10-1-2021

Neurologic Complications in Transcatheter Aortic Valve Replacement

Abel Ignatius
Henry Ford Health, aignati2@hfhs.org

Marvin H. Eng
Henry Ford Health, meng1@hfhs.org

Tiberio M. Frisoli
Henry Ford Health, TFRISOL1@hfhs.org

Recommended Citation
Ignatius A, Eng MH, and Frisoli TM. Neurologic Complications in Transcatheter Aortic Valve Replacement. Interv Cardiol Clin 2021; 10(4):519-529.

Neurologic Complications in Transcatheter Aortic Valve Replacement

Abel Ignatius, MD[a], Marvin H. Eng, MD[a], Tiberio M. Frisoli, MD[b,c,*]

KEYWORDS

• Stroke • TAVR • Cerebral embolic protection • Atrial fibrillation

KEY POINTS

- Stroke remains a source of significant mortality, morbidity, and disability in the transcatheter aortic valve replacement (TAVR) population.
- Acute periprocedural and remote strokes have differing mechanisms, hence mitigation strategies.
- Although the use of cerebral embolic protection devices did not meet statistical significance for preventing stroke, larger analyses suggest they have value in preventing stroke.
- Post-TAVR stroke prevention is controversial and limited by the bleeding profile of patients as routine use of Factor Xa inhibitors and even dual antiplatelet therapy were a source of significant morbidity in prospective studies.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has become the most commonly performed treatment for symptomatic severe aortic stenosis (AS) in patients across all surgical risk profiles.[1] TAVR provides a life-saving and lifestyle-improving treatment for patients across all surgical risk profiles.[2–5] Advancements in technology and operator experience have resulted in diminishing rates of mortality, paravalvular aortic insufficiency, postprocedure pacemaker implantation, and vascular complications.[6]

However, despite those advancements, the rate of postprocedural stroke has remained relatively stable over time, with multiple studies demonstrating a stroke rate in the 2% to 3% range at 30 days post-TAVR in procedures performed between 2007 and 2018.[7–10] These TAVR stroke rates are lower than the comparator surgical aortic valve replacement.[2,11]

Stroke is one of the most feared, debilitating, and costly complications of TAVR. Further reducing stroke remains a central objective in the treatment of aortic valve stenosis. In later discussion, the authors synthesize the state-of-the-art and future of post-TAVR stroke and its prevention.

DEFINITIONS AND DISTINCTIONS

Standardized criteria for the definition of stroke endpoints for TAVR clinical trials have been published by the Valve Academic Research Consortium. Diagnostic criteria involve "rapid onset of a focal or global neurological deficit with at least 1 of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphagia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke."[6] In addition, there should be no readily identifiable nonstroke cause for the

[a] Center for Structural Heart Disease, Henry Ford Hospital, 2799 W Grand Boulevard, Detroit, MI 48202, USA; [b] Interventional Structural Cardiology, Center for Structural Heart Disease, Heart and Vascular Institute, Henry Ford Hospital, 2799 W Grand Boulevard, Detroit, MI 48202, USA; [c] Henry Ford Allegiance Hospital, 205 N East Avenue, Jackson, MI 49201, USA

* Corresponding author. Center for Structural Heart Disease, Henry Ford Hospital, 2799 W Grand Boulevard, Detroit, MI 48202.

E-mail address: tfrisol1@hfhs.org

Intervent Cardiol Clin 10 (2021) 519–529
https://doi.org/10.1016/j.iccl.2021.06.006

clinical presentation. Minor stroke is characterized by a modified Rankin score less than 2, whereas major stroke is characterized by a score $\geq$2.

Although the definition of stroke is relatively clear, how stroke has been defined and studied in TAVR is quite more complex.

True Incidence of Stroke Depends on the Definition and Adjudication

Different TAVR trials have adjudicated the stroke endpoint differently: some as disabling, others inclusive of those detected after careful examination, often by a neurologist, of subtle signs and symptoms and that may yield no lifestyle-limiting disabilities, and others detected with imaging, such as MRI, sometimes in asymptomatic patients.

Analysis of the transcatheter valve therapy (TVT) registry of about 100,000 TAVR procedures through the middle of 2017 shows stable stroke rates (TVT registry represents site-reported stroke rates) despite improvements in operator experience and device technology, of about 2% to 2.5%.[9] In comparison, trials (ie, SENTINEL, DEFLECT III) whereby stroke is adjudicated based on careful neurologic assessment (eg, National Institutes of Health Stroke Scale before and after TAVR), the rates are in the range of 9% to 15%; in trials for which new brain MRI lesions are a principal endpoint (ie, MISTRAL-C, CLEAN TAVI, SENTINEL), the rates are much higher.[10,12–14] Stroke rates in contemporary TAVR trials are shown in Fig. 1.

Importantly, nondisabling strokes should not necessarily be considered benign or truly asymptomatic, as these may be associated with steeper cognitive decline over time, an issue that is of particular importance for the large and growing number of younger low-risk patients that are undergoing TAVR.[14]

Relationship of Stroke to the Transcatheter Aortic Valve Replacement Procedure Itself

Some strokes occur in the periprocedural period, whereas other strokes occur remotely from the procedure. It is critically important to make these distinctions, as they have implications for mitigating the risk of these events. An intraprocedural stroke has a different pathophysiological mechanism, incidence, and potential prevention strategy than a stroke remote from the TAVR.

TIMING, MECHANISM, AND PREDICTORS OF STROKE IN TRANSCATHETER AORTIC VALVE REPLACEMENT PATIENTS

Timing

Post-TAVR strokes have been classified as acute if occurring withing 24 hours, subacute if occurring from 1 day to 30 days post-TAVR, and late if occurring after 30 days. Acute strokes occurring during or shortly after TAVR represent most post-TAVR strokes. In cohort B of the landmark PARTNER trial, nearly two-thirds of the strokes related to TAVR at 1 year occurred within 30 days post-TAVR. In PARTNER, 85% of the 30-day strokes occurred within the first week, with the peak rate by day 2.[15] Several other studies have shown that stroke incidence following TAVR has a peak in the immediate period after the procedure (24–48 hours), with some studies reporting half of the total events occurring within 1 month.[16,17] Among 3191

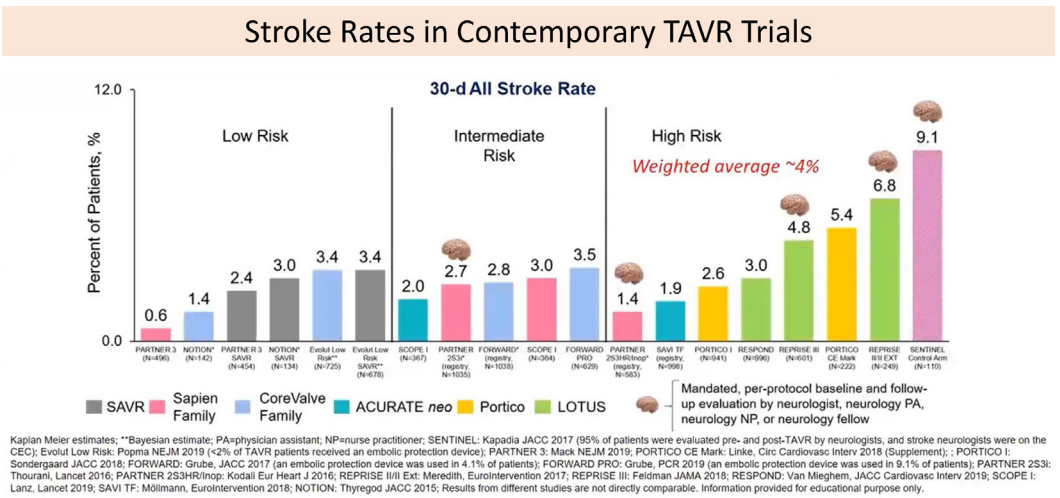

Fig. 1. Stroke rates vary across various contemporary TAVR trials, in part related to the definition of stroke used in the trial protocol. *, refers to Kaplan Meier estimates.

patients from the FRANCE-2 registry, strokes were reported in 4%, with 48.5% of these events occurring within the first 48 hours.[17]

Mechanism

Acute strokes are thought to be due to embolism of thrombus or fibrocalcific debris from the valve site or because of atherothrombotic emboli originating from ulcerative plaques in the aortic arch or great cerebral vessels. Such particles can be dislodged during wire/catheter/device manipulation across the aortic arch, during attempts to traverse the aortic annulus with wire and device, during balloon valvuloplasty, or valve deployment. Other potential causes of stroke caused by TAVR include hypotension associated with rapid ventricular pacing or hemodynamic instability during the procedure, especially in someone with preexisting cerebrovascular disease.[6] Less than 5% of acute strokes after TAVR are reported as hemorrhagic.[18]

Stroke that occurs after many days to weeks or months after TAVR is presumably less related to the TAVR procedure and more so to the patient's underlying stroke risk factors. Many patients who have AS also have other comorbidities that predispose them to ischemic stroke, such as advanced age, hypertension, diabetes, atherosclerotic and calcific arterial disease of the aorta and cerebral vessels, and atrial fibrillation.

Predictors/Risk Factors

It is important to establish reliable predictors of stroke after TAVR so that periprocedural and postprocedural care can be tailored on an individual basis. There are patient risk factors and procedural risk factors. Table 1 summarizes some of the reported risk factors, with more detailed discussion later.

In a meta-analysis, female sex and underlying chronic kidney disease (CKD) were baseline characteristics that were associated with higher risk of stroke post-TAVR.[19] Female sex is associated with smaller aortic annuli and left ventricular outflow tract dimensions, and therefore, higher mechanical interaction between the native and aortic valve prosthesis. This finding is supported by the PARTNER trial, which demonstrated a higher rate of strokes (6.3% vs 2.8%) in patients with smaller aortic annuli and valve area.[15] CKD was also identified as a patient-related risk factor (relative risk [RR]: 1.29; $P = .03$), thought to be related to its inherent role in atherogenesis and/or the absence of established guidelines regarding anticoagulation therapy for stroke prevention in these patients.[19]

Table 1
Reported stroke risk factors in TAVR, categorized as patient- or procedure-related

Patient-Related	Procedure-Related
Female Gender	Valve dislodgement/ embolization
Older Age	Non-transfemoral TAVR Access
Atrial fibrillation	
Chronic kidney disease	
Smaller aortic annular area	
Degree of aortic valve calcification	
Bicuspid aortic valve	
Carotid artery disease	
Peripheral arterial disease	
Prior Stroke	

There was a nonstatistically significant signal that balloon postdilation was associated with higher risk of stroke. The strongest procedure-related predictor of stroke occurring 1 to 30 days post-TAVR was new-onset atrial fibrillation (RR: 1.85; $P = .005$).

In a real-world sample of commercial TAVRs performed in 2017, for which the ischemic stroke rate was 2.4%, factors independently associated with post-TAVR ischemic stroke included a history of carotid artery disease, peripheral artery disease, atrial fibrillation or flutter, older age, bicuspid aortic valve, and female sex.[20,21]

Atrial fibrillation has been consistently reported in studies investigating risk factors for postprocedural stroke. New-onset atrial fibrillation has been identified as an independent predictor for 30-day stroke (odds ratio [OR] 2.27, $P = .018$) and chronic atrial fibrillation as a major contributor to late (>30 days) strokes occurring in 3.3% of patients after a median follow-up of 12 months.[16]

Other potential risk factors for stroke after TAVR include implantation of 2 valves, prior stroke, coronary artery disease, valve dislodgement/embolization, degree of aortic valve calcification, and small index aortic valve area (cutoff value of 0.4 cm^2/m^2).[16,17,22,23]

Presently, the balloon-expandable Sapien valve (Edwards Life Sciences, Inc, Irvine, CA, USA) and the self-expandable CoreValve Evolut system (Medtronic, Inc, Minneapolis, MN, USA)

are the 2 devices primarily used for the TAVR procedure, with no strong evidence to suggest statistically significant differences in stroke rates between valve types.[17,19,24] A meta-analysis of transfemoral versus nontransfemoral (in this analysis, transcarotid and transsubclavian approaches) TAVR revealed an increased risk of stroke for the nontransfemoral route (OR 1.53; confidence interval 1.05–2.22) when adjusting for confounding factors.[21] It is possible that the risk adjustment does not fully account for the higher stroke predisposition of patients that require nontransfemoral TAVR. These nontransfemoral arterial alternative accesses were not associated with an increased risk of adjusted 30-day death, bleeding, or vascular complication. Current data suggest no difference in stroke rate with regard to transfemoral versus transapical approach.[19,24,25,26]

IMPLICATIONS OF STROKE TO THE PATIENT AND HEALTH CARE SYSTEM

Stroke has been shown to increase mortality in TAVR patients, with a 30-day mortality of 16.7% compared with 3.7% in patients without stroke.[8] One meta-analysis revealed periprocedural stroke associated with a more than 6 times greater risk of 30-day mortality.[27,28]

Silent or asymptomatic infarctions, as assessed by brain MRI, have been associated with steeper decline in cognitive function, including impairments in memory performance, psychomotor speed, and global cognitive function resulting in increased risk of dementia and depression.[29,30] Furthermore, stroke patients who survive to hospital discharge are significantly less likely to go home following TAVR (36.1% vs 78.9% in those without strokes, $P<.001$).[8]

In an analysis of younger patients (age <65), stroke was associated with significant financial strains in 33%, an inability to return to work in 56%, and a decrease in participation in social activities in 79%.[31] After a stroke, the additional annual change in disability increases at a faster rate than in those age-matched who did not have stroke.[32] Given the steep growth in TAVR volume, the impact is further amplified with wide-reaching consequences.

The financial burden of TAVR-related stroke also cannot be understated, with an estimated incremental cost of approximately $16,272 per patient and an added length of stay of about 2.5 days for major stroke.[33] In another analysis, stroke is associated with a 33% increase in average TAVR hospitalization cost (+$19,658), a 6-day average increase in length of index hospitalization stay, and a 121% increase in nursing home and intermediate care facility discharge.[34]

STROKE PREVENTION

As discussed, post-TAVR strokes can be acute and often related to the procedure itself, or subacute-late and more related to the inherent stroke-predisposing milieu of the patient and the transcatheter heart valve.

Efforts to reduce rates of acute stroke have centered on meticulous intraprocedural technique, improved device technology, and intraprocedural cerebral embolic prevention device use. Prevention of subacute and late stroke revolves around pharmacologic antiplatelet or anticoagulant therapy as it relates to the transcatheter prosthesis and to the patient's inherent stroke risk factors, such as atrial fibrillation and atherosclerotic vascular disease. Device therapy with, for example, left atrial appendage closure is also under investigation for the prevention of subacute and late stroke after TAVR.

Intraprocedural Device Therapy

Cerebral embolic protection devices (CEPDs) were developed to reduce the risk of strokes and silent emboli by preventing procedural debris from reaching cerebral vasculature. Currently, the SENTINEL Cerebral Protection System (Boston Scientific, Natick, MA, USA) is the only Food and Drug Administration (FDA)-approved device available for use in the United States. It consists of 2 filters within a single 6F delivery catheter percutaneously placed from the right radial or brachial artery over a 0.014-in guidewire.[14] The filters are positioned in the brachiocephalic and the left common carotid arteries before TAVR (Fig. 2), covering about 90% of cerebral vascular circulation. The filters are then withdrawn into the catheter and removed after TAVR. The Sentinel device has been shown to capture debris, including thrombus, valve tissue, calcified debris, artery wall, myocardium, and foreign material, in 99% of TAVR patients, which weighed heavily in the decision by the FDA to approve the device. Fig. 3 shows debris as captured during TAVR, and Fig. 4 shows fluoroscopic examples of in vivo Sentinel deployment during TAVR and illustrates some techniques used to overcome more challenging anatomies.

The SENTINEL trial randomized 363 patients undergoing TAVR at 17 centers in the United States and 2 centers in Germany to CEPD versus no protection. The device, although

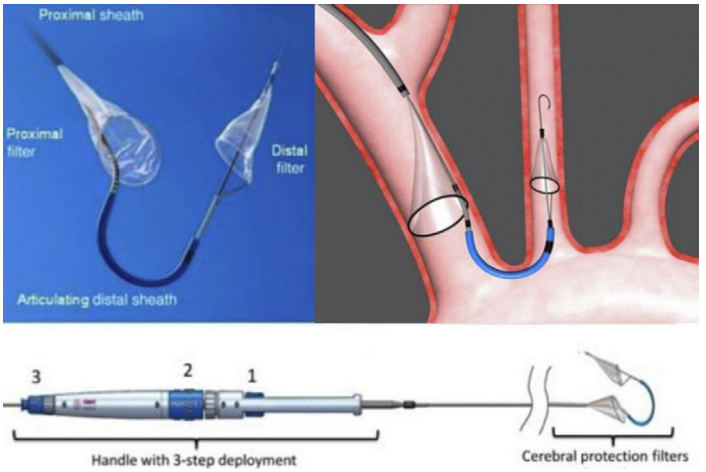

Fig. 2. The Sentinel cerebral embolic protection filter device.

manipulated and positioned in the great cerebral vessels, was shown to be safe: Sentinel-related complications were 0.4%. The rate of major adverse cardiac and cerebrovascular events at 30 days was 7.3% and not statistically different than that of the control group (9.9%).[14] Strokes at 30 days were 9.1% in control subjects and 5.6% in patients with devices, also statistically not significant (P = .25), in what was an underpowered study for this endpoint. Despite not achieving statistical significance, the 72-hour data demonstrate 63% relative risk reduction and 5.2% absolute risk reduction in stroke.

The primary efficacy endpoint for this trial, importantly, not stroke but rather new lesion volume on diffusion-weighted MRI in protected territories, was lower in the device arm (178.0 mm^3) as compared with the control arm (102.8 mm^3) but did not meet statistical significance

Fig. 3. Examples of debris retrieved from the Sentinel device during TAVR. (*Courtesy of* Tiberio Frisoli MD.)

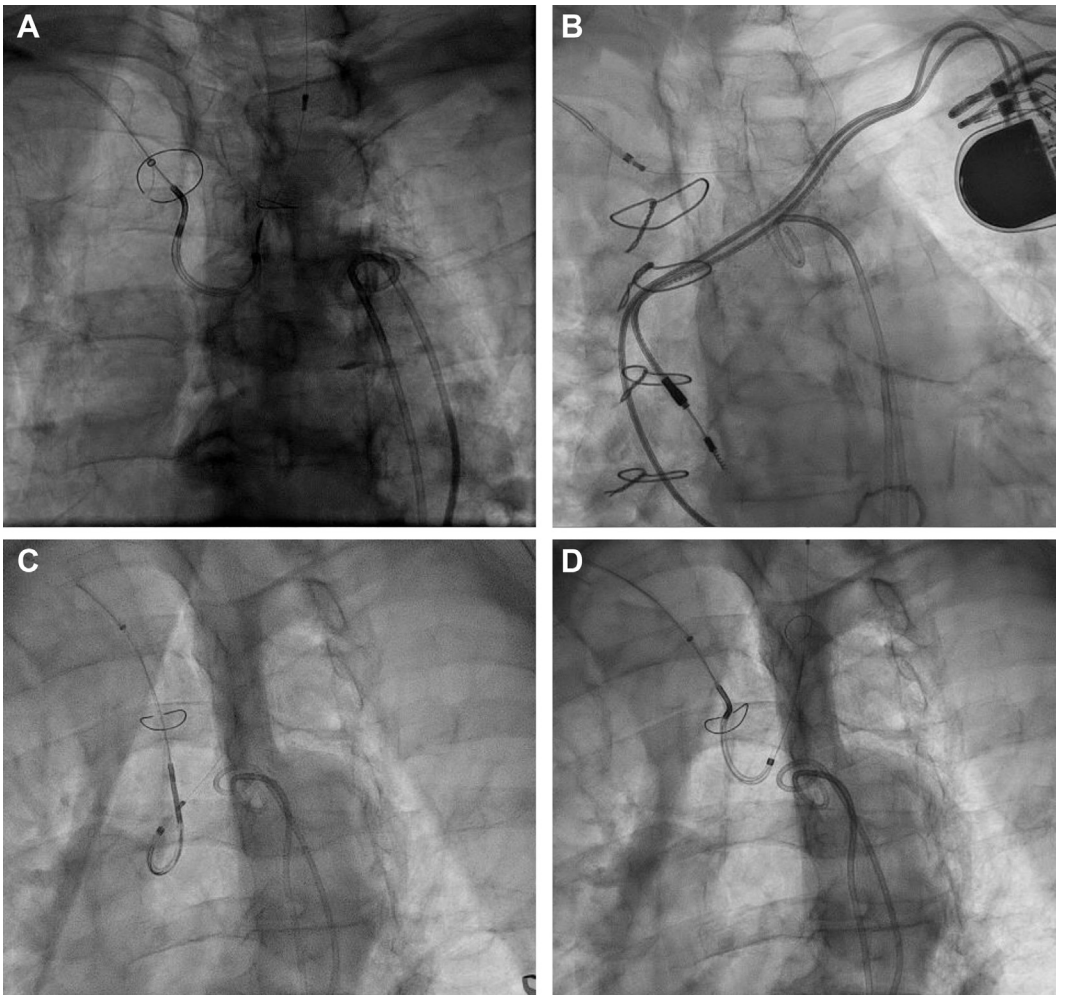

Fig. 4. Fluoroscopic images during TAVR that serve as examples of Sentinel deployment. (*A*) Typical appearance of Sentinel after deployment, with distal filter in left common carotid artery and proximal filter in brachiocephalic artery. (*B*) Example of how, in a bovine arch anatomy, the guidewire can be passed directly into the left carotid rather than into the ascending aorta, for delivery of the Sentinel. (*C*) Example of how, in bovine arch anatomy, when one is unable or prefers not to pass the guidewire directly into the left common carotid artery, the device can be flexed and turned around on itself in the distal ascending aorta to become coaxial with the left common carotid to allow wiring. (*D*) After the operator does what is shown in panel (C), the rotation that was applied to the device can be undone as it is pulled up into the left common carotid, after which the distal filter is pushed forward.

($P = .33$). Thus, the SENTINEL trial was a negative trial. However, after adjusting for valve type and baseline T2/FLAIR lesion volume in a post hoc analysis, there were significant differences in new lesion volumes favoring embolic protection. There was also a correlation between lesion volume and neurocognitive decline at 30 days.

In the MISTRAL-C randomized controlled study, the Sentinel device had fewer new lesions and a smaller total lesion volume (95 mm^3 vs 197 mm^3). Neurocognitive deterioration was present in 4% of Sentinel CPS patients versus 27% without embolic protection.[10] In the randomized controlled CLEAN-TAVI trial, the number of new lesions was lower in the filter group compared with controls (4.00 vs 10.00), as was the new lesion volume (242 mm^3 vs 527 mm^3).[12] Meta-analysis data from the SENTINEL, MISTRAL-C, and CLEAN-TAVI trials showed a statistically significant reduction ($P = .017$) in new brain lesions favoring Sentinel, ultimately leading to FDA approval. Of note, the Sentinel device does not provide complete cerebrovascular protection, as there is no filter in the left vertebral artery territory.

Real-world registry data have been favorable for the Sentinel device. Stroke rates (disabling and nondisabling) at 7 days after TAVR were reduced by 70% (1.4% vs 4.6%; $P = .03$) at the University of Ulm and by 78% (1.4% vs 6.3%; $P<.01$) at Cedars-Sinai.[35,36] When patients from the SENTINEL trial were combined with the CLEAN-TAVI and SENTINEL-Ulm studies in a patient level pooled analysis of 1306 patients with propensity score matching, all stroke was significantly lower (1.88% vs 5.44%; $P = .003$; relative risk reduction (RRR) 65%).[37] A recently published retrospective analysis of the Nationwide Inpatient Sample database from 2017, of 525 patients who underwent TAVR with CEPD and 1050 propensity score-matched patients who underwent TAVR without CEPD, revealed a lower ischemic stroke risk (1% vs 3.8%; $P = .003$) and a higher cost of index hospitalization ($47,783 vs $44,578; $P = .002$), without an increased risk of procedural complications.[20]

A major barrier to widespread Sentinel use has been cost, as the Centers for Medicare and Medicaid Services did not reimburse for its use. As of October 2018, an add-on payment went into effect for Sentinel use during TAVR. Maximum new technology add-on payment for a case involving Sentinel was $1400 for fiscal year 2019. Cost is still a commonly cited barrier for use of this device.

The TriGuard (Keystone) Embolic Deflection Device is another form of cerebral embolic protection for use during TAVR. It is a nitinol mesh filter positioned in the aortic arch across the right brachiocephalic, left common carotid, and left subclavian arteries and is designed to deflect emboli away from cerebral circulation during TAVR. The DEFLECT III trial randomized 85 subjects undergoing TAVR at 13 centers in Europe and Israel from February 2014 to 2015 to TriGuard protection versus no protection. Results from this prospective study showed that the device was safe to use, and patients who underwent TAVR with TriGuard protection had fewer ischemic brain lesions, fewer neurologic deficits, and improved cognitive function at discharge and at 30 days compared with controls.[13] However, results from the late-breaking REFLECT II trial reported at the Transcatheter Cardiovascular Therapeutics Connect 2020 virtual conference showed that the TriGuard 3 failed to demonstrate a statistically significant difference in in-hospital and 30-day stroke compared with controls.[38]

Only about 20% of all TAVR procedures in the United States is performed with cerebral embolic protection; in Germany over the past 3 years, only 3.8% of all TAVR cases were done with cerebral protection.[39]

Many who do not use cerebral embolic protection regularly argue: it is a device that has never been proven in a randomized trial to reduce stroke; it does not protect all cerebral vessels; cost is significant if not prohibitive.

Many who do use cerebral embolic protection regularly tend to argue: the SENTINEL study was underpowered; although it did not meet its primary endpoint, the findings from registries and meta-analyses such as those discussed above are compelling; for such a devastating complication as stroke, the use of a device that is proven safe and effective at least at catching debris simply makes too much sense to be dismissed. A common rhetorical question cited by proponents is: "If your mother were to undergo TAVR, would you want cerebral embolic protection for her?"

At this time, a paucity of prospective randomized data showing a clinical stroke benefit, coupled with a significant cost has led to a lack of universal adoption of cerebral embolic protection in TAVR. The multicenter PROTECTED-TAVR trial aims to address this controversial issue. It is an ongoing randomized controlled trial scheduled for completion in 2022; the primary endpoint is clinically adjudicated stroke at 72 hours or discharge.

Post–Transcatheter Aortic Valve Replacement Medical Therapy for the Mitigation of Stroke Risk

Subclinical leaflet thrombosis, defined as hypoattenuated leaflet thickening (HALT) as detected by high-resolution computed tomography (CT) has been investigated as a potential risk factor for post-TAVR stroke. The prevalence of HALT among TAVR patients in PARTNER 3 was 10% and 24% at 30 days and 1 year after TAVR, respectively; spontaneous resolution of 30-day HALT occurred in 54% of patients at 1 year.[40] Although the individual endpoint of stroke was not different between HALT and no HALT groups, the pooled rates of stroke, transient ischemic attack (TIA), and thromboembolic complications were higher in HALT than no HALT groups (8.6 vs 1.6%; RRR 5.3). An analysis of the RESOLVE and SAVORY registries revealed no statistically significant difference in stroke rates between those with (4.12 strokes per 100 person-years) or without (1.92 strokes per 100 person-years) CT-adjudicated reduced leaflet motion.[41] However, they did note that subclinical leaflet thrombosis was associated with increased rates of TIAs (4.18 TIAs per 100

person-years vs 0.60 TIAs per 100 person-years). An analysis of the OCEAN-TAVI registry with CT data out to 3 years after TAVR showed that early HALT was present in 45 patients (9.3%) at a median time of 3 days.[42] The investigators found that the presence of early leaflet thrombosis was not associated with in-hospital stroke. Furthermore, the rates of ischemic and hemorrhagic stroke were similar between patients with and without early leaflet thrombosis at a mean follow-up of 1.8 years post-TAVR (0% vs 0.6%, $P = .57$; 0% vs 0.7%, $P = .52$, respectively). Overall, the association between HALT and stroke is still unclear.

Atrial fibrillation is common in patients undergoing TAVR and represents a major risk factor for acute, subacute, and late post-TAVR stroke.[43,44] Reported incidences of stroke among atrial fibrillation patients after TAVR range from 3% to 12% in the first year after TAVR, with a quarter of the strokes occurring within the first 24 hours and half within 30 days.[45,46] Guidelines recommend vitamin K antagonist with or without antiplatelet therapy for 3 to 6 months after TAVR in patients with indication for anticoagulation, with the antiplatelet intended to prevent thromboembolism before valve endothelialization.

In the POPular TAVI trial, cohort B, which looked at patients with an already-established indication for long-term anticoagulation, the addition of 3 months of clopidogrel to oral anticoagulation (either vitamin K antagonist or direct-acting oral anticoagulant) increased bleeding (34.6% vs 21.7% for all bleeding; 16.7% vs 8.9% for major, life-threatening, or disabling bleeding) without reducing stroke (5.8% vs 5.1% for ischemic stroke).[47] The Kaplan-Meier curves for bleeding separate almost immediately after TAVR and continue to separate out to 90 days when clopidogrel was discontinued, with most of the bleeding occurring within 1 week of TAVR.

The GALILEO trial, involving patients without an established indication for oral anticoagulation after TAVR, showed that rivaroxaban 10 mg daily with aspirin was associated with more bleeding and more death or thromboembolic complications than aspirin with clopidogrel.[48] Another analysis found that for patients with hemorrhagic late strokes (>30 days postprocedure), the use of anticoagulation was more common than antiplatelet therapy (48.3% vs 27.2%).[49]

The aforementioned studies raise an important question: how do we adequately mitigate the potential of late strokes in patients who have undergone TAVR without putting them at increased risk for bleeding? The ongoing prospective WATCH-TAVR randomized controlled trial aims to address this dilemma by investigating the safety and effectiveness of left atrial appendage occlusion with the WATCHMAN device in prevention of stroke and bleeding in patients with atrial fibrillation undergoing TAVR. It is tentatively scheduled for completion in November 2022.

In patients *without* an indication for long-term anticoagulation, practice guidelines recommend clopidogrel in addition to aspirin for the first 3 to 6 months after TAVR, for the purpose of mitigating the stent-mediated risk of thromboembolization before the valve has endothelialized. This intensified dual antiplatelet regimen has been shown in several series to result in major or life-threatening bleeding in up to 15% of patients 1 year after TAVR.[2,3,11] TAVR patients are particularly prone to bleeding, as they tend to be older with comorbidities that predispose to bleeding, such as gastrointestinal angiodysplasia, and with postprocedure conditions, such as transient thrombocytopenia, that further augment this risk. Balancing stroke prevention related to the transcatheter prosthesis and the patient's inherent stroke risk factors, with the bleeding tendencies that many TAVR patients possess, is a prominent focus of research.

Prospective studies, such as the ARTE trial, showed a lower incidence of bleeding with aspirin than with aspirin plus clopidogrel at 3 months.[50] In cohort A of POPular, a comparison of aspirin with clopidogrel to aspirin alone, for 3 months after TAVR, revealed that bleeding was significantly higher (26.6% vs 15.1% for all bleeding; 10.8% vs 5.1% for major, life-threatening, or disabling bleeding), without a benefit in ischemic outcomes (5.4 vs 5.1% for ischemic stroke; 9.9 vs 9.7% for composite of cardiovascular death, ischemic stroke, or myocardial infarction), for the patients with a dual antiplatelet regimen.[51] The quality of these pieces of data may call for a revision of post-TAVR guideline recommendations.

SUMMARY

Stroke remains an issue for the TAVR procedure. TAVR-related strokes are devastating to patients and their families, and very costly for health care systems. With the growth of TAVR volumes and the expansion of TAVR indications to lower-risk, younger, and often less symptomatic patients, the mission to bring TAVR stroke rates down is even more important. The predictors of stroke

in TAVR are not yet well defined, although older age and female gender, carotid and peripheral arterial disease, bicuspid aortic valve anatomy, and atrial fibrillation are emerging as risk factors across studies; the detection and appropriate and prompt treatment of preexisting or newly diagnosed atrial fibrillation represent a central objective in the mitigation of stroke risk. For acute stroke, there is an evolving body of evidence suggesting cerebral embolic protection may mitigate the risk; more randomized controlled data are forthcoming. For subacute and late stroke, treating the intrinsic stroke-predisposing milieu of patient and transcatheter prosthesis requires careful individualized pharmacologic and nonpharmacologic therapy, balancing risk of stroke with that of bleeding.

CLINICS CARE POINTS

- When counseling patients on risks and benefits of TAVR, it is important to explain that TAVR has a proven excellent safety and efficacy profile, but that there is still a roughly 2% risk of clinically significant stroke.
- Patients should know that improving stroke rates is a priority among those performing and developing TAVR. Stroke prevention strategies currently being utilized and studied include devices placed during the TAVR procedure into or near the arteries that supply the brain, blood thinning medications, early diagnosis and treatment of atrial fibrillation, and further improved operator experience and TAVR device technology.

DISCLOSURE

Dr T.M. Frisoli is a physician proctor for Edwards Lifescience, Boston Scientific, and Medtronic.

REFERENCES

1. Carroll JD, Mack MJ, Vemulapalli S, et al. STS-ACC TVT registry of transcatheter aortic valve replacement. J Am Coll Cardiol 2020;76:2492–516.
2. Mack MJ, Leon MB, Thourani VH, et al, PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380(18):1695–705.
3. Leon MB, Smith CR, Mack MJ, et al, PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374(17):1609–20.
4. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. The Lancet 2015;385:2477–84.
5. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.
6. Holmes DR Jr, Mack MJ, Kaul S, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiol 2012;59(13):1200–54.
7. Vlastra W, Jimenez-Quevedo P, Tchétché D, et al. Predictors, incidence, and outcomes of patients undergoing transfemoral transcatheter aortic valve implantation complicated by stroke. Circ Cardiovasc Interv 2019;12(3):e007546.
8. Huded CP, Tuzcu EM, Krishnaswamy A, et al. Association between transcatheter aortic valve replacement and early postprocedural stroke. JAMA 2019;321(23):2306–15.
9. Carroll JD, Vemulapalli S, Dai D, et al. Procedural experience for transcatheter aortic valve replacement and relation to outcomes: the STS/ACC TVT registry. J Am Coll Cardiol 2017;70(1):29–41.
10. Van Mieghem NM, van Gils L, Ahmad H, et al. Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial. EuroIntervention 2016;12(4):499–507.
11. Popma JJ, Deeb GM, Yakubov SJ, et al, Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med 2019;380(18):1706–15.
12. Haussig S, Mangner N, Dwyer MG, et al. Effect of a cerebral protection device on brain lesions following transcatheter aortic valve implantation in patients with severe aortic stenosis: the CLEAN-TAVI randomized clinical trial. JAMA 2016;316(6):592–601.
13. Lansky AJ, Schofer J, Tchetche D, et al. A prospective randomized evaluation of the TriGuard™ HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial. Eur Heart J 2015;36(31):2070–8.
14. Kapadia SR, Kodali S, Makkar R, et al, SENTINEL Trial Investigators. Protection against cerebral embolism during transcatheter aortic valve replacement. J Am Coll Cardiol 2017;69(4):367–77.
15. Kapadia S, Agarwal S, Miller DC, et al. Insights into timing, risk factors, and outcomes of stroke and transient ischemic attack after transcatheter aortic valve replacement in the PARTNER trial (Placement

of Aortic Transcatheter Valves). Circ Cardiovasc Interv 2016;9(9):e002981.
16. Nombela-Franco L, Webb JG, de Jaegere PP, et al. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. Circulation 2012;126(25):3041–53.
17. Tchetche D, Farah B, Misuraca L, et al. Cerebrovascular events post-transcatheter aortic valve replacement in a large cohort of patients: a FRANCE-2 registry substudy. JACC Cardiovasc Interv 2014;7(10):1138–45.
18. Miller DC, Blackstone EH, Mack MJ, et al, PARTNER Trial Investigators and Patients; PARTNER Stroke Substudy Writing Group and Executive Committee. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. J Thorac Cardiovasc Surg 2012;143(4):832–43.e13.
19. Auffret V, Regueiro A, Del Trigo M, et al. Predictors of early cerebrovascular events in patients with aortic stenosis undergoing transcatheter aortic valve replacement. J Am Coll Cardiol 2016;68(7):673–84.
20. Megaly M, Sorajja P, Cavalcante J, et al. Ischemic stroke with cerebral protection system during transcatheter aortic valve replacement. JACC Cardiovasc Interv 2020;13(18):2149–55.
21. Faroux L, Junquera L, Mohammadi S, et al. Femoral vs nonfemoral subclavian/carotid arterial access route for transcatheter aortic valve replacement: a systematic review and meta-analysis. J Am Heart Assoc 2020;9:e017460.
22. Takagi K, Naganuma T, Tada N, et al. The predictors of peri-procedural and sub-acute cerebrovascular events following TAVR from OCEAN-TAVI registry. Cardiovasc Revasc Med 2020;21(6):732–8.
23. Doerner J, Kupczyk PA, Wilsing M, et al. Cerebral white matter lesion burden is associated with the degree of aortic valve calcification and predicts periprocedural cerebrovascular events in patients undergoing transcatheter aortic valve implantation (TAVI). Catheter Cardiovasc Interv 2018;91(4):774–82.
24. Athappan G, Gajulapalli RD, Sengodan P, et al. Influence of transcatheter aortic valve replacement strategy and valve design on stroke after transcatheter aortic valve replacement: a meta-analysis and systematic review of literature. J Am Coll Cardiol 2014;63(20):2101–10.
25. Thomas M, Schymik G, Walther T, et al. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2010;122(1):62–9.
26. Rodés-Cabau J, Dumont E, Boone RH, et al. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. J Am Coll Cardiol 2011;57(1):18–28.
27. Muralidharan A, Thiagarajan K, Van Ham R, et al. Meta-analysis of perioperative stroke and mortality in transcatheter aortic valve implantation. Am J Cardiol 2016;118(7):1031–45.
28. Vlastra W, Chandrasekhar J, Vendrik J, et al. Transfemoral TAVR in nonagenarians: from the CENTER collaboration. JACC Cardiovasc Interv 2019;12(10):911–20.
29. Hassell ME, Nijveldt R, Roos YB, et al. Silent cerebral infarcts associated with cardiac disease and procedures. Nat Rev Cardiol 2013;10(12):696–706.
30. Vermeer SE, Prins ND, den Heijer T, et al. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348(13):1215–22.
31. Daniel K, Wolfe CD, Busch MA, et al. What are the social consequences of stroke for working-aged adults? A systematic review. Stroke 2009;40(6):e431–40.
32. Dhamoon MS, Longstreth WT, Bartz TM, et al. Disability trajectories before and after stroke and myocardial infarction. JAMA Neurol 2017;74(12):1439–45.
33. Arnold SV, Lei Y, Reynolds MR, et al. Costs of periprocedural complications in patients treated with transcatheter aortic valve replacement: results from the Placement of Aortic Transcatheter Valve trial. Circ Cardiovasc Interv 2014;7(6):829–36.
34. Alqahtani F, Sengupta PP, Badhwar V, et al. Clinical and economic burden of acute ischemic stroke following transcatheter aortic valve replacement. Struct Heart 2018;3(1):72–3.
35. Seeger J, Gonska B, Otto M, et al. Cerebral embolic protection during transcatheter aortic valve replacement significantly reduces death and stroke compared with unprotected procedures. JACC Cardiovasc Interv 2017;10(22):2297–303.
36. Makkar RR, Thourani VH, Mack MJ, et al, PARTNER 2 Investigators. Five-year outcomes of transcatheter or surgical aortic-valve replacement. N Engl J Med 2020;382(9):799–809.
37. Seeger J, Kapadia SR, Kodali S, et al. Rate of periprocedural stroke observed with cerebral embolic protection during transcatheter aortic valve replacement: a patient-level propensity-matched analysis. Eur Heart J 2019;40(17):1334–40.
38. Presented by Dr. Jeffrey W. Moses at the Transcatheter Cardiovascular Therapeutics Virtual Meeting (TCT Connect), October 14-18, 2020.
39. Stachon P, Kaier K, Heidt T, et al. The use and outcomes of cerebral protection devices for patients undergoing transfemoral transcatheter aortic valve replacement in clinical practice. JACC Cardiovasc Interv 2021;14(2):161–8.

40. Makkar RR, Blanke P, Leipsic J, et al. Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves: PARTNER 3 cardiac computed tomography substudy. J Am Coll Cardiol 2020; 75(24):3003–15.
41. Chakravarty T, Søndergaard L, Friedman J, et al, RESOLVE, SAVORY Investigators. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet 2017;389(10087):2383–92.
42. Yanagisawa R, Tanaka M, Yashima F, et al. Early and late leaflet thrombosis after transcatheter aortic valve replacement. Circ Cardiovasc Interv 2019;12(2):e007349.
43. Kirchhof P, Benussi S, Kotecha D, et al, ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37(38):2893–962.
44. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. Circulation 2019;140(2):e125–51.
45. Abdul-Jawad Altisent O, Durand E, Muñoz-García AJ, et al. Warfarin and antiplatelet therapy versus warfarin alone for treating patients with atrial fibrillation undergoing transcatheter aortic valve replacement. JACC Cardiovasc Interv 2016;9(16): 1706–17.
46. Jochheim D, Zadrozny M, Ricard I, et al. Predictors of cerebrovascular events at mid-term after transcatheter aortic valve implantation - results from EVERY-TAVI registry. Int J Cardiol 2017;244: 106–11.
47. Nijenhuis VJ, Brouwer J, Delewi R, et al. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. N Engl J Med 2020;382(18):1696–707.
48. Dangas GD, Tijssen JGP, Wöhrle J, et al, GALILEO Investigators. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. N Engl J Med 2020;382(2):120–9.
49. Muntané-Carol G, Urena M, Munoz-Garcia A, et al. Late cerebrovascular events following transcatheter aortic valve replacement. JACC Cardiovasc Interv 2020;13(7):872–81.
50. Rodés-Cabau J, Masson JB, Welsh RC, et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve: the ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) randomized clinical trial. JACC Cardiovasc Interv 2017;10(13):1357–65.
51. Brouwer J, Nijenhuis VJ, Delewi R, et al. Aspirin with or without clopidogrel after transcatheter aortic-valve implantation. N Engl J Med 2020; 383(15):1447–57.