Received: 30 March 2023 | Revised: 18 June 2023 | Accepted: 20 June 2023

DOI: 10.1002/hsr2.1391

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Safety and efficacy of cerebral embolic protection devices for patients undergoing transcatheter aortic valve replacement: An updated meta-analysis

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Abstract

Background and Aims: Cerebral embolic protection (CEP) devices are employed to capture embolic debris and reduce the risk of stroke during transcatheter aortic valve replacement (TAVR). Evidence is mixed regarding the safety and efficacy of CEP. We aimed to summarize the safety and effectiveness of CEP use during TAVR.

Methods: Electronic databases, including PubMed, PubMed Central, Scopus, Cochrane Library, and Embase, were searched using relevant search terms for articles relating to CEP. All relevant data from 20 studies were extracted into a standardized form. Statistical analyses were performed using Revman 5.4. Odds ratio (OR) or mean differences (MDs) were used to estimate the desired outcome with a 95% confidence interval (CI).

Results: Twenty studies (eight randomized controlled trials [RCTs]) involving 210,871 patients (19,261 in the CEP group and 191,610 in TAVR without the CEP group) were included. The use of CEP was associated with a lower odds of 30-day mortality by 39% (OR: 0.61, 95% CI: 0.53–0.70) and stroke by 31% (OR: 0.69, 95% CI: 0.52–0.92). Comparing devices, benefit in terms of mortality and stroke was observed with the use of the Sentinel device (Boston Scientific), but not among other devices. No differences were observed in the outcomes of acute kidney injury, major or life-threatening bleeding events, or major vascular complications between groups. When only RCTs were included, there were no observed differences in the primary or secondary outcomes for CEP versus no CEP use during TAVR.

Conclusions: The totality of evidence suggests a net benefit for the use of CEP, weighted by studies in which the Sentinal device was used. However, given the RCT subanalysis, additional evidence is needed to identify patients at the highest risk of stroke for optimal decision-making.

KEYWORDS

cerebral embolic protection devices, stroke, transcatheter aortic valve replacement

1 | INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an established treatment method for severe symptomatic aortic stenosis. TAVR has shown to be associated with improved clinical outcomes compared with medical therapy and surgical aortic valve replacement (SAVR) in patients with an elevated risk for mortality with surgery.[1–3] Despite a very high procedural success rate, cerebral ischemic events remain unpredictable and substantially impact long-term morbidity and mortality after TAVR.[4,5] During the TAVR, there is a possibility of debris embolizing from the aorta and aortic valve, which may result in cerebrovascular events (CVEs).[6,7] Several studies have demonstrated a high incidence of new cerebral ischemic lesions (~70%) following TAVR, identified by diffusion-weighted magnetic resonance imaging (DW-MRI).[8–10]

Transcranial Doppler studies during TAVR have revealed that embolic phenomena occur most commonly during the positioning of the prosthetic valve and valve insertion.[11–13] Approximately half of the periprocedural CVEs become clinically apparent at least 24 h after TAVR.[14–16]

TAVR is shown to be associated with improved post-procedural outcomes compared with standard medical therapy, including lower mortality and better quality of life in surgically high-risk population,[2,17] and the rate of overt stroke following TAVR is also relatively low (~2%) in current practice.[18] However, the burden of micro-embolization and small ischemic cerebral injuries may still contribute to cognitive decline.[19–21]

Cerebral embolic protection (CEP) devices have been employed to capture embolic debris and mitigate adverse neurological events. Several observational and randomized controlled trials (RCTs) have been conducted, but the safety and efficacy of using CEPs during TAVR remain inconclusive. Thus, we have conducted this systematic review and meta-analysis to evaluate the safety and efficacy of CEPs during TAVR.

2 | METHODS

2.1 | Literature search strategy

This systematic review and meta-analysis followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[22] Our protocol for this meta-analysis is available in the publicly available international prospective register of systematic reviews (PROSPERO) registry (CRD42022325385). We searched for relevant articles from web-based medical libraries, including PubMed, PubMed Central, Scopus, Cochrane Library, and Embase. We used the terms "cerebral protection system," "transcatheter aortic valve replacement," and "TAVR," as the keywords for search. The reference list of the retrieved article was then imported into Covidence software.[23]

2.2 | Selection criteria

Title and abstract screening and full-text screening were the two initial steps applied to filter the desired papers and exclude irrelevant articles for our study. Three independent researchers (SL, AB, and MS) were involved in screening and conflict management. Discrepancies were further resolved by mutual discussion and consensus.

We included the published articles such as RCTs, prospective and retrospective cohort studies, and cross-sectional studies that had compared TAVR with or without CEP through 1/9/2023.

This study did not include case reports, case series, review articles, editorials, expert opinions, studies with poorly defined outcomes, or meta-analyses. In addition, abstracts with no available full text, unpublished studies, and single-arm studies whose results had evaluated the feasibility of TAVR with only CEP were also excluded during the full-text review.

2.3 | Data extraction

We extracted variables under sub-headings including baseline characteristics (participant number, mean age, male population, and other comorbid medical and surgical conditions), procedural characteristics (TAVR site, valve type, CEP type, procedural time, imaging assessment time frame, and neurocognitive assessment). Primary endpoints were 30-day all-cause mortality and 30-day stroke. Secondary endpoints were related to imaging evidence of emboli after TAVR, as measured by DW-MRI, acute kidney injury (AKI), significant or life-threatening bleeding, and major vascular complications. Imaging endpoints included the number of patients with new ischemic lesions, the total volume of lesions (TVL), and the number of new lesions.

2.4 | Data analysis

Data were analyzed using RevMan 5.4.[24] Random/fixed-effects models were used to determine the pooled odds ratio (OR) to estimate the outcome with a 95% confidence interval (CI) based on heterogeneity. We used the mean difference (MD) for DW-MRI findings for the volume of lesions and the number of new lesions. The median and standard deviations were calculated using the median and interquartile range, if those values were not provided in the studies.[25] A forest plot was used to represent the degree of variation between studies.

2.5 | Assessment of risk of bias in included studies

Risk of bias assessment was performed using the Cochrane Risk of Bias (ROB) 2.0 tool for RCTs, shown in the (Supporting Information: Figure S1). We used the Joanna Briggs Institute critical appraisal checklist for non-RCT studies (Supporting Information: Table 1).[26,27]

RevMan 5.4 was used to summarize biases for RCTs using the Cochrane ROB 2.0 tool.

2.6 | Assessment of heterogeneity

The I-squared (I^2) test was employed to assess heterogeneity, and interpretation was done based on the Cochrane Handbook for Systematic Reviews of Interventions.

2.7 | Subgroup analyses and sensitivity analysis

Subgroup analyses were performed between RCTs and observational studies and between types of CEP devices to evaluate their impact on the overall result. A sensitivity analysis was performed by excluding studies with fewer than 50 patients in a particular group to omit the skewed result based on the shared weight in the result.

3 | RESULTS

3.1 | Study selection and study population

A total of 1057 studies were identified after the databases were searched. After removing 125 duplicates, the title and abstract of 932 studies were screened, and 106 studies were eligible for full-text review. A total of 86 records were excluded for reasons described in Figure 1. We included 20 studies for our quantitative synthesis, as represented in the PRISMA flow diagram (Figure 1).

Among 20 studies, 8 RCTs and 12 cohort studies were included comparing the efficacy of CEP with no CEP in patients undergoing TAVR. These studies included a total of 210,871 patients, with 19,261 undergoing TAVR with CEP and 191,610 undergoing TAVR without CEP. 53.3% were male.

Baseline characteristics of the participants in the included studies are shown in Table 1. Procedural and outcome details are shown in Table 2.

4 | QUANTITATIVE SYNTHESIS

ORs were used to measure outcome estimation for 30-day all-cause mortality and stroke as co-primary outcomes. DW-MRI findings (number of patients with new lesions, volume of lesions, and number of new lesions) and other complications (AKI, significant/life-threatening bleeding, and major vascular complications) were secondary outcome variables.

4.1 | Thirty-day all-cause mortality

Pooling data using a fixed effect model from 20 studies demonstrated a 39% lower odds of 30-day mortality amongst patients undergoing TAVR with CEP (OR: 0.61, 95% CI: 0.53–0.70; $n = 202{,}189$; $I^2 = 2\%$). Analysis including only RCTs did not show a significant difference (OR: 1.04, 95% CI: 0.51–2.10; $n = 4029$; $I^2 = 0\%$). Thirty-day mortality was significantly lower among patients undergoing TAVR with CEP group compared with patients undergoing TAVR without CEP when only observational real-world studies were included (OR: 0.60, 95% CI: 0.52–0.69; $n = 198{,}160$; $I^2 = 18\%$; Figure 2).

4.2 | Thirty-day stroke events

Overall analysis using random effect models demonstrated a significant reduction in the occurrence of stroke at 30 days in TAVR with the CEP group in comparison to TAVR only (OR: 0.69, 95% CI: 0.52–0.92; $n = 202{,}251$; $I^2 = 51\%$). However, when only RCTs were included, there was no significant benefit of CEP over no CEP (OR: 0.84, 95% CI: 0.60–1.19; $n = 4025$; $I^2 = 0\%$; Figure 3).

4.3 | Sensitivity analysis

A sensitivity analysis excluding studies with fewer than 50 patients demonstrated a lower odds of mortality in TAVR with CEP group compared to those without CEP, however when only RCTs were included, this became nonsignificant (Supporting Information: Figure 2).

Excluding studies with fewer than 50 patients, there was a reduction in stroke when CEP was used with TAVR versus no CEP (OR: 0.72, 95% CI: 0.53–0.98; $n = 201{,}368$; $I^2 = 60\%$). When only RCTs were included, this finding did not reach significance (OR: 0.86, 95% CI: 0.60–1.22; $n = 3845$; $I^2 = 0\%$; Supporting Information: Figure 3).

4.4 | Subgroup analysis

Thirty-day mortality based on CEP device: We performed a subgroup analysis to compare individual CEP devices. Thirteen studies used the Sentinel (Boston Scientific) device, 4 studies used Triguard (Keystone Heart) device and the rest used the Embrella (Edwards Lifesciences) and Embol-x systems (Edwards Lifesciences). In subgroup analysis performed based on the device used, using fixed effect model from 13 studies, 4 RCTs and 9 non-RCTs, we noted a 39% lower odds of 30-day mortality in the TAVR with CEP group when the Sentinel device was used as the CEP while comparing TAVR without CEP (OR: 0.61, 95% CI: 0.53–0.70; $n = 201{,}515$; $I^2 = 21\%$). However, analysis performed only on the four RCTs showed no significant difference. The analysis on other devices showed no significant difference. (Supporting Information: Figure 4).

A subgroup analysis using a random effect model from the 13 studies using the Sentinel device showed a 37% lower odds of 30-day stroke in TAVR with the CEP group where the Sentinel device was used as the CEP while comparing TAVR without CEP (OR: 0.63, 95% CI: 0.46–0.87; $n = 201{,}577$; $I^2 = 61\%$; Supporting Information: Figure 5).

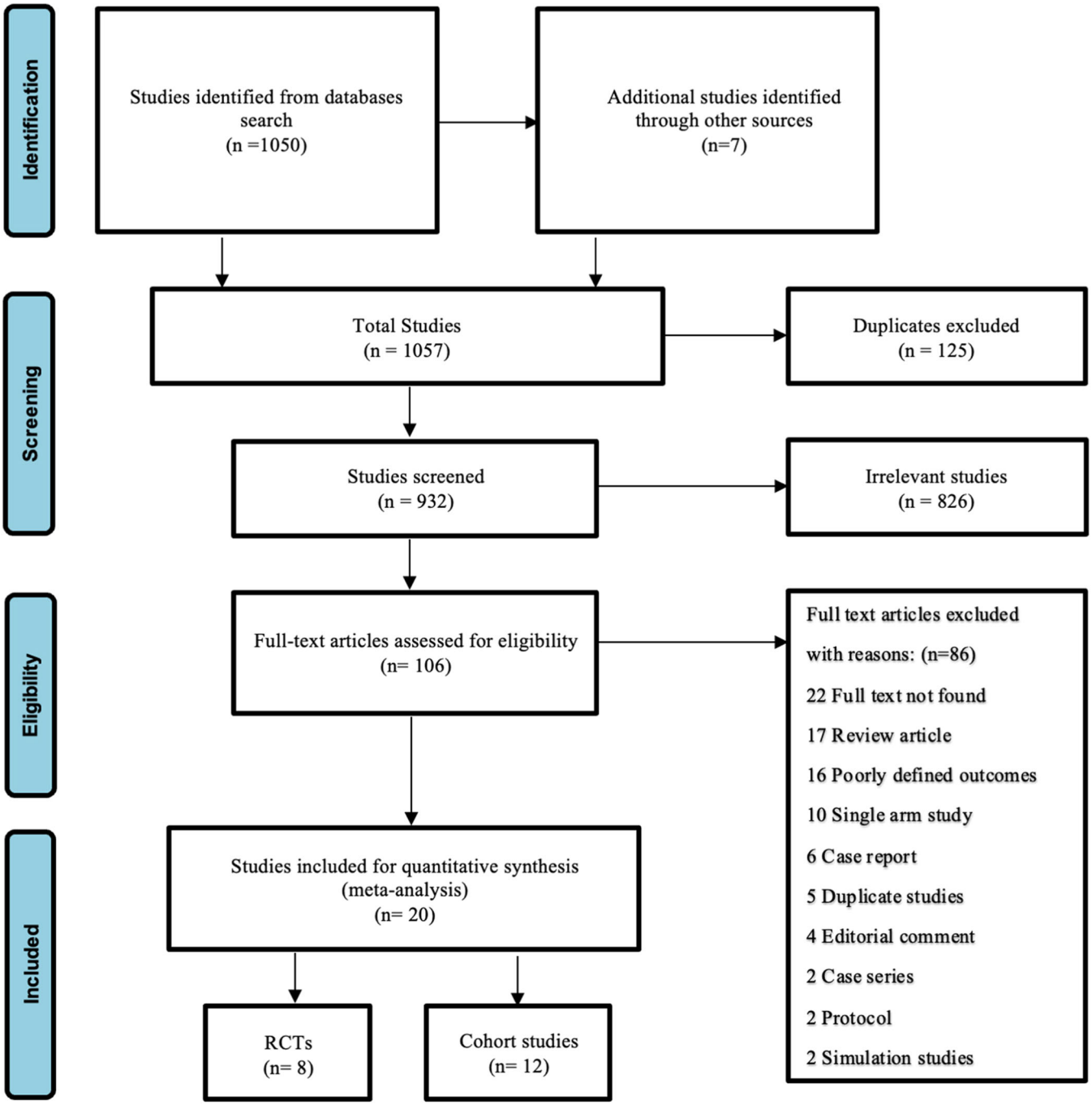

FIGURE 1 PRISMA flow diagram. PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCT, randomized controlled trial.

4.5 | DW-MRI assessment

4.5.1 | Patients with new lesions

DW-MRI was performed in seven studies, five RCTs and two non-RCTs that included a total of 586 patients. The overall incidence of a patient with a new lesion was 85.1% (274/322) with the use of CEP and 86.7% (229/264) in patients without the use of CEP. The statistical analysis showed no difference in the number of new lesions (MD: 0.79, 95% CI: 0.49–1.28; $n = 586$; studies = 7; $I^2 = 0\%$; Supporting Information: Figure 6).

4.5.2 | Total volume of lesions

The TVL was 88–511 mm^3 in patients with CEP and 168–942 mm^3 in patients without CEP. The use of CEP during TAVR was not associated with lower total volume of lesions (MD: −76.03, 95% CI:

TABLE 1 Baseline characteristics of the included population.

Study	Year	Type of study	Intervention	*N*	Mean age (years)	Sex (male)	DM	HTN	CKD	CAD	PVD	H/O CVD (stroke, TIA)	TAVR access site
Wendt et al. (EMBOL-X)[28]	2015	RCT	With CEP	14/30	(81.0 ± 5.0)	4/14	–	–	6/14	–	5/14	1/14	Transaortic 100%
			Without CEP	16/30	(82.1 ± 4.1)	8/16			6/16		6/16	3/16	
Lansky et al. (DEFLECT III)[29]	2015	RCT	With CEP	46/85	(82.5 ± 6.5)	20/46	10/46	37/46	11/46	6/46	6/46	6/46	Transfemoral 96.47%, Transapical 3.53%
			Without CEP	39/85	(82.3 ± 6.0)	19/39	9/39	28/39	10/39	8/39	5/39	7/39	
Kapadia et al. (SENTINEL)[30]	2017	RCT	With CEP	244/363	82.8	113/244	82/244			127/244	37/244	17/244	Transfemoral 94.7%
			Without CEP	119/363	85	61/119	45/119			66/119	18/119	7/119	
Lind et al.[31]	2022	Retrospective study	With CEP	18/51	(91.7 ± 2.1)	8/18	3/18	–	10/18	10/18	3/18	8/18	Transfemoral
			Without CEP	33/51	(92 ± 1.85)	14/33	8/33	–	22/33	27/33	11/33	5/33	
Butala et al.[32]	2021	Retrospective study	With CEP	12,409/ 123,186	79.0 ± 8.9	7341/ 12,409	–	–	–	–	3059/ 12,398	1253/12,396	Transfemoral
			Without CEP	110,777/ 123,186	79.4 ± 8.8	60,571/ 110,777					25,793/ 110,657	10,180/ 11,0 628	
Megaly et al.[33]	2020	Retrospective study	With CEP	525/36,220	81 (76–87)	280/525	210/525	105/525	165/525	65/525	85/525	60/525	
			Without CEP	35,695/ 36,220	81 (75–86)	19,215/ 35,695	13,590/ 35,695	9505/ 35,695	11,685/ 35,695	4695/ 35,695	8310/ 35,695	4195/35,695	
Rodés-Cabau et al. (PROTAVI-C)[34]	2014	Pilot N.R. study	With CEP	41/52	83 (79–86)	19/41	14/41	36/41	18/41	24/41	6/41	0	Transfemoral
			Without CEP	11/52	84 (78–89)	8/11	5/11	10/11	6/11	5/11	1/11	0	
Samim et al.[35]	2015	Retrospective study	With CEP	15/52	84 (73–87)	8/15	5/15	8/15	-	8/15	1/15	3/15	Transfemoral 100%
			Without CEP	37/52	81 (78–84)	21/37	9/37	21/37		25/37	3/37	5/37	
Stachon et al.[36]	2021	Retrospective study	With CEP	1564/ 41,654	80.62 ± 6.36	722/1564	539/1564	935/1564	45/1564	822/1564	174/1564		Transfemoral
			Without CEP	40,090/ 41,654	81.14 ± 6.02	18,778/ 40,090	13,009/ 40,090	25,437/ 40,090	1800/ 40,090	19,528/ 40,090	3311/ 40,090		
Van Mieghem et al. (MISTRAL-C)[37]	2016	RCT	With CEP	32/65	82 (79–84)	17/32	4/32	21/32	–	2/32	9/32	6/32	Transfemoral
			Without CEP	33/65	82 (77–86)	17/33	9/33	23/33		2/33	11/33	6/33	
Seeger et al.[38]	2017	Prospective study	With CEP	280/802	80.6 ± 6.0	128/280	84/280		81/280	166/280	18/280	26/280	Transfemoral 100%
			Without CEP	522/802	80.5 ± 6.2	256/522	155/522		180/522	330/522	53/522	63/522	

(Continues)

TABLE 1 (Continued)

Study	Year	Type of study	Intervention	*N*	Mean age (years)	Sex (male)	DM	HTN	CKD	CAD	PVD	H/O CVD (stroke, TIA)	TAVR access site
Seeger et al. (RESPOND)[39]	2020	Prospective study	With CEP	92/996	80.0 ± 6.4	37/92	21/92	80/92		53/92		11/92	Transfemoral
			Without CEP	904/996	80.0 ± 6.5	452/904	202/904	709/904		505/904		83/904	
Voss et al.[40]	2019	Retrospective study	With CEP	39/391	79.1 ± 7.3	18/39	–	–	–	23/39	–	2/39	Radial (35), brachial (4)
			Without CEP	352/391	79.5 ± 7.2	174/352				192/352		28/352	
Haussig et al. (CLEAN TAVI)[41]	2016	RCT	With CEP	50/100	80 ± 5.1	21/50	20/50	44/50	43/50	26/50	2/50	1/50	Transfemoral
			Without CEP	50/100	79.3 ± 4.1	22/50	25/50	47/50	39/50	25/50	4/50	3/50	
Dona et al.[42]	2022	Prospective study	With CEP	213/411	80.4 ± 6.7	118/213	71/213	189/213	–	133/213	27/213	15/213	Transfemoral
			Without CEP	198/411	80.4 ± 6.8	98/198	65/198	175/198		127/198	19/198	15/198	
Nazif et al. (REFLECT II)[43]	2021	RCT	With CEP	157/214	80.31 ± 7.73	86/157	61/156	–	36/157	–	20/155	27/157	Transfemoral 100%
			Without CEP	57/214	78.05 ± 8.19	35/57	23/57		17/57		11/57	3/57	
Lansky et al. (REFLECT I)[44]	2021	RCT	With CEP	141/204	79.8 ± 7.3	80/141	60/140	–	27/136	–	15/134	18/137	Transfemoral
			Without CEP	63/204	81.5 ± 7.1	42/204	20/63		11/62		8/59	7/62	
Kemp et al.[45]	2022	Prospective study	With CPS	78/157	84 ± 4	43/78	25/78	60/78			28/78	13/78	Badial. Brachial Transfemoral
			Without CPS	79/157	84 ± 4	36/79	26/79	59/79			26/79	9/79	
Isogai et al.[46]	2022	Retrospective cohort study	With CPS	1802/2839	78.6 ± 9.4	1081/1802	678/1802	1611/1802	45/1802	344/1802		385/1802	Transfemoral
			Without CPS	1037/2839	80.2 ± 9.5	581/1037	379/1037	948/1037	43/1037	274/1037		238/1037	
Kapadia et al. (PROTECTED-TAVR)[47]	2022	RCT	With CPS	1501/3000	78.9 ± 8.0	870/1501	501/1501	1306/1500		850/1493	165/1484	114/1496	Transfemoral
			Without CPS	1499/3000	78.9 ± 7.8	933/1499	522/1499	1312/1497		880/1493	162/1481	122/1491	

TABLE 2 Clinical outcome of TAVR with or without CEP.

Study	Intervention	Type of valve	Type of CEP	All-cause mortality	All stroke	Major bleeding complications	AKI (Stage II/III)	Major vascular complications	Procedural success	30-day events				
										All-cause mortality	Overt stroke	Life-threatening bleeding	AKI	Major vascular compli-cations
Wendt et al. (EMBOL-X)[28]	With CEP	SAPIEN-XT	EMBOL-X	0	0	–	–	–	100%	NA	–	–	–	–
	Without CEP			0	0					NA				
Lansky et al. (DEFLECT III)[29]	With CEP	SAPIEN-XT	TriGuard	1/46	1/46	1/46	1/46	7/46	88.90%	1/46	2/46	2/46	1/46	8/46
	Without CEP	SAPIEN-XT, CoreValve		2/39	2/39	2/39	0/39	6/39		2/39	2/39	3/39	0	8/46
Kapadia et al. (SENTINEL)[30]	With CEP	SAPIEN-XT, SAPIEN-3, CoreValve, Evolut-R	Sentinel						94.40%	3/234	13/231		1/231	21/244
	Without CEP									2/111	10/110		0/111	7/119
Lind et al.[31]	With CEP	CoreValve Evolut, Sapien S3	TriGuard 3	–	–	7/18	2/18	–	100%	0/18	2/18	–	–	–
	Without CEP					17/33	1/33	–	100%	4/33	10/33			
Butala et al.[32]	With CEP	CoreValve, Sapien	Sentinel	99/12,409	158/12,409	491/12,266	–	–	96.90%	162/11,658	216/11,682	–	–	–
	Without CEP			1317/ 110,777	1716/ 110,777	4808/108,858			97.30%	2297/ 102,877	2224/ 102,919			
Megaly et al.[33]	With CEP		Sentinel	0/525 (in hospital)	5/525	–	–	0/525	–	–	–	–	–	–
	Without CEP			510/35,695	920/35,695			30/35,695						
Rodés-Cabau et al. (PROTAVI-C)[34]	With CEP	SAPIEN-XT	Embrella Embolic Deflector	–	–	–	–	–	100%	3/41	3/41	3/41	3/41	5/41
	Without CEP									0/11	0/11	0	0	1/11
Samim et al.[35]	With CEP	Medtronic core valve, Edwards SAPIEN XT	Embrella Embolic Deflector System	-	0/15	–	–	–	100%	0/15	0/15	–	–	–
	Without CEP				0/37				100%	0/37	0/37			
Stachon et al.[36]	With CEP			30/1564 (in hospital)	44/1564	–	123/1564	–		–	–	–	–	–
	Without CEP			1033/40,090	849/40,090		2897/ 40,090							
Van Mieghem et al. (MISTRAL-C)[37]	With CEP	SAPIEN-XT, SAPIEN-3,	Sentinel						93.75%	1/32	0/32	1/32	0/32	0/32
	Without CEP									3/33	2/33	5/33	1/33	6/33

(Continues)

TABLE 2 (Continued)

Study	Intervention	Type of valve	Type of CEP	All-cause mortality	All stroke	Major bleeding complications	AKI (Stage II/III)	Major vascular complications	Procedural success	30-day events				
										All-cause mortality	Overt stroke	Life-threatening bleeding	AKI	Major vascular compli-cations
		Medtronic CoreValve, Balloon dilatation, Portico												
Seeger et al.[38]	With CEP		Claret dual valve sentinel type	2/280 (7-day follow-up)	4/280	4/280	3/280	5/280	91.8%	–	–	–	–	–
	Without CEP			11/522	22/522	21/522	7/522	19/522						
Seeger et al. (RESPOND)[39]	With CEP	lotus valve			1/92						1/92	NA	NA	
	Without CEP				30/904						31/904			
Voss et al.[40]	With CEP	Medtronic CoreValve, Edwards Sapien 3 valve	Claret Sentinel	–	–	1/39	3/39	1/39	94.90%	–	–	–	–	–
	Without CEP					11/352	39/352	9/352						
Haussig et al. (CLEAN TAVI)[41]	With CEP	Medtronic Core Valve	Claret Montage Dual Filter System	–	5/50	–	–	–	90%	0	4/50	1/50	1/50	5/50
	Without CEP				5/50					1/50	4/50	1/50	5/50	6/50
Dona et al.[42]	With CEP		Sentinel	1/213 (in hospital)	5/213	–	–	–	88.7%	19/213	–	–	–	–
	Without CEP			1/198	13/198					32/198				
Nazif et al. (REFLECT II)[43]	With CEP	Medtronic Core Valve, Edwards SAPIEN	TriGuard 3	4/157	13/157	9/157	4/157	11/157	67.60%	4/157	13/157	9/157	4/157	11/157
	Without CEP			1/57	3/57	0/57	0/57	0/57		1/57	3/57	0/57	0/57	0/57
Lansky et al. (REFLECT I)[44]	With CEP	Medtronic Corevalve	TriGuard HDH	0/141	13/141	4/141	0/141	16/141	93.40%	2/131	14/131	4/130	0/129	16/130
	Without CEP			0/63	4/63	0/63	0/63	1/63		0/59	4/59	0/59	0/59	1/59
Kemp et al.[45]	With CPS	Boston Accurate Neo, Boston Lotus Edge and	Sentinel	0/78	0/78		3/78			0/78				
	Without CPS			2/79	5/79		6/79		99.00%	2/79				

TABLE 2 (Continued)

Study	Intervention	Type of valve	Type of CEP	All-cause mortality	All stroke	Major bleeding complications	AKI (Stage II/III)	Major vascular complications	Procedural success	30-day events				
										All-cause mortality	Overt stroke	Life-threatening bleeding	AKI	Major vascular complications
		Medtronic evolut R												
Isogai et al.[46]	With CPS		Sentinel	2/1802	8/1802					2/1802	8/1802			
	Without CPS			8/1037	15/1037					8/1037	15/1037			
Kapadia et al. (PROTECTED-TAVR)[47]	With CPS		Sentinel	8/1501	34/1501		8/1501		94.4%					
	Without CPS			4/1499	43/1499		7/1499							

−169.44 to 17.38; $n = 765$; studies = 8; $I^2 = 69\%$; Supporting Information: Figure 7).

4.5.3 | Number of new lesions per patient

Meta-analysis of the number of new lesions per patient among those treated with CEP with TAVR versus TAVR only showed no statistical difference between the two (MD: −0.26, 95% CI: −2.08 to 1.56; $n = 728$; studies = 7; $I^2 = 80\%$;Supporting Information: Figure 8).

4.6 | Major complications

4.6.1 | Acute kidney injury

There was no statistical difference in the odds of AKI among those treated with CEP with TAVR versus TAVR only (OR: 1.06, 95% CI: 0.89–1.27; $n = 47{,}101$; studies = 13; $I^2 = 0\%$; Supporting Information: Figure 9).

4.6.2 | Major or life-threatening bleeding

The odds of major or life-threatening bleeding on Day 30 did not differ between the two groups (OR: 0.86, 95% CI: 0.70–1.06; n = 123,073; $I^2 = 3\%$; Supporting Information: Figure 10).

4.6.3 | Major vascular complications

There was no difference in the odds for developing major vascular complications among those treated with CEP with TAVR versus TAVR only (OR: 1.08, 95% CI: 0.59–1.95; $n = 38{,}488$; studies = 10; $I^2 = 30\%$; Supporting Information: Figure 11).

4.7 | Publication bias

Publication bias of included studies was assessed using Egger's funnel plots (Supporting Information: Figures 12 and 13).

5 | DISCUSSION

The transcatheter approach to aortic valve replacement reduces cardiac symptoms, hastens recovery time, and has been shown to reduce the 1-year mortality rate by 20% in patients at high surgical risk.[2] However, the risk of stroke remains a substantial concern, with rates of stroke around 5% in RCTs comparing TAVR with SAVR in high-risk patients.[1,2] Thus, the CEP was developed to diminish the risk of CVEs, shorten the length of stay, and improve the overall survival rate.[32,33,38,42] This meta-analysis investigated the safety and

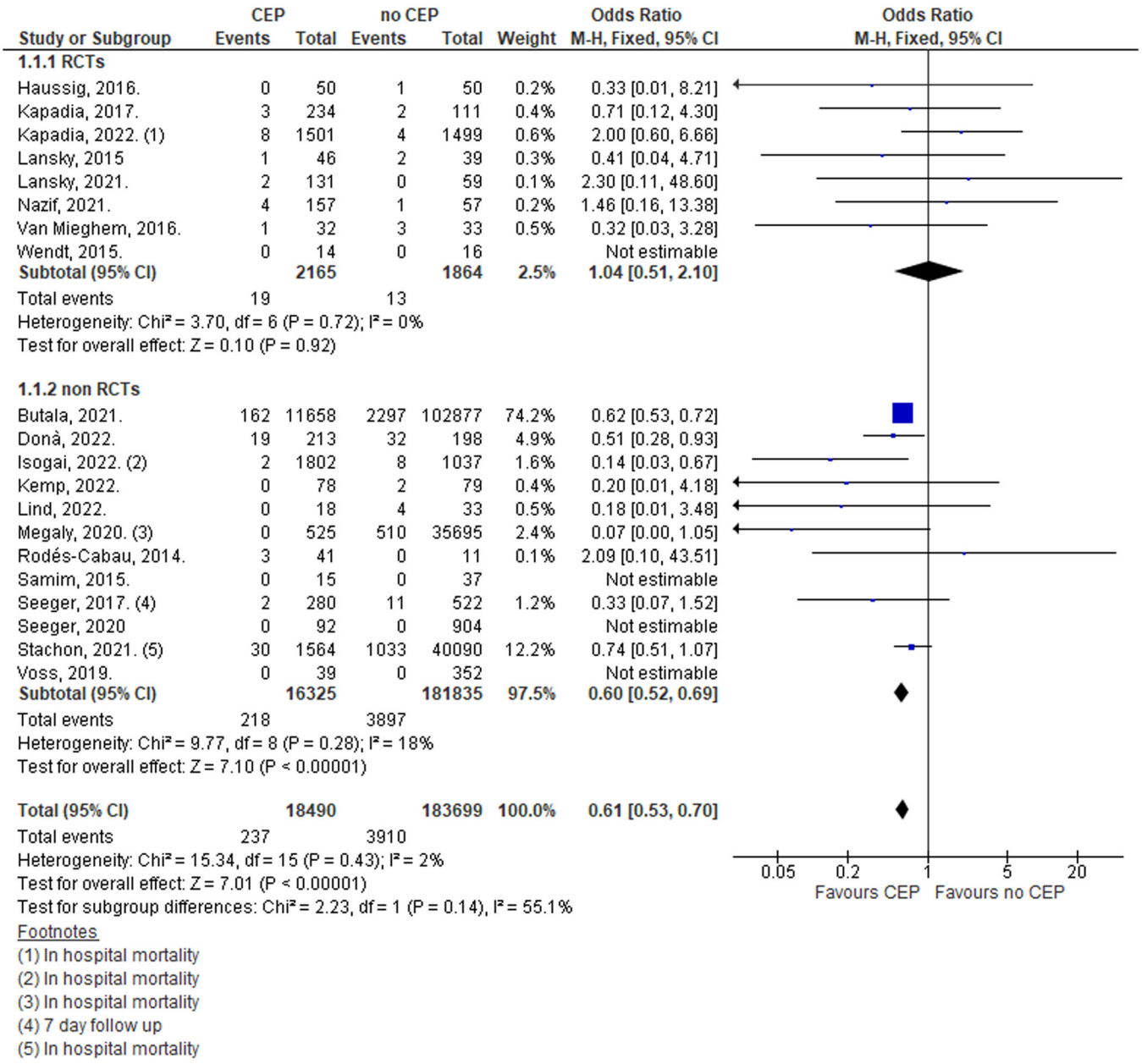

FIGURE 2 Forest plot showing 30-day mortality comparing patients undergoing TAVR only versus those undergoing TAVR with CEP using a fixed effect model. CEP, cerebral embolic protection; TAVR, transcatheter aortic valve replacement.

efficacy of CEP use during TAVR. Our analysis showed overall 39% lower odds in 30-day mortality (OR: 0.61, 95% CI: 0.53–0.70), and 31% lower odds of stroke at 30 days (OR: 0.69, 95% CI: 0.52–0.92). In our subgroup analysis, these findings were weighted by the findings from the Sentinel CEP; however, four RCTs including Sentinel devices did not reach significance. These findings are congurent with previous results of Butala et al. which study described lower odds of mortality and lower trend in stroke in national inpatient registry-based data.[32] Giustino et al. previously did not observe any significant reduction in clinically overt stroke or all-cause mortality.[48] We believe that the differences between our findings and Giustino et al. can be explained by inclusion of only four RCTs with total population of 252.

Despite similar stroke rates with and without the use of CEP, disabling stroke is thought to occur less commonly among the CEP group.[47] CEP devices are designed to primarily protect the carotid arterial system and current studies are inconclusive about the stroke distribution and stroke size. Further RCTs that compare stroke distribution and stroke severity should be conducted to assess the potential benefit of CEP devices.

In this study, the secondary outcomes of imaging-based embolic phenomena did not show significant differences between

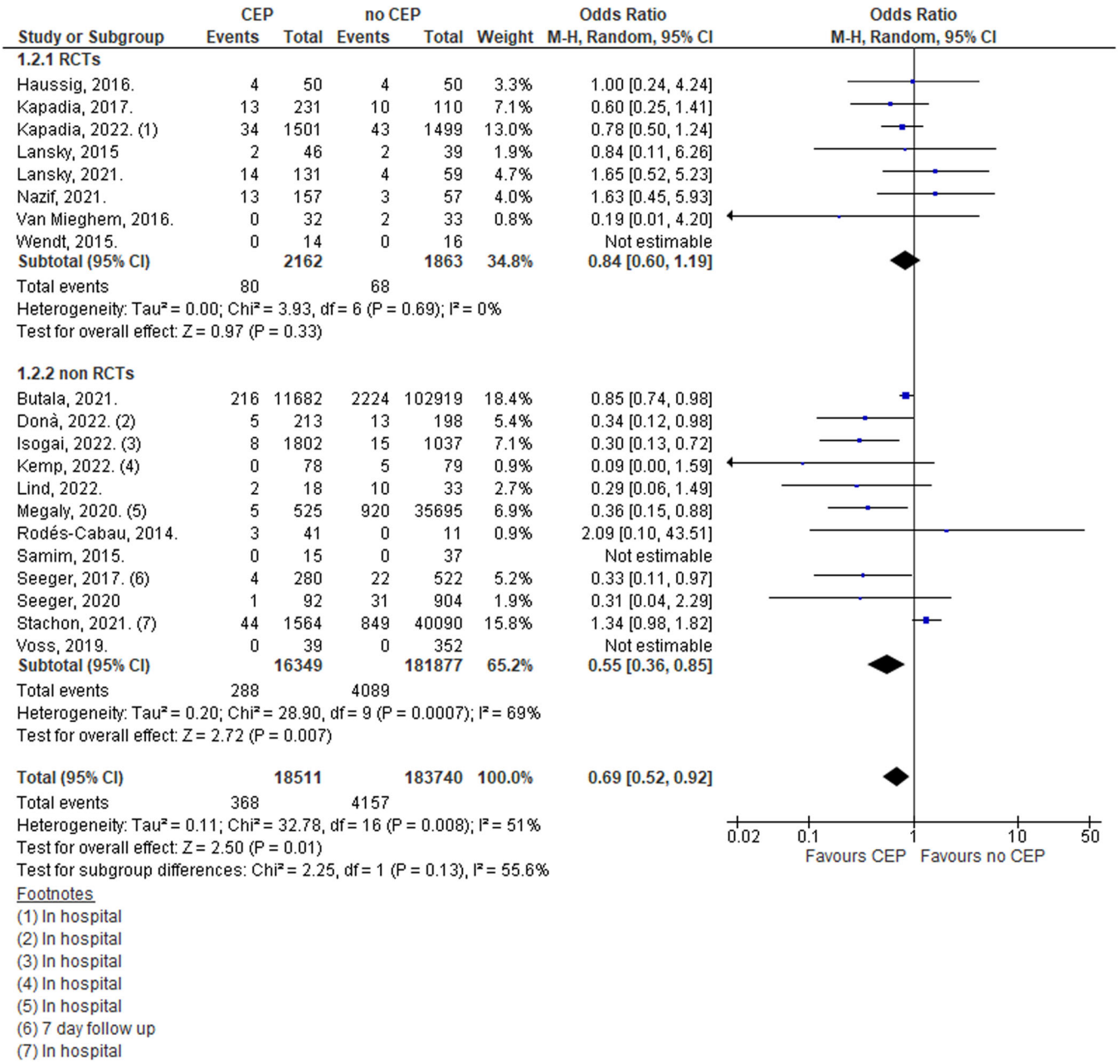

FIGURE 3 Forest plot demonstrating 30-day stroke event rates for patients undergoing TAVR only versus TAVR with CEP, using a random-effect model. CEP, cerebral embolic protection; TAVR, transcatheter aortic valve replacement.

patients treated with or without CEP during TAVR. Among prior studies, only Haussaig et al.[41] described a statistically significant decrease in the volume of lesions, while all other studies failed to show differences.[28,30,34,35,37,43,44] Most RCT studies have used 3 T DW-MRI brain imaging, aside from a study by Wendt et al.[28] that used 1.5 T DW-MRI, which is maybe less sensitive. Studies consistently obtained postprocedure MRIs at 7- and 30-day post-TAVR; some studies were limited by not having access to preprocedural MRIs.[29]

We did not observe any differences in the odds of major or life-threatening bleeding, acute kidney injury, or major vascular complications. Our findings can be compared with the results of Ndunda et al. for AKI and major vascular complications.[49]

5.1 | Limitations

Inclusion of only randomized studies failed to show a reduction in mortality or stroke when CEP was used in conjunction with TAVR versus TAVR alone. It is possible that the findings are due to insufficient total sample size and are not powered adequately enough to show significant differences. The relative infrequency of clinically

evident strokes and also heterogeneity among the studies may have contributed to this lack of differences. Included studies used real-world data and included different CEP devices, which may differ in their design and efficacy. Also, included studies did not analyze the neurocognitive outcome of patients due to the limited availability of data.

6 | CONCLUSIONS

This meta-analysis suggests that the use of CEP is associated with lower odds of 30-day mortality only when non-randomized studies were pooled with data from RCTs. There was no overall reduction in stroke when CEP was used with TAVR compared with patients treated only with TAVR. Our subanalysis suggests that outcomes were more compelling when the Sentinel CEP device was used. Operators will need to determine CEP use based on clinical judgment until new iterations of the device are available, or additional studies compel more or less utilization.

AUTHOR CONTRIBUTIONS

Dhan Bahadur Shrestha: Conceptualization; data curation; formal analysis; methodology; project administration; resources; software; validation; visualization; writing—original draft; writing—review and editing. **Jurgen Shtembari**: Conceptualization; methodology; visualization; writing—original draft; writing—review and editing. **Sandesh Lamichhane**: Data curation; investigation; methodology; project administration; resources; software; writing—original draft; writing—review and editing. **Abinash Baniya**: Data curation; investigation; resources; software; writing—original draft; writing—review and editing. **Manoj Shahi**: Data curation; investigation; methodology; project administration; resources; software; writing—original draft; writing—review and editing. **Swati Dhungel**: Project administration; supervision; writing—review and editing. **Kailash Pant**: Project administration; supervision; validation; writing—review and editing. **Nadia R. Sutton**: Conceptualization; investigation; methodology; project administration; supervision; validation; visualization; writing—review and editing. **Pedro Villablanca**: Investigation; methodology; project administration; supervision; validation; writing—review and editing. **Sudhir Mungee**: Project administration; supervision; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data are available in the manuscript and Supporting Information files.

TRANSPARENCY STATEMENT

The lead author Abinash Baniya affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

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How to cite this article: Shrestha DB, Shtembari J, Lamichhane S, et al. Safety and efficacy of cerebral embolic protection devices for patients undergoing transcatheter aortic valve replacement: An updated meta-analysis. *Health Sci Rep*. 2023;6:e1391. doi:10.1002/hsr2.1391