Cerebral Embolic Protection During TAVR

A Clinical Event Meta-Analysis

Embolic protection (EP) is a strategy to prevent embolization of thrombotic or calcific debris during transcatheter aortic valve replacement (TAVR). Randomized controlled trials (RCT) investigating the efficacy and safety of EP devices have been underpowered for clinical endpoints (1–5). Whereas preliminary data suggest that EP may reduce cerebral infarction markers or improve early cognition, any effect on hard clinical endpoints remains unclear.

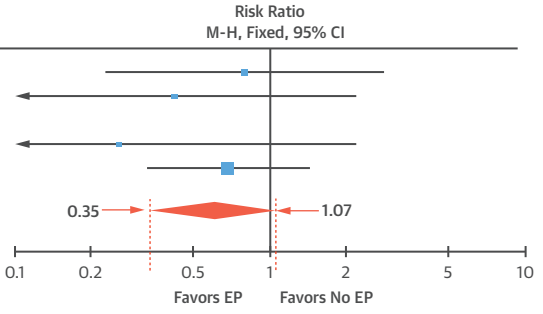
With the release of new evidence (1), we performed an updated systematic review and aggregate data meta-analysis of RCT that evaluated EP during TAVR according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The research protocol of this study was registered in PROSPERO (International Prospective Register of Systematic Reviews) (CRD42016049057). Study groups were defined by the random assignment to EP versus not. The primary clinical endpoint was the risk of death or stroke at longest follow-up available according to the intention-to-treat principle. Risk for bias in each trial was systematically evaluated with the Cochrane tool. We estimated risk ratio (RR) with 95% confidence intervals (CI). We also estimated the absolute risk differences (ARD) (with 95% CI) and number needed to treat (NNT), to evaluate the public health impact of the intervention. Given the lack of observed heterogeneity across trials, the primary analytic method was with fixed effects. Heterogeneity across trials was estimated with I2 statistics (I^2 < 50% indicating lack of heterogeneity). Analyses were conducted using STATA (version 14, STATA Corp., College Station, Texas) and Review Manager (version 5.3; Cochrane Collaboration, Copenhagen, Denmark) software.

A total of 5 RCT with 625 patients were included (1–5); 376 patients were randomized to EP (different devices, but same device within each trial) and 249 to no EP. Overall risk of bias was deemed low in all 5 trials. EP had a nonsignificant trend towards lower risk of death or stroke on relative (6.1% vs. 9.6%; RR: 0.61; 95% CI: 0.35 to 1.07; p = 0.08; I^2 = 0%) and absolute (ARD: −3.5%; 95% CI: −7.9% to 0.9%; NNT = 28) terms (**Figure 1**). Results were potentially consistent following stratification by type of EP device used ($p_{interaction}$ = 0.64). The magnitude and direction of the effect was also consistent with sequential exclusion of each included RCT. Concordant effect estimates were found for all-cause mortality on relative (1.3% vs. 3.6%; RR: 0.42; 95% CI: 0.14 to 1.26; p = 0.12; I^2 = 0%) and absolute (ARD: −2.28%; 95% CI: −4.88% to 0.31%; NNT = 44) terms; as well as for stroke on relative (5.1% vs. 7.3%; RR: 0.66; 95% CI: 0.36 to 1.23; p = 0.20; I^2 = 0%) and absolute (ARD: −2.2%; 95% CI: −6.1% to 1.7%; NNT = 46) terms.

FIGURE 1 Clinical Outcomes in Patients Undergoing TAVR With Versus Without Embolic Protection Devices

Study or Subgroup	Embolic Protection Events	Embolic Protection Total	No Embolic Protection Events	No Embolic Protection Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CLEAN-TAVI	4	50	5	50	17.7%	0.80 [0.23, 2.81]
DEFLECT-III	2	46	4	39	15.4%	0.42 [0.08, 2.19]
EMBOL-X	0	14	0	16		Not estimable
MISTRAL-C	1	32	4	33	14.0%	0.26 [0.03, 2.18]
SENTINEL	16	234	11	111	52.9%	0.69 [0.33, 1.44]
Total (95% CI)		**376**		**249**	**100.0%**	**0.61 [0.35, 1.07]**
Total events	23		24			

Heterogeneity: Chi^2 = 1.10, df = 3 (P = 0.78); I^2 = 0%
Test for overall effect: Z = 1.73 (P = 0.08)



Pooled effect estimates for the risk of death or stroke according to the use of cerebral embolic protection versus not during TAVR. CI = confidence interval; CLEAN-TAVI = Claret Embolic Protection and TAVI; DEFLECT-III = A Prospective, Randomized Evaluation of the TriGuard HDH Embolic Deflection Device During TAVI; EP = embolic protection; M-H = Mantel-Haenszel; MISTRAL-C = MRI Investigation With Claret; SENTINEL = Cerebral Protection in Transcatheter Aortic Valve Replacement; TAVR = transcatheter aortic valve replacement.

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In this clinical event meta-analysis including the totality of RCT on this subject to date, EP was associated with a nonsignificant trend towards lower risk for death or stroke, which might correspond to a 3.5% absolute risk reduction and NNT of ~28 (i.e., for every ~28 patients assigned to an EP device, 1 death or stroke event may be averted). These findings suggest that EP may be a clinically relevant adjunctive strategy in patients undergoing TAVR. It is plausible that the magnitude of the benefit may be accentuated in patients at high risk for cerebrovascular complications. Additionally, because subclinical ischemic brain injury is associated with both cognitive and functional neurological impairment over time, prevention of subclinical embolization may be particularly important when treating younger and lower risk patients with severe aortic stenosis.

The present findings are subject to the inherent limitations of the included RCT: study design, sample size, treatment crossover, imaging and neurocognitive assessment drop-out, and endpoint ascertainment (underscoring the logistic challenges of this type of studies). Meta-analyses complement but do not replace adequately powered RCT. Therefore, additional evidence on EP effectiveness in routine practice is warranted, particularly on individual EP device performance and safety.

In conclusion, the totality of the data suggests that use of EP during TAVR appears to be associated with a nonsignificant trend towards reduction in death or stroke.

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Edoxaban Versus Warfarin

Bone Fractures Due to Falling

Steffel et al. (1) found that elderly atrial fibrillation patients receiving anticoagulation therapy and at increased fall risk had increased rate of bone fractures due to falling, which was similar between the use of 2 anticoagulants, edoxaban and warfarin (adjusted hazard ratio: 0.94; 95% confidence interval: 0.55 to 1.61). From an expert's point of view, this is an important finding that should be discussed.

Age-related fractures result generally from bone fragility and minor trauma such as a fall from a standing position; falling is closely linked to nonvertebral fractures such as in the hip that cause significant morbidity and mortality. Warfarin is a vitamin K antagonist (VKA) that inhibits γ-carboxylation of glutamic acid residues not only of blood coagulation proteins but also of osteocalcin, the most abundant noncollagenous bone protein, but evidence for deleterious effects of VKAs on bone health is weak (2). Of note, a number of clinical studies have independently and consistently shown that warfarin use is not associated with the risk of hip fracture (3) and that the meta-analysis suggests that anticoagulation with VKAs is unlikely to result in increased risk of such a fall-related fracture (4). This can be theoretically explained by natural homeostatic system in the skeleton (i.e., adaptation of bone to mechanical strain) (3,5). Consequently, the similar rates of bone fractures due to falling between use of non-VKA edoxaban and warfarin (1) are reasonable and seem to internally validate the results that anticoagulation with edoxaban was associated with lower rates of severe bleeding and mortality than with warfarin (1).