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EDITORIAL COMMENT

Filtering the Truth Behind Cerebral Embolization During Transcatheter Aortic Valve Replacement*

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Although transcatheter aortic valve replacement (TAVR) has evolved as a genuine therapeutic option for patients with severe symptomatic aortic stenosis, periprocedural stroke rates still remain relatively high. In fact, of all percutaneous cardiac interventions at the interventional cardiologist's disposal, TAVR is associated with the highest stroke rate: averaging ~3% within the 30 days following the procedure in large registries and hovering at 4% to 5% in the 2 randomized clinical trials comparing TAVR and surgical aortic valve replacement (SAVR) in high-risk patients (1-3). Following a 10-year evolution in transcatheter valve design and refinements in procedural techniques, stroke rates during TAVR have been relatively stagnant over time (4,5). In addition to the occurrence of clinically-apparent stroke, several studies utilizing serial brain magnetic resonance imaging (MRI) systematically demonstrated silent new cerebral lesions in at least two-thirds of individuals undergoing TAVR (3). Although these findings may, to some extent, simply reflect the nature of TAVR in a high-risk patient substrate with extensive comorbidities, this may also reflect a fundamental limitation of contemporary TAVR techniques. Yet, the quest for TAVR to emerge as a viable alternative to SAVR in lower-risk, younger patients with severe aortic stenosis is inevitable. Therefore, minimizing peri-TAVR stroke risk to levels equivalent to or even lower than those following SAVR looms as an important challenge.

A critical appraisal of the mechanisms associated with cerebrovascular events during TAVR is important for implementing effective measures to curb its incidence. The multiple and diffuse distribution of silent cerebral lesions evident on brain MRI post-TAVR strongly suggests an embolic etiology (3). Transcranial Doppler studies performed during TAVR highlighted the occurrence of cerebral embolization at virtually all time-points during the procedure, but yet seem particularly frequent during valve positioning and implantation, suggesting an important role of the mechanical interaction between transcatheter and native aortic valves (6). From a clinical perspective, several studies found mechanical factors, such as balloon post-dilation, valve dislocation, or embolization, or the need for a second valve each associated with a higher cerebrovascular event rate (7-9), particularly within the first 24-h post-TAVR period (7). Indeed, ~50% of all 30-day cerebrovascular events occurred after the first 24-h post-TAVR period, and these events appeared to be more related to atrial arrhythmias and the underlying systemic burden of atherosclerotic disease.

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With this background information in hand, in this issue of *JACC: Cardiovascular Interventions*, Van Mieghem et al. (10) present an extension of their prior observations of the pathology of embolic debris captured with the Montage Dual Filter embolic protection (Claret Medical, Inc., Santa Rosa, California) during TAVR. After initially recruiting 40 patients, this group previously demonstrated that embolic debris was captured in 75% of TAVR cases, consisting of fibrin/thrombus, amorphous calcium, or connective

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tissue (11). The authors subsequently enrolled an additional 41 patients undergoing TAVR with the Montage Dual Filter embolic protection system, and they now present an expanded analysis aimed at identifying patient and procedural factors associated with cerebral embolization. Across 81 patients undergoing TAVR using either a balloon or self-expanding valve, embolic debris were ultimately captured in 86% of the study population, ranging in size from 0.1 to 9 mm. Thrombotic and tissue-derived debris were retrieved in 74% and 63% of patients, respectively. The source of tissue embolizations mostly ranged from native aortic valve leaflets, the aortic wall, or left ventricular myocardium. Intriguingly, 10% of embolic fragments were deemed to be foreign body-derived. The frequency of captured debris was marginally greater in balloon- versus self-expanding transcatheter valves; however, the rate of captured thrombus did not differ according to valve type. On multivariable logistic regression analysis, the use of balloon-expandable valves and a greater cover index (indicative of valve oversizing) were independently associated with tissue embolization.

This analysis provides important mechanistic insights that further illuminate the nature and reality of TAVR-related cerebral embolization. First, the high rate of captured debris is consistent with prior transcranial Doppler and brain MRI studies, confirming the seemingly inevitable occurrence of cerebral emboli during TAVR. Second, the near systematic presence of thrombus among the captured debris is somewhat surprising and appeared to be more frequent compared with other interventional procedures using filter devices (e.g., carotid stenting) (12,13), highlighting the need to improve peri-TAVR anticoagulation strategies. Consistent with this notion were the suboptimal mean ACT levels (<250 to 300 s) reported by the authors, and future studies will need to focus on identifying the optimal periprocedural anticoagulation strategy that associates with a lower rate of thromboembolism. Furthermore, such a high rate of thrombus within the filters raises the question of whether thrombi could have been generated de novo within the filter. Third, tissue debris were captured in about two-thirds of patients, which confirms the mechanical interaction between catheters, delivery systems, transcatheter valve, and the vascular system as important contributory factors in cerebral embolization during TAVR. Of note, tissue debris not only were related to the aortic valve (valve tissue, calcific material), but also involved upstream (aortic wall) and downstream (myocardium) structures, emphasizing once again the complexity of the pathophysiology behind cerebral embolization during TAVR. Additionally, the authors found that a balloon-expandable system and a greater degree of valve oversizing increased the risk of tissue emboli.

Although these findings are novel and thought-provoking, they should nevertheless be considered hypothesis-generating due to some important caveats (some of which have been acknowledged by the authors). This single-center study was likely underpowered to draw meaningful conclusions with respect to the interaction between valve type and the nature and frequency of debris (evidenced by extremely wide confidence intervals in multivariable analyses). The finding of more frequent tissue embolization with balloon- versus self-expanding valves is at slight odds with a prior (similar-sized) transcranial Doppler study, which suggested that microemboli were more frequent during self-expanding transcatheter valve implantation (6); it also seems to be somewhat contradictory with larger-scale clinical data showing no differences in stroke rate between the 2 valve systems (14).

Furthermore, no differentiation was made between the different origins of tissue debris, making it difficult to draw definitive conclusions regarding the mechanisms behind the apparently higher tissue emboli rate with balloon-expandable systems and a higher degree of valve oversizing.

However, a number of clinical implications of this study warrant consideration. The optimal periprocedural anticoagulation strategy during TAVR remains empirical. The ubiquitous presence of captured thrombus suggests the need for prospective evaluations of various types and intensities of periprocedural anticoagulation strategies during TAVR. The frequent nature of captured emboli also raises the issue of whether embolic protection devices will ultimately find a role during TAVR. Two pilot studies with deflector devices (the Embrella Embolic Deflector device [Edwards Lifesciences, Irvine, California], and the TriGuard Embolic Deflection device [Keystone Heart, Caesarea, Israel]) highlighted the feasibility and safety of these systems during TAVR (15,16). Although preliminary data showed a trend toward a reduction of cerebral embolic lesion volume with such devices, the number of new brain lesions detected on brain MRI did not differ from historical MRI data (15,16). However, the results of the prospective randomized CLEAN-TAVI (Claret Embolic Protection and TAVI) trial were recently presented (17) showing the Montage Dual Filter embolic protection system's ability to significantly lower both the volume and number of new brain lesions post-TAVR. Importantly, early (day 2 post-TAVR) ataxia rates were significantly lower, favoring the group receiving

the embolic protection system. Another randomized trial using this device and with surrogate brain MRI endpoints is currently ongoing in the United States (SENTINEL trial; NCT02214277).

The work by Van Mieghem et al. (10,11) represents a step forward in understanding the burden and pathophysiology of cerebral emboli during TAVR and would intuitively support the systematic use of embolic protection devices during TAVR. However, the utility of such devices as an adjunct during TAVR will ultimately depend on their ability to lower clinically-meaningful endpoints in a cost-effective manner. The exceptionally high frequency of TAVR-related cerebral embolism provides a unique opportunity to develop and standardize cerebral imaging endpoints as a reliable surrogate biomarker of clinical efficacy. This would enable the medical community to more readily conduct smaller-scale trials testing novel devices, refine procedural techniques, and evaluate the effect of novel pharmacotherapeutic regimens at a lesser cost while exposing lesser numbers of patients to a potentially inferior or futile clinical strategy. This is the path that has been followed to prove the efficacy of embolic protection devices in TAVR, with promising preliminary results. If ultimately positive, surrogate cerebral imaging data could then either result in direct implementation of such devices in routine clinical practice or to inform the decision to invest in larger, prospective, randomized clinical trials powered for clinical endpoints. Meanwhile, we should continue to investigate mechanisms underlying TAVR-related cerebral embolism as a mandatory step in the process of ultimately reducing TAVR-related cerebrovascular events.

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