JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 13, NO. 18, 2020

EDITORIAL COMMENT

Cerebral Embolic Protection

Burden of Proof*

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Establishing proof for the clinical benefit of cerebral embolic protection (CEP) devices after transcatheter aortic valve replacement (TAVR) has been challenging. The SENTINEL CEP device (Boston Scientific, Marlborough, Massachusetts) demonstrated capture of embolic debris (leading to approval in the United States) and may reduce ischemic brain injury detected by diffusion-weighted magnetic resonance imaging (DW-MRI) (1–4). However, whether such surrogate effectiveness measures translate into a lower incidence of ischemic stroke (or improved neurocognition) remains a matter of debate. In addition, the clinical significance and long-term sequelae of acutely asymptomatic cerebral injury detected on DW-MRI affecting most patients undergoing TAVR have not been defined (5).

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The paper by Megaly et al. (6) in this issue of *JACC: Cardiovascular Interventions* should be commended for attempting to address this question using a largescale retrospective analysis of hospitalized U.S. patients derived from the National (Nationwide) Inpatient Sample (NIS). In a propensity-matched analysis, Megaly et al. demonstrate that compared with TAVR with no CEP, use of the SENTINEL CEP device significantly reduced in-hospital mortality (0% vs. 1.9%; $p < 0.001$), ischemic stroke (1.0% vs. 4.8%; $p < 0.001$), and hemorrhagic stroke (0% vs. 1.0%; $p = 0.037$), at the expense of higher post-procedure bleeding (2.9% vs. 0.5%; $p < 0.001$) and a higher cost of hospitalization ($47,783 vs. $43,969; $p = 0.017$). The observed reduction in hemorrhagic stroke is unexpected with use of any CEP device; however, it may represent a reduction in hemorrhagic conversion of ischemic strokes.

Individual randomized controlled trials (RCTs) evaluating CEP devices (1–3,7,8) were designed to demonstrate device safety and effectiveness on the basis of surrogate endpoints including debris capture and DW-MRI brain lesion volumes. Completed RCTs have had significant limitations. First, they have not had sufficient power to identify differences in ischemic stroke, which occur with relatively low frequency. At least 3,000 patients would be needed to provide sufficient power to detect a difference in ischemic stroke in a randomized CEP trial: a prohibitively large sample size in the early-stage approval of these accessory devices. Furthermore, most RCTs have evaluated outcomes at 30 days (rather than in-hospital), which likely dilutes the direct benefit of embolic protection during the TAVR procedure. Finally, RCTs tend to exclude extreme-risk patients such as those with prior stroke, carotid artery disease, porcelain aorta, bicuspid valves, or valve-in-valve procedures, which further reduces the ability to detect significant differences. For example, most CEP RCT populations include <5% of subjects with prior stroke, whereas most real-world observational studies report prior stroke rates of more than 10% (9,10). In an attempt to address sample size limitations of individual trials, a previous meta-analysis of RCT CEP trials (N = 625; 376 with CEP and 249 without) identified numerical, but not significant, reductions in mortality (1.3% vs. 3.6%; $p = 0.12$),

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the Section of Cardiology, Yale School of Medicine, New Haven, Connecticut. Dr. Lansky received speaker fees from Keystone Heart. Dr. Pietras has received consulting fees from Keystone Heart. Dr. Shah has reported that he has no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2020.06.030

stroke (5.1% vs. 7.3%; p = 0.20), and their composite (relative risk = 0.61; p = 0.08) with CEP compared with unprotected TAVR (11).

There have been 2 other large observational studies addressing CEP effectiveness. One single-center German study, comparing 280 patients with SENTINEL CEP to 280 propensity-matched controls, reported results consistent with those of Megaly et al. (6), including similar effect sizes for reductions in 7-day mortality (0.7% vs. 2.9%; p = 0.06) and all stroke (1.4% vs. 4.6%; p = 0.03) (8). By contrast, a more recent retrospective analysis derived from the Vizient database of over 400 U.S. academic centers, comparing 2,725 patients with the SENTINEL CEP device to 2,725 matched controls, found no significant differences in in-hospital mortality (0.9% vs. 1.1%; p = 0.58) or ischemic stroke (1.5% vs. 1.7%; p = 0.58) (9).

The lack of consistent evidence, particularly in observational studies, likely results from inherent limitations that introduce bias, such as inconsistent ascertainment methods across institutions, lack of data standards, and bias in selecting which patients receive CEP (12,13). Although the previously cited German study (9) included a clear definition for stroke and had neurologist-reviewed imaging in all symptomatic patients, neither of the other 2 observational studies employed standardized definitions or reporting methods. Additionally, the non-CEP arms in observational studies tend to include higher-risk patients before matching, suggesting systematic differences in patient selection for CEP. In turn, clinicians may be more likely to start stroke evaluations in higher-risk patients, particularly if they did not receive embolic protection during TAVR. This could result in more complete ascertainment of stroke in unprotected patients in comparison with protected patients. For instance, before matching, Megaly et al. (6) found that compared with 45 patients in the non-CEP arm, none of the patients in the CEP arm had carotid artery disease—the strongest predictor of stroke in their study. Lastly, a propensity-matched analysis cannot control for all confounding variables; indeed, even in the matched cohort, the non-CEP arm in Megaly et al. (6) had a lower proportion of white patients (75% vs. 87%) and more patients from the southern U.S. region (27% vs. 5%), both of which are associated with increasing incidence of stroke (14).

In addition to uncertainties regarding the effect of CEP on symptomatic stroke, even the evidence for a reduction in brain injury documented by DW-MRI has been weak in individual trials (1–3,7,8). A meta-analysis of 3 RCTs comparing TAVR with and without use of SENTINEL CEP, which included systematic protocol mandated DW-MRI, did demonstrate a reduction in the total volume of brain injury with CEP after TAVR (4). However, MRI lesion volume is subject to wide variation on the basis of methods of acquisition and measurement. In the SENTINEL randomized trial, even in territories protected by the device, there was no significant reduction in total lesion volume, as was the case for the whole brain (1). Although several observational population-based studies have shown that an increased burden of "silent brain infarcts" increased the risk of future dementia, stroke, and transient ischemic attacks (15,16), that link has yet to be definitively proven after TAVR.

The study by Megaly et al. (6) is an important addition to the CEP literature, supporting CEP's clinical benefit in reducing stroke risk in patients undergoing TAVR. In the context of conflicting results from current RCTs and other observational studies, the results of Megaly et al. reinforce the need for a definitive, well-powered RCT to characterize the clinical benefit of CEP devices and to determine their appropriate use in TAVR. The large PROTECTED TAVR (Stroke PROTECTion With SEntinel During Transcatheter Aortic Valve Replacement; NCT04149535) randomized trial will provide these answers.

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KEY WORDS embolic protection, stroke, TAVR,