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OPINION

A Meaningful Therapy to Reduce Ischemic Brain Injury

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The evolution of transcatheter aortic valve replacement (TAVR) as an integral part of the treatment algorithm for severe aortic stenosis has been accelerated by the reduction of procedural complications. Although procedural stroke rates appear to have decreased with refinements in technique and device iteration, it still remains a concern, as noted by Dr Lansky in this issue. Perhaps what is most relevant is not only the impact of stroke on clinical outcomes but the perceived impact by patients, many of whom describe it as a "fate worse than death." Over the last few years, several devices (Figure 1) designed to reduce cerebral embolic events have been studied in trials evaluating the effectiveness of the therapy at reducing MRI measures of cerebral injury and clinical events. Whether these therapies have demonstrated a "meaningful" reduction in ischemic brain injury and thus should be recommended for routine use has been debated.

The concept of embolic protection is one employed in other arenas of cardiovascular intervention, including saphenous vein graft intervention and carotid artery stenting. It is a therapy that makes intuitive sense: preventing embolic debris from causing end organ injury should be beneficial. In fact, its routine use has been mandated for reimbursement in carotid stenting. This was despite the fact that there had been no randomized trials demonstrating clinical benefit prior to approval, but rather multiple registries showing lower stroke rates when compared with historical data, as well as high rates of debris capture. The rationale behind using embolic protection during TAVR is analogous to the use of filters during carotid stenting (i.e. protecting the brain from embolic injury). Two devices have already been evaluated in randomized clinical trials. The first is the Claret Medical Sentinel device, a 6 French compatible dual filter system that is placed from the right radial artery and designed to capture and remove embolic debris from the great vessels (Figure 1, panel A). The second is the Keystone Medical TriGuard device, which is a "deflector" placed in the aortic arch via a 9 French femoral sheath designed to prevent debris from reaching the cerebral circulation (Figure 1, panel B). It is important to note that neither device is a permanent implant and only remains in place for the duration of the TAVR procedure.

Several important questions must be answered in order to evaluate whether embolic protection devices (EPDs) provide meaningful benefit. First and foremost, one must define "meaningful benefit." Is it necessary for studies of cerebral embolic protection (CEP) to show a significant reduction in clinical stroke to demonstrate utility? If not, what surrogate endpoints are meaningful: debris capture, reduction in diffusion weighted magnetic resonance imaging (DW-MRI) abnormalities, or neurocognitive benefits? Given that EPDs are accessory devices, how rigorous does the data need to be demonstrating benefit, especially if the safety profile is excellent? Finally, should other factors such as patient demand, device cost and the ongoing desire to simplify the TAVR procedure play a role in the decision-making process? Interpreting the existing trial data in the context of these questions will demonstrate the favorable risk/benefit profile of CEP in TAVR.

The most obvious question is whether embolic protection reduces clinical stroke rates. Thus far, 625 patients (376 with embolic protection and 249 without protection) have been randomized across five trials evaluating embolic protection during TAVR.[1–5] The largest of these was the SENTINEL trial (345 patients), which demonstrated a 38% reduction in stroke (5.6% vs. 9.1%, $p = 0.25$) at 30-days with embolic protection utilizing the Claret Medical device.[4] The lack of statistical significance is not surprising given the size of this study, and lack of statistical power to demonstrate a reduction in stroke. In fact, based on the observed event rate, a study would have to randomize ~1856 patients to have 80% power to demonstrate a significant reduction in stroke (FDA Panel, Gaithersburg, MD, February 23, 2017). Although none of the five randomized trials demonstrated a *statistically* significant reduction in stroke at 30 days, they all reported fewer strokes in the arm with embolic protection. A recent meta-analysis combining these trials demonstrated a significant reduction in all-cause mortality or stroke (6.4% vs. 10.8%; RR: 0.57; 95% CI: 0.33–0.98, $p = 0.04$).[6] This benefit was consistent even after stratification for the specific EPD used. In addition, although not statistically significant, concordant effects were seen for the individual endpoints of mortality and stroke.

An important factor to consider is that the etiology of stroke after TAVR can be multifactorial in this elderly population with multiple comorbidities. Although the primary embolic risk is during the procedure, studies have demonstrated that the risk of neurologic events following TAVR may remain elevated up to 30 days after the procedure.[7] These late events are less likely attributable to procedural embolic events and may be related to other factors such as atrial fibrillation,

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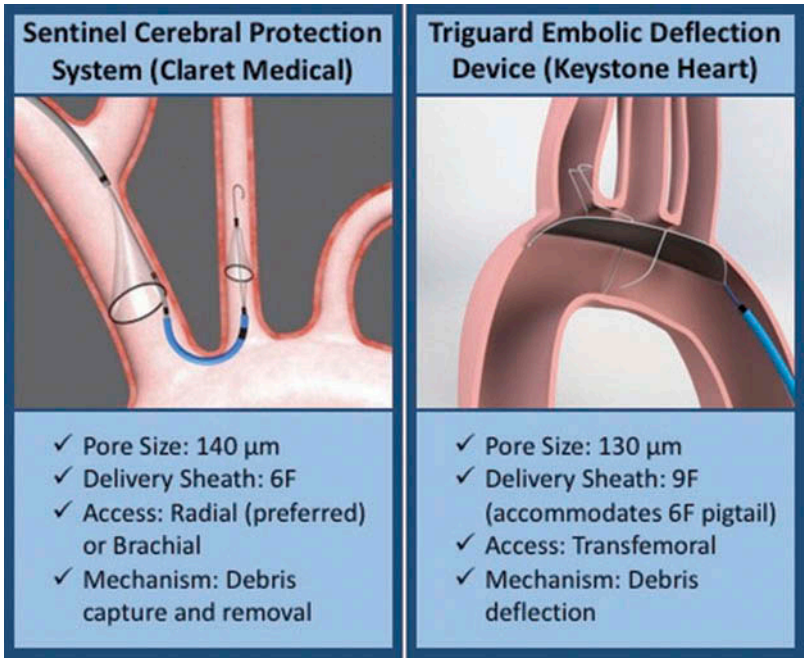

Figure 1. Comparison of devices designed to reduce cerebral embolic events.

which occurs in approximately 25% of TAVR patients. Therefore, when evaluating the benefit of EPDs, which will only reduce procedural events, it may be necessary to focus on a shorter time window such as 72 hours after the procedure. In the SENTINEL trial, there was a 63% reduction in stroke at 72 hours in the embolic protection arm (3.0% vs. 8.2%, $p = 0.05$) (FDA Panel, Gaithersburg, MD, February 23, 2017).

Due to the challenges of adequately powering studies for *hard* clinical endpoints such as death and stroke, studies have used DW-MRI abnormalities, a marker of cerebral injury, as a surrogate endpoint. Earlier studies have demonstrated that DW-MRI abnormalities are found in at least two thirds of patients following TAVR.[8,9] The CLEAN-TAVI trial, the first randomized study evaluating embolic protection during TAVR, demonstrated a 65% reduction in median new lesion volume in protected territories at 7 days on DW-MRI with the Claret Medical device (292 mm^3 vs. 101 mm^3, $p = 0.002$).[5] The subsequent SENTINEL trial, utilizing a similar device, showed a comparable reduction in new lesion volume (43%) with embolic protection but this did not achieve statistical significance (178 mm^3 vs. 101 mm^3, $p = 0.33$).[4] In the DEFLECT III study, CEP utilizing the TriGuard device resulted in a higher percentage of patients without new ischemic brain lesions (21.2% vs. 11.5%), but it also failed to reach statistical significance.[3] There are multiple reasons why this may be the case. First, there is likely significant variability in the burden of baseline cerebral disease amongst the patients. In a post hoc analysis from the SENTINEL trial, baseline disease burden was found to be the strongest predictor of new DW-MRI lesion volume. Secondly, the timing of post-procedure MRI acquisition window was variable across patients, and given that DW-MRI lesions represent acute injury and decrease over time, this likely increased variability in the results. Whereas in the CLEAN-TAVI trial, DW-MRIs were rigorously obtained at 2 and 7 days, there was greater variability in the other studies which may have diluted the effect. Finally, it may once again be an issue of study size and adequate statistical power to demonstrate a difference. Similar to the clinical outcomes, a patient level meta-analysis of the three studies utilizing the Claret Medical Sentinel device demonstrated a significant reduction in total new lesion volume in 319 patients who received embolic protection [−114.4 (−218.2 to −10.5), $p = 0.03$].[10]

However, the question still remains whether DW-MRI is an adequate surrogate endpoint. The advantage of DW-MRI, as an endpoint, is that it is readily quantifiable. However, there are significant challenges with its use. First, there is significant variability in MRI technique, magnet strength (1.5 Tesla vs. 3 Tesla) and window of image acquisition and processing between different studies affecting the ability to compare across studies and pool data. Second, due to both clinical and logistic issues, including pacemaker implantation, there is significant patient drop-out in MRI acquisition. Finally, and perhaps most importantly, whether new lesion volume is an important clinically relevant endpoint remains unclear. Just as in real estate, location is perhaps the most important factor. A small lesion in an eloquent area can produce a profound deficit while a large lesion in a different location may not cause a clinically apparent defect. Therefore, although using MRI as a surrogate may be tempting, it may be challenging for both the clinical and technical reasons noted above.

In the end, the goal of embolic protection is to prevent embolic debris from entering the cerebral circulation. One of the strongest pieces of data supporting its use are the histologic and morphometric analyses from the Claret Medical studies demonstrating that embolic debris is captured during TAVR in almost all patients and includes valve tissue, calcium, thrombus, vessel wall, and foreign material (Figures 2A and 2B).[4] Indeed, one in four patients in the SENTINEL study had an average of 25 pieces of debris greater than 500 microns in size, which are visible to the naked eye. It makes logical sense that if it is feasible and safe, embolic debris should be removed rather than allowed to enter the cerebral vasculature. This clear benefit of embolic protection devices

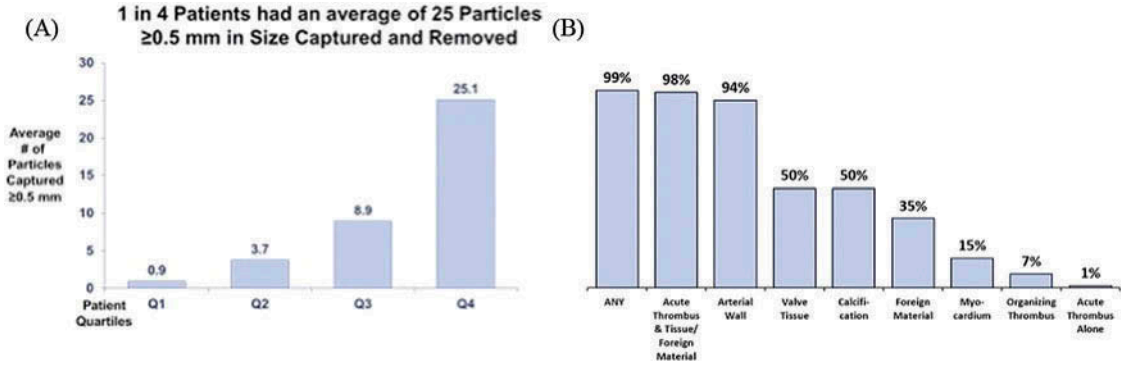

Figure 2. (A) Histologic, and (B) morphometric analyses from the Claret Medical studies demonstrating that embolic debris is captured during TAVR.

should be weighed against device safety, which has been proven to be excellent. Across all existing trials, there has been no evidence of significant safety concerns, which is extremely reassuring and supports the routine use of these devices.

The critical question of whether transcatheter embolic protection should be utilized in all or some patients during TAVR cannot be answered conclusively based upon any one of the existing trials. However, the totality of the data demonstrating clear safety as well as evidence of efficacy with reduced death and stroke, reduced DW-MRI abnormalities, and high rates of debris capture do support routine use. In fact, given this data, why would one not use it in every case? Two reasons that have been argued include cost constraints and the continued drive to simplify the TAVR procedure. Although adding additional costs to an already costly procedure is a concern, it is important to note that complications such as a death and stroke have significant financial and patient welfare implications. Analysis from the PARTNER I trial demonstrated that procedural complications account for 24.5% of the non-implant-related costs of TAVR.[11] Therefore, reducing these complications can have a financial benefit. Furthermore, the impact of a neurologic complication can extend far beyond the financial costs. Often it results in loss of independence and worsening quality of life, that may be viewed by many patients as a "fate worse than death." Therefore, in a desire to reduce costs and simplify the procedure, one must not reject a therapy that can provide meaningful benefit. Any stroke is one too many and embolic protection should be recommended for routine use in all patients. We would never drive without a seat belt and we should never do TAVR without embolic protection.

Disclosure statement

The author reports no conflict of interest. The author alone is responsible for the writing and content of this article.

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