital and 1 post-discharge). Discharge to home tended to be more likely in patients with stroke after TAVR with CEP than those without CEP (50.0% vs. 16.7%).

3.4 | Distribution of stroke-involved vascular territories with or without CEP

Stroke-involved vascular territories were determinable by CT or MRI images in 20 patients (6 CEP users, 14 CEP nonusers) out of 23 patients who developed stroke after TAVR (Figure 3); in the remaining three patients with stroke (2 CEP users, 1 CEP nonusers), stroke-involved vascular territories could not be determined due to the absence of acute ischemia finding in CT images without MRI performed. In unadjusted analysis, the rate of stroke in any protected territories was significantly lower in CEP users than in CEP nonusers (0.22% vs. 0.96%, $p = 0.010$), driven by a lower rate of stroke in distal filter-protected territories (0.17% vs. 0.87%, $p = 0.012$). In the stabilized IPTW analysis, the difference became statistically insignificant, but the rates of stroke in any protected territories (0.27% vs. 0.79%, $p = 0.078$) and stroke in distal filter-protected territories (0.22% vs. 0.69%, $p = 0.064$) were still numerically lower in CEP users than in CEP nonusers (Table 2).

4 | DISCUSSION

The present study demonstrated an association between Sentinel CEP use and a lower incidence of moderate or severe stroke following TF-TAVR (0.11% vs. 0.69%, $p = 0.013$) despite a statistically nonsignificant difference in overall stroke risk (0.49% vs. 1.18%, $p = 0.064$). Although not statistically significant, stroke after TAVR with CEP tended to be less severe than stroke after TAVR without CEP. Further, no patient with stroke after TAVR with CEP died within 30 days following TAVR, whereas 4 (26.7%) out of 15 patients with stroke after TAVR without CEP died within 30 days.

4.1 | CEP and incidence of overall stroke following TAVR

The primary mechanism of stroke following TAVR is embolization of debris from the degenerated aortic valve or the aorta.[9,13,23] Prior studies consistently demonstrated the capture of heterogeneous debris in the Sentinel CEP filters of almost all patients.[9,13,14] Also, prior investigations have confirmed that Sentinel CEP use reduces the amount of embolization into protected territories of brain.[9,14,24] However, the efficacy of CEP use in reducing the incidence of procedural stroke remains uncertain due to the lack of evidence from an adequately powered randomized trial. The present study did not demonstrate an association between CEP use and overall stroke rate following TAVR in a risk-adjusted population, consistent with the findings in recent large-scale observational studies.[10–12] One possible reason for this negative result is that stroke can occur even in protected territories among CEP users, as demonstrated by the present study as well as prior studies.[9,14,24,25] Since the overall risk of stroke with TAVR was less than 2%, the risk difference between CEP use and nonuse in terms of overall stroke rate was −0.69% in the

TABLE 2 Comparison of outcomes between TAVR with or without CEP

	Before stabilized IPTW				After stabilized IPTW			
	TAVR without CEP (*n* = 1037)	TAVR with CEP (*n* = 1802)	*p* value[a]	Risk difference (95% CI)	TAVR without CEP (*n* = 1037)	TAVR with CEP (*n* = 1802)	*p* value[a]	Risk difference (95% CI)
Stroke, overall	15 (1.45)	8 (0.44)	0.007	−1.00% (−1.95% to −0.29%)	12 (1.18)	9 (0.49)	0.064	−0.69% (−1.59% to −0.02%)
Moderate or severe stroke (NIHSS ≥ 6)	10 (0.96)	2 (0.11)	0.001	−0.85% (−1.66% to −0.33%)	7 (0.69)	2 (0.11)	0.013	−0.58% (−1.31% to −0.12%)
Severe stroke (NIHSS ≥ 15)	5 (0.48)	0 (0)	0.006	−0.48% (−1.12% to −0.13%)	3 (0.29)	0 (0)	0.046	−0.29% (−0.86% to −0.01%)
Stroke or TIA	16 (1.54)	8 (0.44)	0.004	−1.10% (−2.07% to −0.37%)	12 (1.18)	9 (0.49)	0.064	−0.69% (−1.59% to −0.02%)
Ischemic stroke	15 (1.45)	8 (0.44)	0.007	−1.00% (−1.95% to −0.29%)	12 (1.18)	9 (0.49)	0.064	−0.69% (−1.59% to −0.02%)
Hemorrhagic stroke	0 (0)	0 (0)	(-)	(-)	0 (0)	0 (0)	(-)	(-)
TIA	1 (0.10)	0 (0)	0.37	−0.10% (−0.54% to 0.13%)	1 (0.10)	0 (0)	0.36	−0.10% (−0.55% to 0.13%)
In-hospital death	8 (0.77)	2 (0.11)	0.006	−0.66% (−1.41% to −0.18%)	6 (0.59)	4 (0.22)	0.18	−0.37% (−1.07% to 0.10%)
In-hospital death or severe stroke	11 (1.06)	2 (0.11)	0.001	−0.95% (−1.78% to −0.40%)	7 (0.69)	4 (0.22)	0.064	−0.47% (−1.20% to 0.02%)
Stroke by territories								
Stroke in any protected territories	10 (0.96)	4 (0.22)	0.010	−0.74% (−1.56% to −0.18%)	8 (0.79)	5 (0.27)	0.078	−0.51% (−1.28% to 0.02%)
Proximal filter-protected territories	3 (0.29)	4 (0.22)	0.71	−0.07% (−0.64% to 0.33%)	3 (0.29)	5 (0.27)	1.00	−0.02% (−0.61% to 0.39%)
Distal filter-protected territories	9 (0.87)	3 (0.17)	0.012	−0.70% (−1.48% to −0.18%)	7 (0.69)	4 (0.22)	0.064	−0.47% (−1.20% to 0.02%)
Stroke in partially-protected territories	7 (0.68)	4 (0.22)	0.11	−0.45% (−1.18% to 0.04%)	4 (0.39)	5 (0.27)	0.73	−0.12% (−0.75% to 0.32%)
Stroke in unprotected territories	1 (0.10)	1 (0.06)	1.00	−0.04% (−0.49% to 0.23%)	0 (0.0)	1 (0.05)	1.00	0.05% (−0.32% to 0.31%)

Note: Values are n (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; other abbreviations as in Table 1.

[a]Fisher's exact test.

TABLE 3 Characteristics, management, and outcomes of stroke after TAVR with or without Sentinel CEP use

	Stroke after TAVR without CEP (*n* = 15)	Stroke after TAVR with CEP (*n* = 8)	*p* value
Stroke characteristics			
NIHSS at the time of diagnosis	7.0 (4.5–19.0)	4.0 (2.0–7.0)	0.087
Severe stroke (NIHSS ≥ 15)	5 (33.3)	0 (0.0)	0.12
Moderate or severe stroke (NIHSS ≥ 6)	10 (66.7)	2 (25.0)	0.089
Symptoms			
Aphasia	9 (60.0)	2 (25.0)	0.19
Dysarthria	9 (60.0)	5 (62.5)	1.00
Motor weakness or hemiparesis	10 (66.7)	5 (62.5)	1.00
Confusion/altered mental status/unresponsive	11 (73.3)	4 (50.0)	0.37
Visual abnormality	10 (66.7)	3 (37.5)	0.22
Facial droop	7 (46.7)	1 (12.5)	0.18
Severity of impaired consciousness			0.23
Mild (GCS 13–15)	10 (66.7)	8 (100.0)	
Moderate (GCS 9–12)	3 (20.0)	0 (0.0)	
Severe (GCS 3–8)	2 (13.3)	0 (0.0)	
Imaging modality for diagnosis			
CT head	15 (100.0)	8 (100.0)	(-)
CT angiography	10 (66.7)	8 (100.0)	0.12
MRI	9 (60.0)	4 (50.0)	0.69
Magnetic resonance angiography	3 (20.0)	0 (0.0)	0.53
Infarct volume,[a] ml	3.60 (0.50–21.80) [*n* = 13]	3.28 (0.24–13.20) [*n* = 6]	0.42
Impaired cerebral circulation			0.16
Anterior circulation alone	8 (53.3)	1 (12.5)	
Posterior circulation alone	4 (26.7)	4 (50.0)	
Both anterior and posterior	3 (20.0)	2 (25.0)	
Indeterminable	0 (0.0)	1 (12.5)	
Treatment			1.00
Conservative medical management	11 (73.3)	7 (87.5)	
Thrombolysis alone	0 (0.0)	0 (0.0)	
Thrombectomy alone	3 (20.0)	1 (12.5)	
Both thrombolysis and thrombectomy	1 (6.7)	0 (0.0)	
Outcomes			
In-hospital death	3 (20.0)	0 (0.0)	0.53
Discharge disposition[b]			0.16
Home	2/12 (16.7)	4/8 (50.0)	
Rehabilitation center or SNF	10/12 (83.3)	4/8 (50.0)	
30-day death	4 (26.7)	0 (0.0)	0.26

Note: Values are *n* (%) or median (IQR).

Abbreviations: CT, computed tomography; GCS, Glasgow Coma Scale; MRI, magnetic resonance imaging; SNF, skilled nursing facility; other abbreviations as in Table 1.

[a]Unavailable in four patients without any infarct in CT who did not receive MRI assessment.

[b]Includes only patients discharged alive.

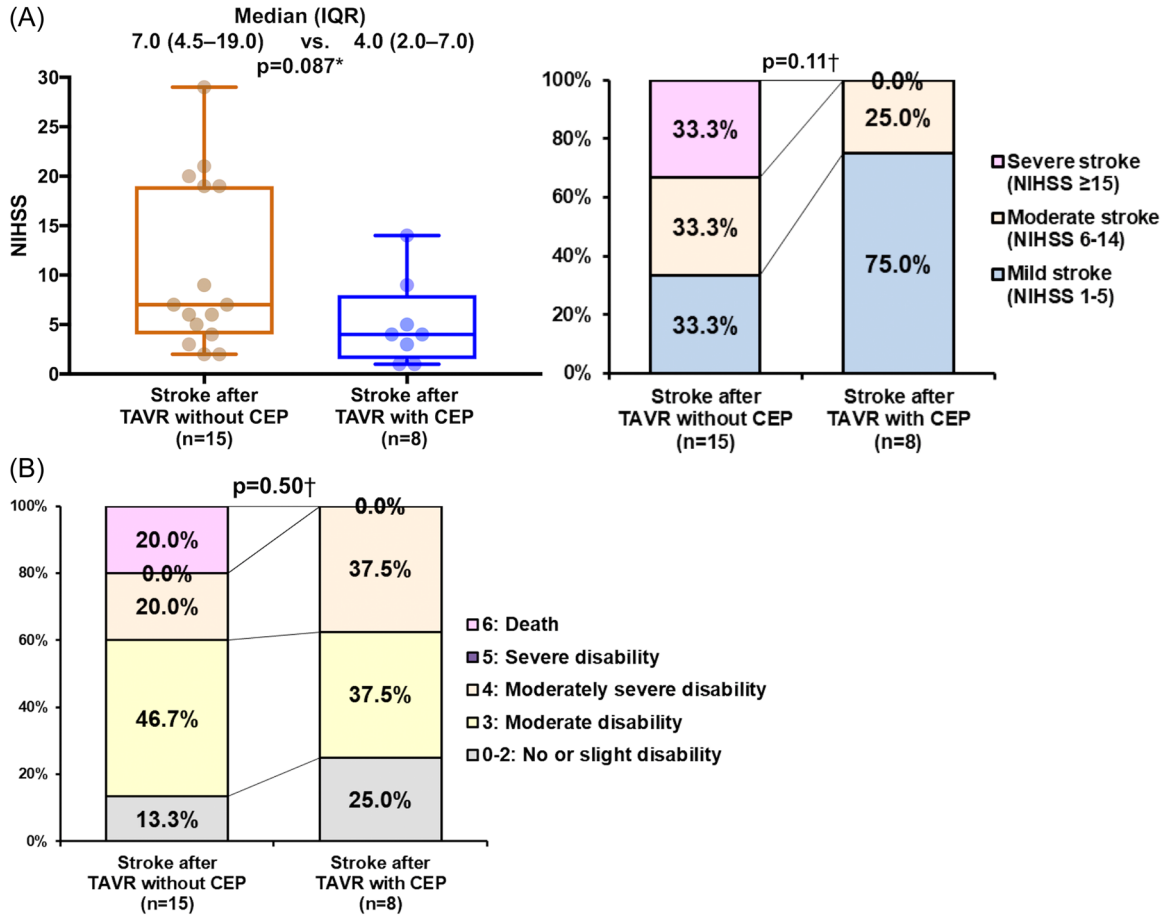

FIGURE 2 NIHSS and modified Rankin Scale among patients who developed stroke after TF-TAVR with or without CEP. (A) NIHSS at the time of diagnosis. (B) Modified Rankin Scale at discharge. *Mann–Whitney *U* test. †Fisher's exact test. NIHSS, National Institutes of Health Stroke Scale; other abbreviations as in Figure 1.

present stabilized IPTW analysis, comparable to that (<−1%) in the recent Transcatheter Valve Therapy registry study.[10] However, the value of our study is to demonstrate the clinical significance of this small absolute change in overall stroke risk resulting in significant reduction in severity of stroke.

4.2 | CEP and severity of stroke following TAVR

Although recent observational studies included a much larger number of patients in a nationwide study setting,[10–12] their findings were limited by the lack of data on neurological assessments and imaging data. Notably, the present IPTW analysis demonstrated an association between CEP and a lower incidence of moderate or severe stroke following TAVR despite no statistically significant difference in overall stroke rate. The risk reduction for moderate or severe stroke by CEP (−0.58%) was comparable to that for overall stroke (−0.69%), possibly suggesting that the stroke risk reduction by CEP is mainly from prevention of moderate or severe stroke. The present study also found that the NIHSS (albeit not statistically significant) tended to be lower in stoke following TAVR with than without CEP. These findings suggest that CEP may reduce the neurological severity of stroke following TAVR, possibly indicating an important role of CEP in the management and prognosis of stroke following TAVR.

The Sentinel CEP can functionally capture large debris that may cause severe stroke. In contrast, tiny debris may go through the gaps between the filters and arteries, leading to stroke even in CEP-protected territories, but such a stroke may be less likely to cause severe symptoms. In the Sentinel trial, there was a significant correlation between new lesion volume in MRI and neurological dysfunction[9]; that is, the reduction of new brain lesion volume by CEP can lead to less clinical sequelae of stroke. The occurrence of stroke following TAVR leads to poor short- and long-term survival in TAVR recipients.[4–7] In the present study, the NNTs for overall stroke and moderate or severe stroke (146 and 173, respectively) were relatively large from the clinical standpoint of the device efficacy and may suggest that we should use CEP specifically for only patients at high risk of stroke to improve the NNTs. Importantly, however, stroke after TAVR is largely unpredictable due to the lack of established predictors,[26,27] and its risk does not change with increasing procedural experience.[28] Hence, it appears clinically reasonable to make efforts to attenuate stroke-related mortality risk

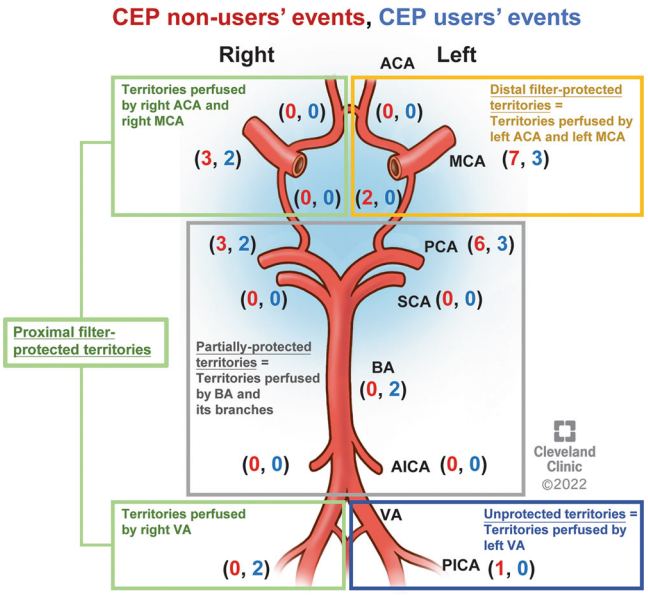

FIGURE 3 Distribution of stroke-involved vascular territories. Stroke-involved vascular territories were determinable by computed tomography or magnetic resonance images in 20 out of 23 patients who developed stroke (6 CEP users, 14 CEP nonusers). Each parenthesis in the figure shows the numbers of stroke involved in a corresponding vascular territory; the left number in red is the number of events in the CEP nonusers and the right number in blue is that in the CEP users. ACA, anterior cerebral artery; AICA, anterior inferior cerebellar artery; BA, basilar artery; MCA, middle cerebral artery; PCA, posterior cerebral arteries; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery; VA, vertebral artery; other abbreviations as in Figure 1.

by using CEP during TAVR in case that stroke occurs post-procedurally. Recently, our group reported that the CEP may be associated with a lower risk of stroke-related mortality among patients who developed stroke following TAVR using a nationwide database.[29] This potential positive effect of CEP on stroke-related mortality might be supported by the present result that CEP was associated with a lower incidence of moderate or severe stroke. In this context, our data are considered hypothesis-generating due to the small number of stroke events, warranting further investigations on the impact of CEP on the severity of stroke and subsequent mortality risk. An ongoing large-scale randomized trial (PROTECTED TAVR NCT04149535) will answer the question of whether CEP provides clinical benefits on the incidence and severity of stroke in patients undergoing TAVR.

5 | STUDY LIMITATIONS

Several limitations should be noted in the present study. First, this was a retrospective, non-randomized study, which could be subject to residual or unmeasured confounders even after adjustments by stabilized IPTW. Although the overall stroke rate was statistically not significantly different between the CEP uses and nonusers, it is possible that with a larger sample size, the difference may have reached statistical significance. Second, pre-TAVR neurological findings (e.g., pre-TAVR NIHSS and MRI) were not available because neurological evaluations were not routinely performed as part of pre-TAVR management. Third, the number of patients with stroke following TAVR ($n = 23$) could be underpowered to examine the differences in NIHSS and modified Rankin Scale between stroke after TAVR with and without CEP. Also, the number was too small to allow for multivariable adjustment to compare stroke characteristics and outcomes between the two stroke groups. Fourth, the subgroup analyses were likely underpowered. Fifth, learning curve phenomenon of operator experience may affect the outcomes. Lastly, the present study was conducted at a single high-volume center with a predominant use of balloon-expandable valves. Given the lower stroke rate in the present study (0.81%) than in the US nationwide registry (1.5%–2.0%),[2] the findings of the present study may not be generalizable to other institutions.

6 | CONCLUSIONS

The present study demonstrates that the use of Sentinel CEP may be associated with lower risk of moderate or severe stroke despite no significant difference in overall stroke incidence following TF-TAVR. The present study provides a hypothesis that the clinical benefit of CEP use may lie in the effect of attenuating the severity of stroke. Further large-scale prospective studies are needed to address this hypothesis about the role of CEP use during TAVR and confirm our findings.

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CONFLICT OF INTEREST

Dr. Samir R. Kapadia has served as the study principal investigator for the ongoing PROTECTED TAVR trial (NCT04149535). The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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