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EDITORIAL COMMENT

Routine Use of Embolic Protection During Transcatheter Aortic Valve Replacement*

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Transcatheter aortic valve replacement (TAVR) has become an important treatment option for patents with aortic stenosis (1). Stroke and paravalvular leak were initially recognized as the 2 most important complications of this therapy. Appropriate device and patient selection along with improvement in technology have brought these risks into an acceptable range. With that said, stroke risk with TAVR, although comparable to that with surgical AVR (SAVR), remains to be a serious complication of AVR (2). Recently, the U.S. Food and Drug Administration (FDA) has approved the Sentinel Cerebral Protection System (Claret Medical, Santa Rosa, California), a first in its class. It is indicated for use as an embolic protection device to capture and remove thrombus/debris while performing TAVR procedures. The diameters of the arteries at the site of filter placement should be between 9 and 15 mm for the brachiocephalic artery and 6.5 and 10 mm in the left common carotid artery. This indication labeling is primarily based on the SENTINEL (Cerebral Protection in Transcatheter Aortic Valve Replacement) trial (3). Primary endpoint of the SENTINEL trial was magnetic resonance imaging–measured new brain lesion volume, with limited power to study clinical events. Dr. Wöhrle's group provides valuable clinical data from consecutive patients who underwent TAVR with the Sentinel device (Seeger et al. [4] in this issue of *JACC: Cardiovascular Interventions*). They successfully deployed both filters of the Sentinel device in 280 of 305 (91.8%) patients. The reasons for not using the device were lack of radial access (n = 18), anatomy of the arch vessels (n = 6), or carotid stenosis (n = 1). They report lower risk of all strokes in patients with use of embolic protection compared with unprotected propensity-matched patients (1.4% vs. 4.6%; p = 0.03). This study provides clinical data to the TAVR community, which does not have a consensus on whether the cerebral protection device should be used in all or selected patients. It is important to note that this is a retrospective, propensity-matched study after successful implantation of the Sentinel device from a single center. Several questions arise when we consider the use of embolic protection for a TAVR procedure and attempt to interpret these additional data.

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In the PARTNER (Placement of Aortic Transcatheter Valves) trial, the risk of stroke with TAVR was almost 2-fold higher than SAVR (4.7% for TAVR vs. 2.4% for SAVR at 30 days; p = NS), resulting in a concern for the future of TAVR therapy (5). It is important to note that SAVR stroke was at its lowest in this trial (2.4%). In subsequent randomized trials, the stroke rate with SAVR has been higher (5.6% to 6.2%) (6–8). Neurological assessment was not mandatory in this first PARTNER trial (PARTNER 1A), raising the possibility that strokes could have been under-recognized. Subsequent studies using systematic, independent neurological evaluation have shown that risk of stroke with TAVR is not higher than SAVR and may even be lower. However, that risk is still in the 4% to 10% range for all strokes, and 2% to 3% for major strokes. Although this risk is considered "acceptable" when compared with the gold standard therapy of SAVR, the question remains whether such a risk is really acceptable to patients. For other transcatheter therapies (such as percutaneous coronary intervention), the risk of stroke is much smaller (0.1% to 0.2%), which can potentially

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serve as a benchmark for future TAVR studies. With careful neurological examination, the total stroke rate with TAVR is even higher (e.g., 9.1% in the control group of the SENTINEL trial), but the impact of minor strokes on quality of life, health care cost, and patient satisfaction remains unknown. In the study from Ulm (4), systematic use of Sentinel device resulted in a 1.4% stroke rate with independent neurological assessment. In light of these data, a major stroke rate of 2% to 3% and for all strokes of 4% to 10% in TAVR without embolic protection may not be acceptable.

In the SENTINEL trial (3), the device was safe with no neurological complications attributable to the device use. In the current study (4), there were no neurological complications that were attributed to device manipulation, underscoring the safety of the Sentinel device. There were 4 strokes despite embolic protection, 3 of 4 were in protected territories and 3 of 4 were noted on day 1 after the procedure, raising the possibility of a device-related neurological event. However, investigators did not report any difficulty placing the device or neurological symptoms at the time of procedure. There are other potential mechanisms of stroke, other than emboli from Sentinel device manipulation, including occurrence of emboli after the procedure, inadequate coverage of the vessel due to large vessel size or tortuosity, emboli in unprotected territories, and so on.

Several studies have tried to identify predictors of stroke in patients undergoing TAVR. Aortic valve calcification, arch calcification, old age, and severe aortic stenosis are some of the risk factors for early stroke after TAVR. Because all patients have aortic valve calcification, and many have some degree of vascular calcification, it is difficult to identify patients who are completely safe or at the highest risk of stroke. Some studies have implicated the need for additional procedural manipulation such as pre- and post-dilatation as a risk factor for stroke. Furthermore, all valve types have been associated with a similar procedural stroke risk. Considering these factors, one could surmise that stroke remains an unpredictable complication of TAVR irrespective of device use.

The SENTINEL trial missed the primary endpoint because it failed to show a statistically significant decrease in magnetic resonance imaging–detected new lesion volume in protected territories. There are 2 possible explanations for this result: first, the device was ineffective; and second, the decrease in lesion volume (44%) was not statistically significant because the study was underpowered. Power calculation for this study was based on limited prior data. Interestingly, the clinical strokes in the first 72 h (now defined as procedural stroke by NeuroARC definition) were significantly reduced with the use of the Sentinel device (3.0% vs. 8.2%; $p = 0.053$) (9). This finding together with the fact that 99% of the patients had material captured in filters provides evidence for efficacy. The current study adds to the argument that with systematic use of this device, there appears to be a clinical benefit in stroke reduction and possibly mortality reduction.

Although Sentinel is the first device approved by the FDA for embolic prevention during TAVR, there are several other embolic protection devices that are in development and testing for this indication. Currently, the TriGuard deflection device (Keystone Heart, Herzliya, Israel) was being studied in a randomized pivotal trial (REFLECT [Cerebral Protection to Reduce Cerebral Embolic Lesions After Transcatheter Aortic Valve Implantation] trial; NCT02536196). The study was stopped prematurely. This device also has clinical data from the DEFLECT (A Prospective, Randomized Evaluation of the TriGuard™ HDH Embolic Deflection Device During TAVI) I to III trials showing safety and efficacy in smaller trials outside of the United States (10,11). This device covered the origin of all cerebral vessels in patients with appropriate anatomy, which is a potential advantage of the system. The second-generation device will address the need for smaller than 9-F femoral access (needed for current device) and need to protect a wider range of anatomies with more certainty.

Several facts should be taken into consideration when deciding whether the device should be routinely used in practice as implemented successfully by Dr. Wöhrle's group (4). There is cost associated with the device because there is no reimbursement for its use in the United States at this time. Device use takes a small amount of additional time, which can be considered a significant percentage of time for a short TAVR procedure; however, with routine use, only 5 to 15 additional minutes are added to the procedure. Although additional contrast use and radiation exposure have been mentioned, these are usually not clinically significant increments. About 10% of patients may not be candidates for the use of this device because of anatomic considerations (need for right arm access, size of vessels, anatomic variations in arch vessels, calcification and tortuosity, and so on). In anatomically eligible patients, if the procedure is performed without an emboli prevention strategy and the patient has a procedural stroke, one could argue that this adverse event could have been potentially prevented with the use of this device. The level of evidence for this argument can be classified as B, including the current study. The FDA label to

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"capture and remove thrombus/debris while performing TAVR" and IFU (instruction for use) indicating "A post hoc analysis showed a 63% relative reduction in peri-procedural stroke rates in favor of the Sentinel System (3.0% vs 8.2%)", and that the device is deemed safe to use, may make patients and operators question their decision for not using the device. On the other hand, if the patient has a stroke despite using embolic protection, device manipulation can be considered as a possible mechanism even though there were no safety concerns in the trials. Widespread adoption of the embolic protection during TAVR will require consideration of all these arguments and will be facilitated by adequate training of the operators in device use along with additional data from post-market use.

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