Routine Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement: A Meta-Analysis of RCTs

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Disclosure of Relevant Financial Relationships

I, Mahmoud Ismayl DO NOT have any financial relationships to disclose.

Background

- TAVR has emerged as a standard therapeutic approach for patients with severe symptomatic AS across all surgical risk categories.[1]
- Although advancements in technique and technology have led to a reduction in many procedure-related complications, the incidence of periprocedural stroke has remained relatively unchanged.[2]
- This persistent risk has spurred considerable interest in cerebral embolic protection (CEP) strategies aimed at minimizing cerebrovascular events associated with TAVR procedures.[3]

[1]Otto CM et al. *J Am Coll Cardiol*. 2021;77:450-500
[2]Ismayl M, et al. *Am J Cardiol*. 2023;199:59-70
[3]Kharbanda RK et al. *N Engl J Med*. 2025;392:2403-2412

Background

- Data from the TVT Registry indicate that CEP devices are used in approximately 28% of TAVR centers and 13% of procedures nationwide.[1]
- Despite this uptake, the recent **BHF PROTECT-TAVI** trial reported no significant reduction in stroke rates with CEP use.[2]
- We performed an updated meta-analysis of RCTs to comprehensively evaluate the clinical effectiveness and safety profile of CEP devices during TAVR.

[1]Butala NM et al. *Circulation*. 2021;143:2229-2240
[2]Kharbanda RK et al. *N Engl J Med*. 2025;392:2403-2412

Methods

- A systematic search of 3 electronic databases—PubMed, EMBASE, and ClinicalTrials.gov—to identify RCTs comparing clinical outcomes of CEP devices versus standard care during TAVR.
- Search terms and keywords: “Cerebral Embolic Protection,” “Embolic Protection,” “Transcatheter Aortic Valve Replacement,” “TAVR,” “Stroke,” and “Cerebrovascular Accident.”
- Studies were included if they reported data on at least one of the predefined clinical endpoints.

Methods

- Primary outcome:
  - Stroke (including disabling and nondisabling strokes)
- Secondary outcomes:
  - Disabling stroke
  - All-cause mortality
  - New ischemic lesions on post-TAVR brain MRI
  - Major vascular complications
  - Life-threatening bleeding
  - Acute kidney injury

Methods

- For dichotomous outcomes, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated from the available data in the included studies, and study-specific RRs were combined using the DerSimonian and Laird random-effects model with the estimate of heterogeneity taken from the Mantel−Haenszel model.
- Risk of bias among included trials: Cochrane risk of bias tool.
- Quantify statistical heterogeneity: Higgins *I*-squared (I^2) statistic.
- Publication bias: funnel plots.

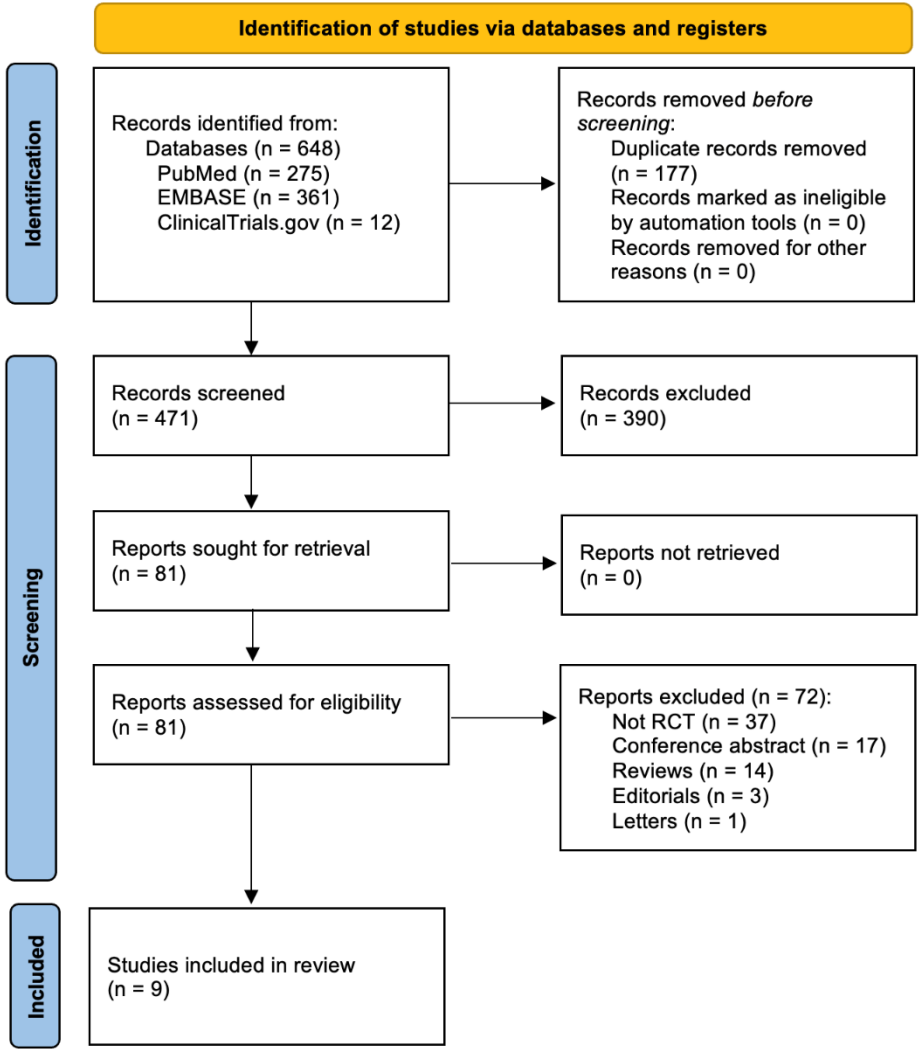
Methods

- All statistical analyses were performed using the Cochrane Review Manager (RevMan) version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).
- For all analyses, $p < 0.05$ was considered statistically significant.
- Results were reported according to the PRISMA Protocol 2020 statement.

Results

- PRISMA flow diagram for study search and selection.

- 9 RCTs with 11,641 patients undergoing TAVR
  - 5,970 **with** CEP
  - 5,671 **without** CEP



Results

- All studies reported outcomes at 30 days except 2 trials—**BHF PROTECT-TAVI**[1] and **PROTECTED TAVR**[2]—which reported outcomes at 72 hours post-procedure or at the time of hospital discharge (if discharge occurred sooner).
- All included studies were of acceptable methodological quality, with no evidence of significant publication bias or substantial heterogeneity (I^2 > 50%).

[1]Kharbanda RK et al. *N Engl J Med*. 2025;392:2403-2412
[2]Kapadia SR et al. *N Engl J Med*. 2022;387:1253-1263

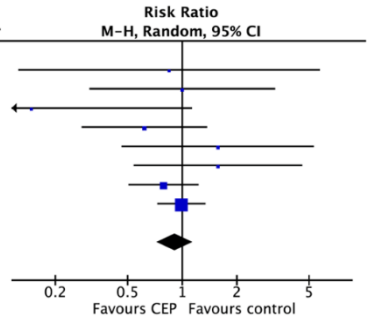
Results

- **No significant differences** between CEP and control groups in terms of:
  - Stroke
  - Disabling stroke

A: Stroke

Study or Subgroup	CEP group Events	CEP group Total	Control group Events	Control group Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
TAo-EmbolX 2015	0	14	0	16		Not estimable	2015
DEFLECT III 2015	2	46	2	39	1.3%	0.85 [0.13, 5.74]	2015
CLEAN-TAVI 2016	5	50	5	50	3.6%	1.00 [0.31, 3.24]	2016
MISTRAL-C 2016	1	32	7	33	1.2%	0.15 [0.02, 1.13]	2016
SENTINEL 2017	13	231	10	110	7.8%	0.62 [0.28, 1.37]	2017
REFLECT II 2021	13	157	3	57	3.3%	1.57 [0.47, 5.32]	2021
REFLECT I 2021	14	131	4	59	4.3%	1.58 [0.54, 4.59]	2021
PROTECTED TAVR 2022	34	1501	43	1499	25.0%	0.79 [0.51, 1.23]	2022
BHF PROTECT-TAVI 2025	81	3795	82	3799	53.4%	0.99 [0.73, 1.34]	2025
Total (95% CI)		**5957**		**5662**	**100.0%**	**0.91 [0.73, 1.14]**	
Total events	163		156				

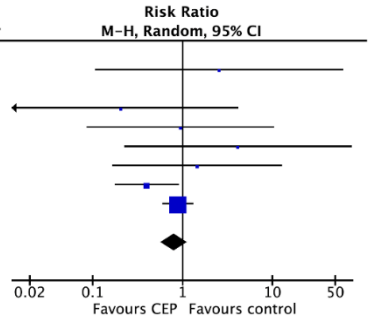
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.48$, df = 7 (P = 0.48); $I^2 = 0\%$
Test for overall effect: Z = 0.82 (P = 0.41)



B: Disabling stroke

Study or Subgroup	CEP group Events	CEP group Total	Control group Events	Control group Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
TAo-EmbolX 2015	0	14	0	16		Not estimable	2014
DEFLECT III 2015	1	46	0	39	1.1%	2.55 [0.11, 60.95]	2015
CLEAN-TAVI 2016	0	50	0	50		Not estimable	2016
MISTRAL-C 2016	0	32	2	33	1.3%	0.21 [0.01, 4.13]	2016
SENTINEL 2017	2	231	1	109	2.0%	0.94 [0.09, 10.30]	2017
REFLECT I 2021	4	130	0	59	1.3%	4.12 [0.23, 75.35]	2021
REFLECT II 2021	4	157	1	57	2.4%	1.45 [0.17, 12.72]	2021
PROTECTED TAVR 2022	8	1501	20	1499	17.1%	0.40 [0.18, 0.90]	2022
BHF PROTECT-TAVI 2025	47	3795	53	3799	74.8%	0.89 [0.60, 1.31]	2025
Total (95% CI)		**5956**		**5661**	**100.0%**	**0.80 [0.57, 1.12]**	
Total events	66		77				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.88$, df = 6 (P = 0.44); $I^2 = 0\%$
Test for overall effect: Z = 1.32 (P = 0.19)



Results

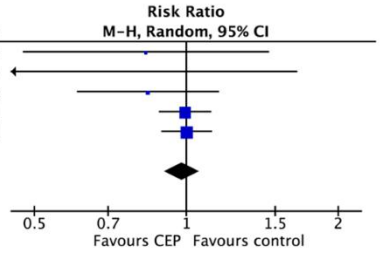
- **No significant differences** between CEP and control groups in terms of:
  - New ischemic lesions on post-TAVR brain MRI

C: New MRI lesions

Study or Subgroup	CEP group Events	Total	Control group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
TAo-EmbolX 2015	8	14	11	16	2.0%	0.83 [0.47, 1.46]	2015
DEFLECT III 2015	1	33	4	26	0.1%	0.20 [0.02, 1.66]	2015
MISTRAL-C 2016	16	22	13	15	6.0%	0.84 [0.61, 1.16]	2016
REFLECT I 2021	97	111	51	58	44.5%	0.99 [0.88, 1.12]	2021
REFLECT II 2021	85	100	90	106	47.4%	1.00 [0.89, 1.12]	2021
Total (95% CI)		**280**		**221**	**100.0%**	**0.98 [0.91, 1.06]**	
Total events	207		169				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.00$, $df = 4$ ($P = 0.41$); $I^2 = 0\%$

Test for overall effect: $Z = 0.46$ ($P = 0.64$)



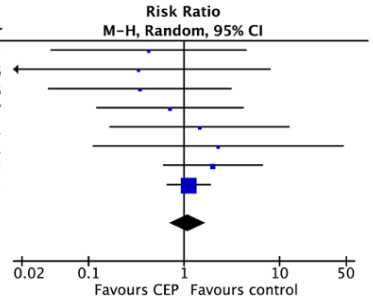
Results

- **No significant differences** between CEP and control groups in terms of:
  - All-cause mortality
  - Major vascular complications

A: Mortality

Study or Subgroup	CEP group Events	CEP group Total	Control group Events	Control group Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
DEFLECT III 2015	1	46	2	39	3.3%	0.42 [0.04, 4.50]	2015
CLEAN-TAVI 2016	0	50	1	50	1.8%	0.33 [0.01, 7.99]	2016
MISTRAL-C 2016	1	32	3	33	3.8%	0.34 [0.04, 3.13]	2016
SENTINEL 2017	3	234	2	111	5.9%	0.71 [0.12, 4.20]	2017
REFLECT II 2021	4	157	1	57	3.9%	1.45 [0.17, 12.72]	2021
REFLECT I 2021	2	131	0	59	2.0%	2.27 [0.11, 46.62]	2021
PROTECTED TAVR 2022	8	1501	4	1499	12.9%	2.00 [0.60, 6.62]	2022
BHF PROTECT-TAVI 2025	29	3795	26	3799	66.4%	1.12 [0.66, 1.89]	2025
Total (95% CI)		**5946**		**5647**	**100.0%**	**1.09 [0.71, 1.67]**	
Total events	48		39				

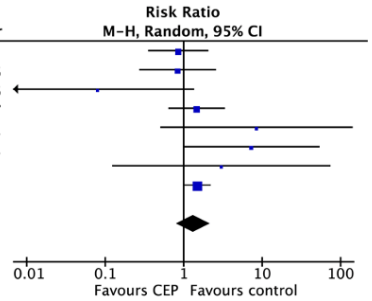
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.70$, df = 7 (P = 0.81); $I^2 = 0\%$
Test for overall effect: Z = 0.39 (P = 0.70)



B: Major vascular complications

Study or Subgroup	CEP group Events	CEP group Total	Control group Events	Control group Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
DEFLECT III 2015	8	46	8	39	18.4%	0.85 [0.35, 2.05]	2015
CLEAN-TAVI 2016	5	50	6	50	13.6%	0.83 [0.27, 2.55]	2016
MISTRAL-C 2016	0	32	6	33	2.9%	0.08 [0.00, 1.35]	2016
SENTINEL 2017	21	244	7	119	19.8%	1.46 [0.64, 3.34]	2017
REFLECT II 2021	11	157	0	57	2.9%	8.44 [0.51, 141.00]	2021
REFLECT I 2021	16	130	1	59	5.4%	7.26 [0.99, 53.48]	2021
PROTECTED TAVR 2022	1	1501	0	1499	2.3%	3.00 [0.12, 73.49]	2022
BHF PROTECT-TAVI 2025	64	3772	43	3776	34.7%	1.49 [1.02, 2.19]	2025
Total (95% CI)		**5932**		**5632**	**100.0%**	**1.32 [0.81, 2.18]**	
Total events	126		71				

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 10.55$, df = 7 (P = 0.16); $I^2 = 34\%$
Test for overall effect: Z = 1.11 (P = 0.27)



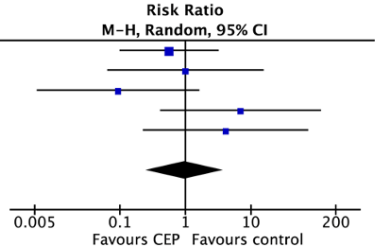
Results

- **No significant differences** between CEP and control groups in terms of:
  - Life-threatening bleeding
  - Acute kidney injury

C: Life-threatening bleeding

Study or Subgroup	CEP group Events	Total	Control group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
DEFLECT III 2015	2	46	3	39	31.6%	0.57 [0.10, 3.21]	2015
CLEAN-TAVI 2016	1	50	1	50	17.9%	1.00 [0.06, 15.55]	2016
MISTRAL-C 2016	0	32	5	33	16.9%	0.09 [0.01, 1.63]	2016
REFLECT II 2021	9	157	0	57	17.1%	6.97 [0.41, 117.94]	2021
REFLECT I 2021	4	130	0	59	16.5%	4.12 [0.23, 75.35]	2021
Total (95% CI)		**415**		**238**	**100.0%**	**0.99 [0.25, 3.86]**	
Total events	16		9				

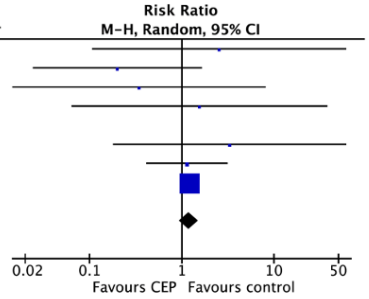
Heterogeneity: $Tau^2 = 0.75$; $Chi^2 = 5.79$, df = 4 (P = 0.22); $I^2 = 31\%$
Test for overall effect: Z = 0.02 (P = 0.98)



D: Acute kidney injury

Study or Subgroup	CEP group Events	Total	Control group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
DEFLECT III 2015	1	46	0	39	0.5%	2.55 [0.11, 60.95]	2015
CLEAN-TAVI 2016	1	50	5	50	1.2%	0.20 [0.02, 1.65]	2016
MISTRAL-C 2016	0	32	1	33	0.5%	0.34 [0.01, 8.13]	2016
SENTINEL 2017	1	231	0	119	0.5%	1.55 [0.06, 37.80]	2017
REFLECT I 2021	0	129	0	59		Not estimable	2021
REFLECT II 2021	4	157	0	57	0.6%	3.30 [0.18, 60.42]	2021
PROTECTED TAVR 2022	8	1501	7	1499	5.3%	1.14 [0.41, 3.14]	2022
BHF PROTECT-TAVI 2025	137	3414	113	3417	91.2%	1.21 [0.95, 1.55]	2025
Total (95% CI)		**5560**		**5273**	**100.0%**	**1.19 [0.94, 1.50]**	
Total events	152		126				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.09$, df = 6 (P = 0.66); $I^2 = 0\%$
Test for overall effect: Z = 1.45 (P = 0.15)



Results

- A subgroup analysis based on the type of CEP device showed similar outcomes between CEP and control groups, regardless of the type of CEP device used.

Discussion

- The absence of demonstrable benefit in stroke or mortality reduction raises important questions.
- It remains unclear whether this reflects inherent limitations of first-generation CEP devices, suboptimal trial design that did not specifically target high-risk stroke populations, or a true lack of therapeutic efficacy.

Discussion

- **BHF PROTECT-TAVI** [1]:
  - Short follow-up duration
  - Use of a device that did not provide complete protection of all cerebral territories.
- **PROTECTED TAVR**[2]:
  - The observed stroke rates were lower than anticipated, potentially limiting the study's power.

[1]Kharbanda RK et al. *N Engl J Med*. 2025;392:2403-2412
[2]Kapadia SR et al. *N Engl J Med*. 2022;387:1253-1263

Discussion

- Importantly, neither the TVT Registry analysis nor prior trials have identified specific patient subgroups that clearly benefit from CEP on stratified analyses.[1,2]
- Unmet research need: to better define high-risk populations who may derive clinical benefit from CEP during TAVR.
- Until such evidence becomes available, selective and judicious use of CEP devices may be reasonable in individual cases, but current data do not support its routine application in all patients undergoing TAVR.

[1]Kharbanda RK et al. *N Engl J Med*. 2025;392:2403-2412
[2]Butala NM et al. *Circulation*. 2021;143:2229-2240

Limitations

- Inherent limitations to the included RCTs, such as low event rates and the absence of patient-level data, which limited our ability to perform subgroup analyses and identify populations that may derive benefit from CEP devices.
- Furthermore, 2 of the 9 trials (**BHF PROTECT-TAVI** and **PROTECTED TAVR**)[1,2] were very large in size and therefore the weights of these studies largely influenced the pooled estimates for the RRs.

[1]Kharbanda RK et al. *N Engl J Med*. 2025;392:2403-2412
[2]Kapadia SR et al. *N Engl J Med*. 2022;387:1253-1263

Conclusions

- In this meta-analysis of RCTs, CEP during TAVR was **not** associated with significant reductions in stroke or mortality.
- These findings do **not** support the routine use of CEP devices in all patients undergoing TAVR.
- Future studies are warranted to identify subgroups that may benefit from selective CEP use and to evaluate the efficacy of next-generation devices.