Journal of Cardiothoracic and Vascular Anesthesia 000 (2022) 1–3

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Editorial

Judgment Reserved: The Evolving Development of Cerebral Embolic Protection Devices in Transcutaneous Aortic Valve Replacement

TRANSCUTANEOUS AORTIC VALVE REPLACEMENT (TAVR) has revolutionized the care of patients with severe aortic stenosis—within a matter of <15 years, TAVR now provides a safe therapeutic intervention across an expansive scope of patients with severe aortic stenosis, from prohibitive perioperative risk for surgical aortic valve replacement (SAVR) to a less-invasive management option for persons deemed high-, intermediate-, or even low-perioperative risk for SAVR.[1] Patients who undergo TAVR typically avoid several of the less-desirable features that are routine in the conduct of most SAVR procedures—there is (usually) no endotracheal tube or general anesthesia and no sternotomy or cardiopulmonary bypass run. The advancement of TAVR, from its introduction to its current contemporary practice, has been extremely fast, and the rapid change has been buoyed by concurrent advances in TAVR device technology and aggressive efforts to improve safety and reduce complications that are associated with the procedure. The incidence of severe adverse events from the first-generation devices (eg, early vascular access sheaths and valve types) of TAVR's nascence have dropped significantly when compared to the contemporary devices. When comparing first-generation versus contemporary TAVR valves, a meta-analysis of outcomes in almost 70,000 patients who received TAVR, found periprocedural mortality decreased impressively (1.47 ± 1.73 *v* $5.41 \pm 4.35\%$; $p < 0.001$), as did periprocedural myocardial infarction (0.45 ± 0.97 *v* $1.39 \pm 2.22\%$, $p < 0.001$).[2] Periprocedural stroke decreased over time, too, in a statistically significant manner, favoring the contemporary TAVR devices over first-generation devices (2.09 ± 2.93 *v* $2.73 \pm 2.49\%$, $p = 0.009$); the absolute value of this decrease is much less robust than that noted in the incidence of the aforementioned mortality and myocardial infarction.[2] Stroke remains a potentially devastating complication of TAVR intervention.

Although stroke incidence has decreased since the inception of TAVR, considerable efforts are being made to further reduce stroke occurrence. It is hypothesized that embolic debris (arising from calcification, atheromatous plaques, or both)—largely attributed to that liberated from the stenotic aortic valve or arterial/aortic endothelium during the TAVR procedure—is the etiology for the vast majority of stroke events associated with TAVR in the early/acute periprocedural period (eg, within 24-48 hours of procedure).[3] A 2016 study on neuroimaging findings (using before- and after-TAVR magnetic resonance imaging) reported that 94% of studied patients had imaging evidence of new embolic cerebral infarction after TAVR; this finding did not necessarily equate to clinically-evident stroke, but did illustrate the prevalence of embolic debris burden associated with TAVR.[4] Cerebral embolic protection devices (CEPD) have been created to prevent embolic debris from reaching the cerebral circulation, with the intent of decreasing the incidence of ischemic stroke. Among many CEPD devices created by several manufacturers, the Sentinel Cerebral Protection System (Boston Scientific, Marlborough, MA) is one of the more widely studied. The Sentinel device is placed via transcutaneous arterial access of either the right radial or brachial artery, after which 2 umbrella-like filter cones are deployed in the proximal left common carotid and brachiocephalic arteries. The intent of these filters is to allow continued perfusion of the brain while offering a barrier filter with which to capture embolic debris during the TAVR procedure.

In October 2022, the *New England Journal of Medicine* published the results of the PROTECTED TAVR trial that reported the outcomes of a large, multicenter, randomized clinical trial in which the intervention group had the Sentinel CEPD deployed during TAVR compared to the outcomes of patients who underwent TAVR without cerebral protection.[5] The trial was international (sites in North America, Australia, and Europe), randomized, and prospective. A total of 3,000 patients undergoing transfemoral TAVR were assigned randomly to TAVR with the placement of the Sentinel CEPD or TAVR without. The primary endpoint of the study was "stroke within 72 hours after TAVR or before discharge (whichever came first) in the intention-to-treat population." Also assessed

https://doi.org/10.1053/j.jvca.2022.11.005

and reported were the incidences of disabling stroke, death, transient ischemic attack, delirium, major and/or minor vascular complications at the CEPD access site, and acute kidney injury. Neurologic assessment was made by a neurology professional to establish a baseline status before TAVR and to provide post-TAVR evaluation. Of the 3,000 patients randomized, 2,953 total patients were followed through the follow-up period; of the initial 1,489 patients included in the CEPD treatment arm, 1,406 (94%) had the CEPD successfully deployed. In the intention-to-treat population, the primary endpoint of stroke was met in 34 of the 1,501 patients (2.3%) of the CEPD group and 43 of 1,499 patients (2.6%) in the control arm (95% CI -1.7 to 0.5; p = 0.30). There was no statistical difference between the groups for this primary endpoint. Secondary endpoints without statistical difference between the groups included acute kidney injury, delirium, and all-cause mortality. It should be highlighted that the secondary endpoint of disabling stroke (defined in this study as a modified Rankin scale score of $\geq$2 and an increase of at least 1 point in the modified Rankin scale from the baseline score) was diagnosed in fewer patients who received CEPD placement—8 patients in the CEPD group had disabling stroke compared to 20 patients in the control arm of the study (0.5% *v* 1.3%; 95% CI -1.5 to -0.1).[5]

This trial is informative for physicians caring for patients undergoing TAVR. There were several important favorable features of this study—PROTECTED TAVR was a large randomized trial that involved >50 TAVR centers on 3 continents, and the patients included in the study underwent TAVR with both sedation and general anesthetics, included both balloon-expandable and self-expanding valve types, and included TAVR for trileaflet, bicuspid, or bioprosthetic aortic valves.[5] The aforementioned characteristics reflect real-world conditions and suggest generalizability across much of the practice of transfemoral TAVR practices. Although the results suggest a "negative" study when looking at the primary endpoint, it is an important update and contribution to the available body of knowledge on cerebral protection—with this embolic protection device at least—during TAVR.

There is, of course, room for reflection on this study and on the concept of cerebral protection at large. In regard to the PROTECTED TAVR trial itself, perhaps the most striking endpoint between the CEPD and the control groups was the discrepancy in the number of patients who suffered disabling strokes, in whom several fewer disabling strokes were found in the group that received CEPD placement. The study was not powered to determine a difference in disabling stroke, but even so, the variation is notable. The determination of the clinical features of stroke severity may be confounded by some inconsistency, however, as the experience and expertise of the neurology professional assigned to evaluate the neurologic status of the patients was widely varied, the "neurology professional" performing neurologic assessment was defined as a board-certified or board-eligible neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner.[5] Although the large sample size and broad geographic range made it nearly impossible to expect a small group of experienced neurologists to evaluate every patient, the broad expanse of neurologic evaluators may have contributed to unintended variability in the reported results. Moreover, although the results of the PROTECTED TAVR trial may seem disappointing, as the trial did not find superior protection from a stroke when using a protection device; in fact, the study (and its results) may help guide efforts at reducing stroke events in the future. The Sentinel device serves to filter debris—and it does indeed do that—but it only can filter debris of a certain size, and it only does so for 2 of the 3 great vessels off the aortic arch; very small debris (or air) will pass the Sentinel device even when deployed perfectly, and there is incomplete protection of the posterior cerebral circulation system with the Sentinel device, as the left subclavian artery is not given any protective cover. Outside of this specific trial with this singular protection device, perhaps the Sentinel device is not the optimal device (or the best iteration of this device concept) for stroke protection. Perhaps a device with the ability to filter even smaller particles will improve stroke protection efforts, or protection for the left subclavian artery will reduce neurologic event rates. Several other CEPDs are available and/or under investigation; some are "filter-type" devices, like the Sentinel, that aim to capture debris within a filter to prevent the passage of said debris to the brain. The other CEPD design is a "deflection-type" design, which is intended to block the passage of debris into the great vessels of the aortic arch, and thus "deflect" the debris distally into the descending aorta.[6] There are at least 7 clinical trials that are recruiting patients for further study of CEPD devices for use during TAVR as of the time of this editorial. These investigations should serve to further inform on the benefits (or lack thereof) of CEPD.[7]

At present, compulsory use of the Sentinel device to significantly reduce the incidence of embolic stroke during TAVR is not supported by the PROTECTED TAVR study. There is a promising signal that the occurrence of disabling stroke may be reduced with CEPD use, and that may, in fact, be worth evaluation in future studies. In summary, however, there are still more questions that need to be answered before an evidence-based case can be made to compel CEPD use for every transfemoral TAVR procedure so as to reduce the incidence of periprocedural stroke.

Conflict of Interest

None.

Daniel S. Cormican, MD, FCCP*
Division of Cardiothoracic Anesthesiology, Division of Surgical Critical Care, Anesthesiology Institute, Allegheny Health Network, Pittsburgh, PA

References

1 Figulla HR, Franz M, Lauten A. The history of transcatheter aortic valve implantation (TAVI)-A personal view over 25 years of development. Cardiovasc Revasc Med 2020;21:398–403.

2 Winter MP, Bartko P, Hofer F, et al. Evolution of outcome and complications in TAVR: A meta-analysis of observational and randomized studies. Sci Rep 2020;10:155–68.
3 Davlouros PA, Mplani VC, Koniari I, et al. Transcatheter aortic valve replacement and stroke: A comprehensive review. J Geriatr Cardiol 2018;15:95–104.
4 Lansky AJ, Brown D, Pena C, et al. Neurologic complications of unprotected transcatheter aortic valve implantation (from the Neuro-TAVI Trial). Am J Cardiol 2016;118:1519–26.
5 Kapadia SR, Makkar R, Leon M, et al. Cerebral embolic protection during transcatheter aortic-valve replacement. N Engl J Med 2022; 387:1253–63.
6 Cubero-Gallego H, Pascual I, Rozado J, et al. Cerebral protection devices for transcatheter aortic valve replacement. Ann Transl Med 2019;7:584.
7 Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/results?cond=embolic&term=TAVR%2C+TAVI&cntry=&state=&city=&dist=. Accessed October 28, 2022.