Stroke After Aortic Valve Replacement
The Known and Unknown

Ron Waksman, MD; Sa’ar Minha, MD

Stroke after aortic valve surgery is known as a devastating complication and is associated with increased morbidity and mortality. Transcatheter aortic valve replacement (TAVR) has emerged as a valid alternative for surgical aortic valve replacement (SAVR) both in inoperable patients and in those at high risk for surgery; however, the encouraging results were hampered by various complications, including stroke. In the pivotal Placement of Aortic Transcatheter (PARTNER) trial, the initial stroke rates of TAVR patients were almost double the stroke rates in patients who underwent SAVR (3.8% versus 2.1%; \( P=0.2 \)), and this potentially affected the decision to choose 1 procedure over the other. However, continued follow-up to 3 years equated the stroke rates in SAVR and TAVR. More recent SAVR and TAVR data indicate that stroke rates in both procedural alternatives has declined, with rates of 1.7% to 2.5% from large registries such as the Society for Thoracic Surgeons and the German Aortic Valve registries. However, the unknowns with respect to stroke after AVR are numerous. In evaluations of neurological complications, overt clinical and obvious disabling stroke is only 1 potential neurological event that could occur after the procedure, and as opposed to permanent neurological deficits, these events either are clinically silent or go unnoticed because physicians are not performing tests to rule out these events (ie, cognitive deficits). The incidence and impact of these events on outcome are unknown. Furthermore, the role and impact of magnetic resonance imaging (MRI) detection of silent strokes also remain unknown.

In the current issue of Circulation, Messé and colleagues prospectively assessed the incidence of both clinical stroke and silent neurological events in 196 patients ≥65 years of age who underwent SAVR as recorded by serial neurological examinations and MRI. The incidence of clinically overt stroke was 17%, whereas silent infarct was identified in 54% of patients with no neurological symptoms by MRI. These rates are alarming, especially compared with the stroke rates reported in the literature. Overall, stroke in this cohort was not significantly associated with increased mortality, but moderate to severe strokes (National Institutes of Health Stroke Scale score ≥10) were strongly associated with mortality. These results highlight most of the unknowns in neurological events after AVR.

First, the true incidence of clinical stroke after SAVR is still unclear because this contemporary report recorded a higher incidence than was previously reported in surgical literature. These discrepancies probably stem from a lack of uniform definitions for stroke. This is reflected in the article by Messé et al, who reported a stroke rate of 17% using the study’s definitions. However, with the use of the Society for Thoracic Surgeons definitions, the recorded stroke rate was only 7%. This difference is due to the discrepancy in stroke definitions used across studies and emphasizes the challenges with the definition of stroke. Although the Society for Thoracic Surgeons score records only “permanent neurological deficit,” the study’s definitions for stroke also included events that lasted <24 hours but were documented by imaging in the corresponding territory.

A second explanation for the discrepancy lies in the number of neurological tests performed. The fact that 3 complete neurological examinations were performed by a neurologist for every patient at follow-up potentially decreased the threshold for diagnosing neurological deficits, which may lead to a higher diagnosis rate (the more you look, the more you find). These 2 issues call for a uniform definition for neurological events, similar to what was implemented for TAVR by the Valve Academic Research Consortium. These definitions should also address who should evaluate a patient’s neurological status and when it should be evaluated. With the uncertainty in the reported rates of postprocedural stroke, in comparisons of TAVR and SAVR, stroke rates should not be taken for granted, and the decision to choose 1 alternative over the other should be based on other clinical metrics.

Neurological events other than clinical stroke are even harder to define and thus to report and explore. Both SAVR and TAVR literature reported cognitive decline after the operation, but the clinical implication of these deficits is not well established. This uncertainty is also true for silent neurological events (ie, events recorded by imaging modalities with no apparent clinical symptoms). Messé et al report a 54% incidence of silent brain infarcts that were demonstrated by diffusion-weighted imaging after the procedure in patients with no clinical neurological event. This is in concordance with this group’s prior report and with reports in the TAVR literature of high rates of silent brain infaracts (demonstrated by diffusion-weighted MRI with incidences exceeding 70%). Conflicting evidence exists on the clinical implication of these imaging findings, with some authors reporting no association with cognitive impairment and others claiming an
association between new lesion burden and neurological outcome. This controversy is complicated by the evolution or resolution of stroke at the long-term follow-up. Resolution of the cognitive impairment was noted in patients with both post-procedural cognitive impairment and new findings on MRI. Because most of the data are based on relatively small-scale studies, with different definitions and tests used for establishing cognitive function, it is still unknown whether diffusion-weighted MRI is overly sensitive for the detection of new, clinically irrelevant lesions or whether, in fact, these lesions imply a meaningful clinical issue.

The etiologic factors leading to neurological events are also controversial. It is reasonable to assume that the embolic events result from dislodgement of atherosclerotic material during the manipulation of the aorta and the aortic valve. Even in the face of preventive measures such as epiaortic ultrasound before cannulation, the surgical technique necessitates some aortic manipulation. Similarly, TAVR requires the manipulation of relatively large delivery systems across the aortic arch, which in turn leads to atherosclerotic plaque dislodgement. This was the main driver of the development of a variety of embolic protection devices. These devices, deployed percutaneously, are designed to filter and stop debris from reaching the brain. Although this seems promising from a technical standpoint, no evidence exists to establish the clinical merits of these devices. A designated prospective clinical trial, the Prospective Randomized Outcome Study in Patients Undergoing TAVI to Examine Cerebral Ischemia and Bleeding Complications (PROTAVI-C), will examine the effect of the umbrella embolic protection system by randomizing patients to TAVR with and without protection and in a second randomization exploring the differences in neurological events with single versus dual antiplatelet therapy after TAVR.

Beyond the embolic causes, Messé et al suggest that longer cardiopulmonary bypass time was independently associated with increased stroke risk. This suggests that stroke after SAVR results from the hemodynamic alternations associated with cardiopulmonary bypass and that this risk cannot be mitigated by embolic protection devices and thus is unique to the surgical arena. It should be mentioned that hemorrhagic stroke is also reported after SAVR and TAVR, although in a minority of cases (6% in the Messé et al study and 4% in the pivotal PARTNER trial). Hemorrhagic stroke should be attributed to overcoagulation and suggests the unmet need of safe anticoagulation protocols for this TAVR population.

Beyond technical and mechanical measures, the prevention of postoperative stroke may be feasible with an adequate anti-thrombotic or anticoagulant regimen, but this is yet another unresolved issue. In patients who underwent SAVR and were randomized to warfarin or aspirin postoperatively, no differences were noted in the rate of ischemic events between regimens; this and other studies have led to the recommendation by the American College of Chest Physicians to use aspirin as the antithrombotic therapy after SAVR for ≥3 months, and the combination of aspirin and clopidogrel is recommended after TAVR without evidence to support this recommendation. The ongoing Aspirin Versus Aspirin+Clopidogrel Following Transcatheter Aortic Valve Implantation (ARTE) clinical trial, randomizing patients after transcatheter aortic valve implantation to either aspirin or aspirin and clopidogrel, will potentially shed some light on this issue. This decision is complicated by a significant rate of atrial fibrillation in patients undergoing AVR (either chronic or postoperative), which increases the risk for thromboembolic events.

Timing of stroke after AVR has an interesting pattern. In several surgical series, it was demonstrated that 55% to 72% of stroke occurred during the first 24 hours after the procedure. Data from the PARTNER trial randomizing high-risk patients to either TAVR or SAVR have demonstrated that 51% of neurological events occurred during the first 10 days after the procedure, peaking at day 2 for both TAVR and SAVR. In this series, TAVR was associated with increased risk for early neurological events compared with SAVR (coefficient, 2.21±0.68; P=0.01). During the late term (after the first week), the treatment arm was no longer determined to be a significant risk factor for a neurological event. The risk factors associated with late neurological events were mostly patient-related risk factors such as history of prior stroke and New York Heart Association class. Looking at the yearly incidence of stroke after this early period (1%–2%), we see that this incidence is similar to the natural history incidence of stroke in the general population (>75 years of age). In 2014, we recognize that clinical stroke after AVR remains a devastating event, that there are no differences in stroke rates between TAVR and SAVR, and that the overall rate of stroke after AVR is trending to lower rates for both treatment modalities. Although the article by Messé et al adds important insights into the incidence of both clinically overt and silent neurological events after SAVR, the study highlights the numerous unknowns with regard to stroke after AVR, including the true incidence, the value of MRI in diagnosing silent strokes, the causes and correlates of stroke after AVR, and what measures should be taken to further minimize stroke incidence. AVR, either via SAVR or TAVR, is a lifesaving procedure that remains the most viable modality for the treatment of aortic stenosis. Therefore, it is imperative that rigorous, prospective, well-designed clinical trials be conducted to address the unknowns of stroke-related issues after AVR and to better understand how we can further minimize this unwarranted event.

Disclosures

None.

References


**KEY WORDS**: Editorials ■ aortic valve ■ heart valve prosthesis implantation