Transcatheter aortic valve replacement (TAVR) has been established as a standard of care worldwide in patients with degenerative severe aortic stenosis deemed at high or prohibitive risk for surgical aortic valve replacement. Since its early inception, stroke has been the most feared potential complication. In the early experience, rates of clinical stroke at 30 days after TAVR ranged between 4% and 6%. The substantial improvements in case selection, procedural technique, device technology development, and operator experience overtime dropped this rate substantially.

Of note, in a large high-risk TAVR trial with a self-expandable device, the risk of stroke over 3 years was higher in the control group undergoing surgical aortic valve replacement. Despite the availability of surgical aortic valve replacement for long time, the issues discussed hereafter have not yet been investigated in prospective, randomized fashion. Although we focus on TAVR, owing to the 2 papers we are commenting upon, we should acknowledge upfront that cerebrovascular event (CVE) prevention remains a common theme for all kinds of bioprosthetic aortic valves, via surgical or transcatheter implantation.

See Articles by Kapadia et al and Kleiman et al

CVE during or after TAVR is a multifactorial phenomenon with clinical, anatomical, procedural, and pharmacological factor contributions. During TAVR, the predominant pathological mechanisms may be cerebral embolism of calcific or atherothrombotic debris during positioning and implantation of the valve prosthesis. After TAVR, thromboembolic mechanisms may include endovascular thrombosis (including upon small size emboli), late embolization of calcific or atheromatous debris from the native aortic valve, ongoing thrombotic pannus (or mural thrombus layer) formation on the surface of the implanted prosthesis, and other mechanisms, including new-onset atrial fibrillation or the progression of atherothrombotic vascular disease. However, definitive scientific evidence characterizing the CVE risk peri-TAVR is still lacking.

In this issue of Circulation: Cardiovascular Interventions, 2 important reports on the incidence, predictors, and impact of CVE after TAVR have been published. Notably, these 2 analyses stem from the 2 major randomized trials and continuous access registries in this field, namely the PARTNER-1 (Placement of Aortic Transcatheter Valves) and the CoreValve studies.

Kapadia et al report on a total of 2621 patients who had TAVR with the balloon-expandable Edwards SAPIEN valve; in-hospital CVEs were identified by the treating physician. At follow-up visits, neurological status was systematically assessed with the National Institutes of Health Stroke Scale by trained examiners. All events were adjudicated by a dedicated multidisciplinary clinical events committee. The incidence of stroke was 3.8%, 5.4%, and 6.9% at 30 days, 1 year, and 3 years, respectively. At 30 days, 85% of strokes occurred within the first week and 64% within the first 2 days. The instantaneous risk for stroke was significantly greater within the first 2 to 3 days and then declined. There were no significant differences in rates of stroke according to the TAVR procedure access (transfemoral or transapical). Both 30-day and later stroke risks were higher for patients with a CHA2DS2-VASc score above 3 compared with patients with lower CHA2DS2-VASc score; this is not surprising. Predictors of early stroke included higher aortic valve peak gradient for transfemoral-TAVR, pure aortic stenosis (without aortic regurgitation), and postdilation for transapical-TAVR. Predictors of late stroke included dementia at baseline and use of smaller TAVR valve size (23 mm versus 26 mm) for transfemoral-TAVR, and non-white race, lower ejection fraction, and atrial fibrillation for transapical-TAVR. Risk factors for stroke were analyzed with bootstrap (1000 bootstraps) aggregation to mitigate type II errors in model selection with the threshold of <50% to define statistically significant (P<0.05) unreliable predictors. By doing so, lack of use of dual antiplatelet therapy and early experience were unreliably associated with increased risk for stroke.

Kleiman et al report on a total of 3687 patients who underwent TAVR with the self-expandable Medtronic CoreValve in the randomized pivotal trials and continuous access registries. CVE was diagnosed using a clinical algorithm, implementing the National Institutes of Health Stroke Scale plus appropriate imaging at baseline, post procedure, at hospital discharge, at 30 days, and then yearly. Stroke severity was graded using the modified Rankin scale. Events were adjudicated by a multidisciplinary clinical events committee. Rates to first stroke (any type) were 4.8%, 7.1%, and 8.4% at 30 days, 6 months, and 1 year, respectively. Among the 270 strokes that occurred at 1 year, 54.4% (147) occurred within 10 days after TAVR. Of note, among patients who had a stroke within the first year, 19...
(7%) had a second stroke during the same year of follow-up. Distribution of the hazard function indicates that the risk of stroke is highest within the first days after the procedure and then declines. By inspection of the distribution of the modified Rankin scale, at least 30% of the strokes were associated with severe disability or death. In this study, independent predictors of early stroke (from day 0 to day 10) were clinical factors (National Institutes of Health Stroke Scale score ≥1 at baseline, prior CVE, peripheral artery disease, absence of prior coronary artery bypass surgery, presence of angina, low body mass index, and falls within the prior 6 months) and procedural factors (longer procedural time, total delivery catheter time in the body, rapid pacing during preparatory valvuloplasty, and Medtronic CoreValve repositioning with a snare); no imaging covariates predicted early stroke, and operator experience did not emerge as a predictor. Predictors of later stroke were smaller body surface area, severe aortic calcifications (of borderline significance), and falls within the past 6 months. In both studies, not surprisingly, the occurrence of a CVE (either a stroke or TIA) was associated with increased risk for subsequent mortality.4,5

What are the main take-home messages from the great sets of data outlined above? First, the risk of CVEs is greater early after TAVR (within few days). Second, clinical, anatomic, and procedural factors can predict the risk for CVE. Procedural factors are more important in predicting earlier CVEs and, rather, frailty, and other clinical–anatomic factors more strongly correlate with later CVEs. Third, CVEs are associated with increased morbidity and mortality, a finding that may reflect either correlation (patients having strokes are more frail and sicker) or causality (stroke is a true mediator that may reflect either correlation (patients having strokes are more frail and sicker) or causality (stroke is a true mediator of mortality in this population). These 3 messages seem to be uniformly applicable to both balloon-expandable and self-expandable valves.4,5

Although these 2 articles provide substantial, novel, and high-quality data to the field, several important limitations should be outlined. First and foremost is the lack of uniform definitions in the timing, severity, classification, and ascertainment of stroke. For example, in the report of Kleiman et al,4 stroke severity was assessed with the modified Rankin scale, whereas in the study of Kapadia et al,5 it was not. Common definition of neurological events and cognitive function would be useful in comparing data across literature. Second, the importance of pharmacological factors, both periprocedural (ie, platelet inhibitor type and loading dose or anticoagulation details) and postprocedural (ie, intensity and duration of dual antiplatelet therapy or type/strategy of oral anticoagulation) remain unknown because patients were not randomized to different pharmacological strategies, and medications were heterogeneously prescribed, tracked, and often not reported. Third, in both studies, early-generation TAVR device types have been used, and sick patient populations had been included. It is conceivable that new-generation TAVR devices likely reduce the risk of stroke, and procedure- or device-related factors are significant contributors to thromboembolic risk in a low or intermediate risk population; these need to be better understood because their clinical ramifications can be different in a high/prohibitive risk population versus lower-risk patients. Finally, there is always uncertainty on reliable tracking and reporting of CVEs in depth of time in such sick, advanced age patients. Inclusion of cognitive impairment in future studies further raises the bar for comprehensive clinical investigation.

Nevertheless, the intrinsic limitations of these studies are indicative of future areas of clinical investigation in this field. First, we should reach a consensus to better characterize, track, and report CVEs in TAVR patients and apply the same in surgical aortic valve replacement as well. Such definitions should satisfy (1) accuracy, (2) ease of use (ie, noncomplex tools in diagnosis), and (3) ascertainment capability by as many healthcare professionals as possible to overcome the important barrier of incorrect or missing diagnosis and correctly guide further diagnostic evaluation for pathogenesis ascertainment (eg, stroke because of atrial fibrillation versus device thrombosis).

Second, the importance of antithrombotic drugs in mitigating stroke risk after TAVR, especially on the mid- to long-term, require evidence from high-quality randomized controlled trials. For example, in the ongoing GALILEO trial [NCT02556203], patients who undergo successful TAVR and do not require full done anticoagulation upfront are randomized to a low-dose (10 mg orally once daily) rivaroxaban-based anticoagulation strategy (rivaroxaban plus aspirin for the first 3 months followed by aspirin alone) versus an antiplatelet-based strategy (aspirin plus clopidogrel for the first 3 months followed by aspirin alone), with the hypothesis that low-level anticoagulation with rivaroxaban will be more effective in reducing the composite of mortality or thromboembolic event rate without substantially increasing bleeding. This hypothesis stands on the rationale that stroke is an important contributor of mortality after TAVR and that anticoagulants are more effective than antiplatelets in preventing thromboembolism in high-risk patients (ie, high CHA2DS2-VASc score); in addition, low-dose anticoagulation may protect from potential thrombotic pannus formation.6

A somewhat different hypothesis is tested in the ongoing ATLANTIS trial (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis, NCT02664649) in Europe, which randomizes patients after TAVR to full-dose anticoagulation with apixaban versus different control groups according to the requirement of upfront anticoagulation with warfarin or not (based on non–TAVR related indications as per the treating physician).

In both articles published concurrently in this issue of the journal,4,5 the composite end point of cardiovascular and CVEs as well as bleeding rates are examined at 1-year follow up. On the contrary, the duration and intensity of antiplatelet therapy should be also clarified. In the PARTNER trial, lifelong aspirin (75–100 mg per day) and clopidogrel (75 mg per day) for 6 months were recommended (no special action on any deviations is explained). The American College of Cardiology/American Association for Thoracic Surgery/Society for Cardiac Angiography and Interventions/Society of Thoracic Surgeons panel recommends dual antiplatelet therapy with aspirin and clopidogrel to reduce the risk of thromboembolic events after TAVR, but the optimal duration of such treatment is not specified.7 Because of (expected) enhanced bleeding risks with clopidogrel therapy in TAVR patients, it may be reasonable to require that the more intensified combination
therapy should mitigate the risk of cardiovascular and CVEs by at least 25% to have a favorable benefit-to-risk ratio over a monotherapy.

Third, modifiable baseline and procedural risk factors for periprocedural stroke have to be clearly characterized to identify patients who may benefit of intraprocedural embolic protection devices, which seem to be associated with lower risk of cerebral embolization and neurological outcomes in early studies with different devices. For example, routine use of embolic protection devices may only/mostly be beneficial in patients with complex anatomic characteristics (eg, highly calcified native valves, large aortic arch atheromas, or angulated aorta) or expected challenging-longer procedures.

The currently identified predictors have to be placed in perspective with those identified in earlier studies. For example, in a previously published study from a large multicenter real-world experience, balloon postdilation and valve embolization were identified as the 2 strongest predictors for acute CVEs. Balloon postdilation, which is often implemented as antiparavalvular leak procedure, had been described as a strong predictor of both CVEs and conduction disturbances requiring permanent pacemaker. Persistent new-onset and paroxysmal subclinical episodes of atrial fibrillation have also been important thromboembolic risks after TAVR, thereby, reinforcing the potential benefits of intensified antithrombotic therapy in suitable subjects.9

Finally, a recent trial on intraprocedural anticoagulation with approved, contemporary TAVR device types indicated low, yet, finite rate of early stroke and a lower level of cerebral embolization than other trials.10,11 The notable variability of these events, along with other CVE types and cognitive impairment, should be considered in future investigations. Ascertainment bias may lead to low CVE rates in longitudinal, self-reporting registry-based data12 and to higher embolization rates in studies focused on embolic protection device use. We expect that these would ultimately settle overtime, but relevant efforts should be taken to improve the quality control of all relevant research operations.

In conclusion, although high-quality scientific evidence from randomized controlled trials is needed to establish the role of CVE prevention strategies during and after TAVR, a deep understanding of CVE pathophysiology in this particular population is necessary to appropriately implement available tools and techniques. The translation of this evidence basis in clinical practice may often be confronted by uncaptured or even unmeasurable factors that narrow the applicability of the research data. The clinician judgment has to go beyond statistical models, risk scores, and randomized controlled trials at the time of individualized decision-making. An overview of the possible strategies for stroke prevention after TAVR is illustrated in the Figure. The quest for the future will be the art of applying in daily clinical practice what is deduced on a population basis, particularly in the complex TAVR patients.

**Disclosures**

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References


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