REVIEW

Cerebral embolic protection in patients undergoing transcatheter aortic valve implantation: Recent advances

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ABSTRACT

Despite major advances in transcatheter aortic valve implantation (TAVI) technology during the last years, stroke remains one of the most serious complications of TAVI, tremendously increasing mortality and the loss of neurocognitive function. Since TAVI is expected to further spread into lower-risk patient groups, there will be greater emphasis to obviate such serious complications. One possible technique for preventing stroke is using cerebral embolic protection devices (CEPDs). CEPDs are designed for capturing or deflecting emboli that are en route to the brain and hence to protect the brain from embolism. Although their clinical utilization is increasing, the evidence for using CEPDs is not yet clear. Since this is a rapidly growing field with recent advances, and the impact of CEPD on preventing neurological events is still limited, there is an urgent need for understanding the role of CEPD in preventing clinically significant strokes. In this review, we present an overview of the available literature on CEPDs in patients undergoing TAVI and outline recent advances within this field.

Key words: aortic stenosis, cerebral embolic protection, stroke, transcatheter aortic valve implantation

INTRODUCTION

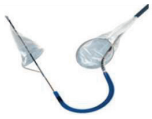
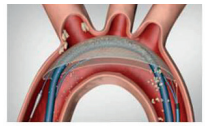
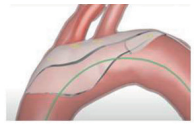
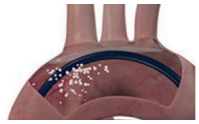
Despite the technical progress in transcatheter aortic valve implantation (TAVI) and the steadily increasing operator experience, stroke remains one of the main complications limiting the life expectancy and resulting in a tremendous deterioration of physical and neurocognitive function as well as affecting psychosocial aspects [1]. Neurological events are observed in 1%–11% of patients undergoing TAVI [2]. The highest risk for embolization of debris into the brain has been shown to be periprocedural during valvuloplasty, valve positioning, and implantation of the new valve and is mainly described as a result of manipulation at highly calcified structures or embolization of intraaortic atheromatous material or thrombi. In addition, emboli can originate from the aortic arch, the left ventricular outflow tract, or even from particles of the equipment used during the procedure [3].

Apart from clinical strokes, subclinical strokes, defined as new ischemic brain lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) without any clinical signs, are found in approximately 90% of patients undergoing TAVI. Nonetheless, the clinical significance of these "silent" strokes remains unclear [4].

Since TAVI is expected to further expand into lower-risk patient groups [5] and patients undergoing TAVI want to maintain their ability to independently practice their daily activities instead of simply staying alive [6], special efforts to prevent embolic stroke or other neurological events remain of utmost importance.

One option for protecting brain structures from embolization of debris is using cerebral embolic protection devices (CEPDs). CEPDs are intended to reduce the risk for embolic events by filtering and capturing particles or by deflecting embolic debris downwards into the descending aorta. Even though using CEPDs is steadily increasing and new technologies are constantly arising, the evidence for the widespread use of CEPDs and prevention of stroke is not yet clear [7]. The available literature is mainly based on observational studies

Table 1. Overview of currently available and investigational CEPD

	Sentinel (Boston Scientific, Corp., US)	Emblok (Innovative cardiovascular solutions, Grand Rapids, MI, US)	Emboliner (Emboline Inc., Santa Cruz, CA, US)	TriGuard 3 (Keystone Heart, Caesarea, Israel)	Point-guard (Transverse medical Inc., US)	Protembo (Protembis GmbH, Germany)
Device						
Access	Right radial, 6 F	Femoral, 11 F	Femoral, 9 F	Femoral, 8 F	Femoral, 10 F	Left radial, 6 F
Coverage	2-vessels capture	3-vessel capture	3-vessel and body capture	3-vessel coverage	3-vessel coverage	3-vessel coverage
Pore size	140	125	150	145	105	60
Main trials	MISTRAL-C (2017) SENTINEL (2017) CLEAN-TAVI (2017) PROTECTED-TAVR (ongoing) PROTECT-HF (ongoing)	European study (ongoing)	SafePass trial (planned)	DEFLECT I–III REFLECT I–II (2021)	CENTER-Trial (ongoing)	PROTEMBO SF Trial (ongoing)
Regulatory status	CE mark/FDA approved	Investigational	Investigational	CE mark/investigational	Investigational	Investigational

Abbreviations: CEPD, cerebral embolic protection device; CE, Commiteé Europeenne; FDA, Food and Drug Administration

and small-sized randomized trials, which are not powered to provide clear evidence for the use of CEPDs. Furthermore, most of the studies assessed imaging endpoints instead of major clinical events, which raises further uncertainties.

In the current review, we summarize current knowledge and describe recent advances in CEPDs in patients undergoing TAVI.

TYPES OF EMBOLIC PROTECTION SYSTEMS

Currently available CEPDs

Currently, there are mainly two mechanisms of protecting brain structures from embolic debris during TAVI. There are deflector devices that redirect debris towards the descending aorta, and there are filter devices that retain embolic material and debris (Table 1).

The dual filter device Sentinel CEPD (Boston Scientific, Marlborough, MA, US) is the most studied (Table 2) and the only device that is approved for clinical use in both Europe and the US. The system is advanced through a 6 F sheath through the right radial or brachial artery. The two 140 µm pore polyurethane filters are placed proximally in the brachiocephalic trunk and distally in the left common carotid artery before TAVI. The left vertebral artery remains unprotected so that 9 of 28 brain territories are protected by the filter system. There is only one size available resulting in some anatomical variations where sufficient protection cannot be provided.

The Sentinel device was studied in several observational studies and randomized trials. The largest randomized trial (SENTINEL) [8] was published in 2017 and randomized 363 patients in a 1:1:1 fashion (the safety arm n = 123 [use of CEPD and assessment of clinical events without imaging or neurocognitive testing]; the imaging device arm n = 121; the control arm n = 121). After the procedure, embolic debris was found in 99% of all filters. However, the trial could not show a significant reduction of median total new lesion volume in the protected brain areas (102.8 mm^3 in the device arm vs. 178 mm^3 in the control arm; $P = 0.33$) using DW-MRI 2–7 days after TAVI.

The efficacy of the Sentinel CEPD was also investigated in the single-center randomized CLEAN-TAVI trial [9] which included 100 patients undergoing TAVI. The study performed brain MRI at baseline, two and seven days after TAVI and observed a significant reduction in the number of new lesions in the CEPD group as determined by DW-MRI (4 in the CEPD arm vs. 10 in the control arm; $P < 0.001$) and a significant decrease in the volume of new cerebral lesions after 48 hours (242 mm^3 in the CEPD arm vs. 527 mm^3 in the control arm; $P < 0.001$). Despite these promising results, there was no significant reduction in clinical stroke (n = 5 in the CEPD arm vs. n = 5 in the control arm; $P > 0.05$).

The multicenter randomized MISTRAL-C trial [10] evaluated the Sentinel CEPDs in 65 patients and found debris in 100% of the filters. The trial further showed a significantly lower rate of patients with neurocognitive deterioration when using CEPDs (4% vs. 27%; $P = 0.017$). Even though multiple lesions (>10 lesions on DW-MRI) were only seen in patients without CEPDs (20% vs. 0%; $P = 0.03$), there was only a numerical, non-significant reduction in the number of new brain lesions in DW-MRI (73% vs. 87%; $P = 0.31$).

The TriGuard CEPD (Keystone Heart Ltd., Caesarea, Israel) is the only deflector device, that received CE marking (however, without Food and Drug Administration approval yet). It is inserted through an 8 F sheath in the femoral artery (contralateral to the main access site) and placed within the inner curvature of the aortic arch allowing maximal blood flow to the brain arteries and covering all

Table 2. Randomized controlled trials evaluating CEPD

Trial	Study population (n)	Main objectives	Assessment of the main endpoints	Main results
Sentinel (2017)	363 Multicenter RCT	Efficacy and safety of Sentinel CEPD	Assessment: DW-MRI at 2-7 days NE at baseline, at discharge, 30 days 30-day safety (VARC-2)	• Debris in 99% of all filters • Numerically less strokes at 72h (3% vs. 8.2%; $P = 0.053$) • Numerically less new lesion volume (102.8mm^3 vs. 178 mm^3; $P = 0.33$) • No significant difference in neurocognitive function at 30 days • Numerically lower stroke rate at 30 days (5.6 vs. 9.1; $P = 0.25$) • At 30 days lower lesion volume of protected areas • Correlation between lesion volume and neurocognitive decline ($P = 0.0022$)
Clean TAVI (2016)	100 Single center RCT	Effect of Sentinel CEPD on number of new lesions on DW-MRI	Assessment: DW-MRI at baseline, 2 days and 7 days NE 2 at and 7 days	• Lesions in 98% of patients • Less new lesions (4 vs. 10; $P < 0.001$) • Lower volume of new cerebral lesions after 48 hours (242 mm^3 vs. 527 mm^3; $P < 0.001$) • No difference in clinical stroke (10% vs. 10%; $P = 1.0$) • New neurological symptoms similar (n = 5; $P = 1.0$ in both groups)
Mistral-C (2016)	65 Multicenter RCT	Efficacy and performance of Sentinel CEPD	Assessment: MRI baseline and 5–7 days NE baseline and 5–7 days	• Debris found in 100% of filters • Lesions found in 78% of patients • Numerically less new lesions (73% vs. 87%; $P = 0.31$) • Numerically lower lesion volume (95 mm^3 vs. 197 mm^3; $P = 0.171$) • ≥10 lesions only in control group ($P = 0.03$) • Sign reduction in patients with multiple lesions (20 vs. 0 %; $P = 0.03$) • Neurocognitive deterioration 4% vs. 27% ($P = 0.017$)
Deflect III (2015)	85 Multicenter RCT	Safety, efficacy, and performance of TriGuard HDH	Primary endpoint: in hospital procedural safety (death, stroke, disabling bleeding, acute kidney injury, major vascular complications) Assessment: MRI at 2–6 days NE at baseline, pre-discharge, 30-days	• Primary endpoint numerically lower (21.7% vs. 30.8%; $P = 0.34$) • Full coverage 89% • Per treatment population analysis: • Freedom from new lesions at discharge: 26.9% vs. 11.5%; P = not specified • Freedom from new lesions at 30 days: 11.5% vs. 9.1%; $P = 0.78$) • Numerically lower NIHSS at discharge (3.1 vs. 15.4%; $P = 0.16$)
REFLECT II (2020)	220 Multicenter RCT	Efficacy & safety of TriGuard 3	Assessment: MRI 2–5 days Death or stroke at 30 days NIHSS worsening 2–5 days	• Primary efficacy 45.7% vs. 54.3%; $P = 0.857$ • Full coverage 60% • Technical success 71%, • Numerically lower total lesion volume (215.4 mm^3 vs. 188.1 mm^3; $P = 0.405$) • Sign. more vascular complication in CEPD group, according to author TAVI associated (7% vs. 0%; $P = 0.04$) • Numerically higher event rate in CEPD group (15.9 vs. 7%; $P = 0.11$)

Abbreviations: DW-MRI, diffusion-weighted magnetic resonance imaging; MRI, magnetic resonance imaging; NE, neurological examination, NIHSS, National Institutes of Health Stroke Scale; RCT, randomized controlled trial; TAVI, transcatheter aortic valve implantation; VARC, Valve Academic Research Consortium; other — see Table 1

3 cerebral vessels. It is a single-wire nitinol frame and mesh filter with a pore size of 130 µm. DEFLECT III [11] was the first randomized multicenter trial for the first-generation TriGuard HDH including 85 patients. TriGuard HDH was shown to be safe and achieved full coverage of the brain arteries in 89% but failed to show a significant reduction in new lesions on DW-MRI in the intention-to-treat analysis when compared to the control group. In the per treatment group (subjects with complete brain vessel coverage), there was a trend toward greater freedom from new DW-MRI lesions (26.9% in the CEPD arm vs. 11.5% in the control arm) and an improved cognitive function in patients with CEPDs (65.4% vs. 30.4%; $P = 0.02$), but the explorative study was not powered to detect statistically significant effects on safety and efficacy outcomes. In a pooled analysis, including 142 subjects from DEFLECT I and III and the Neuro-TAVR (transcatheter aortic valve replacement) registry [12], there was a Valve Academic Research Consortium (VARC-2) defined significant reduction of in-hospital stroke (6% vs. 0%; $P = 0.05$), a reduced incidence of stroke as defined by worsening of the National Institutes of Health Stroke Scale (NIHSS) combined with new ischemic lesions on DW-MRI (0 vs. 19%; $P = 0.002$), and lesion volume on DW-MRI (315 + 620 mm^3 vs. 511 + 893 mm^3; $P = 0.04$), as well as an improved cognitive function favoring the protected groups.

TriGuard HDH was subsequently investigated once more within the REFLECT I trial, enrolling 258 patients. It met the safety endpoints but did not meet the predefined hierarchical composite effectiveness endpoint of all-cause mortality or any stroke at 30 days, Montreal Cognitive Assessment worsening at 30 days, or NIHSS worsening at 2–5 days, and total volume of cerebral ischemic lesions detected by DW-MRI at 2–5 days after TAVI compared with unprotected controls. Full coverage of the brain arteries was achieved in only 57%, and the trial was terminated early which led to the development of the next generation TriGuard 3 [13], providing an easier use and a larger, self-stabilizing filtration surface, which was further investigated in the multicenter, randomized REFLECT II trial [14]

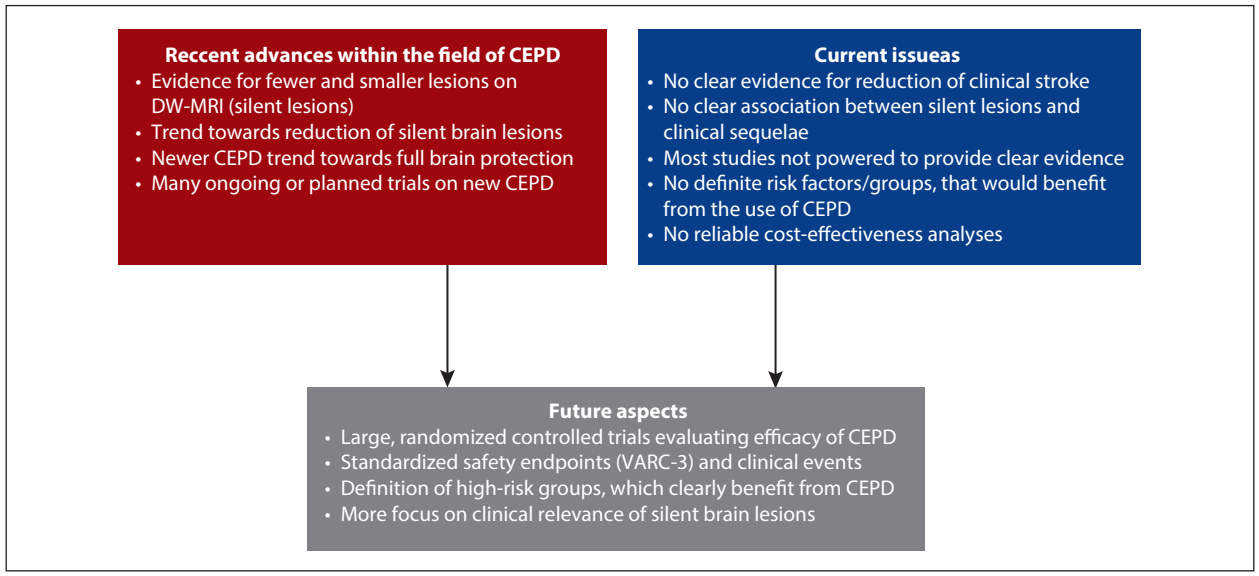


Figure 1. Recent advances and open questions
Abbreviations: see Tables 1 and 2

evaluating performance and safety in 220 TAVI patients. The trial met its safety endpoint (a composite of all-cause mortality, stroke, life-threatening or disabling bleeding, stage 2/3 acute kidney injury, coronary artery obstructions with subsequent intervention, major vascular complication, and valve-related dysfunction requiring intervention), defined by VARC-2, which was compared with a historical performance goal. However, there was a numerically higher number of life-threatening bleedings (5.7% vs. 0%; $P = 0.12$) and a significantly higher number of major vascular complications (7% vs. 0%; $P = 0.04$). Full coverage of the brain arteries was 60% and the primary hierarchical composite efficacy endpoint (including death or stroke at 30 days, National Institutes of Health Stroke Scale score worsening in hospital, and cerebral ischemic lesions on DW-MRI at 2 to 5 days) was not met with TriGuard 3 compared to the control group.

Investigational CEPD

Several CEPDs are being developed. These devices have different mechanisms of action and are in different stages of clinical evaluation.

The deflector device Embrella was studied in the non-randomized PROTAVI-C study including 93 patients [15] and showed a lower volume of new lesions on DW-MRI in the device group compared with the control group ($P = 0.003$). Nevertheless, new brain lesions were observed in 100% of the patients.

Another deflector device is the Embol-X CEPD (Edwards Lifescience, Irvine, CA, US). A randomized trial by Wendt et al. [16] evaluated 30 patients receiving Embol-X CEPD and showed significantly smaller lesion volumes in the supply region of the middle cerebral artery (33 mm^3 vs. 76 mm^3; $P = 0.04$), as well as in the vertebral and basilar artery territory.

PointGuard (Transverse Medical Inc., Denver, CO, US) is a complete cerebral embolic protection deflector system with a dynamic stabilization spring for positioning and minimizing debris migration. It provides full perimeter edge and sidewall conformity while providing maximum blood flow to the brain. The CENTER trial is currently investigating its performance and safety.

ProtEmbo (Protembis GmbH, Aachen, Germany) is another deflector device that is advanced through the left radial artery and, therefore, avoids the way along the carotid arteries, which are commonly heavily calcified in elderly patients. In the same way, it avoids interference with TAVI. The device has a low-profile design and has a very small pore size of 60 µm, hence protecting the brain from small-sized embolizing particles. The PROTEMBO SF trial is evaluating feasibility, safety, and efficacy of the ProtEmbo system for patients undergoing TAVI. First results are expected soon.

Emblok (Innovative Cardiovascular Solutions, LLC., Grand Rapids, MI, US) is an 11 F sheath device containing a 4 F pigtail catheter advanced through femoral access. It is a 125 µm pore-size nitinol filter system that allows the embolic filter and a radiopaque pigtail catheter to be advanced simultaneously through femoral access. It fits in various anatomies of the aorta with a diameter up to 35 mm. Currently, the system is available only for investigational use. The results of the clinical trial evaluating feasibility and safety are expected in the near future.

Further ideas for protecting the brain from embolization tend to include the protection of peripheral arteries and especially the renal arteries (Emboliner and Captis).

Results from initial studies which evaluate feasibility and safety are expected soon.

CURRENT ISSUES AND RECENT ADVANCES

Definition of standardized study endpoints

The incidence of postprocedural neurologic events and stroke is highly dependent on the definition, ranging from predominantly clinical to imaging-based definitions that include new lesions detected on DW-MRI without any neurocognitive alterations (silent strokes). As a result, stroke can be underreported as well as overreported within different trials. Depending on the assessment and on the definition applied, it is reported in around 5% when defining stroke based on clinical symptoms to >90% when focusing on silent lesions detected by DW-MRI [3, 17]. Systematic evaluation by an experienced neurologist can further increase the incidence [18].

Historically, there has been a lack of uniform definition which inhibited comparability. Recently, VARC-3 introduced updated definitions of neurologic events associated with TAVI, which represents a step towards standardization in future studies and provides harmonization with previous Neurologic Academic Research Consortium (NeuroARC) definitions.

According to VARC-3, stroke is classified as overt CNS (central nervous system) injury (NeuroARC type 1) with either ischemic stroke, hemorrhagic stroke, or stroke that is not otherwise specified. Covert CNS injury (NeuroARC type 2) is described by pathological evidence or by imaging. Neurologic dysfunction without CNS injury (NeuroARC type 3) is defined as transient focal neurological signs lasting <24 hours (transient ischemic attack) or delirium without CNS injury. Furthermore, periprocedural events are classified as acute (<24 hours) or subacute (24 hours–30 days) [19].

Assessment of stroke remains complex since neurological tests remain challenging in the elderly and could lead to false-positive or false-negative results. A neurologic assessment is recommended to be performed by an experienced neurologist to detect slight deviations. An assessment by a non-neurologist may still be acceptable in clinical practice. However, for clinical trials on CEPDs, VARC-3 clearly recommends neurologic assessment by an experienced neurologist.

The need for routine performance of MRI or a transcranial doppler examination is not yet clear. MRI usually detects 68%–100% of ischemic brain lesions but is limited to the time span after TAVI [4]. Procedural transcranial doppler ultrasound detects 100% of cerebral embolic signals, which mainly arise during valve deployment [20]. Studies, investigating the optimal method for detecting stroke using imaging are still missing.

Even though there is evidence for a reduction of new brain lesions and volume of new lesions, there is no clear evidence for prevention of clinical sequelae. The clinical impact of embolized debris detected by MRI is controversial, but silent infarction has been described to be associated with premature neurocognitive deterioration and dementia [21, 22]. Studies evaluating these effects should follow soon.

Risk factors for stroke

To date, there is no clear evidence on whether to use CEPDs for all patients, for specific groups at high risk, or for none of the patients undergoing TAVI. In clinical practice, CEPDs are often used in patients thought to be at high risk for cerebral embolism.

Risk factors for developing TAVI-related stroke include patient-related characteristics such as age, prior stroke, and atrial fibrillation, as well as procedure-related factors, such as long procedure time, rapid pacing, or valve repositioning. Whereas procedure-related factors are related to an increase in the risk of early stroke, patient-related risk factors are associated with late stroke (>10 days) [23]. Furthermore, there could be an increased risk for cerebral embolism in the bicuspid valve or valve-in-valve procedures. In addition, there are reports about different stroke rates for different valves [24] and the modulating effect of oral anticoagulation on preventing cerebral embolism during TAVI should be investigated in large studies.

Currently, however, conditions that could increase the risk for cerebral embolic events are still ill-defined. A preprocedural model for risk assessment to identify patient groups that would benefit most from CEPD is missing.

Reasons for stroke despite using CEPDs

Reasons for embolic events despite using embolic protection are multiple. One possible reason could be incomplete sealing due to specific features of the device or individual anatomy. Further reasons include an unprotected left vertebral artery which originates from the left subclavian artery and the fact that there is only one available filter size when focusing on the Sentinel device.

Second, since not only manipulation at the valve but also the placement of protection devices could mobilize different structures, this could be identified as a possible source for emboli or debris causing cerebral embolism [3, 25].

One additional mechanism for cerebral events that has been described is hemodynamic instability and the resulting hypotension during TAVI procedures, where CEPDs would not contribute to increased safety. Hemodynamic instability could arise, for example, in the case of rapid pacing in patients with reduced left ventricular ejection fraction and general anesthesia as a potential factor, increasing the number of neurological events. These mechanisms need to be studied in the future.

Cost-effectiveness

One point that needs to be elucidated in this context is cost-effectiveness, which is of importance since the

number of TAVI procedures is rapidly increasing and the procedure is expected to further expand into younger and lower-risk patient groups. Specifically for those patients, prevention of serious complications such as periprocedural stroke needs specific attention. The market for CEPDs is expected to increase rapidly and several trials on new CEPDs will follow soon. Since more than 50% of patients experiencing stroke are unable to return to work, and most of them end up with serious financial problems, sequelae such as permanent disability and psychosocial issues should be specifically taken into account [18, 26]. The benefit of preventing stroke should be balanced against the costs of the device. Since healthcare expenditures for periprocedural stroke with all its subsequent annual costs and psychosocial consequences could potentially tremendously exceed the costs of CEPDs, there should be evaluations on cost-effectiveness and the number needed to treat (NNT) from large, randomized trials.

Currently, analyses about cost-effectiveness and clear evidence for the benefit of routine use of CEPD are missing.

Future aspects for clinical trials on CEPD

Until now, there is limited evidence on the routine use of CEPDs in all patients, and clear recommendations on which patients might benefit from the use of CEPD are still lacking. The low event rate in most of the trials precludes definite conclusions as to the clinical benefit of CEPDs. Although evidence for efficacy has been provided by registries and pooled analyses [26, 27], no convincing evidence from large randomized controlled trials is currently available, and it seems that at least 3000 patients are needed for an adequately powered randomized controlled trial (RCT).

In addition, the time span for diagnosing TAVI-related stroke differs between the currently available studies and ranges between 24 hours and 30 days. Since not only the TAVI procedure but also new-onset atrial fibrillation or other conditions can lead to stroke, results may be confounded. Kahlert et al. [28] showed that most embolic events occur during valve implantation. Therefore, timing up to 7 or even 30 days could distort the rate of periprocedural stroke due to the impact of atrial fibrillation or the periprocedural management of oral anticoagulation.

Results of the large randomized PROTECTED TAVR (Stroke PROTECTion With Sentinel During Transcatheter Aortic Valve Replacement) trial (NCT04149535) are expected in 2022. The trial randomized 3000 patients to either the use of Sentinel CEPD or no use of CEPD with the primary endpoint of neurologist-assessed in-hospital stroke within the first 72 hours. The BHF PROTECT-TAVI (British Heart Foundation Randomised Trial of Routine Cerebral Embolic Protection in Transcatheter Aortic Valve Implantation, n = 7730, ISRCTN16665769) is set to compare TAVI with filter protection versus unprotected TAVI for the endpoint of any new stroke within 72 hours. These results will provide further important answers.

Besides this, there should be large studies on the effects and clinical sequelae of subclinical or silent strokes. Available data mainly focus on clinical stroke, whereas the clinical significance and long-term sequelae of asymptomatic lesions after TAVI have not been defined.

Third, most of the studies excluded patients with a very high risk for embolic events such as prior stroke, carotid artery disease, porcelain aorta, bicuspid valves, or valve-in-valve procedures. Future trials should include these high-risk groups so that clear evidence for the use of CEPD could be provided at least for specific patient groups.

New CEPDs are in development with a trend toward full-brain and even full-body protection. Access site, sheath size, and mesh pore size differ between these devices. The perfect protection device should protect the entire brain and offer easy delivery and positioning with stability throughout the whole procedure; it should be clinically effective and safe.

CONCLUSIONS

Whether to use CEPDs in all patients, in a selective group of patients, or in none of the patients remains a matter of debate. Although current results indicate a reduction in the number and size of silent lesions, hard evidence of clinical efficacy of CEPD during TAVI is still missing. Results from large RCTs are expected soon, and these will provide information on the effect of CEPDs in terms of clinical stroke after TAVI. The clinical relevance of protection from silent lesions of brain injury requires further studies.

In conclusion, currently available results from RCTs and observational trials show consistent device safety but clear evidence for routine use of CEPD during TAVI is still missing. Furthermore, available studies show substantial limitations and should be interpreted carefully. Large, RCTs will follow soon and will provide the essential information still missing.

Article information

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