Stroke after Aortic Valve Replacement: The Known and Unknown

Running title: Waksman et al.; Stroke after AVR: The Known and Unknown

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Stroke following 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) in both 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 TraNscatheterER (PARTNER) trial, the initial stroke rates of TAVR patients were almost double in comparison to patients who underwent SAVR (3.8% vs. 2.1%; p=0.2); and this potentially impacted the decision to choose one procedure over the other. However, continued follow-up up to 3 years equated the stroke rates in SAVR and TAVR. More recent surgical and TAVR data indicate that stroke rates in both procedural alternatives had declined, with rates of 1.7-2.5% from large registries, such as the Society for Thoracic Surgeons (STS) and the German Aortic Valve registries. However, the unknowns with respect to stroke following AVR are numerous. When evaluating neurological complications, overt clinical and obvious disabling stroke is only one potential neurological event that could occur after the procedure, and as opposed to permanent neurological deficit, these events are either clinically silent or go unnoticed due to the fact that physicians are not performing tests to rule out these events (i.e., cognitive deficits). The incidence and impact of these events on outcome is unknown. Further, the role and impact of magnetic resonance imaging (MRI) detection of silent strokes also remains unknown.

In the current issue of Circulation, Messe 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 exams and MRI. The incidence of clinically overt stroke was 17% while silent infarct was identified in 54% of patients with no neurological symptoms by MRI. These rates are alarming especially when compared to the
stroke rates reported in the literature. Overall, stroke in this cohort was not significantly
associated with increased mortality but moderate-severe strokes (National Institutes of Health
Stroke Scale ≥10) were strongly associated with mortality. These results highlight most of the
unknowns regarding 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 manuscript, with a reported stroke rate of 17% using the study’s definitions.
However, by using the STS definitions, the recorded stroke rate was only 7%. This is due to the
discrepancy in stroke definitions used across studies and emphasizes the challenges with the
definition of stroke. While the STS 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 three complete neurological exams 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
two issues call for a uniform definition for neurological events, similarly to what was
implemented for TAVR by the Valve Academic Research Consortium (VARCH).6 These
definitions should also address who should evaluate a patient’s neurological status and when.
With the uncertainty in the reported rates of post-procedural stroke, when comparing TAVR to
SAVR, stroke rates should not be taken for granted and the decision to choose one alternative
over the other should be based upon other clinical metrics.
Neurological events other than clinical stroke are even harder to define and thus to report and explore. Both surgical and TAVR literature reported on cognitive decline after the operation but the clinical implication of these deficits is not well established.7–9 This uncertainty is also true for ‘silent neurological events’ (i.e., events that were recorded by imaging modalities with no apparent clinical symptoms). In the current manuscript by Messe et al., the authors report a 54% incidence of silent brain infarcts that were demonstrated by diffusion-weighted imaging (DWI) post procedure in patients without any clinical neurological event. This is in concordance with this group’s prior report10 and with TAVR literature reporting high rates of silent brain infarcts (demonstrated by DWI-MRI with incidences exceeding 70%).11, 12 Conflicting evidence exists regarding the clinical implication of these imaging findings with some authors reporting no association with cognitive impairment11, 13 and others claiming an association between new lesion burden and neurological outcome.14 This controversy is complicated by the evolution or resolution of stroke at long-term follow-up. Resolution of the cognitive impairment was noted in patients with both post-procedural cognitive impairment and new findings on MRI.13 Since 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 DWI-MRI imaging is over-sensitive for detection of new, clinically irrelevant lesions or that in fact, these lesions imply a meaningful clinical issue.

The etiological 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 prior to cannulation, 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 toward the development of a variety of embolic protection devices. These devices are deployed percutaneously and are designed to filter and stop the 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, 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 a second randomization will explore the differences in neurological events with single- versus dual antiplatelet therapy after TAVR.

Beyond the embolic etiology, the presented manuscript by Messe et al. suggests 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 can’t be mitigated by embolic protection devices and is thus unique to the surgical arena. It should be mentioned that hemorrhagic stroke is also reported after SAVR and TAVR, although this is reported in a minority of cases (6% in Messe et al. and 4% in the pivotal PARTNER trial). Hemorrhagic stroke should be attributed to over coagulation and suggests the unmet need of safe anticoagulation protocols for this TAVR population.

Beyond technical and mechanical measures, prevention of post-operative stroke may be feasible with adequate antithrombotic or anticoagulant regimen but this is yet another unresolved issue. In patients who underwent SAVR and were randomized to warfarin or aspirin post-operatively, no differences were noted in the ischemic events rates 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 $\geq 3$ months, while the combination of aspirin and clopidogrel is recommended after TAVR without evidence to support this recommendation.\textsuperscript{17} The ongoing Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation (ARTE) clinical trial randomizing patients after TAVI 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 post-operative), which increases the risk for thromboembolic events.

Timing of stroke after AVR has an interesting pattern. In several surgical series it was demonstrated that 55-72\% of stroke occurred during the first 24 hours after the procedure.\textsuperscript{18, 19} 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 post-procedure, peaking at day 2 for both TAVR and SAVR.\textsuperscript{15} 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. By looking at the yearly incidence of stroke after this early period (1-2\%), it seems that this incidence is similar to the natural history incidence of stroke in the general population (aged $>75$ years).\textsuperscript{20}

In 2014 we recognize that clinical stroke after AVR remains a devastating event, that there are no differences in the rates between TAVR and SAVR, and that the overall rate of stroke post AVR is trending to lower rates for both treatment modalities. While the manuscript by
Messe et al. adds important insights regarding the incidence of both clinically overt and silent neurological events after SAVR, the study highlights the numerous unknowns with regard to stroke post-AVR, including the true incidence, the value of MRI in diagnosing silent strokes, the etiologies and correlates of stroke following 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 are conducted to address the unknowns of stroke related issues post AVR and to better understand how we can further minimize this unwarranted event.

Conflict of Interest Disclosures: None.

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