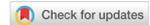


Review

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Routine use of cerebral protection devices during transcatheter aortic valve implantation: what does the evidence say?

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How to cite this article: Saadi EK, Saadi RP, Tagliari AP, Taramasso M. Routine use of cerebral protection devices during transcatheter aortic valve implantation: what does the evidence say? *Vessel Plus* 2020;4:41.
<http://dx.doi.org/10.20517/2574-1209.2020.54>

Received: 9 Oct 2020 **First Decision:** 9 Nov 2020 **Revised:** 14 Nov 2020 **Accepted:** 20 Nov 2020 **Published:** 18 Dec 2020

Academic Editor: Frank W. Sellke **Copy Editor:** Cai-Hong Wang **Production Editor:** Jing Yu

Abstract

Transcatheter aortic valve implantation (TAVI) is a well-established treatment for symptomatic severe aortic stenosis in intermediate and high-risk patients. However, as TAVI indications increase, concerns regarding adverse events and complications rise in the same proportion. Stroke is one of the most feared TAVI complications and a hard endpoint present in all TAVI studies. TAVI-related stroke incidence becomes even more relevant with TAVI indications spreading to younger, low/intermediate-risk patients. Several devices have been developed to prevent this catastrophic event, some of them being broadly used. Nevertheless, the evidence for routine use of cerebral embolic protection devices is still controversial.

Keywords: Transcatheter aortic valve replacement, transcatheter aortic valve implantation, cerebral protection device, cerebral protection system, Sentinel Cerebral Protection System, stroke prevention



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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is a well-established and widespread option to treat severe aortic stenosis in intermediate and high-risk patients. However, its increased use brings some intrinsic concerns, especially in low-risk and younger patients, a population in which even a low rate of adverse events can be catastrophic^[1-7]. In this setting, to reduce or, ideally, to eliminate neurological complications is especially relevant.

To mitigate neurological events risk, cerebral embolic protection devices (CEPD) were developed aiming to capture embolized debris and/or to prevent them from reaching the cerebral circulation. Even with some evidence supporting CEPD benefits and safety, the lack of a single randomized clinical trial demonstrating reduction in hard outcomes, such as stroke and mortality, has limited the widespread acceptance of CEPD and its routine use.

This article offers an updated state-of-the-art review on CEPD use and which patient profile is most likely to benefit from this therapy.

Issue relevance

The incidence of clinically relevant neurological events after TAVI varies from 1 to 10%, but it can be as high as 94% if silent events detected by brain imaging are also considered^[8]. The majority of post-TAVI strokes have an embolic origin and occur in the early post-TAVI period (64% and 85% at 2 and 7 days, respectively). These are referred to as procedure-related neurological events.

Calcium debris embolization can happen during catheter and wire manipulation, valve implantation, pre-dilatation, and/or post-dilatation^[2,5]. Compared to native valves, valve-in-valve and bicuspid aortic valve are associated with higher stroke rates due to the need for increased valve manipulation or the presence of highly calcified anatomies. Debris embolization can also be secondary to small thrombus formation or embolization from atherosclerotic plaques in the ascending aorta and aortic arch.

Regarding the clinical relevance, patients who suffer a stroke are at high risk for mortality and severe morbidity including physical disability^[9,10]. In a meta-analysis conducted by Eggebrecht *et al.*^[11], patients with cerebrovascular events presented a 3.5-fold higher 30-day mortality than those without events (25.5% vs. 6.9%, respectively). In another study, short- and long-term mortality risks were incremental according to cerebrovascular events severity, with a significantly higher mortality rates in the presence of major stroke [30-day mortality: odds ratio (OR) = 7.43; 95% confidence interval (CI): 2.45-22.53; $P = 0.001$, late mortality: hazard ratio (HR) = 1.75; 95%CI: 1.01-3.04; $P = 0.043$]^[12]. Similarly, a meta-analysis of 29,034 patients showed a 30-day mortality following stroke of 12.27%, with stroke-related mortality of 28.22%, compared with 6.4% mortality in patients without a stroke (OR = 6.45; 95%CI: 3.9-10.66; $P < 0.0001$)^[13]. Furthermore, it is valid to emphasize that 30-day permanent disability is found in around 50% of patients who have suffered a stroke^[14] and that even silent cerebral emboli are associated with worse outcomes, three times higher risk of clinical stroke, two times higher risk of dementia and declined cognitive function.

Notwithstanding, cerebrovascular events present a high impact on patient's quality of life, a consequence even more feared than death. Interesting research showed that, in terms of postoperative perspectives, the majority of patients undergoing TAVI had as their primary objective the maintenance of their independence and being able to practice daily hobbies, but only 7% had staying alive after the procedure as their main goal^[15]. These results highlight the importance of patients' quality of life as endpoint, which should be considered during the TAVI decision-making process.

Table 1. Main cerebral protection devices

	Coverage	Access site	Delivery sheath	Pore size	Mechanism
Sentinel	BCT, LCCA	Radial	6F	140 μm	Capture
TriGUARD	Full arch	Femoral	8F	115 × 145 μm	Deflection
Embella	BCT, LCCA	Radial	6F	100 μm	Deflection
ProtEmbo	Full arch	Radial	6F	60 μm	Deflection
Emblok	Full arch	Femoral	11F	125 μm	Capture
Embol-X	Full body	Transaortic	17F	120 μm	Capture
Emboliner	Full body	Femoral	9F	150 μm	Capture

BCT: brachiocephalic trunk; LCCA: left common carotid artery; μm: micrometers

CEREBRAL PROTECTION SYSTEM

Recent data suggested that CEPD use is associated with less overt strokes, lower total lesion volume, and a smaller number of new ischemic lesions detected by post-procedural magnetic resonance imaging (MRI) studies^[10,16-19].

So far, several CEPD have been developed by many manufactures, including ProtEmbo, Sentinel, TriGUARD, Emblok, Emboline, Embrella, and Embol-X^[20-22]. They vary not only in the mechanism for protection, for instance, capture versus deflection, but also in the access site and delivery sheath size [Table 1]. However, only the Sentinel is already approved by the Food and Drug Administration (FDA), being the most used and studied device. A summary of the current published and ongoing trials regarding cerebral protection during TAVI is presented in Table 2.

Sentinel CPS^R [Claret Medical (Boston Scientific, Corp, USA)]

The Sentinel CPS is the most studied cerebral protection device. It is made of 2 inter-connected filters deployed into the brachiocephalic trunk and left common carotid artery through a 6 French size sheath^[23]. The most commonly used access is the right radial artery [Figures 1 and 2]^[18].

Three randomized clinical trials (RCT) evaluating the Sentinel's role during TAVI were published in 2016, the MISTRAL-C, the CLEAN-TAVI, and the SENTINEL trial^[22,24,25]. These trials demonstrated device's safety and suggested that Sentinel was associated with fewer and smaller brain lesions on postoperative MRI than unprotected TAVIs.

The MISTRAL-C was the first study to enroll 65 TAVI patients submitted to a protected or unprotected TAVI procedure. New brain lesions on MRI studies were found in 78% of patients, with fewer new lesions number (73% vs. 87%; $P = 0.31$) and total lesion volume [95 mm^3 (IQR 10-257) vs. 197 mm^3 (95-525); $P = 0.171$] in the protected group. Ten or more new brain lesions were found only in the control cohort (0% vs. 20%; $P = 0.03$), and neurocognitive deterioration was present in 4% of patients with received Sentinel during TAVI vs. 27% in those who did not ($P = 0.017$)^[24]. Similarly, the CLEAN-TAVI study randomized 100 patients in 1:1 fashion to TAVI with or without Sentinel insertion. Post-procedure MRI revealed new cerebral lesions in 98% of patients, with a significant smaller new lesion volume [242 mm^3 (95%CI: 159-353) vs. 527 mm^3 (95% CI 364-830); $P = 0.001$] and lower number of new lesions two days post-TAVI [4.0 (IQR: 3.00-7.25) vs. 10.0 (IQR 6.75-17.00); $P < 0.001$] in the Sentinel group. These neuro-imaging differences, however, were not translated into a significant reduction in clinical stroke incidence (10% in each group)^[22]. The randomized SENTINEL trial, by its time, included 363 patients with a 2:1 randomization for CEPD vs. no CEPD. Although statistical significance was not achieved, the study demonstrated a strong trend toward stroke reduction within 72 h post-TAVI in the CEPD group compared to the unprotected group (3.0% vs. 8.2%; $P = 0.053$)^[25].

Table 2. Main trials evaluating the use of cerebral embolic protection devices during TAVI

Trial	Year of publication	Device studied	Study design	Endpoints	Population	Main results (device vs. no device)
Published trials						
MISTRAL-C	2016	Sentinel (CE mark and FDA approval)	Randomized clinical trial	Primary endpoint: new cerebral lesions by DW-MRI 5 to 7 days after TAVI	From January 2013 to July 2015, 65 patients randomized 1:1 to transfemoral TAVI with or without Sentinel	Device success: 93% New brain lesions: 78% Absence of new lesions: 13% vs. 27%; $P = 0.31$ Total lesion volume: 95 mm ³ (10-257) vs. 197 mm ³ (95-525) U 10 new brain lesions: 0 vs. 20%; $P = 0.03$ Neurocognitive deterioration: 4% vs. 27%; $P = 0.017$
CLEAN-TAVI	2016	Sentinel	Randomized clinical trial	Primary endpoint: numerical difference in new positive postprocedure DW-MRI brain lesions at 2 days after TAVI in potentially protected territories. Secondary outcome: difference in volume of new lesions after TAVI in potentially protected territories	From April 2013 to June 2014, 100 patients randomized 1:1 to TAVI with or without Sentinel	Device success: 92% New cerebral lesions: 98% Number of new lesions: 4 (3-7.25) vs. 10 (6.75-17); $P < 0.001$ New lesion volume: 242 mm ³ (159-353) vs. 527 mm ³ (364-830); $P = 0.001$ Stroke incidence: 10% vs. 10%
SENTINEL trial	2017	Sentinel	Randomized clinical trial	Primary safety endpoint: MACCE at 30 days Primary efficacy endpoint: reduction in new lesion volume in protected brain territories by MRI at 2 to 7 days after TAVI	19 centers 363 patients randomized 2:1 to TAVI with or without Sentinel	Device success: 94.4% Debris found within filters: 99% MACCE: 7.3% vs. 9.9%; $P = 0.41$ New lesion volume: 102.8 mm ³ vs. 178 mm ³ ; $P = 0.33$ 30 days stroke: 5.6% vs. 9.1%; $P = 0.25$
DEFLECT I	2015	TriGuard (CE mark approval; applied for FDA approval)	Prospective, multicentre trial	Primary safety endpoint: in-hospital device- or procedure-related cardiovascular mortality, major stroke disability, life-threatening bleeding, distal embolisation, major vascular complications, or need for acute cardiac surgery	37 consecutive patients undergoing TAVI with the TriGuard	Successful cerebral coverage: 80% Primary outcome: 8.1% New cerebral ischaemic lesions on post-procedure DW-MRI: 82% Per-patient total lesion volume: 34% lower than historical cohorts (0.2 cm ³ vs. 0.3 cm ³)
DEFLECT III	2015	TriGuard	Randomized clinical trial	Primary endpoint: in-hospital procedural safety (death, stroke, life-threatening or disabling bleeding, stage 2/3 acute kidney injury, or major vascular complications) Secondary device performance endpoint: technical success (successful device deployment, positioning with complete three-vessel coverage)	13 centers in Europe and Israel From February 2014 to March 2015, 85 patients randomized to TAVI with ($n = 46$) or without TriGuard ($n = 39$)	Primary endpoint: 21.7% vs. 30.8%; $P = 0.34$ Technical success: 88.9% Per Treatment population (subjects with complete three-vessel cerebral coverage): new ischaemic brain lesions 26.9 vs. 11.5%; new neurologic deficits 31 vs. 15.4%
REFLECT II	2020	TriGuard 3	Randomized clinical trial	Primary safety endpoint (composite of all-cause mortality, stroke, life-threatening or disabling bleeding, stage 2/3 acute kidney injury, coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring intervention at 30 days) Primary efficacy endpoint (composite of all-cause mortality or stroke at 30 days, National Institute of Health Stroke Scale worsening, absence of DWI-MRI lesions post-procedure, and total volume of cerebral lesions by DWI)	25 US centers 295 patients randomized 2:1 to TAVI with or without TriGuard	Device successful deployment: 100% Technical success: 71% Primary safety endpoint: 15.9% device vs. 34.4% performance goal; P non-inferiority = 0.0001 Primary efficacy endpoint: 45.7% vs. 54.3%; $P = 0.857$ Median total lesion volume: 215.39 mm ³ vs. 188.09 mm ³ ; $P = 0.405$

PROTAVI-C Pilot	2014	Embella (CE Mark approval)	Prospective and nonrandomized trial	Periprocedural cerebral lesions assessed by DW-MRI	52 patients who underwent transfemoral TAVI with (n = 41) or without (n = 11) Embrella	Device successfully deployed: 100% 7 days DW-MRI new ischemic lesions: 100% vs. 100% Median number of defects per patient: 8 (3-13) vs. 4 (2-8); P = 0.41 Lesion volume per lesion: 30 mm ³ (20- 50) vs. 50 mm ³ (30-70); P = 0.003 New foci of restricted diffusion: 57% vs. 67%; P = 0.7 Lesion size: 88 ± 60 mm ³ vs. 168 ± 217 mm ³ ; P = 0.27 Lesion volumes in the supply region of the middle cerebral artery: 33 ± 29 mm ³ vs. 76 ± 67 mm ³ ; P = 0.04	
EMBOL-X trial	2015	EMBOL-X	Prospective, single-center, randomized-controlled trial	Periprocedural cerebral lesions assessed by DW-MRI at baseline and within 7 days post-TAVI	From July 2012 to April 2014, 30 patients randomized 1:1 to TAVI with (n = 14) or without (n = 16) EMBOL-X	Device successfully positioned: 100% Significant debris capture: 90% 30-day MACCE: 0% New ischemic defect post-procedural DW-MRI: 95% Median number of new lesions per patient: 10 (4.75-15.2) Total new lesion volume: 199.9 mm ³ (83.9-447.5) Mean lesion volume per lesion: 42.5 mm ³ (21.5-75.6) Primary safety endpoint: 0% Primary technical performance endpoint: 100% Debris capture: 100%	
Embolc Embolic study	2020	Embolc	Prospective, nonrandomized, multicenter, first-in-man pilot study	Primary endpoint: technical success and immediate cerebral embolic burden after TAVI (number and volume of new brain lesions detected by DW-MRI at days 2 to 5 post-TAVI compared with baseline)	20 patients submitted to TAVI with Emblok	Device successfully positioned: 100% Significant debris capture: 90% 30-day MACCE: 0% New ischemic defect post-procedural DW-MRI: 95% Median number of new lesions per patient: 10 (4.75-15.2) Total new lesion volume: 199.9 mm ³ (83.9-447.5) Mean lesion volume per lesion: 42.5 mm ³ (21.5-75.6) Primary safety endpoint: 0% Primary technical performance endpoint: 100% Debris capture: 100%	
SafePass 2	Early clinical results presented at TCT 2019	Emboliner	Prospective, non-randomised, multicentre, open-label study	Primary safety endpoint: 30-day MACCE incidence Technical performance: technical success (ability to successfully access the aortic arch, position the device and retrieve and remove it)	3 centers in New Zealand 24 patients submitted to TAVI with Emboliner	Device successfully positioned: 100% Significant debris capture: 90% 30-day MACCE: 0% New ischemic defect post-procedural DW-MRI: 95% Median number of new lesions per patient: 10 (4.75-15.2) Total new lesion volume: 199.9 mm ³ (83.9-447.5) Mean lesion volume per lesion: 42.5 mm ³ (21.5-75.6) Primary safety endpoint: 0% Primary technical performance endpoint: 100% Debris capture: 100%	
Ongoing trials							
PROTECTED TAVR	Recruiting	Sentinel	Prospective randomized trial	Primary endpoints : rate of stroke through 72 hours post-TAVR or discharge (whichever comes first)	Estimated enrollment: 3000 patients randomized to TAVR with or without Sentinel	Device successfully positioned: 100% Significant debris capture: 90% 30-day MACCE: 0% New ischemic defect post-procedural DW-MRI: 95% Median number of new lesions per patient: 10 (4.75-15.2) Total new lesion volume: 199.9 mm ³ (83.9-447.5) Mean lesion volume per lesion: 42.5 mm ³ (21.5-75.6) Primary safety endpoint: 0% Primary technical performance endpoint: 100% Debris capture: 100%	
PROTECT TAVI	Recruiting	Sentinel	Prospective randomized trial	Primary endpoint: total new lesion volume in protected brain regions detected by MRI Secondary endpoint: number of new cerebral lesions detected by MRI; occurrence of clinical stroke and/or neurocognitive dysfunction; postoperative outcome according to VARC 2 criteria	Estimated enrollment: 328 patients submitted to TAVI with or without Sentinel	Device successfully positioned: 100% Significant debris capture: 90% 30-day MACCE: 0% New ischemic defect post-procedural DW-MRI: 95% Median number of new lesions per patient: 10 (4.75-15.2) Total new lesion volume: 199.9 mm ³ (83.9-447.5) Mean lesion volume per lesion: 42.5 mm ³ (21.5-75.6) Primary safety endpoint: 0% Primary technical performance endpoint: 100% Debris capture: 100%	
PROTEMBO SF Trial	Recruitment completed, not published	ProtEmbo	Prospective, observational, multi-center, intention-to-treat study	Primary endpoint: procedural success (successful access, delivery to, deployment within, and retrieval of the ProtEmbo System from the aortic arch, adequate coverage of side branch vessels and maintenance of position for duration of the TAVR procedure) In-hospital procedural safety up to 7 days (MACCEs, including device-related safety outcomes) Stroke severity at 3 and 30 days Occurrence of Serious Adverse Events at 3 and 30 days	Original estimated enrollment: 10 patients submitted to TAVI with ProtEmbo	Device successfully positioned: 100% Significant debris capture: 90% 30-day MACCE: 0% New ischemic defect post-procedural DW-MRI: 95% Median number of new lesions per patient: 10 (4.75-15.2) Total new lesion volume: 199.9 mm ³ (83.9-447.5) Mean lesion volume per lesion: 42.5 mm ³ (21.5-75.6) Primary safety endpoint: 0% Primary technical performance endpoint: 100% Debris capture: 100%	

MACCE: major adverse cardiac and cerebrovascular events; DWI-MRI: diffusion-weighted magnetic resonance imaging



Figure 1. Sentinel cerebral protection system. Image provided courtesy of Boston Scientific. © 2020 Boston Scientific Corporation or its affiliates. All rights reserved

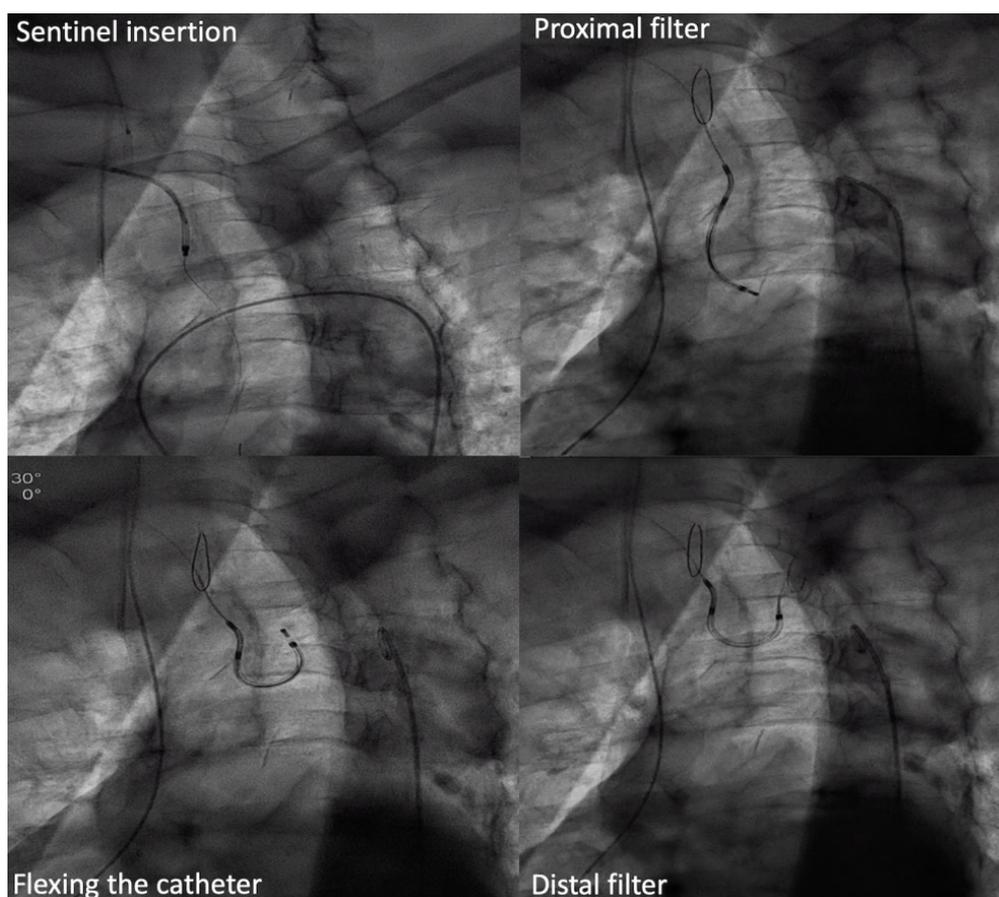


Figure 2. Sentinel implantation

Regardless of the fact that none of these trials have, individually, demonstrated superiority in terms of hard outcomes, such as stroke and mortality, recent meta-analyses showed that CEPD use was associated with lower rates of stroke and 30-day mortality^[18,23]. A propensity-matched patient cohort including 533 patients also showed lower rates of procedural all-stroke (1.88% *vs.* 5.44%, OR = 0.35, 95%CI: 0.17-0.72, relative risk reduction 65%; $P = 0.0028$), and the combined endpoint of all-cause mortality and all-stroke (2.06% *vs.*

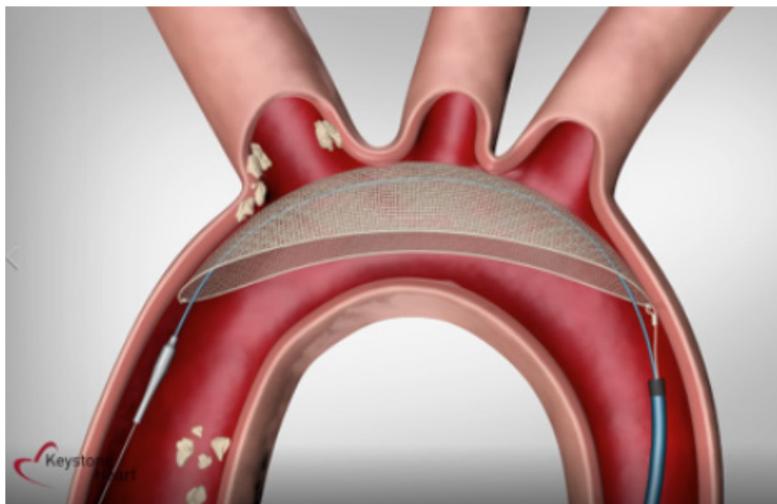


Figure 3. TriGUARD device

6.00%, OR = 0.34, 95%CI: 0.17-0.68, relative risk reduction 66%; $P = 0.0013$) in the protected TAVI group. The rate of disabling stroke was also substantially lower in the Sentinel group (0.38% vs. 2.44%; $P = 0.0045$)^[26].

Furthermore, in the last months, evidence from two large US databases has suggested that Sentinel use during TAVI was associated with statistically significant reduction in stroke risk. In the Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) TVT Registry, the rate of in-hospital stroke was not significantly lower when the Sentinel device was used according to an instrumental-variable analysis (1.39% vs. 1.54%; RR = 0.90; 95%CI: 0.68-1.13). A secondary propensity-weighted analysis of the data, however, indicated that cerebral protection was associated with a reduction in the rates of in-hospital stroke (1.30% vs. 1.58%; RR = 0.82; 95%CI: 0.69-0.97), in-hospital death or stroke (2.1% vs. 2.5%; RR = 0.84; 95%CI: 0.73-0.98), 30-day stroke (1.9% vs. 2.2%; RR = 0.85; 95%CI: 0.73-0.99), and 30-day death (1.7% vs. 2.2%; RR = 0.78; 95%CI: 0.64-0.95)^[27]. Corroborating these findings, a propensity-weighted analysis of the National Inpatient Sample showed that Sentinel use was associated with a lower risk of in-hospital ischemic stroke (1.0% vs. 3.8%; OR = 0.24; 95%CI: 0.09-0.62) and in-hospital death (0% vs. 1%; $P = 0.036$)^[28].

Despite the aforementioned, it is essential to remember that the Sentinel does not protect the left vertebral artery since it is a branch of the left subclavian artery. There are still concerns about leaving the left vertebral artery unprotected, thus some companies are developing devices to eliminate this blind spot.

TriGUARD™ (Keystone Heart, Herzliya, Israel)

The TriGUARD is the only CE mark approved system designed to cover and protect all three major cerebral aortic arch vessels [Figure 3]. Currently, the device is only in investigational use in the US, planning to apply for FDA approval.

The TriGUARD is inserted through a transfemoral 8F sheath, via the femoral artery access already in use during TAVI, usually at the pigtail insertion side, thus eliminating the need for a third arterial puncture. The device is made of nitinol and consists of a self-positioning, self-stabilizing polymetric mesh with pore sizes 115×145 micrometers (μm) opened in the aortic arch, covering the three aortic arch vessels^[29].

There are clinical trials already published showing the efficacy and safety of the device. The DEFLECT I and DEFLECT III trial demonstrated that the technical success, which included complete 3-vessel cerebral coverage, was achieved in 80%-90% of the patients. The DEFLECT III demonstrated that this device use is

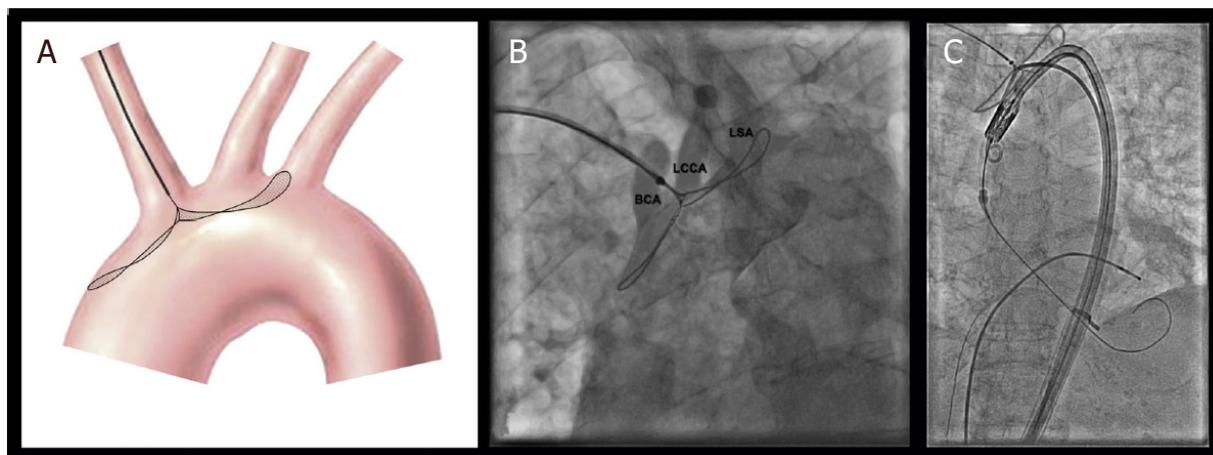


Figure 4. Embrella device. Reproduced from Samim *et al.*^[35]. A: the Embrella Embolic Deflector System; B: device positioned in the aortic arch; C: TAVI deployment

associated with greater freedom from new ischemic brain lesions, fewer new neurologic deficits, and better performance on a delayed memory task at hospital discharge^[30,31]. From DEFLECT I to DEFLECT III study, the device has changed from a 250 μm to 130 μm pore size. The REFLECT trial is another randomized clinical trial with larger population, designed to study the TriGUARD 3 device. The TriGUARD 3 is the new generation device, designed to bring some improvements such as a simplified frame design, which eliminates the need for a dedicated stabiliser. It is fully visible via fluoroscopy, contains a reduced filter mesh pore size for deflection of smaller particles (145 μm \times 115 μm vs. 250 μm \times 250 μm), and has a refined delivery system that reduced the delivery profile (8F instead of 9F)^[32]. Recently, Jeffrey W. Moses presented the results from the Reflect II trial during a late-breaking trial session at TCT Connect 2020. The results showed the safety of the TriGUARD 3, but did not demonstrate superiority for the primary hierarchical efficacy endpoint^[33].

Embrella Embolic Deflector System (Edwards Lifesciences, Irvine, CA, USA)

The Embrella Embolic Deflector (EED) system consists of an oval-shaped nitinol frame (length 59 mm, width 5-25 mm), covered with a porous polyurethane membrane (100 μm pore size). Its porous membrane allows blood flow to the brain while simultaneously deflecting embolic material [Figure 4]. The device is composed of 2 petals and a delivery cable in a 6F sheath system inserted via the right radial or brachial arteries. The two opposing petals are positioned along the aorta greater curvature, protecting the brachiocephalic and common carotid arteries from embolism^[34,35].

The EED System has been assessed in a limited clinical study in Europe and received CE Mark approval in May 2010. Two main RCT have studied the EED system. In these studies, Rodés-Cabau *et al.*^[34] (PROTAVI-C Pilot) and Samim *et al.*^[35] demonstrated the feasibility and safety of using the EED. However, the device failed to prevent cerebral microemboli or new transient ischemic lesions, as evaluated by Diffusion Weighted Imaging Magnetic Resonance Imaging (DW-MRI). In fact, the studies showed a higher number of brain lesions in the EED group compared to the control group, even though the device was associated with lower lesion volume^[34,35]. The PROTAVI-C editorial comment also raises doubts about the real utility of the device^[36].

ProtEmbo^R (Prtembis, GmbH, Germany)

The ProtEmbo is an intra-aortic embolic protection filter device comprising a filter connected to a delivery unit enabling delivery of the unexpanded device with a 6F sheath via the left radial artery [Figure 5]. The device is delivered in the aortic arch, protecting its three major vessels (i.e., brachiocephalic trunk, left



Figure 5. Illustration of ProtEmbo device

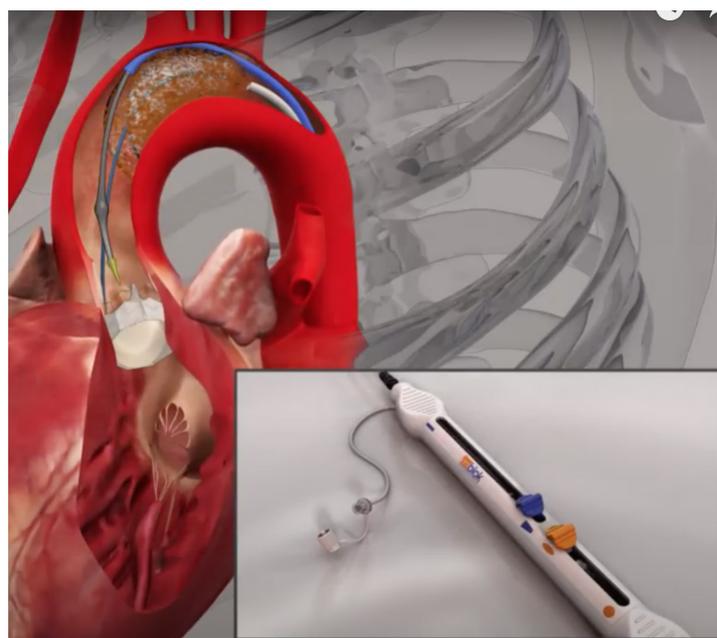


Figure 6. Illustration of Emblok device

common carotid artery, and left subclavian artery). The filter consists of a porous polymeric material with 60 μm pores. The PROTEMBO SF Trial is the first randomized clinical trial to test the ProtEmbo device clinically. It has already completed the recruitment phase, but the results have not been published yet.

Emblok (Innovative Cardiovascular Solutions, Grand Rapids, MI, USA)

The Emblok embolic protection system is an 11F sheath device containing a 4F pigtail, delivered via femoral artery access in the aortic arch [Figure 6]. The device covers all three aortic arch vessels, and the filter consists of 125 μm of polyurethane.

The first trial testing the device was published on JACC, in 2020, by Latib *et al.*^[37]. This prospective, nonrandomized, multicenter study had no control group. Nevertheless, it demonstrated that the use of this device appears to be feasible and safe. It was successfully placed and retrieved in all twenty cases, and no neurological events were observed.

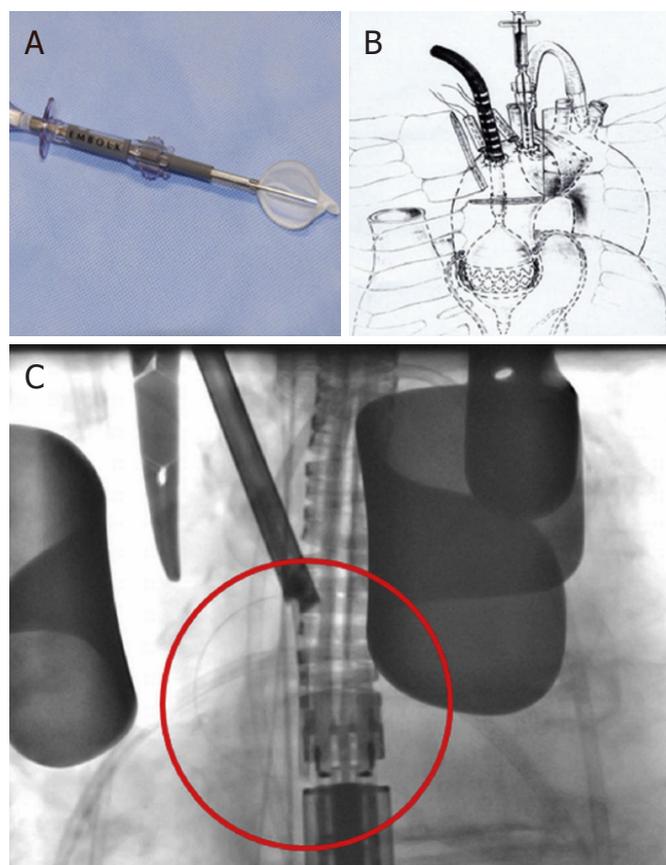


Figure 7. Transaortic Embol-X device. Reproduced from Wendt et al.^[38]. A: EMBOL-X system; B: transaortic TAVI; C: EMBOL-X intraprocedural control

Embol-X (Edwards Lifesciences, Irvine, CA, USA) - Transaortic

The Embol-X device was first developed to be used during open-heart surgery at the aortic cannulation site [Figure 7]. A randomized clinical trial tested its effectiveness in TAVI by a transaortic approach. In this trial, the device was shown to be safe and effective in reducing the incidence and the volume of new cerebral lesions. The device is placed inside the aorta and is available in 5 sizes covering an aortic diameter of 22 to 40 mm. It is delivered by a 17F sheath^[38].

Emboliner Embolic Protection Catheter (Emboliner)TM

The Emboliner Cerebral Protection Catheter is the first device designed to prevent both cerebral and body embolism [Figure 8]. It is delivered through a transfemoral 9F sheath, the same sheath used for the 6F pigtail. Therefore, no additional access is required. Its pore size is 150 μm . The SafePass 2 trial is the first trial with the Emboliner device; it has completed enrollment but has not been published yet. However, the device seems to be safe and effective with little adverse events related to it, capturing up to five times more debris than Sentinel, according to informal data.

Cost-effectiveness analysis

There is no published cost-effectiveness analysis defining the real role of routine cerebral embolic protection device use during TAVI procedures. Therefore, the benefit of preventing a stroke should be balanced against the device costs, taking into consideration that strokes have an unpredictable, but often devastating impact, not only in terms of mortality but also in terms of sequelae (50% of patients develop permanent disability, more than 50% are unable to return to work, and more than 30% end up with serious financial problems). In this setting, Shiyovich et al.^[39] estimated that the cost added by a moderate disability

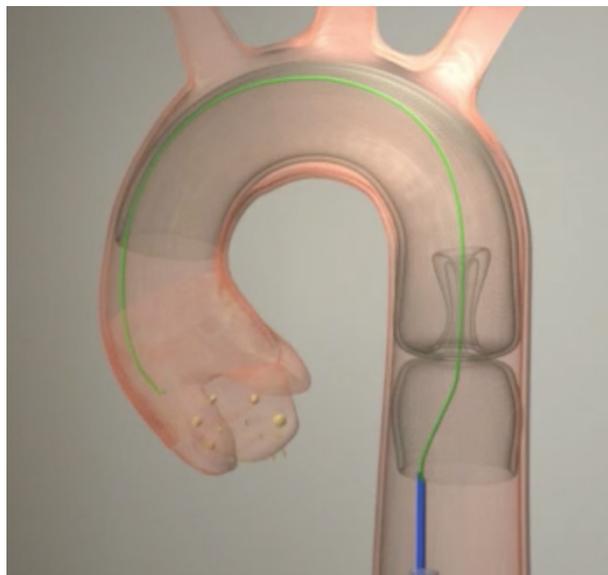


Figure 8. Illustration of Emboliner full body protection device

due to a neurologic event is around \$25,000, followed by a subsequent annual cost increase of up to \$60,000. Hence, as the device cost (Sentinel CPS) is approximately \$2,800, and the CEPD number needed to treat is around 20, CEPD cost-effectiveness is suggested.

DISCUSSION

To critically evaluate the CEPD trials presented above, some critical points should be taken into account. First, the studies showed important discrepancy between imaging and clinical outcomes since the observed reduction in new cerebral lesions number and volume did not reflect the expected benefit in hard outcomes. Trying to explain this discrepancy, it has been hypothesized that the lack of validated models to assess neurocognitive function in TAVI patients, the certain degree of pre-procedural cognitive dysfunction in some patients, and the high prevalence of inter and intra-observer variability for neurological tests, could blunt the real CEPD benefit^[15]. Second, stroke incidence varies according to the study type, being significantly higher when the results are adjudicated based on formal neurologist clinical assessment (up to 10%) than when they are adjudicated by non-neurologists (2%-6%)^[24-26]. Third, CEPD randomized trials have not been designed or powered to demonstrate an unequivocal impact on hard clinical endpoints. These observations make the search for preventive strategies even more relevant, especially in younger patients with longer life expectancy.

Regarding the best procedure strategy, we believe that it is still too early to affirm that CEPD should be universally used or that there is a specific patient population in which protected TAVI is more cost-effective. During the TAVI decision-making process, several factors should be balanced, such as age, the amount of leaflet and/or left ventricular outflow tract calcification, and the presence of aortic plaques or atrial fibrillation^[26]. Therefore, from our perspective and considering the available evidence discussed above, two strategies could be possible:

1. Tailored preventive strategy: If TAVI is performed in a center with limited CEPD availability, one possible strategy could be to limit its use to high-risk scenarios based on preoperative risk factors (e.g., age, previous atrial fibrillation, history of cerebrovascular events, renal failure, concomitant coronary artery disease), transoperative risk factors (e.g., increased catheter and guidewire manipulation, extremely severe aortic stenosis, complex valve-in-valve procedures, multiple valve repositioning maneuvers, need

for pre- and post-dilatation), and highly calcified anatomies (e.g., extensive atherosclerosis, complex aortic atheroma, bicuspid aortic valve, severe left ventricular outflow tract calcification).

2. Routine preventive strategy: If TAVI is performed in a center without CEPD use restrictions, one possible approach could be to offer it routinely as long as there is adequate anatomy, heart team indication, and patient concordance. This approach is based on the fact that captured debris are presented in almost all patients^[40], regardless of preoperative risk factors or type of device used.

CONCLUSION

This review article discusses the pros and cons of cerebral embolic protection use during TAVI procedures. Despite CEPD's high cost, recent evidence, especially with the Sentinel system, has suggested that cerebral protection employment may lower stroke and even mortality rates. Ongoing and upcoming trials will help to fill some of the current evidence gaps related to CEPD use during TAVI.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design and review of this manuscript: Saadi EK, Saadi RP, Tagliari AP, Taramasso M

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Dr. Saadi EK is a consultant and Proctor for Medtronic, Abbott and Edwards and received speaker honoraria from Edwards and Medtronic. Dr. Tagliari AP has received a Research Grant from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (Capes) - Finance Code 001. Dr. Taramasso M is a consultant for Abbott Vascular, Boston Scientific, 4TECH, and CoreMedic; he has received speaker honoraria or Consultant fees from Edwards Lifesciences, CoreMedic, SwissVortex and Mitraltech.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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