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EDITORIAL COMMENT

Cerebral Embolic Protection in Catheter-Based Mitral Interventions

Research or Clinical Tool?*

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Transcatheter MitraClip (Abbott Vascular, Santa Clara, California) implantation has emerged as the single catheter-based technique for mitral valve repair with global adoption. Worldwide, an estimated 25,000 patients have been treated with the MitraClip so far. Typically, the incidence of major stroke after surgical mitral valve repair or replacement is similar to what is seen after surgical aortic valve replacement, and varies between 1% and 5% (1-3). In the only randomized trial comparing MitraClip with mitral valve repair/replacement, major stroke rate at 30 days was 1% after MitraClip and 2% after mitral valve surgery (4). The EVEREST (Endovascular Valve Edge-to-Edge Repair Study) 2 predominantly enrolled patients with degenerative mitral valve disease (4). In the larger European MitraClip registries, patients had more functional mitral regurgitation (MR). The clinically major stroke rate after clipping appeared to be negligible and <1%: 0.7% in 560 patients in the ACCESS EU (ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe) trial, and 0% in 1,064 patients in the German TRAMI (Transcatheter Mitral Valve Interventions) Registry (5,6).

Important lessons were learned after a decade of controversy about stroke rates in patients undergoing surgical or catheter-based aortic valve replacement. The randomized PARTNER (Placement of Aortic Transcatheter Valve) I trial seemed to suggest that the less-invasive transcatheter aortic valve replacement (TAVR) was associated with a higher neurological event rate compared with surgical aortic valve replacement; yet, the randomized U.S. CoreValve high-risk study refuted these findings (7,8). Interestingly, the involvement of competent authorities like the U.S. Food and Drug Administration, efforts by the Valve Academic Research Consortium to determine uniformity in endpoint definitions and trial design, and the advent of embolic protection devices have scrutinized research on neurological events in the field (9). Neurology experts are now involved in most important TAVR trials and assess all enrolled patients undergoing valve replacement before and after the procedure. This scrutiny has revealed more (subtle) neurological changes in significantly more patients. Indeed, new neurological events were detected in 15% of patients in the control arm of the randomized DEFLECT III (A Prospective, Randomized Evaluation of the TriGuard HDH Embolic Deflection Device During TAVI) trial and in 17% of patients undergoing surgical aortic valve replacement in the DeNOVO (Determining Neurologic Outcomes from Valve Operations) prospective cohort study (10,11). Diffusion-weighted magnetic resonance imaging (MRI) studies and histopathology studies have revealed signs of cerebral embolization in over 80% of patients undergoing TAVR (12-14).

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Deflecting and filter-based embolic protection devices (EPDs) are being intensely studied in the field of TAVR, and not surprisingly, interest for EPD also emerges in the MitraClip space (15). In this issue of *JACC: Cardiovascular Interventions,* Frerker et al. (16) study the use of filter-based embolic protection in patients undergoing MitraClip implantation.

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The Sentinel EPD (Claret Medical Inc., Santa Rosa, California) provides filter protection for 3 of 4 arterial contributories to the brain. The filters can be retrieved and microscopically analyzed. Fourteen patients with severe MR were included in the analysis. Most patients had functional MR and concomitant permanent atrial fibrillation. Debris was detected in all patients. Acute thrombus and foreign body material was most common. The presence of acute thrombus is remarkable, especially since optimal per-procedural anticoagulation with heparin was achieved (mean activated clotting time 289 ± 48 s). This raises the question about the etiology of this acute clot formation: device manipulations in the left side of the heart but also the use of the filters themselves may be pro-thrombogenic. Furthermore, procedure times exceeding 90 min may result in transient suboptimal anticoagulation and, thus, promote acute thrombus formation. In fact, MitraClip procedure/device time has previously been associated with more new brain lesions by MRI (17). Conversely, the presence of organizing thrombus in the filters may be associated with the high prevalence of atrial fibrillation that hypothetically may have accounted for the organized thrombus surrounding the mitral valve apparatus. The authors describe the foreign body material as nonpolarizable basophilic material consistent with hydrogel, most probably from the hydrophilic coating of the transseptal sheath, guide delivery catheter, or the clip delivery system and thus inherent to the procedure. In more than one-half of the patients, mitral valve and atrial tissue was found. The authors do not discuss the effect of the number of attempts to grasp both mitral leaflets to eventually close and deploy the MitraClip. One can only wonder whether more attempts could dislodge more tissue. Furthermore, would there be a difference between functional and degenerative MR, with the latter displaying an excess of tissue? The finding that the use of more clips seemed to generate larger debris is intriguing.

In comparison to what typically is captured after TAVR, debris seemed smaller with MitraClip: 295 μm (interquartile range: 104 to 509 μm) versus 1 μm (interquartile range: 0.6 to 1.5 mm) (14). Smaller particle size may reflect the preponderance of functional MR in this study with structurally normal mitral valve leaflets. Similarly, this may explain why no calcium particles were captured. This contrasts with the yield after TAVR, with tissue debris in two-thirds of all patients including amorphous calcium.

The current data are complementary to the recent brain MRI study by Blazek et al. (17), in which a median of 3 new brain lesions were found in 85% of patients after MitraClip.

Given the (very) low clinical stroke rates after MitraClip, purists may claim that EPDs are useless in this setting. Others may argue that even subclinical brain infarcts may not be harmless and may increase the risk for dementia and neurocognitive deterioration in the long run (18). Future research efforts may focus on: 1) the difference in cerebral embolization between functional and degenerative MR; 2) the effect of EPD on new brain lesions by MRI; 3) cerebral embolization burden with transcatheter mitral valve implantation, which intuitively seems more traumatic than MitraClip and may thus dislodge more tissue debris; and maybe most importantly, 4) the effect of new brain lesions after structural heart interventions on immediate and late neurocognitive performance.

In aggregate, cerebral embolization seems ubiquitous with structural left-sided heart interventions. The study by Frerker et al. (16) provides complementary histopathological evidence to prior brain imaging data. Only the future can tell whether filter-based cerebral embolic protection is merely an interesting research tool or an essential clinical accessory for superior procedural (brain) safety.

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