

Cerebral Embolic Protection in TAVI: Friend or Foe

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Abstract

Cerebrovascular accidents including stroke or transient ischaemic attack are one of the most feared complications after transcatheter aortic valve implantation. Transcatheter aortic valve implantation procedures have been consistently associated with silent ischaemic cerebral embolism as assessed by diffusion-weighted MRI. To reduce the risk of cerebrovascular accidents and silent emboli, cerebral embolic protection devices were developed with the aim of preventing procedural debris reaching the cerebral vasculature. The authors summarise the available data regarding cerebral embolic protection devices and its clinical significance.

Keywords

Cerebrovascular accidents, stroke, transient ischaemic attack, transcatheter aortic valve implantation, ischaemic cerebral embolism, diffusion-weighted MRI, risk, cerebral embolic protection devices, procedural debris

Disclosure: The authors have no conflict of interest to declare.

Received: 12 August 2018 **Accepted:** 22 November 2018 **Citation:** *Interventional Cardiology Review* 2019;14(1):22–5. **DOI:** <https://doi.org/10.15420/icr.2018.32.2>

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Since its introduction in 2002, transcatheter aortic valve implantation (TAVI) has provided an alternative to surgical aortic valve replacement (SAVR) in patients considered inoperable or either at high or intermediate risk for SAVR.¹ However, one of the most feared complications of TAVI are cerebrovascular accidents (CVA) including stroke or transient ischaemic attack. Further to this, TAVI procedures have been consistently associated with silent ischaemic cerebral embolism as assessed by diffusion-weighted MRI (or high-intensity transient signals) assessed by transcranial Doppler.^{2–7}

To reduce the risk of CVA and silent emboli, cerebral embolic protection devices (CEPDs) were developed. These devices aim to prevent procedural debris reaching the cerebral vasculature. CEPDs have been shown to be effective in the filtration of debris and decreasing the volume of ischaemic embolic lesions,⁸ hence, with the potential for decreasing the risk of clinically evident CVA. In this article, we summarise the available data regarding CEPDs and their clinical significance.

Types of Embolic Protection Devices

CEPDs are mesh filters to prevent embolic material from entering the carotid arteries. They differ in pore size, location of deployment, and chemical composition. With current techniques, successful deployment is achieved over 90% of cases, with success rates ranging from 64%–100%.⁸ Materials captured by the filters include thrombus, arterial wall tissue, valve tissue, calcification and foreign material.^{9–11}

In the Cerebral Protection in Transcatheter Aortic Valve Replacement (SENTINEL) trial, histopathologic debris were found within filters in 99% of patients.¹²

The Embrella Embolic Deflector (Edwards Lifesciences) uses two heparin-coated membranes with 100 µm pores. Once deployed in the aortic arch, it covers the brachiocephalic and left common carotid arteries. This CEPD was the first to be studied for safety and efficacy.^{13–15}

TriGuard (Keystone Heart) is a nitinol-coated device with 250 µm pores. Unlike other embolic protection devices, the TriGuard covers the left subclavian artery in addition to the brachiocephalic and left common carotid.^{16–18} This distinction is of potential clinical relevance, as the distribution of post-TAVI cerebral infarcts may also be weighted towards the posterior circulation.¹⁹

Sentinel (Claret Medical/Boston Scientific, previously named Montage) is a dual filter with 140 µm pores. The two filters are placed into the brachiocephalic and left common carotid arteries.^{11,12,20,21} Sentinel captures procedural debris, in contrast to the above two devices which simply deflect debris and allow its passage to downstream vessels. However, Sentinel does not protect the left vertebral artery which accounts for up to 20% of total brain perfusion.^{22,23} Therefore, it has recently been trialled in combination with the Wirion embolic protection system (Allium Medical) for posterior territory protection.²³

Embolic Protection Devices and Silent Ischaemic Lesions

Several studies have shown that up to 80% of patients who have undergone TAVI were found to have new silent cerebral ischaemic embolic lesions, and these lesions affected the two cerebral hemispheres and circulation territories in most patients.²⁻⁶ In the literature, the rate of new silent cerebral ischaemic lesions can be very high (>90% of patients), but substantial variations are observed, with others reporting lesions in 62% of patients.^{21,24,25} The absence of a centralised core lab for analysis means that comparisons between studies are difficult to make. This is worthy of exploration in future studies.

New persistent clinical neurological impairment has been encountered in approximately 3–6% of patients.²⁻⁶ Hence, beyond the risk of overt CVA after TAVI, there have been concerns regarding silent ischaemic lesions and its clinical consequences. The recent Neurologic Academic Research Consortium (NeuroARC) consensus statement has defined *covert central nervous system (CNS) infarction or Type 2.a* as “brain, spinal cord, or retinal cell death attributable to focal or multifocal ischaemia, based on neuroimaging or pathological evidence of CNS infarction, without a history of acute neurological symptoms consistent with the lesion location”.²⁶

NeuroARC agrees with the lack of a conclusive link between acute procedure-related subclinical brain lesions and long-term neurological or cognitive outcomes.²⁶ In fact, NeuroARC proposed the term “covert CNS infarction” mainly to recognise that these events may not necessarily be free of clinical consequences, and that detection of neurological or cognitive sequelae depends on the nature, sensitivity, and timing of assessments.²⁶

The use of CEPD might be associated with smaller volume of these silent ischaemic lesions, however, data from meta-analysis failed to demonstrate reduction in the number of new-single, multiple, and total number of lesions.⁸ Furthermore, when diffusion-weighted MRI was performed at follow-up, several embolic ischaemic lesions disappeared over time and even shortly after TAVI.^{2,3,14,21}

Embolic Protection Devices and Clinical Outcomes

Cerebrovascular Accidents

Whenever we see reports stating that Sentinel CEPD captures debris in 99% of patients, it is logical to think that the prevention of clinically apparent CVAs (stroke or transient ischaemic attack) should be the primary motivation for the use of CEPD.¹² However, data up to early 2017 from five studies did not show statistically significant differences in effect estimates for TAVI with CEPD, compared to no CEPD, in terms of 30-day stroke (RR 0.70; 95% CI [0.38–1.29]; $I^2=0\%$).⁸ Interestingly, an updated 2018 meta-analysis did find a statistically significant reduction in 30-day stroke rate with CEPD use (OR 0.55; 95% CI [0.31–0.98]; $p=0.04$; $I^2=0\%$).²⁷ The difference between these two meta-analyses was that the latter included a propensity-matched study published at the end of 2017, which found strokes in 1.4% (4/280) of CEPD patients and 4.6% (13/280) of non-CEPD patients at 7 days.²⁸ This study also provided information regarding the severity of strokes, and there was no significant difference in non-disabling stroke rates with EPD versus no-EPD at 7 days. However, among more severe CVA, a significant difference was encountered, with 0.4% (1/280) among CEPD patients and 3.2% (9/280) among non-CEPD patients experiencing disabling strokes at 7 days.²⁸

Even if the 2018 meta-analysis reached statistical significance for 30-day strokes, and even though the authors pointed out that this result was driven by the addition of the propensity-matched study, the upper margin of the CI seems very close to no effect.²⁷

It is also worth mentioning that the incidence of CVAs has considerably declined. Data from the Transcatheter Valve Therapy registry has shown 30-day stroke rates about 2.1%, which slightly decreased over a 4-year period from 2.3% in 2012 and 2013 to 1.9% in 2015 ($p=0.026$).²⁹ In addition, the 1-year stroke rate obtained by linkage with US Centers for Medicare & Medicaid Services administrative data was 3.8% overall.²⁹ Contemporaneous data using different TAVI technologies showed a stroke rate at 30 days below 2% (1.4%–1.9%).³⁰⁻³⁴

Hence, with the growing experience of operators and heart teams and transcatheter valves technology iterations, contemporaneous data further support a decrease in the incidence of CVAs and this should also be taken into consideration at the time of choosing to use a CEPD.

Mortality

The current literature does not support a clear mortality benefit for the use of CEPD in patients undergoing TAVI, but data is limited. The only randomised controlled trial (RCT) that had mortality as a pre-specified primary endpoint was the SENTINEL trial.¹² The primary safety endpoint was the occurrence of major adverse cardiac and cerebrovascular events (MACCE) at 30 days compared to a historical performance goal.¹² MACCE was defined as all death, all strokes (disabling and non-disabling) and acute kidney injury (stage 3) according to the Valve Academic Consortium-2 definitions.³⁵ MACCE in the control arm occurred in 9.9% and was not statistically different compared with the device and safety arms ($p=0.405$).

Our 2017 meta-analysis of five studies showed no significant differences in point-estimate for 30-day mortality (RR 0.58; 95% CI [0.20–1.64]; $I^2=0\%$).⁸ The updated 2018 meta-analysis explored the 30-day mortality rate and included six studies, four RCTs and two non-RCTs, adding the above mentioned propensity-matched study.^{27,28} Nonetheless, no differences in effect estimates were found (OR 0.43; 95% CI [0.18–1.05]; $I^2=0\%$). Of note, four of the six studies included ≤ 50 patients. The largest data comes from the propensity score matched study by Seeger and colleagues, where 0.7% (2/280) of CEPD patients and 2.9% (8/280) of non-CEPD patients died within 30 days of their procedure ($p=0.06$).²⁸ In their multivariable analysis, only the Society of Thoracic Surgeons score for mortality ($p=0.02$) and TAVI procedures with no CEPD ($p=0.02$) were independent predictors for the occurrence of death or stroke.

Neurocognitive Function

The evaluation of neurocognitive function after TAVI has not been systematically assessed in studies comparing CEPD with no CEPD. Moreover, different scores and tests were utilised among comparative studies, precluding therefore, a head-to-head comparison and fair interpretation of the results. The Montreal Cognitive Assessment (MoCA) was used in three studies, and the proportion of patients with CEPD showing worsening neurocognitive function ranged from 11%–27% and from 23%–33% in patients with no CEPD.^{14,17,20} The National Institutes of Health Stroke Scale was used in three studies, and the proportion of patients with CEPD showing worsening neurocognitive function ranged from 0%–18%, and from 4.5%–23%

in patients with no CEPD.^{17,20,21} The Mini-Mental State Examination (MMSE) was used in one study and did not show differences between CEPD versus no CEPD.¹⁴

As previously stated, there are inconsistencies between new ischaemic lesions and clinically apparent neurologic impairment. Indeed, previous studies could not find a measurable neurocognitive impairment in patients with silent ischaemic embolism pre- and post-TAVI.^{2,3,5,6} Two studies have shown a significant improvement in MMSE scores 3 months after TAVI, and one study showed a significant improvement in MoCA score at 30 days compared with baseline in the CEPD group, but no differences over time with no CEPD.^{7,14,36}

The TriGuard HDH Embolic Deflection Device During Transcatheter Aortic Valve Replacement (DEFLECT-III) trial showed no statistical significance between groups of treatment at 30-day follow-up.¹⁷ It is noteworthy that when the authors adjusted for age, the mean MoCA score improved from baseline to discharge and 30 days in patients who received CEPD; however, the mean MoCA score worsened from baseline to discharge and, interestingly, rebounded to approximately the baseline mean score at 30 days in the control group.¹⁷ The SENTINEL trial used a comprehensive neurocognitive assessment tailored for TAVI patients and designed to evaluate seven domains of neurocognitive function. The use of CEPD did not show any change in neurocognitive function, but there was correlation between new lesion volume and number of lesions and neurocognition at 30 days.¹²

Ghanem and colleagues reported a long-term follow-up on this matter and interestingly enough 91% of patients had preserved cognitive skills throughout the first 2 years after TAVI.³⁷ It is important to note that this study also showed that the cognitive trajectory was affected by the patient's age, but not by the absence of silent ischaemic emboli or the use of CEPD.

Statistical Methods for Interpreting Results and Limitations

There were eight pair-wise comparison studies.^{12,14,15,17,20,21,28,38} Five were RCTs.^{12,17,20,21,38} Two were non-randomised studies,^{14,15} and one used a propensity-score matching strategy to adjust for confounders.²⁸ Among the RCTs, one trial³⁸ adequately described the random sequence generation methods, two trials^{21,38} adequately described the allocation concealment, and four trials^{12,20,21,38} adequately described

the blinding methods for adjudication outcomes. Four studies followed the intention-to-treat analysis to handle missing data,^{12,17,20,21} and two of them used a modified intention-to-treat analysis.^{17,21} The rate of loss to follow-up was high in most of the randomised-studies.^{12,17,20,21} In the non-randomised studies, adjustment for confounders was not reported.^{14,15} Due to the nature of observational studies, potential selection bias cannot be ruled out in these studies. Selective reporting bias also could not be ruled out in all studies. Therefore, as previously stated,⁸ the quality of overall evidence was low to very low with the main limitation being serious risk of bias and imprecision.

Future Perspectives

Even though the use of CEPD provide reduction in lesion volume in the protected territories, a significant number of insults can come from territories supplied by the vertebral arteries, i.e. the posterior lobes and the cerebellum/brainstem.^{4,23} In this regard, the Sentinel CEPD protects only nine out of 28 brain regions, because of the dual blood supply of the posterior circulation.^{23,28} Hence, as with TAVI itself, we are still in the early days of CEPD and further research is warranted to determine patients at high risk for systemic embolisation such as those with extensive atherosclerosis or complex aortic atheroma burden.³⁹

New CEPDs are being developed. The Emboliner Embolic Protection Catheter (Emboliner) is designed to provide improved cerebral protection and to capture both cerebral and non-cerebral debris. It also allows for the operator to pass material through the mesh as required. The SafePass trial will include up to 60 patients from five centres in Germany, the Netherlands and Israel and will assess the safety and technical performance of the Emboliner.

Conclusion

The literature supports a reduction in lesion volume and total lesion volume with CEPD use, but this has not been translated into a substantial reduction in post-procedural or 30-day stroke and/or 30-day mortality. The clinical significance of silent ischaemic emboli is another important question that will require further evaluation, especially as TAVI begins to be utilised in younger patient populations, where there is even less evidence regarding a potential protective effect size. At the very least, CEPD is a promising technology and with further refinement may potentially reduce cerebral risk or neurocognitive function impairment in TAVI patients. Specialised neurological assessment following TAVI should be routine and further emphasised. ■

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