Characterization of Neurological Injury in Transcatheter Aortic Valve Implantation

How Clear Is the Picture?

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The application of transcatheter aortic valve implanta-
tion (TAVI) to high-surgical-risk and inoperable patients with severe aortic stenosis (AS) is gaining widespread acceptance with a burgeoning supportive evidence base. The benefits associated with the application of this technique, however, are mitigated by the occurrence of major, disabling stroke with associated increased mortality and early-reduced quality of life. Despite this, the risk/benefit ratio has been considered acceptable in appropriately selected patients given the outcomes of alternate management options in these high-risk and inoperable populations.

The incidence of cerebrovascular events (CVEs) subsequent to TAVI exceeds that after any other cardiac intervention or valve surgery, most notably in the acute periprocedural period, diminishing over the subsequent 2 months. This elevated early risk reflects the increased incidence of ischemic stroke thought secondary to particulate emboli dissloed by the procedure itself or as a result of thromboembolism.

In fact, cerebral embolism is a universal finding associated with these procedures. Most events, however, are subclinical or silent, with clinically apparent CVEs representing but the tip-of-the-iceberg. As a result of the difficulty ascertaining these subclinical events, the true association between TAVI and neurological injury is unknown and the harm potentially underestimated.

This article aims to comprehensively review neurological injury in TAVI, with an emphasis on cerebrovascular disease. Evidence and current concepts regarding pathophysiological mechanisms, risk factors, and prognostic implications will be discussed and risk reduction strategies explored.

Neurological Impairment

CVEs post-TAVI are classified based on clinical severity as illustrated in Figure 1. Incomplete reporting and variable definitions of clinically apparent events and disregard of subclinical events have limited the true evaluation of CVEs associated with TAVI. Consequently, in 2011 the Valve Academic Research Consortium published a consensus report on standardized end point definitions, including stroke, which were expanded and refined in 2012. These criteria, as well as the important omissions of subclinical CVEs are listed in the Table.

Clinically Apparent CVEs

Overall Incidence

Thirty-day stroke incidences reported in the major landmark TAVI studies and registries published to date are represented in Figure 2. Eggerbrecht et al encompassed much of this within a meta-analysis of all TAVI studies published between January 2004 and November 2011. Here, the overall stroke rate was reported as 1.5% (±1.4%), 3.3% (±1.8%), 4.3% (±1.6%), and 5.2% (±3.4%) at 24 hours, 1 month, 6 months, and 1 year after the index procedure, respectively.

A reduction in the attendant stroke incidence was anticipated as the TAVI procedure evolved, devices improved, patient selection processes became more refined, and stroke prevention strategies optimized. Much of the current literature reflects patients recruited, and data collected, from as far back as 2005, and has been criticized for not reflecting modern TAVI practices.

In light of this, recent notable additions to the evidence base have included the second French national transcatheter aortic valve implantation (FRANCE II), the second Placement of Aortic Transcatheter Valves (PARTNER II), the Australian, in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (the European Sentinel, and the
Advance studies/registries. Advance is a large prospective study with recent recruitment (between 2010 and 2011) of patients undergoing TAVI with the Medtronic Corevalve. This study demonstrated an acute stroke rate of 1.8% and a 30-day stroke rate of 2.9%. Similarly, the Sentinel registry, which is the largest to date containing data on 4571 patients who underwent TAVI between January 2011 and June 2012, revealed a procedural/in-hospital stroke rate of 1.8%, although the 30-day stroke rate was not reported. Both of these studies represent a favorable trend toward improvement relative to earlier studies and registries.

Arguing against a reduction in stroke rates with the evolution of TAVI devices, the FRANCE II and Australian registries have identified rates highly consistent with the findings of the above-mentioned meta-analysis, demonstrating 30-day stroke rates of 3.4% and 3.6%, respectively. Direct comparison between the experience with the traditional Edwards SAPIEN valve in the SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry and the contemporary Edwards SAPIEN-XT in the SOURCE-XT registry also indicates little real improvement in the incidence of neurological events in contemporary practice. Likewise, the inoperable cohort of the eagerly anticipated PARTNER II study recently reported a nonsignificant difference between the SAPIEN and the SAPIEN-XT valves with 30-day disabling (major) stroke incidences of 3.0% and 3.2% (P=0.85), respectively, and of 4.6% and 4.5%, respectively, at 1 year. Thus, it remains unclear whether the results of the Sentinel and Advance registries reflect the realization of the anticipated improvement in stroke rate, or are statistical outliers.

The body of data pertaining to stroke risk with TAVI must be interpreted in the context of the underlying risk in this population, achieved through comparison of risk-matched populations undergoing alternate management options for severe AS. Most notable among these studies is the PARTNER study, which initially identified and sparked interest in the increased risk of stroke associated with TAVI. Cohort B of the PARTNER study randomly assigned patients who were ineligible for surgery but suitable for TAVI to receive either TAVI or medical management and reported a 30-day neurological

Table. Standardized Definitions for Perioperative Cerebrovascular Events

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Definition</th>
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<tbody>
<tr>
<td>A. Stroke</td>
<td>Duration of a focal or global neurological deficit ≥ 24 hours; OR &lt;24 hours if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death.</td>
</tr>
<tr>
<td>Etiology</td>
<td>i. Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue. ii. Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. iii. Undetermined: insufficient information to allow categorization as ischemic or hemorrhagic.</td>
</tr>
<tr>
<td>Severity</td>
<td>i. Disabling stroke (major): an mRS of ≥2 at 90 days and an increase in at least 1 mRS category from an individual’s prestroke baseline. ii. Nondisabling stroke (minor): an mRS score of &lt;2 at 90 days or one that does not result in an increase in at least 1 mRS category from an individual’s prestroke baseline.</td>
</tr>
<tr>
<td>B. Transient ischemic attack</td>
<td>Duration of a focal or global neurological deficit &lt;24 hours, any available neuroimaging does not demonstrate a new hemorrhage or infarct. Qualifiers for (A) and (B): • Exclusion of nonstroke causes for clinical presentation • eg, brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences • Determined by or in conjunction with the designated neurologist. • Diagnosis confirmed by at least one of the following: Neuroimaging procedure (CT scan or MRI brain) and neurologist or neurosurgical specialist</td>
</tr>
<tr>
<td>C. Silent Brain Infarction</td>
<td>Cerebral infarcts that are observed on either CT or MRI scans in the absence of any corresponding, clinically apparent cerebrovascular ischemic event.</td>
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</tbody>
</table>

CT indicates computed tomography; mRS, modified Rankin Score; and TIA, transient ischemic attack.
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event rate of 6.7% in comparison with 1.7%, respectively ($P=0.03$). Similarly, cohort A of the PARTNER study randomly assigned patients who were high-risk candidates deemed eligible for surgery to receive either TAVI or surgical aortic valve replacement (SAVR) and demonstrated a 30-day neurological event rate of 5.5% in comparison with 2.4%, respectively ($P=0.04$), despite a higher incidence of new-onset atrial fibrillation (NOAF) with SAVR.

Congruous with the PARTNER results, overall stroke rates before discharge after isolated SAVR have been consistently reported as 1.5% and 2.4% in the general population and those >80 years of age, respectively. The rate of observed stroke has been reported to occur in 2% of high-risk and inoperable patients undergoing balloon aortic valvuloplasty. This was reflected in cohort B of the PARTNER study, in which higher rates of total CVE were seen with TAVI than with medical management, in which 150 balloon aortic valvuloplasties were performed, with 6.7% versus 1.7% ($P=0.03$) and 10.6% versus 4.5% ($P=0.04$) at 30 days and 1 year, respectively.

Delayed stroke has been assessed in a comparatively small number of studies, averaging $4.3\pm 1.6\%$ at 6 months and $5.2\pm 3.4\%$ at 1 year. At 3 years, cohort B of the PARTNER study reported a cumulative stroke incidence of 15.7% in inoperable patients who received TAVI. Interestingly, the recently released 3-year follow-up data for cohort A of the PARTNER study revealed stroke rates of 8.2% and 9.3% ($P=0.763$) in TAVI and SAVR, respectively. The longest follow-up to date—of 5 years in the Canadian multicenter experience—has revealed a cumulative major ischemic stroke incidence of 9.7% (with an annual risk of 2% per annum) and a cumulative hemorrhagic stroke incidence of 7.3%.

**Severity**

Stroke incidence rates reported by most studies are usually a composite of disabling (major) and nondisabling (minor) stroke (see definitions in the Table). Earlier studies that differentiated types of CVEs revealed that the vast majority are major (85%), rather than minor strokes or transient ischemic attacks (TIAs). The validity of this finding has been undermined by the suggestion that minor strokes and TIAs are underreported particularly in observational studies not specifically geared to their detection. Results of more recent safety studies, specifically designed to detect and report minor strokes and TIAs, should provide a more accurate representation. This is supported by the PARTNER study where TIAs and major and minor strokes accounted for 26%, 58%, and 16% of neurological events, respectively. Moreover, the recent ADVANCE study classified only 40% (1.2% overall rate) of strokes as major, versus 60% (1.7%) as minor.

**Difference in TAVI Strategy**

There are 3 different strategies for TAVI insertion: transarterial, most commonly transfemoral (TF); transapical (TA); and transaortic (TAo). Inherently, TA and, to a lesser extent, TAo access limit manipulation of the ascending aorta and aortic arch by guidewires and angiography catheters. Consequently, it has been postulated that these approaches should minimize disruption and embolization of calcific and atheromatous plaques, and therefore be associated with fewer CVEs. Although statistical significance has not been confirmed by larger studies, a trend toward reduced CVEs with the Edwards SAPIEN (ES) valve via the transapical in comparison with the transarterial approach with either the Medtronic CoreValve...
(MCV) or Edwards SAPIEN valve is noted (2.7±1.4%, 3.1±2.2%, and 4.2%±2.2% at 30 days, respectively). Importantly, this was evident despite a higher-risk population with a mean EuroSCORE of 29.10% for the transapical approach with MCV and ES, respectively. Although less apparent, this trend is also seen in the previously mentioned European Sentinel registry, where the access routes were associated with an equivocal stroke risk (TF=1.9% versus TA=1.6%; \( P=0.68 \)) despite a TA-TAVI group of higher risk (EuroSCORE for TF=19.6% versus TA=22.2%; \( P=0.01 \)).

Similarly, subgroup analysis of cohort A of the PARTNER study revealed a statistically significant, 3-fold increase in overall stroke risk with TF-TAVI with ES versus SAVR (4.6% versus 1.4%, \( P=0.04 \) at 30 days; 6.1% versus 1.9%, \( P=0.03 \) at 1 year), but a nonsignificant difference between TA-TAVI and SAVR (7.9% versus 5.5%, \( P=0.5 \) at 30 days; 14.1% versus 9.7%, \( P=0.37 \) at 1 year). The disparity between approaches, however, was lost when comparing the incidence of major stroke (2.9% versus 1.7%; \( P=0.37 \) for TF-TAVI in comparison with the control SAVR group and 5.8% versus 3.2%; \( P=0.37 \) for TA-TAVI in comparison with control SAVR). The notable difference in the absolute incidence of stroke between the TF and TA-TAVI groups has been attributed to a TF-first approach—a practice that extends across most TAVI centers worldwide. This is supported by the equivalent effect seen in the risk-matched SAVR arms of the study. To date, comparative trials between equivalent risk groups have not been performed.

Furthermore, the suggestion that TA-/TAo-TAVI may be associated with a lower incidence of stroke in comparison with TF-TAVI must be considered in light of the anesthetic and early postoperative differences between strategies. Universally, TA-/TAo-TAVI is performed under general anesthesia followed by postoperative intensive care admission, resulting in longer periods of intubation and sedation in comparison with TF-TAVI, where early awakening after general anesthesia or procedural sedation is routine. Such a difference potentially confounds the detection of early neurological events, particularly of TIAs and minor strokes. Subsequent underreporting of these events among TA-TAVI cohorts may explain the discrepancy between approaches when evaluating overall stroke incidence.

Evidence of reduced stroke risk with increased operator experience is apparent for both the TA- and TF-TAVI approaches, with early results reflecting the initial experiences of the enrolling sites and clouding the true nature of the relationships between access routes and stroke. The relevance of this is suggested by the PARTNER nonrandomized continued access study where, despite comparable risk profiles, the incidence of stroke was half that of the original randomized trial at 30-days (2.3% versus 5.8%) out to 2 years (6.1% versus 12.5%) by using the ES device via the TA delivery route. Similarly, comparison between the inoperable cohorts (cohort B) of the PARTNER and PARTNER II studies demonstrates a reduction in major stroke rates from 5.0% to 3.2%, respectively, again by using the ES valve, however, via the TF route.

Although the implications of access route on stroke rate remains unclear, studies assessing deployment techniques demonstrate no significant difference between either the balloon-expandable ES or the self-expandable MCV via the transarterial approach. An equivalent stroke risk with the 2 types of prosthesis is also supported by the Belgian registry, in which half of the hospitals performed transarterial TAVI with the ES and the other half performed transarterial TAVI with the MCV, such that the prosthesis selected for implantation was hospital determined. Similarly, the aforementioned European Sentinel Registry failed to identify a significant difference between the valves selected (MCV=2.1% versus ES-XT=1.7%; \( P=0.4 \)).

The Pooled Rotterdam-Milano-Toulouse In Collaboration (PRAGMATIC) Plus initiative, the first and most recent study comparing the 2 valve types via the TF approach, reported a difference in 30-day stroke incidence favoring the ES (MCV=3.5% versus ES=1.5%), although this did not reach statistical significance (hazard ratio, 3.0; 95% confidence interval, 0.61–15.364; \( P=0.174 \)).

Timing of CVEs

The temporal pattern of neurological events after AS intervention is similar for both SAVR and TAVI management strategies with the disparity in overall CVE incidence appearing to be an acute phenomenon (Figure 3). An early hazard phase or high-risk period for acute CVEs exists after TAVI, with up to 50% occurring within the first 24 hours. Patients remain vulnerable for up to 2 months after the procedure with declining incidence, before transitioning to a late, constant hazard phase. This late phase is similar among patients with aortic valve disease, irrespective of the management strategy initially used, and likely reflects the background risk of this population.

Although the timeframes used to differentiate acute, subacute, and late stroke are relatively arbitrary and definitions differ between studies, such classification permits a better understanding of the varied etiologies of stroke after TAVI.

Etiology

Early (Acute) Stroke

Acute strokes are considered procedure related, and are almost exclusively ischemic in nature, with <5% reported as
Figure 4. Etiology of embolization secondary to TAVI. A and B, Acute embolization. Disruption of calcific/atheromatous plaques and valve/vascular tissue associated with: passage of guidewires and large-bore catheters and during valvuloplasty and device delivery (A), and device positioning and implantation with thrombus formation on catheter (B). C, Subacute embolization. Persistent nidus of calcium on native valve leaflets provides source for further calcific embolization: thrombus formation secondary to structural changes to native leaflets, presence of prosthetic device, and altered rheology attributable to both apposition of native leaflets to aortic wall and atrial fibrillation.

hemorrhagic.\textsuperscript{31,32} Where hemorrhagic stroke does occur, it is often the result of transformation of an ischemic infarct or secondary to anticoagulation. In the PARTNER trial, for example, the etiology was ischemic in 72\%, ischemic evolving into hemorrhagic in 4\%, and unknown in 24\%, with no primary hemorrhagic strokes.\textsuperscript{2}

Traditionally, the dominant etiology of periprocedural ischemic stroke is of embolization arising from particulate matter (valve/vessel wall tissue, calcific material, and atheromatous plaque) disrupted from within the vasculature and from the native aortic valve complex itself (Figure 4A and 4B).\textsuperscript{6} Cardiac catheterization studies have demonstrated this, showing an association between cerebral embolization and the retrograde passage of even simple guidewires. This is particularly pronounced in patients with severe AS and with longer duration of catheterization.\textsuperscript{33,34} Intuitively, the larger caliber and stiffer catheters used in TAVI result in comparatively worse disruption and, therefore, increased embolic load.\textsuperscript{35} Furthermore, repeated attempts to cross the often friable calcified valve, a higher degree of manipulation of the aortic valve annulus, longer procedural duration, and the forces of valve deployment and balloon pre/postdilation all potentially worsen this disruption.

Recently, thrombotic microembolization potentiated by the TAVI procedure and equipment has been shown to be of equal importance during this acute period (Figure 4B).\textsuperscript{6} The wires and catheters used are known to be prothrombotic. Additionally, iatrogenic damage to endothelium results in activation of the coagulation cascade, platelet activation, and inflammation, all resulting in thrombus formation.

Interestingly, in addition to calcific, atheromatous, tissue, and red/white thrombotic emboli, studies examining the captured debris material from embolic protection devices (EPDs) have also identified myocardial tissue and TAVI delivery catheter shavings (plastic).\textsuperscript{6} Air emboli also are associated with the use and exchange of large catheters and contrast injection, and, if large, can precipitate stroke. Although air microemboli have been associated with neurological dysfunction, this is mostly temporary and, as such, generally considered benign relative to particulate emboli.

Hemodynamic instability leading to systemic hypotension may impair cerebral perfusion pressure beyond cerebral autoregulatory capacity, resulting in hypoperfusion. Although in itself a cause for ischemia, low cerebral flow magnifies the effects of microemboli by impairing their clearance and permitting small emboli to lodge.\textsuperscript{36}

The largest threat to hemodynamic stability during the intraoperative period is the rapid ventricular pacing (rVP) used to reduce cardiac motion and ventricular ejection during balloon valvuloplasty and valve deployment, thereby minimizing the risk of device embolization and malpositioning. This is usually well tolerated, with minimal impairment in perfusion pressures and rapid recovery. Patients with significantly impaired baseline cardiac function, especially those with concentric left ventricular hypertrophy, may experience prolonged episodes of hypotension necessitating volume resuscitation, inotropic support, and the institution of mechanical circulatory support. This is potentiated by myocardial ischemic deficits in light of the rapid heart rate, myocardial hypertrophy, and low coronary perfusion pressure, further depressing contractility.

The associated compromise in cerebral perfusion during rVP has been demonstrated by using transcranial cerebral oximetry, which noninvasively monitors regional oxygen saturation (rSpO\textsubscript{2}) of both frontal lobes. In a pilot study conducted by Bila et al.,\textsuperscript{37} a mean drop in rSpO\textsubscript{2} of 6.1±3.3% was recorded during valvuloplasty with a mean duration of rVP of 40±32 seconds, and by 3.4 ±1.3% with a mean duration of rVP of 17.5±5 seconds during valve deployment. Baseline recovery occurred at a mean of 47±25 seconds after termination of rVP. Although all patients remained above the absolute safety threshold of 55% in this study, events of desaturation to <55% have been reported. A more recent study revealed a population with a mean baseline rSpO\textsubscript{2} of 54±7, which increased by an average of 23% after intubation; however, one-third then experienced at least a 20% decline during pacing and valve deployment.\textsuperscript{38}

Delayed (Subacute/Late) Stroke

In comparison with the relatively well-described causes of early stroke, the etiology of delayed stroke is poorly understood and likely involves factors other than those directly related to the procedure.
During this period, thromboembolism is believed to be the primary underlying cause of CVEs (Figure 4C). Before endothelialization, the stent of the valve may be thrombogenic—a process that has been shown to be incomplete out to 425 days postimplantation. Additionally, the high forces required for valve crimping and balloon dilation cause structural damage to the prosthetic valve leaflets, resulting in a prothrombotic state with platelet and fibrin aggregation demonstrated within hours of implantation. In addition to acting as a persistent nidus for calcific emboli, the native leaflets too undergo prothrombotic structural changes, including fissuring and endothelial denudation. Altered rheology resulting from native leaflet compression against the aortic wall, paravalvular leak, and apical infarction caused by transapical access may similarly be thrombogenic.

These changes occur in the setting of an acquired thrombophilic state frequently present in TAVI candidates owing to AS, heart failure, and associated factors. This prothrombotic state has been confirmed by echocardiographic studies that have demonstrated a remarkably high incidence of preprocedural intracardiac thrombi (10.6%) and spontaneous echo contrast (24%).

Another source of thromboembolism after the acute period is the occurrence of NOAF, defined as any episode of atrial fibrillation lasting >30 seconds. Although >25% of patients undergoing TAVI have preexisting atrial fibrillation, NOAF occurs as a complication of the TAVI procedure in 14% to 32% of patients without a previous history. This occurrence has been consistently shown to be associated with an increased risk of CVEs, primarily in the subacute period, and to be an independent predictor of stroke—the largest study reporting an odds ratio of 2.76 (95% confidence interval, 1.11–6.83). Suboptimal anticoagulation in the context of NOAF appears to play a significant role, with the rate of stroke reaching 40% in nonanticoagulated patients with NOAF, versus just 2.9% in those adequately anticoagulated. The relevance of NOAF to delayed embolic phenomenon and stroke were highlighted by Nuis et al where NOAF preceded clinical signs of neurological impairment in 100% of delayed strokes, as opposed to just 20% of early strokes. Proportionally, hemorrhagic stroke increases over the duration of postprocedural follow-up, accounting for up to 50% of late strokes. This likely reflects an unchanged rate of hemorrhagic stroke in the setting of ischemic stroke rates returning to baseline levels for this patient population.

**Silent CVEs**

Despite significant association with morbidity and mortality, the incidence of clinically apparent stroke is sufficiently small to obscure its utility as an end point in clinical trials. As such, surrogate markers such as silent neurological injuries have been adopted, albeit with unclear clinical implications.

**Diffusion-Weighted MRI**

New ischemic lesions have been identified in as many as 93% of patients post-TAVI; this rate is up to double that seen in isolated SAVR and quadruple that of diagnostic retrograde aortic valve catheterization in the setting of severe aortic stenosis. Interestingly, however, although more frequent, the size of the lesions after TAVI have been reported to be significantly smaller than those after SAVR (77 versus 224 mm³; P<0.001) despite patients of increased age (78.3–83.8 versus 67.4; P<0.001) and higher risk (logistic EuroSCORE 17.9%–22.8% versus 2.5%; P<0.001).

To date, available data on silent infarction are insufficient for conclusions to be drawn regarding differences between TAVI
devices and approaches (Figure 5). Analysis of diffusion-weighted (DW) MRI studies performed pre- and post-TAVI includes a cumulative total of only 222 patients. TA-TAVI with ES was performed in 68 of these patients, with 52 (76.5%) having newly identified ischemic lesions on MRI postprocedure, and 2 (2.9%) with clinically manifest CVEs. TF-TAVI was performed in 154 patients, with 117 (76%) new silent infarcts and 9 (5.8%) CVEs. Of the TF-TAVI, 80 were performed with the MCV, with 60 (75%) new silent infarcts and 8 (10%) clinical CVEs; meanwhile, 74 were performed with the ES, with 57 (77%) new silent infarcts and 1 (1.4%) CVE. Comparatively, the incidence of new silent lesions with SAVR is consistently reported as <50%, although, again, this is confounded by younger age and lower surgical risk in comparison with TAVI cohorts.

All studies have identified new lesions that are multiple and disseminated, consistent with an embolic source. Initially, a left-hemisphere vulnerability to cerebral insult was postulated given the distal positioning of the left-sided vessels and fluid-mixing studies suggesting stratification of flow. Although early studies using DW-MRI supported this, the association has not been confirmed by more recent studies. Similarly, although findings have been inconsistent, there is the suggestion of increased vulnerability of the anterior circulation in comparison with the posterior circulation, with a preponderance for new ischemic lesions in the middle cerebral artery territories.

Not surprisingly, the incidence and volume of preoperative silent ischemic lesions (present in 70% of patients) predicted the occurrence of new postoperative lesions. Individuals with new neurological signs demonstrated a significantly higher number (26 versus 2.7±3, P=0.004) and volume (11.9±6 mL versus 1.1±1.1 mL, P=0.007) of new cerebral infarcts.

Transcranial Doppler
Transcranial Doppler (TCD) is used for the recognition and quantification of high-intensity transient signals (HITS) and microembolic signals with the use of defined criteria. Studies using TCD during TAVI procedures are few, and comparisons between TCD embolic signals and MRI in the same population have not been undertaken. Drews et al provide the only comparison between radiological evidence of stroke (using computed tomography) and TCD emboli detection during TAVI in the same cohort of patients, with an average procedural total of 730 HITS and 140 microembolic signals, associated with an 8% incidence of new cerebral infarctions.

Microemboli detected by TCD occur at all stages of the TAVI procedure with symmetrical hemispheric distribution, but they are most frequent during stages involving manipulation of the aortic annulus, notably during positioning and implantation of the valve (Figure 6). Kahlert et al, in the largest and most comprehensive study investigating TCD-detected emboli, demonstrated the highest number of HITS during the implantation stage with the MCV, suggesting that the stent acts to scrape calcific debris and valve tissue from the native aortic valve during the slow release of the prosthesis. Conversely, more HITS were identified while positioning the ES valve, which, because of rapid expansion, necessitates more precision and is therefore more time-consuming. The logical inference from this is that the duration of aortic valve manipulation determines the quantity and degree of embolization. This may be an increasingly important consideration in light of the development of newer devices offering the capacity for repositioning, resheathing, and retrieval.

Consistent with other therapies that use a retrograde aortic valve approach, arch atheroma demonstrates correlation with
significantly higher numbers of HITS during wire manipulation of the arch and valve insertion in transfemoral subgroups only, with grade III/IV arch atheroma associated with a doubling of the incidence of HITS. Overall, however, the aortic arch appears to play only a minor role in comparison with the significant embolic burden associated with the manipulation of the aortic valve during device positioning and implantation.

Serological Markers
A small number of studies have examined serological markers as surrogates for neurological injury. Neuron-specific enolase, despite its validity assessing neurological damage in traumatic brain injury, has consistently failed to correlate with DW-MRI after cardiac surgery or TAVI. Associations, however, have been demonstrated between the presence and volume of new DW-MRI lesions and both the postoperative s100B ($r=0.64$; $P<0.01$) and preoperative-minus-postoperative ($\Delta$) s100B ($r=0.59$; $P<0.01$) concentrations of patients undergoing SAVR, although this has not been studied in TAVI. Additionally, the area under the curve of S100B has been correlated with TCD microembolic load during TAVI. Finally, an emerging and promising marker for neurological injury in cardiovascular intervention is the glial fibrillary acidic protein for which validation studies are currently underway.

Risk Factors for CVEs
Numerous risk factors for and predictors of CVEs have been reported to exhibit significant associations with neurological events in TAVI studies (Figure 7). Those identified for silent and acute stroke bestow an increased potential for mechanical disruption of calcific/atheromatous plaques and valve/vessel wall tissue with subsequent embolization. Valve dislodgement/embolization and balloon postdilation were independent predictors of acute stroke on multivariate analysis, with odds ratios of 4.36 (95% confidence interval, 1.21–15.69; $P=0.024$) and 2.46 (95% confidence interval, 1.07–5.67; $P=0.034$), respectively. Intuitively, both of these occurrences result in increased manipulation of the aortic valve annulus and increase embolic load, but adequate sizing and precise positioning of the prosthesis can minimize their incidence. Additionally, atheromatous burden and aortic valve area both correlate with the probability of, and embolic load associated with, plaque disruption. This is particularly significant for the surgical TAVI approaches, because these patients are typically more advanced in the natural disease history.

Similar reasoning also questions the role of balloon predilation, which has traditionally been considered a mandatory preliminary step to free the calcific leaflets and facilitate crossing of the aortic valve and deployment of the device. Here, the relationship with stroke is less clear. On one hand, prolonged time and difficulty crossing the stenosed, undilated native aortic valve results in prolonged manipulation, which has been shown to increase embolization. On the other hand, predilation necessitates $rVP$ and contributes to the overall TCD-determined embolic load of the procedure. Moreover, as previously discussed, isolated balloon valvuloplasty is associated with a 2% risk of stroke. In comparison with an historical control group, omission of balloon prevalvuloplasty in a small cohort of patients ($n=60$) undergoing TF-TAVI resulted in a halving of stroke risk (5% versus 11.9%). Further clarification will come with the results of the ongoing randomized multicenter trial: Use of the self-expanding Medtronic CoreValve prosthesis...
without predilation in patients with severely impaired left-ventricular ejection fraction (SIMPLIFY) TAVI trial. Contrasting the mechanical factors precipitating plaque and tissue dislodgement and primarily responsible for acute stroke, major risk factors for subacute stroke result in abnormal blood rheology and a prothrombotic state, thereby increasing the potential for thromboembolism. Most significantly among these is the occurrence of NOAF, whose correlation with subacute stroke has been discussed above. The causes of NOAF in cardiac intervention/surgery are numerous, but include factors that result in elevated levels of circulating inotropes, metabolic and electrolyte abnormalities, elevated inflammatory mediators, pericarditis, diastolic dysfunction, and enlarged left atrial size. Specific to TAVI, the TA approach has been associated with doubling the incidence of NOAF, possibly consequent to the atrial fibrillation-inducing factors of adrenergic stimulation associated with minithoracotomy and pericardial cavity opening. In addition, moderate-severe aortic stenosis, and non–TF-TAVI candidate stratification have shown a correlation with incidence of subacute stroke.

**Prognosis After CVE**

Neurological deficits have been reported to persist in 50% of patients after major stroke associated with TAVI. This is consistent with findings in the general population. In the largest analysis of TAVI patients to date, Eggerbrecht et al reported 30-day mortality after stroke as ≥3.5 times that of those without stroke, with one-fourth dying within the first 30 days (25.5±21.9% versus 6.9±4.2%). These findings are supported by a recently published prospective study of CVEs in a large cohort of patients undergoing TAVI. Here, Nombela-Franco et al reported a significantly higher all-cause 30-day mortality rate with the occurrence of total CVEs (16.7% versus 8.2%; \(P=0.044\)), stroke (20.0% versus 8.2%; \(P=0.012\)), and major stroke (30.0% versus 8.1%; \(P=0.003\)) relative to stroke-free patients. The 1-year mortality rate also was higher with the occurrence of either stroke (33.1% versus 22.1%; \(P=0.041\)) or major stroke (41.6% versus 22.1%; \(P=0.003\)) within the first 30 days, but not CVEs (29.7% versus 22.2%; \(P=0.152\)).

Some insight into the temporal pattern of this increased mortality risk was gained from the analysis of neurological events that occurred in the PARTNER study (Figure I in the online-only Data Supplement). In the immediate period post-CVE, a high hazard ratio was evident regardless of intervention (SAVR, TF-TAVI, or TA-TAVI). Significant differences in the duration of elevated risk were noted, however, with the hazard ratio returning to expected mortality risk after 6 weeks for SAVR, approaching expected mortality after 1 year for TF-TAVI, and remaining elevated beyond 1 year in TA-TAVI.

Health-related quality of life (HRQoL) is generally considered of equal significance to mortality in this older and frailer group of patients. HRQoL improves significantly after TAVI, primarily in physical domains, with mental domains remaining relatively unaffected or even improved. Data pertaining to HRQoL outcomes in those who have sustained a stroke comes from a subgroup analysis of cohort A of the PARTNER study. Here, although patients who had a 30-day stroke experienced a reduced HRQoL early after the event, those who were alive at 1 year demonstrated an improvement consistent with nonstroke TAVI recipients. Thus, among stroke survivors, benefit from relief of AS (both in functional status and cerebral perfusion) may still outweigh impairment secondary to stroke, although further investigation is required to confirm these findings.

The clinical significance of silent neurological injury remains controversial, with mixed results across studies. In the short term, no clear correlation has been established between silent neurological injury and measurable impairment in neurocognitive function or apparent neurological events within the first 3 months after TAVI. This is supported by midterm studies with follow-up of 1 year, which seem to suggest that silent cerebral embolism does not impact prognosis, in terms of either mortality, self-sufficiency, or HRQoL outcomes, although the latter may reflect the relative inattention paid to HRQoL measures until recent times. Postulated longer-term implications including accelerated cognitive decline, dementia, and depression remain to be elucidated.

**Preventative Strategies**

Expansion of the understanding of neurological injury associated with TAVI has fuelled interest into strategies for their prevention. Efforts have predominantly focused on the use of dedicated EPDs and aggressive antithrombotic protocols.

Proof of concept for EPDs in the setting of TAVI was demonstrated in 2010. The rationale for their use relies on the mechanical reduction in cerebral burden of embolic debris by either capturing or deflecting embolized material preventing access to the supraaortic-cerebral trunks. Three such devices are

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**Figure 8. Embolic protection devices (EPDs)**

A. Embrella Deflector (Edwards LifeSciences, Irvine, CA).
B. Montage 2 Capture Device (Claret Medical, Santa Rosa, CA).
C. Triguard Cerebral Deflector (Keystone Heart, Herzliya, Israel; formerly the Shimon Embolic protection filter or SHEF).
currently in the clinical phase (Figure 8). The Embrella deflector (Edwards LifeSciences, Irvine, CA) and the Montage 2 (Claret Medical, Santa Rosa, CA) are both delivered via radial artery access, offer protection to the brachiocephalic and left common carotid arteries, and have received Conformité Européenne mark approval. Conversely, the Triguard cerebral deflector (Keystone Heart, Herzliya, Israel; formerly the Shimon Embolic protection filter or SHEF), is delivered via femoral access and is designed to protect all aortic arch takeoffs.

Although limited, early clinical data have shown considerable promise for these devices in terms of technical success and safety. Efficacy endpoints have also demonstrated potential benefit, but these have been less consistent consequent to a limited number of inadequately powered, nonrandomized, and noncontrolled studies, confounded by potential differences between EPDs. Van Mieghem et al reported the capture of macroscopic embolic debris in 30 of 40 (75%) TAVI cases by using the Claret Montage 2. This was reflected in the recently announced results of the Prospective randomized outcome study in patients undergoing TAVI to examine cerebral ischemia and bleeding complications (PROTAVI-C) pilot study using the Embrella Device (n=41). Here, a reduction in the average volume of ischemic lesions with the use of DW-MRI (42.3 mm3 versus 61–224 mm3 in similar studies without cerebral protection) was reported; however, the incidence of TCD-detected emboli (mean total HITS=638±66) were relatively consistent with previous data from nonprotected TAVI procedures. Similarly, early results from the DEFLECT study demonstrated a reduction in the average and total lesion volumes by 65% and 57%, respectively, when comparing the Triguard-protected patients (0.12, 0–0.39 cm3 and 0.7, 0–3.94 cm3) with historical data (0.34 cm3 and 1.64, 0–70.3 cm3), although the total number of lesions remains unchanged. Ultimately, it is speculated that the success and utility of these devices will depend on improved methods of risk stratification allowing for the adequate identification and selection of high-risk patients who are likely to derive the greatest benefit from their application.

A comprehensive stroke reduction strategy also mandates the implementation of strict antithrombotic and anticoagulant protocols. Intraprocedurally, the use of EPDs has demonstrated that thrombotic material accounts for 70% of captured emboli. This highlights the importance of intraprocedural anticoagulation, with current practice generally employing intravenous heparin targeting an activated clotting time >300 seconds—a point of increasing importance with the longer procedural durations and additional thrombogenic surfaces consequent to the use of EPDs. Additionally, expert consensus guidelines empirically recommend dual-antiplatelet therapy in the postprocedural period with clopidogrel and aspirin, although doses and duration are not specified. Consequently, considerable variability in management is seen across studies/registries with the inconsistent use of loading doses and variable duration of maintenance clopidogrel (75 mg/day) between 1 and 6 months. Aspirin dosing too differs from 80 to 325 mg/day, although it is usually continued indefinitely. It is hoped the results of the ongoing Aspirin versus aspirin + clopidogrel after Transcatheter aortic valve implantation (ARTE) and future studies directed toward novel antiplatelet agents will offer TAVI-specific guidance regarding the optimum regimen.

Antiplatelet therapy, however, is unlikely to be adequate in the setting of previous anticoagulation or the occurrence of post-TAVI NOAF. The significant association between NOAF and stroke suggests the requirement for vigilant monitoring for detection of even short durations of NOAF and, the institution of anticoagulant therapy in its occurrence—although, whether this should occur as triple therapy (aspirin, clopidogrel, and warfarin), dual therapy (aspirin and warfarin), or warfarin alone is yet to be evaluated.

Conclusions

Although the literature supports TAVI use in a subgroup of high-risk and inoperable patients, the understanding of associated neurological injuries is incomplete. As attention shifts to lower-risk populations, the question of risk versus benefit must again be raised, especially in view of the acceptability of conventional aortic valve replacement in this group. It is yet to be determined whether neurological injury will be the Achilles heel that prevents wider application of this technology.

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Supplemental Figure: Prognostic implication of neurological event on mortality

Left = Rate of death (%/month) for A. AVR C. TAVI-TF and E. TAVR-TA. Right = Hazard Ratio for observed compared with expected death for B. AVR C. TAVR-TF and F. TAVR-TA

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Reference: