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EDITORIAL COMMENT

The Pros and Cons of Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement*

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Transcatheter aortic valve replacement (TAVR) continues to grow and flourish with more than 300,000 procedures performed to date worldwide and an expected expansion over the next decade. Currently restricted to high-risk and otherwise inoperable patients (1), recent data favor TAVR rather than surgical aortic valve replacement in intermediate risk patients (2,3). A combination of new-generation devices, increased experience, better understanding of the disease, and improved screening is associated with improved outcomes, and there is a continuous trend to simplifying the procedure (4). Consequently, among early major issues associated with TAVR, paravalvular regurgitation may now be considered as a thing of the past and bleeding/vascular complications are on the decrease thanks to smaller size devices and better selection. Hence, overt stroke remains the most feared complication and is strongly associated with morbidity and mortality.

Early randomized studies have raised concerns about stroke rates with TAVR compared with medical treatment and surgical aortic valve replacement. Indeed, several studies have demonstrated a very high incidence (66% to 90%) of new cerebral ischemic lesions on post-procedural diffusion-weighted magnetic resonance imaging (MRI) and high-intensity transient signals evaluated with transcranial Doppler ultrasonography (5). Cerebral emboli may arise from several sources, such as equipment and materials used for placement of the aortic valve and/or the aortic arch.

Embolic protection devices successfully used in carotid intervention were thus developed in TAVR with the aim of lowering the rate of thromboembolic cerebral clinical and infraclinical events. Although the use of such devices has been explored in several small observational studies and a few randomized studies, their efficacy and safety remain unclear. The consequences of subclinical events on neurologic, functional, and cognitive status are a major concern, especially in the light of the current debate on extending TAVR to lower risk patients. This issue of *JACC: Cardiovascular Interventions* (6) features a contribution on neurologic outcomes with embolic protection devices in patients receiving TAVR. The authors, Giustino et al. from Mount Sinai Hospital in New York, performed a systematic review and study-level meta-analysis of all randomized controlled trials published up to December 2015 that tested the efficacy and safety of such devices during TAVR.

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Out of more than 200 screened articles, only 4 randomized trials met the inclusion criteria: the CLEAN-TAVI (Claret Embolic Protection And TAVI-Trial; n = 100), the DEFLECT-III (A Prospective Randomized Evaluation of the TriGuard HDH Embolic Deflection Device During TAVI; n = 85), the Tao-EmbolX (Intraprocedural Intraaortic Embolic Protection with the EmbolX Device; n = 30), and the MISTRAL-C (MRI Investigation in TAVI with Claret (n = 65) for a total of 280 patients (142 with a protection device).

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By pooling study-level data from randomized trials, the authors sought to investigate both the imaging and clinical neurologic outcomes associated with placement of intraprocedural embolic protection devices in patients with severe aortic stenosis receiving TAVR. Prespecified imaging neurologic endpoints (intention to treat) included total lesion volume in cubic millimeters assessed with diffusion-weighted MRI and number of new ischemic lesions. Pre-specified primary clinical neurological endpoints were any clinical deterioration from baseline according to the National Institute of Health Stroke Scale and the Montreal Cognitive Assessment score at discharge from hospital. Secondary endpoints included overt stroke and parameters related to the protection device, namely, fluoroscopic time and acute kidney injury. When available, data on TAVR devices were compared.

With the use of an embolic protection device, there was a nonsignificant reduction in overt stroke (reported in 3 studies) and all-cause mortality. Total lesion volume (reported in all 4 studies) and mean number of new ischemic lesions (reported in 3 studies) as assessed by diffusion-weighted MRI were lower and there was a trend to a lower number of patients with new ischemic lesions. There was a nonsignificant trend toward improved National Institute of Health Stroke Scale at discharge and patients randomized to embolic device also had a higher Montreal Cognitive Assessment score at discharge. As expected, fluoroscopic time was higher in patients randomized to an embolic device, but the authors reported no difference in acute kidney injury and the procedure appeared safe with no evidence of major complications related to the device. Even though the meta-analysis did not demonstrate any clinical benefit as assessed by a reduction in overt stroke or mortality, the authors suggest that both subclinical imaging and cognitive assessment favor the use of embolic protection devices.

These findings raise several important questions. Do we have enough data on the subject? Do existing data reflect current practice? What types of strokes occur after the procedure? Is there a clear benefit for any given patient and does the cost of the device justify systematic use in all TAVR patients? In the current era of simplifying the TAVR procedure, is a more complex TAVR justified? What is the population at risk and should the device be used in all or selectively? What is the impact of a pharmacologic approach to prevent cerebral emboli? As pointed out by the authors, data are extremely limited with only 4 small randomized trials (including 142 patients with an embolic protection device), significant drop-out in MRI data and no systematic report of all endpoints in each trial. Since this meta-analysis was performed (last publication, December 2015), important additional data have been published suggesting that stroke rate is no longer a major concern (3). The recent PARTNER (Placement of AoRTic TraNscathetER Valve Trial) 2S3 trial reported an overt stroke rate of 2.7% at 30 days, which compares favorably with prior data in particular those reported in the 4 randomized trials and reviewed in this present editorial. As demonstrated in the PARTNER 1 trial (7), stroke is not restricted to the early follow-up post-TAVR or surgical aortic valve replacement and additional overt strokes can occur between 1 and 5 years (all strokes or transient ischemic attacks: 8.6% at 1 year and 15.9% at 5 years). The limited number of patients treated in the 4 trials does not allow for identification of predictive factors. These factors could be extremely useful in view of decreasing additional costs and the added complexity of placement of the embolic protection device versus potential benefits on subclinical events and cognitive function. Furthermore, as suggested by the authors, optimal anticoagulant and antiplatelet therapies need to be defined and may play a major role in the occurrence of neurologic events. Thus, both the cost and complexity of TAVR should be taken into account when adding additional steps to the procedure.

Rightfully, the authors alluded to the need for larger randomized trials to settle the verdict on embolic protection devices because for the time being, it is not clear. A large randomized trial is ongoing (enrollment completed), the SENTINEL trial (Co-PI: S Kopadia & S Kodali from the US, A Linke, Germany) with the aim of randomizing about 300 patients and assessing the efficacy (superiority) and safety (noninferiority) of the Claret Medical Sentinel cerebral protection device in TAVR (SapienXT/Sapien3, Medtronic Corevalve/Evolut) by MRI assessment, neurologic and neurocognitive tests, and histopathology examination.

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KEY WORDS protection device, stroke, transcatheter aortic valve implantation