

# The Role of Cerebral Embolic Protection in Transcatheter Aortic Valve Replacement

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## Abstract

In transcatheter aortic valve replacement (TAVR), stroke remains one of the most devastating complications. As a result, cerebral embolic protection devices (CEPD) have been developed to prevent cerebral embolization in order to lower the stroke risk. Emboli can either be filtered or deflected depending on the type of CEPD. The goal of this review is to provide an overview of all currently available CEPD and to discuss the results of the most relevant studies concerning cerebral embolic protection in TAVR.

**Keywords:** Cerebral embolic protection device, Transcatheter aortic valve replacement, Stroke

**Abbreviations:** TAVR: Transcatheter Aortic Valve Replacement; SBI: Silent Brain Infarcts; DW-MRI: Diffusion-Weighted Magnetic Resonance Imaging; CEPD: Cerebral Embolic Protection Devices; F: French; RCT: Randomized Controlled Trial; NIHSS: National Institutes of Health Stroke Scale.

## Introduction

Stroke is one of the most feared complications of transcatheter aortic valve replacement (TAVR) and is associated with an increased risk of morbidity and mortality [1-4]. Its consequences can be disastrous with permanent significant disability in 40% of the survivors, social isolation and financial problems in up to 80% of the patients and a 6-fold increase in mortality rate during the first month following TAVR [5-8]. It is caused by periprocedural embolization occurring during balloon dilatation, manipulation of the delivery system in the aortic arch, valve positioning and valve deployment [9]. Histopathologic findings have revealed that emboli can consist of native valve tissue, arterial wall tissue, calcification, thrombus and foreign material [10].

Despite improved operator expertise and enhanced valve designs, stroke is still prevalent in about 5% of patients undergoing TAVR [11-13]. Additionally, silent brain infarcts (SBI) occur in the majority of patients

with a reported incidence of 58-100% [14-20]. SBI are characterized by the absence of overt clinical signs in the presence of brain injury (new cerebral embolic lesions) detected with diffusion-weighted magnetic resonance imaging (DW-MRI) [21]. At first glance, these SBI seem harmless, however they can have a detrimental effect with increased risk for cognitive decline and dementia [22]. Consequently, stroke remains an underreported and underdiagnosed clinical entity [23].

Anticipating on the prospect that TAVR is increasingly being performed in the lower surgical risk population it is essential to reduce the risk of cerebral embolization during TAVR [9,10,24,25]. This has led to the development of cerebral embolic protection devices (CEPD) providing a mechanical barrier to the cerebral circulation in which emboli are filtered or deflected to the descending aorta during TAVR.

As a consequence, CEPD have the potential to improve clinical outcomes after TAVR. In this review, an overview

of CEPD in TAVR will be given, highlighting the unique characteristics of each CEPD and its available clinical data.

## Cerebral Embolic Protection Devices

Since the first-in-man study, wherein safety and efficacy of a CEPD in TAVR was assessed, there is growing interest in CEPD and its potential to prevent cerebral embolization and reduce stroke [26]. Cerebral protection can be accomplished by an embolic filter device (i.e., Sentinel CEPD, Boston Scientific, Marlborough, MA, USA) or an embolic deflector device (i.e., TriGUARD, Keystone Heart Ltd, Caesarea, IL, USA).

An embolic filter device utilizes a landing net in order to catch and extract emboli from the circulation, while an embolic deflector device ensures that emboli will deflect away from the cerebral circulation into the descending aorta.

Currently, various CEPD are available with each device having its own strengths and shortcomings (Table 1 and Figure 1). Ideally, A CEPD should be safe, easy to use, able to cover all major cerebral arteries and preserve the calcified and fragile wall of the aortic arch. Importantly, its filtering or deflection capacity should be sufficient in order to prevent cerebral embolization. Moreover, the device should have minimal interaction with the transcatheter heart valve system or other interventional materials. Once deployed, it should stay anchored and provide a stable seal throughout the entire procedure.

## Sentinel CEPD

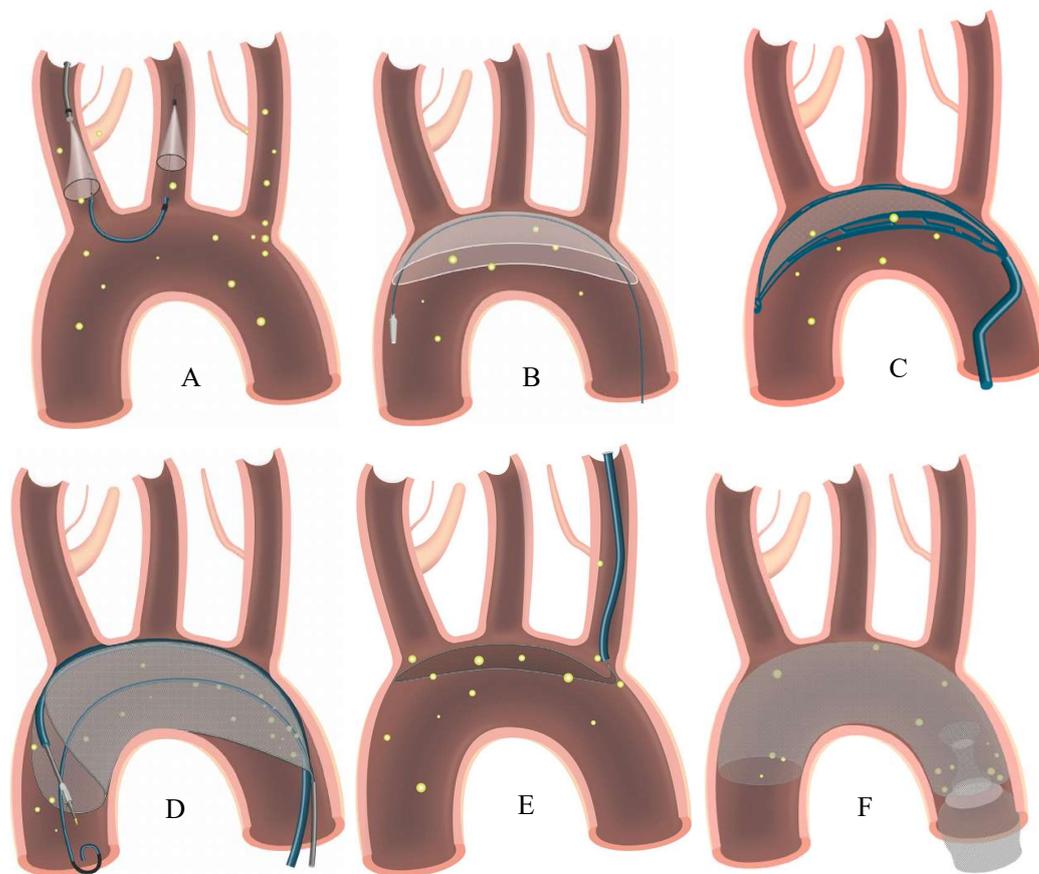
The Sentinel device is the most extensively studied CEPD in TAVR. The third generation Sentinel device received FDA approval in 2017. It can be inserted via a 6 French (F) sheath in the right radial (preferred) or brachial artery and it is easy to use with deployment achieved in less than 10 minutes in 90% of the cases [27-29]. The delivery system contains two filter baskets (140 µm pores), the first filter is placed in the brachiocephalic trunk and the second filter in the left common carotid artery. The left subclavian (and hence left vertebral) artery remains uncovered. As a result, complete cerebral protection is not achieved with the Sentinel device. If complete coverage is preferred, the Wirion filter (CSI, St. Paul, MN, USA) can additionally be placed in the left vertebral artery [30].

**Clinical data:** In 2012, an explorative study confirmed the safety and feasibility of the Sentinel device in TAVR [31]. Two randomized controlled trials (RCT) (CLEAN-TAVI and MISTRAL-C) were conducted in which DW-MRI findings after TAVR revealed a significant reduction in number and volume of new ischemic brain lesions within protected areas in the Sentinel group compared to the unprotected group [29,32]. Additionally, in the MISTRAL-C trial neurocognitive deterioration was less frequently seen in the Sentinel group (4% vs. 27%, p=0.017). A reduction in stroke rate in the Sentinel group compared to the unprotected group was not observed in these studies.

**Table 1:** Strengths and shortcomings of various CEPD.

	Sentinel	TriGUARD 3	Point-Guard	Emblok	ProtEmbo	Emboliner
<b>Principle</b>	Filter	Deflector	Deflector	Filter	Deflector	Filter
<b>Cerebral Protection</b>	Partial	Complete	Complete	Complete	Complete	Complete
<b>Peripheral Protection</b>	No	No	No	Yes	No	Yes
<b>Approach site</b>	Radial	Femoral	Femoral	Femoral	Radial (Left)	Femoral
<b>Access route</b>	TF- & TA-TAVR	TF- & TA-TAVR	TF- & TA-TAVR	TF- & TA-TAVR	TF- & TA-TAVR	TF-& TA-TAVR
<b>Delivery sheath</b>	6F	8F	10F	11F	6F	9F
<b>Mesh pore size</b>	140 µm	115x145 µm	105 µm	125 µm	60 µm	150 µm
<b>EU/USA status</b>	CE Mark/ FDA-cleared	CE Marked and pending FDA 510 (k) clearance	Investigational use	Investigational use	Investigational use	Investigational use

TF: Transfemoral, TA: Transapical, F: French



**Figure 1:** Strengths and shortcomings of various CEPD. **A:** Sentinel device (Boston Scientific); **B:** TriGUARD device (Keystone Heart Ltd); **C:** Point-Guard system (Transverse Medical, Inc.); **D:** Emblok system (Innovative Cardiovascular Solutions); **E:** ProtEmbo system (Protembis GmbH); **F:** Emboliner Embolic Protection Catheter (Emboline Inc.). Ref: Gasior et al. Cerebral embolic protection systems for transcatheter aortic valve replacement. *J Interv Cardiol.* 2018;31:891-8.

Hereafter, the SENTINEL trial (n=363 patients), a multi-center single blinded RCT, showed that debris was found in 99% of the filters. A lower stroke rate at 30 days was seen in the Sentinel group, which however was not statistically significant (5.6% in the Sentinel group and 9.1% in the unprotected group,  $p=0.25$ ) [28]. A reduction in new lesion volume on DW-MRI also was statistically not significant ( $102.8 \text{ mm}^3$  in the Sentinel group and  $178 \text{ mm}^3$  in the unprotected group,  $p=0.33$ ). However, a significant reduction in new lesion volume in protected areas was seen after adjusting for valve type and baseline lesion volume ( $p=0.02$ ). After TAVR, neurocognitive function was similar in both groups with a correlation between lesion volume and neurocognitive decline ( $p=0.022$ ).

Interestingly, device efficacy appeared to vary among the different valve types. CEPD appeared less beneficial with the Sapien S3 valve compared to other valve types (Evolut R or Sapien XT) with respect to lesion volume. Confounding factors such as operator experience, patient selection for

different valve types and lack of routine predilatation in the Sapien S3 group may have influenced this finding.

Importantly, all of these studies were underpowered for hard clinical endpoints such as periprocedural stroke.

In 2017, Seeger et al. performed a large-scale prospective study using propensity score-matched analysis (n=802) [33]. The rate of disabling and nondisabling stroke was significantly lower in the Sentinel group compared to the unprotected group (1.4% vs. 4.6%,  $p=0.03$ ). It should be noted that the endpoint was set at an earlier timepoint compared to the SENTINEL trial (7 days vs. 30 days), thereby excluding some potential nonprocedural related causes of stroke.

A patient level pooled analysis which consisted of patients from the SENTINEL trial, CLEAN-TAVI trial and the SENTINEL-Ulm registry showed similar results after propensity score-matched analysis (n=1066) [34]. In this

study, an even shorter postprocedural period of 72 hours was chosen, at which timepoint, stroke was significantly less prevalent in the Sentinel group compared to the unprotected group (1.88% vs. 5.44%,  $p=0.0028$ ). The major limitation of this study is the heterogenous study population. Also, the reduction in stroke was mainly driven by the SENTINEL-Ulm registry, a non-randomized single center registry, contributing almost two third of the study population. Hence, bias from the SENTINEL-Ulm registry by confounding factors cannot be excluded. Additionally, stroke is defined differently in these three studies and neurologic assessment is not performed consistently among these studies [35]. A meta-analysis consisting of three RCTs and one observational study confirmed these findings and demonstrated that the Sentinel device is associated with a lower 30-day stroke rate after TAVR [36].

Three large retrospective studies utilizing propensity score matched analysis showed mixed results with two studies showing positive results with a lower risk of ischemic stroke after TAVR in the Sentinel group compared to the unprotected group [37-39]. Due to the retrospective nature, selection bias and coding errors of stroke could be present in these studies.

### TriGUARD embolic deflector device

The TriGUARD system is an embolic deflector device which consists of a temporary, single-use, biocompatible nitinol filter mesh (130 x 250  $\mu\text{m}$  pores) on a stabilizing frame [27]. After delivery via a 9F transfemoral sheath the device is deployed in the aortic arch under fluoroscopic guidance. After deployment, the ostia of all three major branches of the aortic arch (right brachiocephalic, left common carotid and subclavian artery) are covered by the device preventing cerebral embolization by means of deflecting debris to the descending aorta. A stable position is ensured with the stabilizer being anchored in the ostium of the right brachiocephalic artery.

**Clinical data:** The TriGUARD system was initially investigated in the DEFLECT I trial, a prospective, multicenter, single-arm study ( $n=37$  patients) [40]. Device safety was confirmed in this study and successful coverage of all three branches could be seen in 80% of the patients. Furthermore, post-procedure DW-MRI findings were promising. Compared to historical data, a 34% reduction of per-patient total lesion volume could be seen with the TriGUARD system. The presence of new cerebral ischemic lesions however was similar compared to historical data (82% vs. 76%,  $p=\text{nonsignificant}$ ).

The TriGUARD HDH, the second-generation device, was then introduced and evaluated in several prospective studies. The DEFLECT III trial, a multicenter RCT ( $n=85$  patients), showed improved cognitive function at discharge in some domains (the International Shopping List Test

(a measure of episodic memory): 65.4% vs. 30.4%;  $p=0.022$ ), less new neurologic deficits, which was defined by worsening in National Institutes of Health Stroke Scale (NIHSS) score from baseline (3.1% vs. 15.4%;  $p=0.16$ ) and greater freedom from new ischemic brain lesions on DW-MRI (26.9% vs. 11.5%; significance levels not provided) in the TriGUARD group compared to the unprotected group [41]. No reduction could be seen in the primary in-hospital procedural safety endpoint (death, stroke, life-threatening or disabling bleeding, stage 2 or 3 acute kidney injury or major vascular complications) (21.7% in the TriGUARD group vs. 30.8% in the control group;  $p=0.34$ ).

The TriGUARD HDH system was further evaluated in a single center prospective study ( $n=14$  patients), wherein its safety and efficacy were confirmed with absence of major adverse cerebral and cardiac events in all patients [42]. A reduction in mean ischemic brain lesion per patient could be shown compared to historical data [13.8 vs. 25.1,  $p=0.049$ ].

In the most recent study, the REFLECT I trial [43], a large RCT ( $n=258$ ), the primary efficacy endpoint (hierarchical composite of all-cause mortality or any stroke at 30 days, NIHSS score worsening at 2-5 days or Montreal Cognitive assessment worsening at 30 days, and total volume of cerebral ischemic lesions detected by DW-MRI at 2-5 days) was statistically not different between the TriGUARD group and the unprotected group. This study has been suspended prior to completing enrollment after introduction of the TriGUARD 3 system and its safety and efficacy being evaluated in the REFLECT II trial.

### TriGUARD 3

The TriGUARD 3 is an update of the current CE-marked TriGUARD HDH and provides extended coverage of the three major branches, less interference with transcatheter heart valve systems and improved ease of use. The device consists of a biocompatible nitinol filter mesh on a self-stabilizing frame. The filter mesh has a reduced pore size (115 x 145  $\mu\text{m}$ ) compared to the TriGUARD HDH preventing smaller particles entering the cerebral circulation. Introduction of the delivery system takes place through an 8F transfemoral sheath in contrast to a 9F sheath for the TriGUARD HDH. Further, a dedicated stabilizer is not needed, since the circumferential device pressure in the aortic arch and support of the nitinol shaft offer sufficient stability throughout the procedure. It is fully visible on fluoroscopy. When positioned correctly, emboli are deflected to the descending aorta.

**Clinical data:** In the REFLECT II trial [44], a large RCT ( $n=220$ ), the composite safety endpoint was numerically higher in the TriGUARD group compared to the unprotected group (15.9% vs. 7.0%,  $p=0.11$ ). The difference was however mainly driven by major

vascular complications related to the TAVR access site. The primary efficacy endpoint (hierarchical composite of all-cause mortality or any stroke at 30 days, National Institutes of Health Stroke Scale (NIHSS) worsening at 2 to 5 days, freedom from any cerebral ischemic lesions detected by DW-MRI at 2-5 days, total volume of cerebral ischemic lesions detected by DW-MRI at 2-5 days) was not statistically different between groups.

In this study, successful device positioning (coverage of all three major branches throughout the procedure) was only achieved in 59.3% of the patients. Further, the study was suspended early resulting in limited statistical power and a small control group with a relatively low rate of serious adverse events.

### **Point-Guard system™ Dynamic Cerebral Embolic Protection**

The Point-Guard system (Transverse Medical, Inc, Denver, CO, USA) is an embolic deflector device, which can be placed via the femoral artery. It is designed to prevent cerebral embolization during structural heart procedures, such as TAVR. It consists of a filter mesh within a flexible nitinol frame. Coverage of the ostia of all major branches (innominate, left common carotid and subclavian artery) of the aortic arch is achieved providing full cerebral embolic protection. It is dynamically stabilized by its isolation zone during positioning. The Point-Guard system is only available for investigational use and clinical data is lacking [45]. The CENTER trial will evaluate the Point-Guard system in the clinical setting.

### **Emblok™ Embolic Protection System**

The Emblok system (Innovative Cardiovascular Solutions, Grand Rapids, MI, USA) is an embolic filter device, which can be used during TAVR and other left-sided heart procedures [45]. Besides cerebral protection the abdominal and peripheral vasculature are protected as well with this device. Access via an 11F transfemoral sheath is obtained after which the system with an incorporated pigtail catheter is advanced into the aorta. The radiopaque pigtail catheter is seated in the non-coronary cusp and the filter system (125- $\mu$ m pore size) is then deployed in the aortic arch. It can accommodate aortic anatomies between 25-40 mm in diameter.

The first in man study (n=20) evaluating the Emblok system during TAVR confirmed its safety and feasibility. In all patients, successful device deployment and retrieval could be observed. 90% of the filters revealed embolized debris. At 30 days follow-up, no major adverse cardiovascular and cerebrovascular events were seen. On DW-MRI, new ischemic brain lesions were present in 95% of the patients. Future studies are needed to elucidate if the Emblok system is efficacious in improving clinical

outcomes after TAVR.

### **ProtEmbo® Cerebral Protection System**

The ProtEmbo system (Protembis GmbH, Aachen, Germany) is an embolic deflector device and is delivered via a 6F sheath in the left radial artery. Its aim is to protect all three major branches of the aortic arch. It consists of a heparin-coated mesh and it has the smallest pore size (60  $\mu$ m) of all CEPD [45]. Safety and feasibility of the device during TAVR will be tested in the PROTEMBO SF Trial.

### **Emboliner™ Embolic Protection Catheter**

The Emboliner Embolic Protection Catheter (Emboline Inc., Santa Cruz, CA, USA) provides cerebral and peripheral embolic protection [45]. The system is introduced via the femoral artery through a 9F sheath. Its pore size is 150  $\mu$ m. The SafePass trial will evaluate the Emboliner Embolic Protection Catheter in a multicenter study.

### **Cerebral Embolic Protection in TAVR: Where do we Stand?**

During recent years, the rapidly increasing number of TAVRs being performed worldwide and the target population expanding to lower surgical risk groups have led to the necessity to optimize clinical outcomes. In TAVR, periprocedural stroke is still a major issue we need to take into consideration. The introduction of CEPD was seen as a logical step in preventing cerebral embolization and lowering the risk of developing stroke after TAVR.

Nevertheless, a significant reduction in stroke rate when utilizing a CEPD has not been proven so far in randomized studies. Importantly, all of these studies were underpowered due to a low sample size and could therefore not detect any significant difference in clinical outcomes [28-29,32,41,43,44].

In contrast to these RCTs, large observational studies using propensity score matched analysis revealed a lower stroke rate when the Sentinel system was used [33,34,37,38]. In these studies, stroke was assessed earlier than 30 days compared to previous studies. Adapting a shorter time frame to diagnose stroke seems reasonable since the majority of neurological events occur within 24 hours. As a result, other potential causes of stroke, such as atrial fibrillation and atherosclerotic disease can be excluded.

The assessment of CEPD has also shifted to surrogate end points in order to prove its value and efficacy. These end points focused on new ischemic brain lesions on DW-MRI and neurocognitive function after TAVR. The rationale behind this is that TAVR is not solely performed to prolong the life expectancy, but also to improve quality of life. The

results nonetheless have been ambiguous. Some studies have showed improved neurocognitive function and a reduction in number and volume of new ischemic brain lesions [29,32,40-42].

A meta-analysis of RCTs (n=252) concluded that the use of CEPD was associated with a lower total lesion volume and fewer new ischemic lesions and better neurocognitive function [46]. In this respect, it might also be of interest to assess the frequency of delirium as a secondary endpoint in CEPD trials. Delirium is frequently observed post-TAVR and is associated with increased morbidity and mortality [47,48].

While there is no doubt about the filtering or deflection capacity of the available CEPD, it is also important to address potential limitations. The Sentinel device only covers two of the three major branches of the aortic arch. Consequently, the left vertebral artery is unprotected, and a significant part of the brain remains unprotected. Furthermore, there is only one filter size available which means that complete sealing of the intended vessels is not established in all aortic anatomies. The TriGUARD 3 device provides full cerebral protection. In spite of that successful device positioning was only achieved in 59.3% of the patients in the REFLECT II trial [44]. Hence, a more reliable and efficacious coverage is crucial to effectively prevent cerebral embolization. Additionally, an improved and safer profile might reduce access-site related vascular complications.

We can therefore conclude that the results of CEPD in TAVR have not been convincing. While high expectations were present with the introduction of CEPD, a clear clinical benefit has not been proven so far.

Nevertheless, we believe that there is still an important role for cerebral embolic protection in TAVR patients at high stroke risk. Technical improvements may be necessary first to optimize CEPD efficacy.

Future large multicenter RCTs, such as the PROTECTED TAVR trial (Stroke Protection With Sentinel During Transcatheter Aortic Valve Replacement, n=3000) and the BHF PROTECT-TAVI (British Heart Foundation Randomized Trial of Routine Cerebral Embolic Protection in Transcatheter Aortic Valve Implantation, n=7730) will evaluate if the use of a Sentinel device is associated with a lower stroke rate at 72 hours. A definitive answer can then be given if there is still a future for CEPD in TAVR.

## Conclusion

In TAVR, the role of cerebral embolic protection still has to be elucidated. Although promising from a pathophysiological point of view, randomized studies have not shown a reduction in stroke rate when a CEPD is used. Future adequately powered RCTs will tell us if cerebral

embolic protection will indeed be beneficial and lead to a lower stroke rate after TAVR.

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