Stroke
An Infrequent but Devastating Complication in Cardiovascular Interventions

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Stroke is a dreadful complication of cardiovascular interventions owing to the clinical manifestations of neurological deficits and the impact on prognosis (Table). Whereas the risk of cerebrovascular events (CVE) is exceedingly low among patients undergoing percutaneous coronary intervention (0.3%),1 it does range from 1.2% to 3.8% among patients undergoing isolated coronary artery bypass grafting,1,2 and is as high as 9.7% among patients undergoing double or triple valve surgery.2 Although transcatheter aortic valve implantation (TAVI) shares many features of a minimal-invasive treatment with other percutaneous techniques, this advantage does not extend to the risk of stroke, which occurs with a frequency of 2.7% to 4.2%.3 In the randomized Placement of Aortic Transcatheter Valves (PARTNER) Trial cohort 1A, rates of stroke and transient ischemic attack were higher among patients undergoing TAVI compared with surgical aortic valve replacement at 30 days (4.6% versus 2.4%; P=0.12), 1 year (8.7% versus 4.3%; P=0.03), and 2 years (11.2% versus 6.5%; P=0.05) of follow-up.4 Similarly, TAVI was associated with an increased risk of CVE compared with medical treatment in the randomized PARTNER 1B study at 30 days (6.7% versus 1.7%; P=0.02), 1 year (11.2 versus 5.5%; P=0.06) and 2 years of follow-up (13.8% versus 5.5%, P=0.01).5

The awareness of this adverse event has been heightened in the recent update of standardized end point definitions for TAVI issued by the Valve Academic Research Consortium.6 CVE are no longer stratified into transient ischemic attack and stroke, but rather into disabling and nondisabling stroke according to the modified Rankin scale. Moreover, rigorous stroke assessment has become an integral part of ongoing trials comparing TAVI with surgical aortic valve replacement among intermediate-risk patients by contributing to the primary end point (composite of death and disabling stroke) and demanding systematic neurological examinations before and after the procedure.

In this issue of Circulation, Nombela-Franco and colleagues7 provide an in-depth analysis of the timing and predictive factors of CVE in 1 of the largest TAVI cohorts studied to date. In a concerted effort of 5 esteemed institutions, individual patient data from 1061 consecutive patients undergoing TAVI were compiled using similar outcome definitions, treatment, and follow-up protocols. Events were categorized as acute when occurring within the first 24 hours after the procedure, as subacute when observed between the first postoperative day and 30 days of follow-up, and as late for any event occurring beyond 30 days after the procedure. The cumulative incidence of CVE of 8.4% (1 in 12 patients undergoing TAVI) during a median follow-up of 1 year is concerning, particularly because only clinically overt events were ascertained in the absence of systematic neurological evaluation before or after the procedure. Notwithstanding, the authors offer important insights into the timing and prediction of CVE, which offer valuable guidance to clinicians performing TAVI.

Acute Risk of CVE
The majority of CVE (54%) in the present study occurred during the acute phase after TAVI (Figure). An embolic mechanism as cause for acute CVE is plausible and supported by MRI studies detecting clinically silent, new intracranial lesions in the majority of patients undergoing TAVI.8 Retrograde passage of a stenosed aortic valve during diagnostic catheterization has been shown to result in new focal cerebral lesions using MRI in 22% of patients.9 In addition, balloon aortic valvuloplasty leads to fracture and denudation of deposits of calcium, which do not only become friable and therefore prone to embolization but also exposed to the circulation with activation of platelets and the coagulation cascade with the attendant risk of thromboembolic complications. Moreover, advancement of the delivery catheter into the aortic annulus and deployment of the valve prosthesis may cause embolization of particulate and calcified debris from previously denuded calcium deposits. Using transcranial Doppler ultrasonography, Erdős et al10 and Kahlert et al11 reported on loads of high intensity transient signals, as surrogate marker for microembolization during different stages of the implantation of self- and balloon-expandable TAVI prostheses. Whereas the balloon-expandable Edwards Sapien prosthesis elicited the highest load of high intensity transient signals during positioning of the valve in the annulus, the self-expanding Medtronic CoreValve prosthesis caused most high intensity transient signals during the process of valve deployment.
A minimal or no-touch technique avoiding any interference with the ascending aorta as well as sparing predilatation of the stenosed aortic valve before prosthesis delivery has been proposed to reduce the risk of periprocedural stroke. Moreover, improvements in the design of delivery catheters, such as enhanced steerability, deflectable catheters, and low cross-sectional profiles, will reduce contact with vulnerable lesions.

Repeat dilatation of the prosthesis to resolve underexpansion of the valve or residual paravalvular aortic regurgitation was associated with a 2.5-fold increased risk of CVE in the present study. An even greater risk (4-fold) during the acute period was related to dislodgement or embolization of the valve prosthesis. This observation suggests that meticulous planning of the procedure in terms of device and size selection is instrumental to avoid valve malposition and paravalvular aortic regurgitation and related CVE. Recent advances in valve technology, including fully repositionable valve types, aim at more precise alignment of the valve prosthesis within the native annulus, which should reduce the risk of valve embolization as well as paravalvular regurgitation. In addition, these devices may allow for less traumatic implantation with accelerated endothelialization attenuating activation of platelets and coagulation. Mechanical cerebral protection devices are yet another approach to reduce periprocedural cerebral embolism during TAVI. Currently, 3 different cerebral protection devices are investigated in ongoing studies, all of which consist of a filter membrane placed either in the aortic arch to deflect particulate debris toward the descending aorta (SMT Embolic Protection Device, Embrella Deflector), or in the large supraaortic branches to filter and retrieve embolized particles from the cerebral circulation (Claret Filter Device). Finally, thrombin-specific anticoagulants may improve the level and consistency of anticoagulation during the procedure, while reducing the risk of bleeding complications.

**Subacute Risk of CVE**

New onset of atrial fibrillation (NOAF) was observed in 12% of patients undergoing TAVI in the study by Nombela-Franco and emerged as single, independent predictor of CVEs during the subacute phase after TAVI (Figure). Atrial fibrillation is a well-known complication after cardiac surgery, and its pathophysiological mechanisms have been related to consequences of the extracorporeal circulation and associated perioperative inflammatory reactions. NOAF affects up to two thirds of patients after open heart surgery and is highest among patients undergoing valve surgery.14 Patients with NOAF after cardiac surgery are more likely to experience CVE, more frequently undergo permanent pacemaker implantation, and require a longer stay in the intensive care unit and in the hospital overall, all of which result in a cost increase of up to $11 000 per patient.14 Considering proce-
dural differences between surgical aortic valve replacement and TAVI, it is somewhat surprising that NOAF has been reported in up to 32% of patients within the first 30 days after TAVI. However, patients undergoing TAVI are typically octogenarians with a higher baseline risk for atrial fibrillation, which may further be precipitated by severe aortic stenosis and underlying diastolic dysfunction. Transapical access is another predictor for NOAF likely related to pericardial dissection and subsequent inflammation. The latter may explain why transapical access has failed to translate into a lower risk of periprocedural stroke. Indeed, neither imaging studies using diffusion weighted MRI nor clinical studies in large patient cohorts showed differences in the number of new intracranial lesions or clinically apparent stroke between patients undergoing transapical as compared with transfemoral TAVI.

Prevention of NOAF and its sequelae should entail careful screening of patients at risk including assessment of a history of atrial fibrillation, echocardiographic evidence of enlarged atria, diastolic dysfunction, and presence of thrombi in the left atrium or atrial appendage. Procedural considerations include the avoidance of triggers of NOAF by minimizing myocardial injury, careful maintenance of electrolyte balance, and aggressive treatment of volume overload. Finally, pharmacological measures such as β-blockers (in the absence of atrioventricular conduction disturbances), amiodarone, angiotensin converting enzyme inhibitors, and angiotensin II receptor antagonists may be considered in patients at increased risk for atrial fibrillation. If NOAF is encountered after TAVI, patients require therapeutic anticoagulation, and restoration of sinus rhythm by pharmacological or electric conversion has been shown successful in the vast majority of patients.

Late Risk of CVE

Chronic atrial fibrillation has emerged as 1 of the principal predictors of late and cumulative CVE after TAVI. Peripheral vascular and previous cerebrovascular disease, as markers of global atherosclerotic burden, were identified as additional independent predictors for the occurrence of late CVE. The frequency and predictors of late CVE point to the spontaneous risk of stroke among elderly patients undergoing TAVI rather than to a risk related to the implanted prosthesis (Figure). The prevalence of stroke is age-dependent, with rates as high as 15% among people ≥80 years of age, and several risk factors, including female sex, arterial hypertension, diabetes mellitus, left ventricular hypertrophy, and smoking, contribute to the spontaneous risk of CVE. Aggressive risk factor modification, including treatment of lipid abnormalities and arterial hypertension, are important treatment goals. In addition, the appropriate antiplatelet and antithrombotic treatment after TAVI remains yet to be defined, requiring a careful balance between prevention of ischemic and bleeding events. Among patients with atrial fibrillation, anticoagulation by means of vitamin K antagonists or novel oral anticoagulants should be implemented, while exclusion of the left atrial appendage by means of percutaneous techniques may be considered in patients at increased risk for bleeding.

CVEs after TAVI adversely impact prognosis, and major stroke in the present study was associated with early and late mortality. However, outcomes may be improved by rapid diagnosis and timely installment of therapy. As a result of the minimally invasive nature of the procedure, TAVI can be performed under light sedation without general anesthesia, which facilitates early recognition of neurological deficits, and frequent neurological check-ups should be extended during postprocedural care. Stroke, particularly during the periprocedural period after TAVI, is amenable to treatment, and dedicated stroke teams can provide immediate access to brain imaging and interventional stroke treatment including intra-arterial thrombolysis or catheter-based recanalization and thrombus extraction, which may favorably impact on prognosis.

The work of Nombela-Franco and colleagues is an important contribution to our understanding of the pathogenesis of stroke after TAVI and will give rise to multiple hypotheses stimulating research in preventive strategies. Although stroke will always remain a nuisance in cardiovascular interventions, careful attention to technical details during TAVI as well as optimal medical treatment after the intervention will help to mitigate this adverse event.

Disclosures

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References


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