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OPINION

Cerebral Embolic Protection: Not Enough Evidence to Support Routine Clinical Use

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"The only thing worse that dying from a stroke is living through a stroke." This statement is attributed to the late Mark Josephson, MD. I heard it many times while discussing anticoagulation for atrial fibrillation with his patients. The statement encapsulates what many TAVR patients believe. Improving or maintaining quality of life is a primary goal, and disabling stroke is often of more concern than death. No member of the TAVR team accepts stroke as an inconvenience that comes at the expense of increasing survival or reducing heart failure. As such, there is keen interest in development of embolic protection devices (EPDs) for reducing the chances of this complication.

There is no doubt that if EPDs can prevent clinical stroke and/or cognitive decline, they will become the standard of care. Indeed, if data on important clinical endpoints favored use of cerebral protection, there would not be much room for debate regarding routine use. The rate of procedural/in-hospital stroke reported in the Sentinel registry was 1.8% (n = 4571) for TAVR patients. This low rate of clinical stroke with TAVR must be viewed in the context of the risk for stroke amongst the population undergoing the procedure. This risk is often extremely high in some elderly patients, and may be negligible in others. We must understand this and resolve a number of other issues before declaring "Mission Accomplished" and endorsing widespread use in all patients.[1] As such, the current debate centers around whether these devices are ready for routine use in all patients based on the current available evidence.

As is pointed out in the articles by the protagonist and moderator, we have moved beyond an era of comparing stroke outcomes in TAVR against SAVR. Instead, we have an imperative to improve all TAVR outcomes, with stroke of paramount interest, particularly as we move to younger and low-risk patients. New ischemic brain lesions have been identified in as many as 93% of patients post-TAVR, with the predominate mechanism related to liberation of calcium and atheroma. These lesions presumably arise from delivery of large bore devices and deployment of the valve. Myocardial tissue, thrombi, air, and even plastic shavings have been implicated in histopathologic analysis of recovered debris.[2] Obviously, no person would choose embolic debris over no embolic debris.

In considering routine use, we have the opportunity to learn from other catheter-based therapies before we embrace EPDs without question. Numerous devices and strategies exist for which initial investigations and proof of concept studies were compelling, but subsequent more vigorous investigation did not bear out the early results. These disparate findings stemmed from a variety of factors, including initial device iterations, operator technique, trial design, use of surrogate outcomes, or simply lack of efficacy. Examples of such procedures include systemic cooling for myocardial infarction, distal embolic protection for native coronary arteries, renal denervation, and routine thrombectomy for acute myocardial infarction. These experiences should serve to temper enthusiasm for new technology. We should not be distracted from the goal of knowing whether EPDs actually work to prevent clinical stroke or cognitive decline.

Meta-analysis of data from four randomized trials (n = 252) showed a reduction in the total volume and number of embolic cerebral lesions, but no reduction in the risk of stroke or mortality with EPDs.[3] A larger analysis of 16 studies involving 1170 patients could not confirm or exclude any difference in clinically evident stroke (relative risk, 0.70; 95% confidence interval [CI], 0.38–1.29; p = 0.26) or 30-day mortality (relative risk, 0.58; 95% CI, 0.20–1.64; p = 0.30). There were no significant differences in new single, multiple, or total number of brain lesions. The use of EPD was associated with a significantly smaller ischemic volume per lesion (standardized mean difference, −0.52; 95% CI, −0.85 to −0.20; p = 0.002) and smaller total volume of lesions (standardized mean difference, −0.23; 95% CI, −0.42 to −0.03; p = 0.02).[3,4] Again, we should be circumspect about making sweeping statements for or against EPD based on the few hundred patients where the EPDs have been implanted if differences in surrogate endpoints are the only identified benefits.

Unfortunately, the relationship of clinical stroke or cognitive decline to imaging evidence of cerebral emboli and volume of infarct, or to recovery of debris from devices, is not well established. The occurrence of subsequent clinical stroke, dementia, reduced quality of life, cognitive decline and even survival with these findings may simply be an acausal correlate. Moreover, the literature is replete with studies finding no or minimal association.[5,6]

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Although embolic lesions on MRI had been considered surrogate markers for clinical stroke, the current American Heart Association guidelines do not define them as such.[7] In fact, the American Heart Association recommends avoiding designating clinically silent cerebral infarctions of undetermined onset as primary or secondary outcomes in most stroke studies, unless all study patients undergo standardized imaging at specific time points.[8] The uncertainty associated with these outcomes likely stems from the fact that these lesions may not represent actual infarcts. In both TAVR[9] and carotid stenting patients,[10] these lesions have been seen to resolve on follow-up imaging. The volume and number of embolic lesions are also difficult to link to clinically important stroke, likely due to the fact that the brain is so heterogeneous with differing thresholds for infarction.[11] Many emboli in one area of the brain may be clinically silent while a few emboli to another can be devastating.

Furthermore, the episodic nature of emboli from TAVR cannot be equated to the cumulative effects of subclinical strokes over decades. In this latter case the etiology is related to both ischemic-embolic stroke and ischemic-lacunar strokes in differing locations. Evidence suggests a disconnect between MRI imaging findings and cognitive changes, indicating that just as the embolic shower is episodic and ubiquitous, cognitive changes are transient and unpredictable.[12,13]

Manipulation of the aorta inherent with use of EPDs is not free of risk. It is difficult to ascertain whether embolic lesions seen on MRI after procedures with EPDs are due to placement of the device itself or are independent of placement. Using evidence from the larger experience of carotid revascularization, parallels can be drawn. With carotid stenting it was found that any manipulation of difficult arch anatomy prior to protection was a significant risk factor for cerebral events, and that operator skill matters.[14] For example, the risk of minor stroke as a consequence of just diagnostic angiography is reported to range from 1.3% to 4.5%, and the risk of major stroke from 0.6% to 1.3%.[15] It is unknown whether these same risks apply when manipulating the aortic arch and great vessels with EPDs for TAVR. Nevertheless, it will be important to ensure that TAVR operators have similar skills to experienced cerebral angiographers and carotid interventionalists to manage the complex arch configurations and variant anatomy associated with increased risk for stroke during procedures.[16,17]

It should be noted that a number of neuroprotective strategies are advocated in cardiac surgery, but EPDs have been largely abandoned due to unsatisfying results. A randomized surgical trial significantly larger than the entirety of the randomized clinical trial experience for EPDs in TAVR (n = 1289) utilized an EPD similar to that used in TAVR. In that surgical study, particulate emboli were found in 96.8% of successfully deployed EPDs. However no significant differences were observed in mortality, stroke, transient ischemic attack, renal insufficiency, myocardial infarction, gastrointestinal complications, or limb threatening ischemia.[8,18]

One should be realistic and recognize that it is impractical in the nascent phases of device development to require comprehensive trials that answer every question to justify approval and dissemination of the technology. This is particularly true of infrequent but important clinical endpoints. Rather, it seems prudent to take a two-pronged approach as has proven beneficial in the past. First, dissemination of these devices within and outside of experienced TAVR centers should occur while procedural and outcomes data are simultaneously collected and reported. In this way, it can be determined whether outcomes from clinical trials can be replicated, as is the case with TAVR, and we can begin to understand whether there are particular patients or factors that confer high-risk and thus high-value for EPDs. For example, a number of factors, in addition to those related to patients, would allow for improved context when using EPDs. Such factors might include valve-related considerations (calcification, nodule location, and mobility, etc.), aortic anatomic variables (complex mobile atheroma, aortic angulation, etc.), type of TAVR device, oversizing, anticoagulation strategy, and procedure duration to name a few.[19]

Second, large and simple trials should be designed to answer basic outcome questions with input from all stakeholders. Such trials can practically be accomplished in a cost-effective manner without stifling innovation due to undue financial burden on our industry partners.[20] Acceptance of innovative trial designs such as linkage of large administrative and clinical datasets to clinical trial data have the promise of reducing the financial burden for device development while still providing validation and insight into the utility of these important devices.

Finally, structural interventionalists are stroke prevention practitioners in addition to being valve implanters. It is our responsibility to implement the proven stroke prevention strategies for which there is similar and even greater evidence for efficacy than EPDs. In fixating on procedural protection, we must recognize the missed therapeutic opportunity of ignoring appropriate management after the procedure amongst patients with bleeding complications or perceived increased bleeding risk. Atrial fibrillation patients should have appropriate anticoagulation to help avoid the >50% of strokes that are not procedural, and if they are not candidates for anticoagulation because of bleeding risk, should be considered for appendage closure. We should understand if there is any relationship of leaflet thrombosis and stroke. Closing as we started, stroke indeed is a devastating complication before, during, and after TAVR. Structural interventionalists should endeavor to refine and develop our armamentarium to avoid this complication. While the efficacy of cerebral protection is not yet established based on existing data, we should be confident that the future of TAVR is dependent in part on success in stroke prevention.

Disclosure statement

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