Transcatheter aortic valve replacement: perioperative stroke and beyond

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ABSTRACT

Introduction: The definition of stroke has changed over time, from a clinical only-based diagnosis to a more complex classification, including both clinical and imaging-based criteria, in part due to widespread use of magnetic resonance imaging (MRI). The increasing number of transcatheter aortic valve replacement (TAVR) procedures in patients with severe aortic valvular stenosis who are considered high-risk surgical candidates has influenced our view on the diagnosis, interpretation, and significance of perioperative stroke during these procedures.

Areas covered: In this perspective, we summarize changes in the definition and diagnostic criteria for stroke and transient ischemic attacks. We examine how the introduction of MRI and standardized cognitive tests has affected our understanding of the safety of TAVR procedures. Finally, we review the growing evidence regarding the role of cerebral protection technology during TAVR procedures on cognitive function.

Expert commentary: Standardized MRI-based protocols and prospective evaluation of neurologic deficits with a battery of cognitive assessment tests are needed to ensure accurate recognition of postprocedural clinical events in patients undergoing TAVR procedures and to confirm the effectiveness of embolic protection technology.

1. Introduction

The increasing number of transcatheter aortic valve replacement (TAVR) procedures in patients with severe aortic valvular stenosis who are considered high-risk surgical candidates for open heart valve replacement surgery has changed our view on the diagnosis, interpretation, and significance of perioperative stroke during these procedures. Stroke and myocardial infarction (MI) are the standard outcome measures for determining the safety of cerebrovascular and cardiovascular procedures and are commonly utilized in clinical trials and registries. Although the definition and diagnostic criteria for acute MI are well established, the classification of stroke and other acute cerebrovascular events is more controversial and has changed over time with advances in neuroimaging, especially the widespread use of magnetic resonance imaging (MRI).

2. The changing definition of ‘stroke’

The classic ‘textbook’ definition of stroke, which implied permanent neurological injury to distinguish it from transient ischemic episodes (referred to as transient ischemic attack, TIA), was originally based on the duration of neurological symptoms. Historically, the diagnosis of stroke was made in cases when neurological deficits lasted for more than 24 h. The 24-hour criterion was introduced into clinical practice at a time when imaging was not available to validate the proposed time-based definition. In 1975, a committee led by the National Institutes of Neurological Disorders and Stroke endorsed such time-based definitions of TIA and stroke [1].

With the development first of computed tomographic (CT) scanning and subsequently of MRI, which was more sensitive than CT imaging in demonstrating acute ischemic injury, it became apparent that imaging markers of brain injury could be detected in many cases that were clinically silent or would be labeled ‘TIAs’ according to the original definition. To improve accuracy in distinguishing a stroke from a TIA and facilitate timely therapeutic interventions, an alternative, tissue-based definition of stroke was proposed, which relied on neuroimaging or other tests capable of providing evidence of cerebral ischemia, rather than the time criterion alone [2,3].

In 2009, the American Heart Association (AHA)/American Stroke Association (ASA) scientific statement on the diagnosis and evaluation of TIA considered the classic 24-hour definition ‘misleading,’ citing studies on patients with transient neurological episodes of different durations who were found to have cerebral infarcts on MRI [4]. The aforementioned
changes in the definition of stroke were reflected in the guidelines for TAVR procedures and its standardized end point definitions adopted within the last few years, such as the Mitral Valve Academic Research Consortium (MVARC) and the Valve Academic Research Consortium (VARC)-2 [5].

In 2013, the AHA/ASA released an expert consensus document with a proposed ‘Updated Definition of Stroke for the 21st Century’ [6]. In addition to an updated definition of cerebral infarction (imaging or pathology based, rather than time based only), ‘silent’ central nervous system (CNS) infarction (that is, imaging or pathological evidence of CNS infarction without corresponding acute neurological dysfunction on clinical examination) was introduced in the proposed classification.

3. TAVR and periprocedural stroke

Early studies evaluating the safety and efficacy of TAVR showed a relatively low rate of periprocedural stroke and TIA. The landmark Placement of Aortic Transcatheter Valves (PARTNER) trial randomly assigned 699 patients with severe aortic valve stenosis to TAVR or surgical aortic valve replacement [7]. At 30 days, the rate of major stroke was 3.8%, the rate of minor stroke was 0.9%, and the rate of TIA was 0.9% in the TAVR group. The study investigators utilized the conventional 24-hour criterion for the definition of stroke versus TIA, relied on retrospective review of progress notes and discharge summaries to grade stroke severity, and did not perform routine brain imaging to evaluate for neuroimaging markers of cerebral ischemia. The overall rate of all neurologic adverse events at 30 days was significantly higher with TAVR than with surgical repair (5.5% vs. 2.4%, \( p = 0.04 \)).

Subsequently, studies that examined early postprocedure MRI of TAVR patients reported a very high rate of diffusion-weighted imaging (DWI)-positive cerebral lesions, often with more than a 10-fold increase in the rate of silent infarction in comparison to the rate of clinical events observed in the PARTNER trial [8–10]. Such events detected on MRI were found predominantly in the immediate postprocedural period (Figure 1). The proposed etiology of TAVR-related strokes is cardioembolic. Histopathological analysis suggests that embolic debris collected during TAVR procedures originates mainly from the native aortic valve leaflets, aortic wall, or left ventricular myocardium [11,12]. Regional distribution of cerebral MRI-DWI lesions supports the embolic mechanism of such infarcts (or ‘events’), because both hemispheres, including anterior and posterior circulation territories, are affected. MRI with its DWI sequence offers excellent sensitivity and specificity in detecting early ischemic injury to the brain, which is far superior to that of CT. With advances in software analysis, researchers are now able to perform quantitative analysis of the number of ischemic lesions, the overall and single-lesion volume, and map the location of DWI lesions according to main vascular territories.

Data on what constitutes the best perioperative medical management of TAVR procedures are scarce. Dual antiplatelet therapy and adequate anticoagulation may be protective against ischemic events, but the effect of these pharmacological agents in the perioperative period thus far has been studied in relation to clinical events only [13,14]. Studies of how pharmacological agents affect the number of MRI lesions in patients undergoing TAVR are lacking.

Studies of serological markers of brain tissue injury, such as neuron-specific enolase and S100\( \beta \) in patients undergoing cardiac surgery, have shown inconsistent results [15–17]. Therefore, unlike brain MRI markers, these markers have not been widely adopted in research or clinical practice to measure the safety of the TAVR procedure.

4. Do all DWI MRI-positive lesions equal stroke?

A major challenge in evaluating the imaging burden imposed by TAVR is the difficulty in standardizing imaging methods. This is not limited to TAVR but has applied to silent brain infarcts, in general [18]. Even minor differences in acquisition protocols, processing methods, and

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**Figure 1.** Embolic strokes post-TAVR. This is an example of multiple ischemic strokes involving bilateral anterior circulation (a) as well as posterior circulation territories (b), indicating the central embolic mechanism. The lesions vary in size and can be immediately detected with diffusion-weighted magnetic resonance imaging (DWI MRI).
interpretation techniques for inclusion of observed lesions may substantially impact results, contributing to the wide range (45–95%) and variability in the incidence of subjects with new lesions among previous studies [8,9,19–22]. Differences in geometry and slice thickness during image acquisition may result in missed lesions or extreme partial volume averaging, as well as standardization of diffusion parameters such as b-value and number of diffusion directions. Post-processing techniques, such as echoplanar imaging distortion correction, can play a major role in eliminating or mitigating artifacts that are often the same size as the lesions being analyzed [23]. Co-registration and direct subtraction of images can also substantially improve both sensitivity and reliability of measurements [24]. Consensus neuroimaging standards for all of these parameters have already been proposed for small-vessel disease, and similar approaches will likely be of great value in the TAVR field [25].

Should such silent DWI lesions detected on MRI be considered truly clinically ‘silent’ infarcts? In clinical trials, stroke severity and the degree of disability are historically evaluated with the National Institutes of Health Stroke Scale (NIHSS). The design of the NIHSS puts greater emphasis on deficits associated with left hemisphere lesions than those associated with right hemisphere stroke. Studies of stroke patients using volumetric analysis of CT- and MRI-detected lesions show that patients with right-sided stroke may have a low NIHSS score despite a higher lesion volume, and right-sided strokes are more difficult to recognize [26–28]. This can be explained by more complex symptoms of right hemispheric strokes (such as neglect, extinction, and spatial disorientation), which are more difficult to recognize than deficits associated with the more striking left hemispheric strokes (such as aphasia), unless a very thorough neurological examination is performed. Indeed, it has become increasingly recognized that the NIHSS under-recognizes disorders of higher cerebral function, such as executive and memory dysfunction, now recognized as important features of vascular cognitive impairment. A relevant example of a series of cases with deceptively ‘benign’ and sometimes bizarre deficits from right hemispheric strokes can be found in the bestselling book by neurologist Oliver Sacks [29].

Yet, right hemispheric strokes might be as – if not more – disabling than strokes affecting the left hemisphere. Neglect as a result of damage to the right hemisphere is a major cause of long-term disability and might explain why patients with right hemispheric strokes require longer hospitalization and have worse rehabilitation outcomes and recovery than those with left hemispheric strokes [30–32]. In a systematic review of studies addressing the influence of neglect on outcomes after stroke, Jehkonen et al. [33] found great variability in the terminology and often a lack of consistency in defining neglect. These authors concluded that neglect should be assessed with a standardized battery of tests, rather than a single test, and a longer duration of follow-up to ensure accuracy in the diagnosis and evaluation of such patients.

5. Discrepancy between clinical and imaging findings after cerebrovascular procedures

It is clear from the aforementioned discussion that there is a major discrepancy between numbers of DWI lesions and measurable clinical effect. This difference is a prime reason for a relative disdain in usage of DWI lesions as an end point for cerebral ischemia. There are reports of reversible DWI lesions that do not manifest in delayed scans as completed strokes noted on fluid level attenuated inversion recovery (FLAIR) sequences [34]. As a corollary, at institutions that utilize MRI during evaluation of intracranial large-vessel occlusion for consideration of endovascular revascularization during acute ischemic stroke, the mismatch between DWI and FLAIR sequences is utilized to measure salvageable brain [35,36]. It is also a valid concern that our clinical measures for neurological deficit, such as the standardized NIHSS or even the individualized independent neurological assessment by a neurologist, are woefully inadequate to accurately and with high sensitivity measure small ischemic lesions in non-eloquent regions of the brain.

Despite the discrepancies, there is widespread agreement that the aspirational goal for all cardiovascular and cerebrovascular procedures is that emboli to the cerebral circulation should be minimized, if not eliminated. That said, for the purposes of measurement of potential harmful cerebral embolic events, which is the desired goal of many of the studies, it is hard to argue against a more sensitive measure than DWI lesions within the first 3–4 days of the index procedure. It can be assumed that some of the DWI lesions will not go on to infarction, but the large number of lesions noted in most procedures will allow us to make comparisons among interventions as well as proposed embolic protection measures more effectively and with smaller sample sizes than if we simply continue to assess neurological deficits lasting more than 24 h.

Another test that has been utilized in some studies of TAVR patients is the Mini Mental State Examination (MMSE). It is designed to rapidly assess orientation, attention, short-term memory, and language and is used in both research and clinical practice, often to evaluate patients with dementia. Its use was documented in some studies of patients undergoing TAVR [8,37]. The MMSE has been shown to have limited sensitivity to subtle brain abnormalities and, therefore, might provide incomplete evaluation of cognitive deficits, especially in patients with acute stroke [38,39].

6. Are ‘silent’ strokes really that silent?

Neurological deficits from silent strokes might not present as readily identifiable syndromes but may have cumulative consequences on neurocognitive function, which would not fit a classic clinical definition of a stroke. A recent case–control study of 305 patients with cognitive impairment and 94 control subjects examined an association between MRI markers of cerebrovascular disease and cognition [40]. A detailed analysis of cognitive domains was performed, including working memory, executive function, language, visuomotor and visuospatial
function, recall and recognition, all of which were evaluated and graded at weekly consensus conferences with neurologists and psychologists. White matter hyperintensities detected on MRI were associated with global neurocognitive deficits. A four-category cerebrovascular disease burden score was established. Patients with scores of ≥2 demonstrated significantly worse global and domain-specific neurocognitive performance than subjects with milder scores.

Several distinct cerebrovascular diseases demonstrate a potential link between cognitive function and procedure-related silent infarction. There is accumulating evidence that surgical revascularization of patients with carotid stenosis who would be classified as asymptomatic according to ‘traditional’ criteria can improve long-term cognitive function through augmentation of cerebral perfusion [41–44]. Conversely, other data suggest that perioperative embolic events occur during carotid endarterectomy and carotid artery stenting (CAS) and can result in cerebral injury, potentially leading to impairment of cognitive function [45]. With CAS, immediate MRI-DWI-positive ‘silent’ lesions were traditionally seen in as many as 30–50% of cases. Improvement in embolic protection devices and, specifically, the use of a flow-reversal approach instead of distal embolic protection devices has shown a significant reduction in the rate of such lesions on postprocedural MRI [44,46].

Another example of the association between cognition and ‘silent’ ischemic disease on postprocedural imaging is found in a study by Patel et al. [47] that investigated the rate of new MRI-positive lesions in patients undergoing coronary artery bypass grafting and surgical valve repair. Overall, new lesions were identified in 31% of cases. New lesions in the right hemisphere were significantly larger than those on the left side (median volume, 128 and 44 mm³, respectively, \( p = 0.034 \)). Seven percent of patients had a clinical perioperative stroke and 46% demonstrated neuropsychological deficits at 6–8 weeks postoperatively. Interestingly, there was no significant association between cognitive deficits and size or number of new MRI-positive lesions. We are left to consider whether the lesion number and volume are crucial variables or there are other vascular factors that relate to overall disease burden.

7. Cognitive function in TAVR patients

Data on neurocognitive function in TAVR patients are scant. Most publications to date [7,8,48–50] have reported the rate of clinical stroke based on the standard set of neurological tests including the NIHSS, MMSE, and modified Rankin Scale (mRS), which have limited capacity to detect and quantify changes in cognitive function. One study that stands out was conducted by Ghanem et al. [37], who applied the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in addition to the standard NIHSS to evaluate changes in cognition after TAVR. Cognitive function was measured at baseline and at 3 days, 3 months, and 1 and 2 years after the procedure. RBANS is used to test language, attention, visual and constructional skills, immediate memory, and delayed memory. These authors reported postprocedural early cognitive decline in 5% of patients. In 91% of patients, sustained cognitive performance was observed throughout the entire duration of the study. It should be pointed out that postprocedural assessment was not performed in 11% of patients because of TAVR-related complications. Criticisms of the trial included its design focusing primarily on global rather than individual neurocognitive domains cognitive score and including patients with impaired cognitive function at baseline, which can result in a measurement error [51]. Nevertheless, the study by Ghanem et al. [37] was a major step forward with its in-depth analysis of the association between TAVR and cognitive function.

8. Cerebral protection technology in TAVR procedures

In a series of recent studies, different types of embolic protection devices have been tested to determine if this specific adjunct technology could decrease the rate of periprocedural embolic events post-TAVR [10,52,53]. Depending on the type and manufacturer, these devices are placed across the aortic arch or inside the great vessels (the innominate and left carotid artery) to capture embolic debris released during the procedure. These devices rely on the same principle as distal embolic protection filters, which are now routinely used in conjunction with CAS. Variable effects of such devices on the overall number of MRI-positive lesions in comparison to unprotected TAVR cases (i.e. those in which no embolic devices were used) were shown; both a reduction and an increase in the total number of lesions with the use of these devices could be seen when compared to cases with ‘unprotected’ TAVR [10,53]. Moreover, it appeared that larger emboli were deflected or captured before intracranial embolization because there was a consistent trend in significant reduction in single-lesion volume and protection from large total infarct volumes.

DEFLECT III: A Prospective Randomized Evaluation of the TriGuard HDH Embolic Deflection Device during TAVI [54], is one of the most recent examples of a study that combined neuroimaging MRI evaluation with a neurocognitive battery of tests to determine the clinical value of cerebral protection technology during TAVR on cognitive function. In addition to a reduction in median per-subject lesion volume in patients in whom cerebral protection was used, there were neurological and cognitive benefits. Among 85 patients who underwent randomization, the cerebral protection group in whom the TriGuard cerebral protection system (Keystone Heart Ltd., Caesarea, Illinois, USA) was used showed improved scores on Montreal Cognitive Assessment (MoCA) tests and delayed memory task at discharge, as well as increased recovery of normal cognitive function measured by the MoCA at 30 days. However, it should be pointed out that no correction was made for multiple observations and that the statistical differences are not considered clinically significant. In a meta-analysis comparing various cognitive screening tests for the detection of dementia, MoCA showed the best diagnostic performance for detection of mild cognitive impairment (MCI), although MCI was a secondary outcome and definitions varied among studies [55].
Table 1 summarizes key features of ongoing and recently completed randomized controlled trials of embolic protection devices in TAVR evaluation: neuroimaging and cognitive outcomes.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study device</th>
<th>Outcome measures</th>
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<tr>
<td>DEFLECT III: A Prospective Randomized Evaluation of the TriGuard HDH Embolic Deflection Device During TAVR NCT02070731</td>
<td>TriGuard embolic deflection device (Keystone Heart Ltd., Caesarea, Illinois)</td>
<td>Volume and number of brain lesions measured with MRI, MoCA</td>
<td>Study completed and published [54]</td>
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<tr>
<td>Claret Embolic Protection And TAVI – Trial (CLEAN-TAVI) ClinicalTrials.gov Identifier: NCT01833052</td>
<td>Claret embolic protection device (Claret Medical, Inc., Rosa, California)</td>
<td>Volume and number of brain lesions measured with MRI, MoCA</td>
<td>Study completed and published [56]</td>
</tr>
<tr>
<td>MRI Investigation in TAVI with Claret (MISTRAL-C) Dutch trial register-ID: NTR4236</td>
<td>Claret embolic protection device (Claret Medical, Inc.)</td>
<td>Volume and number of brain lesions measured with MRI, MoCA, MMSE</td>
<td>Study completed and published [57]</td>
</tr>
<tr>
<td>Neuroprotection in Patients Undergoing Aortic Valve Replacement ClinicalTrials.gov Identifier: NCT02389894</td>
<td>Embol-X embolic protection device (Edwards Life Sciences, Irvine, California) and CardioGard cannula (CardioGard Medical Ltd., Or-Yehuda, Israel)</td>
<td>Volume and number of brain lesions measured with MRI, Hopkins Verbal Learning Test, Trailmaking Tests A and B, MCG Complex Figures, Digit Span, Digit Substitution Test, COWA Verbal Fluency Test, CAM Delirium Assessment</td>
<td>Enrolling</td>
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<tr>
<td>Cerebral Protection in Transcatheater Aortic Valve Replacement (SENTINEL) ClinicalTrials.gov Identifier: NCT02214277</td>
<td>Claret embolic protection device (Claret Medical, Inc.)</td>
<td>Volume and number of brain lesions measured with MRI, Trailmaking Tests A and B, Digit Span, Digit Symbol, COWA, Hopkins Verbal Learning Test, Rey Complex Figure, Brief Visual Memory Test, Geriatric Depression Scale, MMSE</td>
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CAM: Confusion Assessment Method; CES-D: Epidemiologic Studies Depression Scale; COWA: Controlled Oral Word Association; MCG: Medical College of Georgia; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging, TAVI: transcatheter aortic valve implantation.

9. Conclusion

The definition of stroke has changed over time, from a clinical only-based diagnosis to a more complex classification, including both clinical and imaging-based criteria, in part due to the widespread use of MRI. The increasing number of TAVR procedures in patients with severe aortic valvular stenosis who are considered high-risk surgical candidates has influenced our view on the diagnosis, interpretation, and significance of perioperative stroke during these procedures. However, at the present time, data on neurocognitive function in TAVR patients are scant. In a series of recent studies, different types of embolic protection devices have been tested. Although the preliminary data are promising, further studies are needed to demonstrate the protective effect of this new technology on preserving cognitive function in patients undergoing TAVR procedures.

10. Expert commentary

Left heart procedures, including percutaneous coronary interventions, transcatheter valve replacement, and electrophysiological procedures for ablation among others, are known to carry embolic risk to the cerebral circulation. This risk is traditionally assessed using low sensitivity measures, including principally measurable clinical neurological deficit such as stroke or TIA. These measures have perhaps led to a misleading assumption of low embolic risk.

For example, Messé et al. [58] compared the rates of stroke after aortic valve surgery when evaluated by NIHSS-certified neurologists versus other clinical personnel before and after the procedure. The rate of stroke detection was more than double that found in a comparable cohort of patients when...
evaluated by a nonneurologist. On the basis of accumulating data on neuroimaging using principally DWI lesion burden on MRI and sensitive measurements of cognitive function, there is growing awareness for a need for embolic protection. Although this intuitively makes sense, it remains a hypothesis that needs to be confirmed using better standardization of imaging protocols as well as neurocognitive assessment.

Baseline as well as immediate and delayed postprocedural evaluation of cognitive domains together with high-sensitivity MRI sequences are required to accurately determine the clinical consequences of TAVR and the value of currently available preventive strategies. Such a rigorous approach is time-consuming and would require allocation of substantial clinical resources, translating to increased costs. Although it likely would not apply to routine clinical practice, such high standards should be applied in future clinical trials. We look forward to the publication of ongoing studies, several of which are applying many of the proposed measures to further clarify the magnitude of embolic burden, its neurocognitive and clinical consequences, and the effectiveness of embolic protection strategies.

11. Five-year view

To better understand the significance of silent strokes in patients undergoing TAVR on neurocognitive function, similar studies that incorporate both highly sensitive imaging and cognitive evaluations of patients undergoing TAVR and other cardiovascular procedures are needed. To compare the results among such studies, a standard neuropsychological battery to measure cognition needs to be developed, which will be utilized and tested consistently to reduce the effect of inter-study variability. As shown in Table 1, the ongoing trials currently incorporate a variety of cognitive tests. Prospective evaluation of neurological deficits by a neurologist or a neuropsychologist with expertise in cognitive assessment would ensure accurate recognition and documentation of postprocedural clinical outcomes.

Key issues

- The definition of stroke has changed from a clinical only-based diagnosis to a more complex classification, including both clinical and imaging-based criteria.
- Cerebral infarcts are commonly detected with magnetic resonance imaging (MRI) in patients undergoing transcatheter aortic valve replacement (TAVR) procedures.
- Accumulating evidence suggests that careful examination of cognitive function after TAVR detects neurologic deficits in patients who would be classified as asymptomatic according to ‘traditional’ clinical-based criteria for stroke.
- Cerebral protection technology during TAVR procedures shows potential for reducing the burden of procedure-related strokes.
- Standardized MRI-based protocols and prospective evaluation of neurologic deficits with a battery of cognitive assessment tests in patients undergoing TAVR procedures are needed to ensure accurate recognition of postprocedural clinical events.

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Declaration of interest

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References

Papers of special note have been highlighted as either of interest (◦) or of considerable interest (◦◦) to readers.

   ◦◦ This landmark publication endorsed the time-based definition of TIA and stroke.
This expert consensus document emphasized the importance of imaging or pathology based, rather than time based only, definition of stroke and TIA. It also introduced ‘silent’ central nervous system infarction in the proposed classification.


A landmark randomized trial of patients with severe aortic valve stenosis treated with TAVR or conventional surgical aortic valve replacement.


- This prospective study showed a reduction in the number of MRI-positive lesions and neurological deficits with the use of cerebral protection technology during TAVR.

- This study showed a major discrepancy in the documented rate of stroke events after aortic valve surgery depending on the training background of the assessor.