Review Article

Cerebral embolic protection devices during transcatheter aortic valve implantation: clinical versus silent embolism

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Abstract: Cerebrovascular events following transcatheter aortic valve implantation (TAVI) is one of the most devastating complications. Several studies with magnetic resonance or cerebral filters have demonstrated the universal brain embolization after TAVI, in the majority of patients clinically silent. Embolic protection devices (EPD) have been developed as a mechanical barrier to prevent these emboli to reach cerebral vasculature and potentially reduce neurological events. We review the current evidence about EPD in relation to histopathological and cerebral imaging findings and neurological events.

Keywords: Transcatheter aortic valve implantation (TAVI); transcatheter aortic valve replacement (TAVR); stroke, cerebrovascular events; embolic protection device (EPD)

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Introduction

Transcatheter aortic valve implantation (TAVI) is an established therapy for inoperable, high and moderate-risk patients with symptomatic aortic stenosis (1). Therefore, as TAVI has become an important option for an increasing number of patients, its complications should be minimized as much as possible. Cerebrovascular events (CVE) are one of the most feared complications following TAVI due to the enormous impact on patient's quality of life, morbidity and mortality (2-5). In fact, in the first placement of aortic transcatheter valve (PARTNER) randomized clinical trial (RCT) some concerns reached since the incidence of CVE was significantly higher in patients receiving TAVI compare with those undergoing surgical replacement (5.5% *vs.* 2.4% stroke incidence at 30 days, P=0.04) (6). Fortunately, current data showed lower rate of neurological complications with no difference compared to surgery (7,8). Nevertheless, prevention strategies to decrease CVE rate are critical prior to expand TAVI indication to younger, lower risk patients. Several imaging and histopathological studies have demonstrated that the majority of CVE after TAVI have an embolic origin, from debris embolization or thrombus formation (9). Embolic protection devices (EPD) have emerged as a mechanical protection strategy to prevent these emboli to reach the cerebral vasculature and decrease the associated neurological effects. The objective of this article is to provide an overview of the current knowledge of EPD.

Characteristics of EPD

To date, five different types of EPD, in the form of filters or deflectors have been tested and reported during TAVI procedures (*Figure 1*). Main characteristics in terms of design, cerebral protected territories and access routes are summarized in *Table 1*. While, filter devices have the advantage to obtain the embolized material, deflector-type systems are released in the aortic arch rejecting the debris towards the descending aorta, with a theoretically higher probability of peripheral embolism.

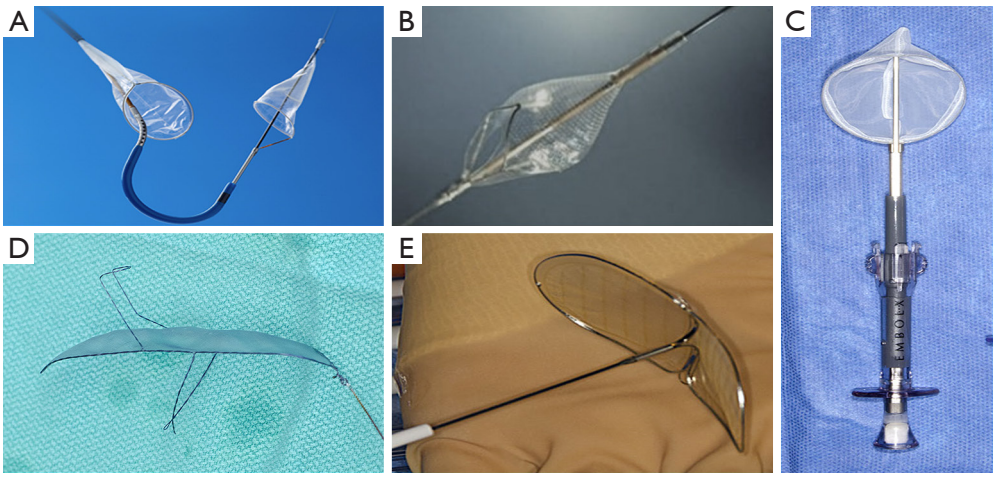

Figure 1 Types of cerebral protection devices. (A) Sentinel (Boston Scientific Corp.); (B) Wirion (Allium Medical Inc.); (C) Embol-X (Edwards Lifesciences); (D) TriGuard (Keystone Heart Ltd); (E) Embrella (Edwards Lifesciences).

Table 1 Main characteristics of the embolic protection devices

Design	Device	Manufacturer	Access	Delivery system	Deployment	Protected cerebral territories	Pore size (μm)
Deflector	Embrella	Edwards Lifesciences, Irvine, CA	Radial or brachial artery	6 F	Aortic arch	Partial protection	100
	TriGuard	Keystone Heart Ltd, Caesarea, Israel	Femoral artery	9 F	Aortic arch	Full protection	140
Filter	Embol-X	Edwards Lifesciences, Irvine, CA	Direct aortic	14 F	Ascending aorta	Full protection	120
	Claret Sentinel	Boston Scientific Corp.	Radial or brachial artery	6 F	1 filter to brachiocephalic trunk and 1 filter to left common carotid	Partial protection*	140
	Wirion	Allium Medical, Inc., Caesarea, Israel	Radial or brachial artery	6 F	1 filter in any vessel of 3.5 to 6 mm diameter	Partial protection*	120

*, Full protection in combination with the Wirion filter in the left vertebral artery.

The Sentinel device (Boston Scientific, Corp.) is a dual system filter, released in the brachiocephalic trunk and the left common carotid advanced in a 6-Fr sheath from the right upper extremity (*Figure 1A*). Using an articulating sheath, the curve of the device can be adjusted to accommodate anatomic variations of the aortic arch. It has received FDA approval in 2017 and it is to date the most widely used EPD in TAVI (it is the only device available in US). One limitation was the incomplete cerebral coverage, which may be solved, in combination with the Wirion Filter (Allium Medical, Inc.) placed in the left vertebral artery for full cerebral coverage (10) (*Figure 1B*). The Embol-X (Edwards Lifesciences, CA) is another filter system that was initially designed to use during conventional cardiac surgery and requires direct access to the ascending aorta (*Figure 1C*). A modified version has been tested in transaortic TAVI with full cerebral coverage. The Triguard device (Keystone Heart, Ltd) is a deflector device placed through a femoral 9-Fr sheath with a parallel use of a pigtail (*Figure 1D*). It provides full cerebral protection covering the 3 branches of the aortic arch with a semi-permeable mesh that deflects particles larger than 140μm. Finally, the Embrella deflector device (Edwards Lifesciences, CA) (*Figure 1E*), which is no longer under development, but was the earliest dedicated device for TAVI (11). It is used via the right radial (or brachial) artery with a 6-Fr sheath and advance into the

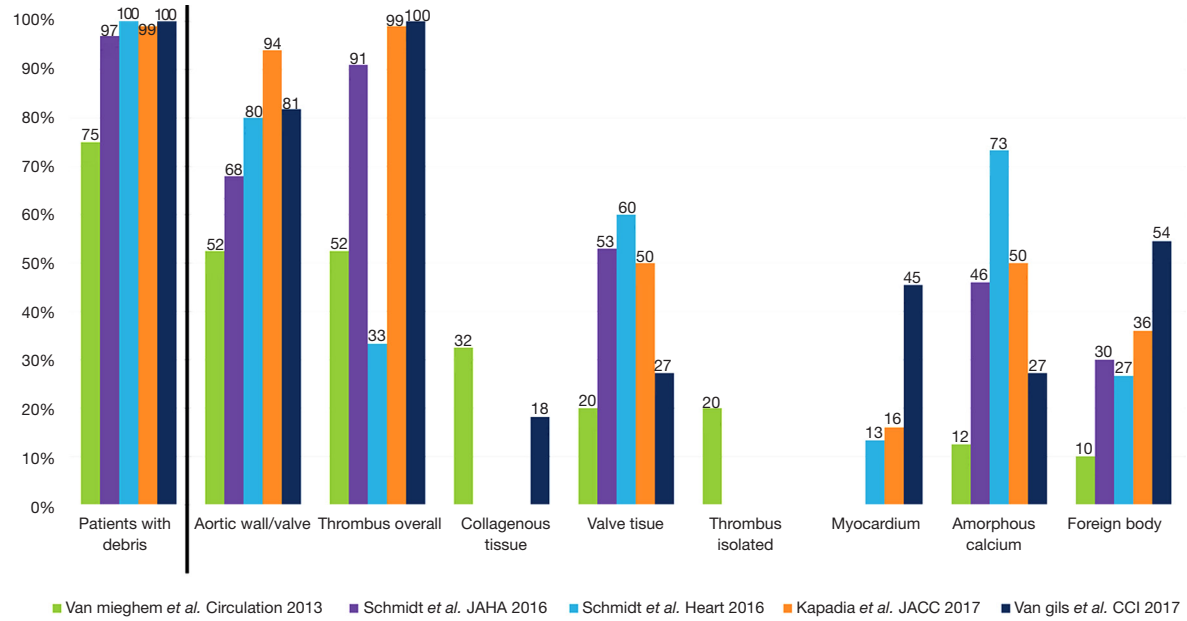

Figure 2 Frequency and distribution of captured debris in histopathologic analysis. Adapted from Armijo *et al.* (9).

aortic arch where the device covered brachiocephalic trunk and left common carotid, leaving left vertebral artery unprotected in most of the cases.

Subclinical data

Filter EPD helped extensively to understand the frequency and nature of the embolized material during the TAVI procedure. Initially, cerebral magnetic resonance imaging (MRI) studies demonstrated that new cerebral lesions, mostly silent, were observed in a high percentage of patients undergoing TAVI (ranging from 60% to 90%) (12-14). These lesions were not associated to the access route or the valve type, and were frequently diffuse and multiple, from anterior and posterior cerebral vascular territories, suggesting an embolic nature. Later, the embolic origin of these lesions was further reinforced by transcranial Doppler studies that quantified high intensity transient signals in the middle cerebral artery during TAVI. While these signals were observed over all phases of the procedure, the greatest number of signals occurred during valve positioning for self-expandable valves and valve implantation during balloon inflation (15,16). Finally, studies using cerebral filters wisely demonstrated that the majority of the patients undergoing TAVI had debris retained in the filter. Initially Van Mieghen *et al.* showed that the emboli were ~1mm size being the majority of fibrin or thrombotic nature (17). Posteriorly, other studies corroborated these findings (10,18-21). The frequency and nature in histopathologic analysis of the debris in different studies are depicted in *Figure 2*.

Clinical data

EPD data in TAVI procedure is based on several observational studies (10,11,22-29) and five randomized clinical trials (20,30-33). Most of them had a very low sample size and were non-powered to detect clinical outcomes. With the intention to detect differences in mortality or neurological events, several meta-analysis combined the results of these studies. Main characteristics and results of observational and randomized studies are summarized in *Table 2*.

Randomized trials

The EMBOL-X trial, which was prematurely interrupted with 30 patients included (only 14 with the filter), had a no effect in the frequency of new brain lesions (57% *vs.* 69%, P=0.70) and volume lesions (88±60 *vs.* 168±217 mm^3, P=0.27) in the MRI performed within 7 days post-procedure (30). However, the filter group had significantly smaller lesion volumes in the supply area of the middle cerebral artery (33±29 *vs.* 76±67 mm^3, P=0.04).

The DEFLECT III multicenter randomized trial with

Table 2 Main characteristics of non-randomized and randomized studies with embolic protection devices

Study	Year	Device	Total n of patients/n of patients with EPD	Design	Objectives/primary outcome	Main results
Observational						
Nietlispach *et al.* (11)	2010	Embrella	4/4	Case series	Describe initial human experience	Correct placement in all the patients Additional procedure time: 13 minutes A 5 mm acute subclinical cortical infarct in one patient
Naber *et al.* (22)	2012	Claret CE Pro + SpiderFX carotid filter	40/40	Case series, prospective, 3 centers	Describe initial human experience Technical success rate	Technical success rate: 87.5% Captured debris: 54% 2 major strokes and 1 minor stroke (30-day)
Onsea *et al.* (23)	2012	SMT embolic deflector	15/15	Case series	Describe first in man experience	Successful placement: 100% Additional procedure time: 7 minutes New cerebral lesions: 3.2 per patient (7.2 in an historical cohort) 1 transient ischemic attack
Rodés-Cabau *et al.* Pro-TAVI C (24)	2014	Embrella	52/41	Prospective, non-randomized, comparative study	Feasibility, safety and exploratory efficacy Control group with HITS and MRI studies	Correct placement in all the patients More HITS in the device group All patients had new lesions (day ≤7) and disappeared at 30-day. Same number of patients with multiple lesions in both groups Device associated with lower lesion volume
Samin *et al.* (25)	2015	Embrella	52/15	Prospective, non-randomized, multi-centre, single-arm study	Compare cerebral injury with and without EPD MRI at day 4 after TAVI	Patients with new brain lesions (100% *vs.* 95%) Increase in number of new ischemic lesions (9 *vs.* 5, P=0.044) in the EPD group Reduction in single lesion volume (9.7 *vs.* 17.8 µL, P<0.001)
Van Mieghem *et al.* (26)	2015	Montage Dual Filter	81/81	Case series	Histopathological analysis of tissue embolization	Debris captured in 86% of patients Thrombotic material (74%) and tissue debris (63%) Tissue material more often with balloon expandable valve and more oversizing

Table 2 *(continued)*

Table 2 *(continued)*

Study	Year	Device	Total n of patients/n of patients with EPD	Design	Objectives/primary outcome	Main results
Baumbach *et al.* DEFLECT I (27)		TriGuard	37/37	Case series	Safety and performance of the TriGuard	Successful coverage in 80%
					MRI and cognitive test pre and post-TAVI	New ischemic lesions in 82% of patients
						Lower volume lesion in complete *vs.* incomplete coverage (0.05 *vs.* 0.45 cm^3, P=0.016)
Schmidt *et al.* (18)	2016	Claret	161/161	Case series	Describe the origin and risk factors of the capture debris	Debris captured in 97% of patients
						Thrombotic material (91%) and tissue debris (68%)
						Risk factors: female sex and diabetes
Samin *et al.* DEFLECT II (28)	2017	TriGuard	14/14	Case series	Safety and performance of the TriGuard	New brain lesions in 91% of patients
					MRI pre and post-TAVI	No reduction in the number of new brain lesions
						Lower volume lesion (13.8 *vs.* 25.1, P=0.049) compare to an historical controls
Seeger *et al.* (29)	2017	Claret Sentinel	560/280	Propensity Matched cohorts	Impact of EPD on stroke and mortality rate	Successful placement: 91.8%
						Primary end-point reduction with EPD (2.1% *vs.* 6.8%, P=0.01)
						Stroke reduction with EPD (1.4% *vs.* 4.6%, P=0.03)
Van Gils *et al.* (10)	2018	Claret Sentinel plus Wirion	11/11	Case series	Evaluate value of left vertebral artery in addition to Claret Sentinel EPD	Successful placement (full coverage): 82%
						Debris obtained in all patients and filters
						Similar debris characteristics in both filters
Randomized						
Wendt *et al.* EMBOL-X (30)	2015	Embol-X	30/14	Single center, prospective, randomized	New brain lesions	No differences in new brain lesions (57% *vs.* 68%, P=0.70) and volume lesion (88 *vs.* 168 mm^3, P=0.27)
					Lesion volume	
Lansky *et al.* DEFLECT III (31)	2015	TriGuard	85/46	Multicenter, prospective, single-blind, randomized	Safety, efficacy and performance	Technical success rate: 88.9%
					Safety endpoint: death, stroke, life-threatening bleeding, AKI (stage 2–3), major vascular complications	No difference in safety endpoint (21.7% *vs.* 30.8%, P=0.34)
						Tendency towards greater freedom from new ischemic brain lesions (26.9% *vs.* 11.5%) and lower neurological deficits by NIHSS (3.1% *vs.* 15.4%) in the EPD group

Table 2 *(continued)*

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Study	Year	Device	Total n of patients/n of patients with EPD	Design	Objectives/primary outcome	Main results
Van Mieghem *et al.* MISTRAL-C (32)	2016	Claret Sentinel	65/32	Multicenter, prospective, double blind, randomized	Evaluate the utility of EPD in new brain lesion and neurocognitive performance	EPD success (94%); material capture (100%) No differences in % of patients with new cerebral lesion and number of lesions Smaller total lesion volume (95 *vs.* 197 mm^3, P=0.17) and less patients with multiple new lesions (0 *vs.* 20%)
Haussig *et al.* CLEAN-TAVI (33)	2016	Claret Montage	50/50	Single center, prospective, randomized	Effect of EPD on the number and volume of cerebral lesions after TAVI	Lower number of new lesions in the EPD group (4 *vs.* 10, P=0.001) Lower new lesion volume in the EPD group (242 *vs.* 527 mm^3, P=0.001) No difference in clinical events
Kapadia *et al.* SENTINEL (20)	2017	Claret Sentinel	363/244	Multicenter, prospective, randomized	Safety and clinical efficacy (MACCE) of EPD during TAVI	EPD success (100%); material capture (99%) No difference in MACCE (7.3 *vs.* 9.9%, P=0.41), volume of new lesion (103 *vs.* 178 mm^3, P=0.33) Early stroke was reduced in the EPD group (3.0% *vs.* 8.2%, P=0.05)

AKI, acute kidney injury; MRI, magnetic resonance imaging; HITS, high-intensity transient signal; MACCE, major adverse cardiac and cerebrovascular events.

85 patients enrolled, evaluated the TriGuard system in terms of clinical and neurocognitive outcomes and MRI findings at baseline, discharge and 1 month follow-up (31). The device was successfully placed to cover full cerebral vasculature in 89% of cases. The primary in-hospital safety endpoint (a composite of death, stroke, major bleeding or major vascular complication and stage 2 or 3 acute kidney injury) occurred in 21.7% of the device group compared to 30.8% in the control group (P=0.34). In patients with complete cerebral coverage, TriGuard was associated with higher rate of freedom from new brain lesions at 1-month (26.9% *vs.* 11.5%, p not reported) and lower neurological deficit in NIHSS scale (3.1% *vs.* 15.4%, P=0.16). The REFLECT trial (NCT02536196) with larger sample size will further test the efficacy of the TriGuard device.

There were three randomized trial with the Sentinel system, accumulating the major evidence to date with this device. The first trial was the MISTRAL-C conducted in four centers in the Netherlands and randomized 65 patients into 1:1 TAVI with or without the device (32). The filter obtained material in all the patients in the intervention group. However, the primary endpoint (percentage of patients with new brain lesions in each group) was not reduced in the device group (73% *vs.* 87%, P=0.31) with a tendency to lower volume lesion (95 *vs.* 197 mm^3, P=0.171). Multiple brain lesions (≥10) were only observed in the group without the device (0% *vs.* 20%, P=0.03) as well as higher cognitive impairment (4% *vs.* 27%, P=0.017). Major limitation of the study was that MRI images and neurocognitive test were only obtained in 57% and 80% of patients, respectively. The second trial was the CLEAN-TAVI that randomized one hundred patients (1:1) in a single center in Germany to perform TAVI with or without the Claret Sentinel device (33). The number of new post-procedure cerebral lesions was significantly lower in the protected brain areas compared to the control group

(4 *vs.* 10, P=0.001) at 2 days after the intervention. Also, new lesion volume was lower in the filter group compared to the control group (242 *vs.* 527 mm^3) (difference 234 mm^3, 95% CI: 91–406; P=0.001). There was not difference in the number of CVE (5 minor strokes in each group). Finally the landmark study with EPD was the SENTINEL multicenter, prospective and randomized trial, which included 363 TAVI patients from 19 centers in US and Germany (20). Patients were distributed in 1:1:1 into a safety arm with the device and two imaging arms that randomly underwent TAVI with and without the device. Neurocognitive assessment and neurologist evaluation was rigorously scheduled before, at 30- and 90-day follow-up with an independent adjudicated clinical events committee. The primary safety endpoint included major adverse cardiac and CVE (MACCE) at 30-day with the primary efficacy endpoint of reduction in new lesion volume in protected cerebral territories on MRI performed at 2–7 days post-TAVI. The device was successfully implanted in all the patients, and debris were obtained in 99% of the patients. MACCE was non-inferior in the device group (7.3% *vs.* 9.9%, P=0.41). Volume of new cerebral lesions was also similar in both groups (102.8 *vs.* 178.0 mm^3, P=0.33). The stroke rate was numerically lower in the device group (5.6% *vs.* 9.1%, P=0.25). In a post-hoc analysis, periprocedural (≤72 hours) stroke rate was reduced in the device group (3.0% *vs.* 8.2%, P=0.05). Although there was a correlation between lesion volume and neurocognitive impairment, the device did not demonstrate any benefit in neurocognitive function. The authors concluded that Sentinel device could be safely used and captured material in almost all the patients leading to a non-significant reduction in new lesion volume in MRI studies and no change in neurocognitive function.

It is worth mentioning a recent single-center, non-randomized study that included 280 patients treated with the Sentinel device and compared to an historical cohort of 522 patients without the device (29). After a propensity score matching (n=280 in each group), the primary end-point (a composite of mortality or stroke within 7 days) was significantly reduced in the protected group (2.1% *vs.* 6.8%, P=0.01). Also in multivariate analysis, TAVI without the device was an independent predictor for the primary end-point.

Meta-analysis

Several meta-analyses have combined the results of the randomized controlled trials and some comparative observational studies (33-40). Main characteristics and findings of published meta-analysis are summarized in *Table 3*. The principal limitations of the meta-analysis were the small number of trials, patients and clinical events, and the high rate of loss to follow-up in most of studies. All meta-analysis concluded that EPD did not reduce the number of new ischemic lesions or the number of patients with new ischemic lesions. However, total lesion volume and single lesion volume was significantly reduced by EPD. Results regarding clinical outcomes such as stroke or mortality were more controversial (41). Some studies reported a non-significant tendency in 30-day stroke or mortality rate (34,36,38), while others observed a significant reduction in the combined endpoint of 7- (38) or 30-day (39,40) stroke or mortality rate. Differences in the inclusion and exclusion criteria, time for event evaluation, and different analytic method used for the analysis (fixed versus random effect analysis) may explain these disparities among the studies. Lastly, there are not head-to-head studies between different EPD, which allow comparing filter or deflector devices. Patient-level data analysis would likely be more appropriate to provide more accurate conclusions and the true effectiveness of these devices for stroke prevention in patients undergoing TAVI.

Conclusions

There is no doubt about the clinical importance of CVE in patient's quality of life and mortality. Therefore the goal is to reduce CVE rate following TAVI. The procedure per se is associated with different nature of material embolization and previous reports with MRI, transcranial Doppler and histopathology studies have clearly demonstrated cerebral embolization during the procedure in the majority of the patients. Potential clinical late implications and cognitive decline of these universally "silent" cerebral lesions need to be well defined in the future, especially for younger patients undergoing TAVI. EPD have emerged as mechanical treatment to prevent cerebral embolization. The current research design of EPD focuses on the silent cerebral lesion in MRI studies as a surrogate marker of the clinical disease. While EPD had a reduction in volume of these cerebral lesions, the number of patients with new cerebral lesions or the total number of lesions has not been consistently reduced by EPD across different studies. The beneficial effect of EPD in patients undergoing TAVI is currently based on observational studies or post-hoc analysis of randomized trials. In addition, the advantage of universally

Table 3 Published meta-analysis with embolic protection device during transcatheter aortic valve replacement

Study	Year	Number of included studies	Type of studies	Patients with EPD	Patients without EPD	Main results/conclusion
Giustino *et al.* (34)	2016	4	RCT	142	138	EPD associated with lower total lesion volume and smaller number of new ischemic lesions
						EPD associated with a trend toward lower risk for deterioration NIHSS and MoCA
						No differences in stroke or mortality risk
Pagnesi *et al.* (35)	2016	6	RCT [4] and non-RCT [2]	198	186	EPD associated with a reduction in total lesion volume and single lesion volume
						No differences in the number of new lesions per patient or the number of patients with new lesions or 30-day mortality
Bagur *et al.* (36)	2017	16	RCT [5] and non-RCT [2]	865	305	EPD associated with smaller volume and smaller total volume of silent ischemic lesions
						Not differences in new-single, multiple or total number of lesions
						No differences in stroke (RR 0.70; 95% CI: 0.38–1.29) or mortality (RR 0.58; 95% CI: 0.20–1.64) at 30-day
Giustino *et al.* (37)	2017	5	RCT	376	249	EPD associated with lower risk of the combined endpoint of stroke or mortality (RR 0.57; 95% CI: 0.33–0.98)
						No difference in mortality (RR 0.42; 95% CI: 0.14–1.26) rate
						No difference in stroke (RR 0.66; 95% CI 0.36–1.23) rate
Mohananey *et al.* (38)	2018	6	RCT [4] and non-RCT [2]	570	655	No difference in stroke or mortality (RR 0.70; 95% CI: 0.40–1.21) at 30-day
						Stroke rate within 1 week was lower in EPD group but similar at 30-day
						No differences in mortality (RR 0.59; 95% CI: 0.22–1.59) rate at 30-day and AKI (RR 0.68; 95% CI: 0.28–1.62) rate
						No differences in major or life threatening bleeding or major vascular complication
Wang *et al.* (39)	2018	5	RCT	386	257	Primary composite endpoint (stroke + mortality) at 30-day was lower in the EPD group (OR 0.54; 95% CI: 0.30–0.98)
						Non-significant reduction in mortality, stroke, acute kidney injury
						EPD associated with lower new total lesion volume
Testa *et al.* (40)	2018	8	RCT [5] and non-RCT [3]	698	561	EPD associated with lower stroke rate (OR 0.55; 95% CI: 0.31–0.98) but not with mortality (OR 0.43; 95% CI: 0.18–1.05) at 30-day
						No differences in the number of new lesions
						EPD associated with smaller ischemic volume per lesion and smaller total volume

EPD, embolic protection device; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale; RCT, randomized controlled trial.

versus selected used of EDP in terms of reduction in hard clinical events remains to be defined. Thus, future analysis and adequately powered and randomized studies will have to further clarify the efficacy of EPD in TAVI. The multifactorial nature of CVE following TAVI make the goal of reducing CVE, a multifaceted process with several preventive strategies, not only during the procedure with EPD, but also in the pre- and post-procedural phases with proper antithrombotic regimens and monitoring for other risk factors.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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