White Paper

Clinical Trial Considerations in Cerebral Protection for TAVR Patients

Embolic protection devices and their potential impact on TAVR patients

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Introduction

Transcatheter aortic valve replacement (TAVR) or implantation (TAVI) demonstrably changed the treatment of high-risk patients with severe aortic stenosis, particularly those at high risk for surgical replacement of the aortic valve. However, greater acceptance of TAVR also raised concerns of complications, particularly increased risks for stroke or neurological and cognitive impairments from embolic events. The entry of embolic protection devices (EPD) into the European (EU) market, with designs that deflect or collect potentially damaging micro-debris associated with TAVR, presents an evolving risk-reduction safety strategy to manage patients, who usually are elderly, with frail health or existing comorbidities. This paper explores the potential for such EPDs as well as factors IQVIA MedTech believes sponsors should consider when developing or using EPDs in clinical trials.

TAVR, or TAVI, has become a standard, minimally invasive option for patients whose health status (too sick to undergo surgical replacement) places them at increased risk for surgical aortic valve replacement (SAVR) for severe aortic stenosis. The first TAVR procedures occurred in Europe in 2002[1] and the United States in 2005, with EU and U.S. commercialization approvals in 2007[2] and 2011,[3] respectively. The success of TAVR adoption resulted from clinical trial patient survival rates equivalent to SAVR and improved survival versus medical therapy, and from the subsequent incorporation of the procedure into both U.S. and European treatment guidelines.

The TAVR market

An estimated 300,000[4] patients have received TAVR, and the market is poised to grow not just due to aging patient populations but also to the August 2016 approvals in the EU and U.S. for expanded TAVR indications to include patients with intermediate risk of death or complications.[5] One analyst said this new population could add annual market growth of 7 to 12 percent in the US, about $400 million,[6] and estimates of the global TAVR market in 2025 have reached $7.45 billion.[7] Such growth also could be spurred when initial market innovators, Medtronic and Edwards Lifesciences, are joined by competitors whose devices are in clinical development but aimed for market clearance decisions before 2020, including Boston Scientific and St. Jude Medical (acquired by Abbott January 2017).

Evaluating strokes related to TAVR

Since the adoption of TAVR, stroke rates among patients appear to have declined due to enhanced devices, surgical expertise and patient selection. However, measures vary by stroke classification – major, minor, transient – and whether assessed during the hospital procedure or at a later date. Below are several studies frequently used as indicators of TAVR-related stroke risk.

One of the most recent TAVR stroke evaluations is an April 2016 meta-analysis of eight studies and five registries. This review reported that study-stroke rates 30 days after TAVR ranged from 4.9 to 0.0 percent – and not significantly different from SAVR rates within each study, which varied from 6.2 to 0.5 percent.[23] Similarly, the five registries reported 30-day rates of 2.5 to 4.1 percent and one-year rates of 4.1 to 4.5 percent.[23] The registries included those in France, Germany and the United Kingdom, as well as that of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry (STS/ACC).

Notably, STS/ACC data, published in 2013, often is cited on its own because it represents the largest single-source evaluation of stroke in TAVR patients: 7,710 from the United States. This assessment examined major strokes both during the procedural hospital stay, 2.0 percent, and 30 days after, 2.8 percent.[24]

One of the longest follow-up of stroke rates stems from the five-year data from The Placement of Aortic Transcatheter Valves (PARTNER) study, a randomized trial of TAVR vs. SAVR. The stroke rate at 30-days for TAVR was 3.8 percent, increasing to 5.1 percent at one year and 10.4 percent at five years.[25] Notably, only the one-year rate significantly differed from SAVR.

Other studies have shown increased risk of stroke over time after TAVR. The U.S. CoreValve High Risk Study reported 30-day rates for any strokes at 4.9 percent and major strokes, 3.9 percent. At one year, the rates increased to 8.8 and 5.8 percent, respectively.[26] The study did not find an increased risk of stroke from TAVR compared to SAVR.[26]

The TAVR market growth, however, has been limited by the procedure's higher risk of stroke, cerebral lesions and increased risk for neurological complications.[8] These outcomes are associated with vascular embolization when debris blocks a cerebral artery. Known clot sources during TAVR procedures include degenerative pieces of the calcified aortic valve leaflets and liberated fatty aortic plaque deposits. Several aspects of TAVR may contribute to the creation of such micro-debris: scraping catheter movements, dilation and removal of the balloon from the patient's valve, and the actual device placement.[9]

Because technical factors, as well as surgical experience strongly correlate with cerebral embolization following TAVR, improvements in devices and implantation expertise have reduced related strokes, a trend expected to continue. However, long-term risks remain real because of the accumulation of TAVR-related cerebral micro-debris and the role of patients' health status, such as chronic atrial fibrillation (AF) or cerebrovascular disease.

Hence the development of embolic protection devices (EPDs) to reduce such risks by deflecting or collecting micro-debris during TAVR. Indeed, the Valve Academic Research Consortium-2 (VARC-2) called for the investigation of such devices as well as medications that might reduce the incidence and severity of strokes after TAVR. More than a dozen companies are developing EPDs, also referred to as cerebral protection devices or embolic deflection devices depending on their mode of

action. The devices can function either to deflect micro-debris into the descending aorta and away from the three cerebral arteries or as filters to capture the debris and prevent it from entering these arteries.

WHAT IS A CEREBRAL EMBOLIC STROKE?

About 87 percent of all strokes are ischemic, the kind in which a blood clot blocks blood flow, according to the AHA, in contrast to hemorrhagic strokes from the rupture of a blood vessel due to a malformation or a weakness called an aneurysm.[27] If the clot forms within a brain blood vessel, it's classified as thrombotic, but when the clot travels into the brain from another location, it's embolic.[28]

As of March 2017, three EPDs have EU market clearance for use with TAVR: Keystone Heart Ltd.'s TriGuard™ Embolic Deflection Device, Edwards Lifesciences' Embrella Embolic Deflector System and Claret Medical, Inc.'s Sentinel™ Cerebral Protection System (CPS). Edwards is testing its EMBOL-X, an EPD approved in the U.S. and EU for use during cardiopulmonary bypass surgery, in TAVR patients. Other companies in this space include Innovative Cardiovascular Solutions and TransVerse Medical Inc. If EPDs become standard for TAVR and other interventional cardiac procedures, their market could reach $1 billion.[7]

TriGuard features a collapsible, flexible Nitinol® frame and mesh. The Embrella uses two self-expanding frames covered in a filter mesh. Both devices are positioned via a catheter within the aortic arch to deflect micro-debris; TriGuard is placed via the femoral artery (the same as the TAVR procedure) and Embrella is placed either via the right radial or brachial artery. The Sentinel CPS is the only approved EPD that acts as a filter to collect debris. Delivered by a catheter through the radial artery, the Sentinel EPD features dual filters, one for the brachiocephalic artery and one for the left common carotid artery, that are removed at the end of the TAVR procedure after recapture within the catheter.

In February 2017, the U.S. Food and Drug Administration (FDA) held a public advisory committee meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee to review Claret Medical's de novo request for the Sentinel® Cerebral Protection System. The committee recommended approval for the device, clearing the way for other EPD manufacturers to pursue 510(k) approvals.

Evaluating EPD impact

In order to understand the potential impact that EPDs might contribute to patients, device sponsors must determine what to measure. The quantification of the risk of disabling strokes and the clinical significance of the brain lesions related to TAVR, with or without EPDs, is complicated because of variations in definitions, assessment tools and clinical data, from both trials and registries. In just the past few years, the diagnosis of stroke has changed from clinical symptoms to now including routine use of clinical imaging, permitting the addition of silent strokes.

The definition of a stroke has changed since the initiation of TAVR trials. Beginning in 2009, U.S. and European academic experts, together with representatives from the FDA and device manufacturers, began developing critical TAVR trial endpoints.[10] The resulting Valve Academic Research Consortium (VARC) consensus report, published in 2011 after informal review by members of seven professional cardiology and cardiac surgery societies, advocated consideration of only major – not minor – strokes as one of a trial's critical safety endpoints. Minor strokes and other neurological events were to be recorded as adverse events. The report described strokes using clinical symptoms and the grading of major and minor strokes via patients' scores on the zero-to-six-pointed Modified Rankin Scale,

which assesses a patient's capability to carry out usual activities of daily living, including walking and body function continence.

The following year, VARC-2 reclassified stroke and modified several related endpoints. Instead of distinguishing between "major" and "minor" strokes, VARC-2 defined "disabling" and "non-disabling," based on a patient's Rankin score 90 days after a stroke.[11] Rankin scores greater than two and an increase by more than one point from the patient's pre-stroke evaluation qualified as a disabling stroke.[11] VARC-2 also called for the use of a new composite calculation using all-cause mortality and disabling stroke, as either a primary or secondary endpoint in TAVR trials. Another new composite was the time-related endpoint for valve safety using a combination of valve dysfunction, endocarditis and thrombotic complications data. Moreover, both early safety (30 day) and clinical efficacy (after 30 days) composite endpoints were to include disabling and non-disabling strokes. VARC-2 also recommended involving a vascular neurologist experienced in stroke and clinical research in "all phases of trial planning, execution, and monitoring, including involvement in the Clinical Events Committee and the Data and Safety Monitoring Board."[11]

In describing stroke, VARC-2 offered five groups of clinical symptom criteria. VARC-2 did not, however, define silent strokes, delineate the difference between a clinical stroke and a cerebral infarction or recommend routine use of diffusion-weighted MRI (DW-MRI) neuroimaging as a tool to characterize stroke or neuronal injuries, noting that diagnosis of stroke may be made just using clinical symptoms. One report indicates that VARC-3 plans to add stroke imaging to its next round of guidance.[12]

How did VARC-2 define stroke?[11]

VARC-2 established five main criteria groups for stroke diagnosis in its 2012 guidelines:

1. Acute episode of a focal or global neurological deficit with at least one of the following:
   - Change in level of consciousness
   - Hemiplegia (paralysis), hemiparesis (partial paralysis), numbness or sensory loss on one side of the body
   - Dysphasia (impaired speech) or aphasia (impaired comprehension of speech)
   - Hemianopia (blindness in half the visual field), amaurosis fugax (temporary vision loss)
   - Or other neurological signs or symptoms consistent with stroke

2. Duration of a focal or global neurological deficit of more than 24 hours, or less than 24 hours if available neuroimaging documents a new hemorrhage (bleeding) or infarct (dead tissue due to blocked blood supply) or the neurological deficit results in death

3. Transient ischemic attack having a focal or global neurological deficit of more than 24 hours and any variable neuroimaging does not demonstrate a new hemorrhage or infarct

4. No other readily identifiable non-stroke cause for the clinical presentation, such as brain tumor, trauma, infection, hypoglycemia, peripheral lesion, or pharmacological influences to be determined by or with the designated neurologist

5. Confirmation of the diagnosis by at least one of the following:
   - Neurology or neurosurgical specialist
   - Neuroimaging procedure (CT scan or brain MRI) but stroke may be diagnosed on clinical grounds alone

Such issues, however, have already been addressed by other groups, providing guidance which sponsors can apply to EPD trials with TAVR. In 2013, the Stroke Council of the American Heart Association/American Stroke Association (AHA/ASA) recognized that stroke criteria "for the 21st Century" in clinical practice and research should be detailed, and it distinguished the role of clinical, neurological and cognitive symptoms in stroke criteria and the use of imaging.[12] AHA/ASA defined a central nervous system infarction as "brain, spinal or renal cell death attributable to ischemia, based on neuropathological, neuroimaging and/or clinical evidence of permanent injury."[13]

The Council also clarified that ischemic strokes must have overt symptoms, while silent infarctions cause no known symptoms. The AHA/ASA also recommended a patient can be diagnosed with stroke with just imaging evidence identifying brain abnormalities consistent with ischemic injury even if he or she lacks classic clinical stroke symptoms or a history of stroke or transient ischemic attack (TIA) (i.e., the patient has had a silent stroke). These expanded, clinical and structural 21st Century diagnosis criteria included input from the American Academy of Neurology, the American Association of Neurological Surgeons and Congress of Neurological Surgeons, the FDA, the U.S. Centers for Disease Control and Prevention and the National Institute of Neurological Disorders and Stroke, part of the National Institutes of Health (NIH).

Significance of silent strokes

The use of silent strokes as an endpoint results from their known adverse consequences, which can impair mobility or cause physical decline, depression, cognitive dysfunction, dementia and a two-to-four-fold increase of clinical stroke risk, independent of other vascular and stroke risk factors.[13]

Current EPD trials use silent strokes/brain lesions as a surrogate marker for disease, even though the clinical relevance of such lesions for TAVR patients is not established firmly because of mixed results, likely influenced by variations in use of lesion counts or volumes within trial endpoints, in stroke definitions and in trial durations. While many studies utilizing MRI have documented new cerebral lesion rates in patients after TAVR alone (ranging from 68[14] to 100 percent[15]), related cognitive assessments have shown improvement, preservation and declines in patients. One meta-analysis of six TAVR trials, with lesion incidences from 58 to 86 percent, found patients' global cognition significantly improved or unchanged, with no changes two years post-procedure on select cognition tests. However, the investigators cautioned the improvements might have resulted from patients' improved cardiac function after TAVR.[16]

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As part of its U.S. regulatory pathway for TriGuard, Keystone conducted the first U.S. prospective unprotected TAVR study with systematic use of neurologic and cognitive evaluations and MRI. This Neuro-TAVI trial found one in five (22.6 percent) patients had new neurological deficits at discharge, with 33 percent experiencing increased cognitive impairment.[8] However, by the 30-day assessment, neurological deficits had resolved to 14.8 percent of patients while the cognitive impairment rate rose to 41 percent.[8] The study also found 94 percent had a number of lesions, averaging 10.4 ± 15.3 per patient.[8] The median lesion size was 295 mm^3 in volume and ranged from 71.6 to 799.6

mm^3.[8] Of note, within the brain 1 mm^3 can have "at least 80,000 neurons and 4.5 million synapses,"[17] leading the authors to estimate that a patient's total ischemic lesion volume could represent the death of millions of neurons and a billion synapses.[18]

As sponsors continue to explore different EPD designs and their effects in diverse patient populations, the field will have greater clarity in understanding the significance of stroke occurrence. In the meantime, sponsors should consider the verified data on the three approved EPDs as they design their EPD trial protocols and endpoints.

Designing an EPD trial

Sponsors examining the effectiveness and safety of EPD in TAVR procedures need to consider not only their patient populations and definitions of endpoints, but the technology employed and methods of data assessment. Sponsors seeking appropriate patients for an EPD trial should follow the same site evaluations they would apply for a TAVR trial: 1) the size and health of the potential patient population, and 2) clinical trial expertise with TAVR which the site team possesses.

PATIENTS AND SITE TEAMS

EPD/TAVR study patients must have stable health for 30 days before the procedure and have undergone assessments of the valve severity, comorbidities and mortality risk, which can challenge recruitment procedures compared to other cardiac device trials. For example, knowing the dosing of antithrombotic and antiplatelet medication or existence of carotid stenosis is necessary to determine later if these factors had a role in any post-procedure strokes.

Sponsors should select sites with a track record of commitment to patient enrollment as well as retention while planning for additional time and resources that usually are greater than they are with other device studies. EPDs currently have been assessed in TAVR patients who are at highest risk for SAVR; however, with the expanded indication of TAVR to intermediate risk patients, sponsors will need to document and evaluate patient health carefully to ensure study participants are matched for such characteristics. Metrics should include frailty, severity of aortic atherosclerosis, liver disease and pulmonary hypertension, among other factors such as quality of life and life expectancy. Any meta-analyses or historical comparisons must account for and make appropriate analytical adjustments for heterogeneous characteristics and risks within the patient populations.

A committed, organized and multidisciplinary interventional and surgical heart team can help a sponsor achieve the best patient outcomes, both in study settings as well as in post-approval commercial use of the devices.

Experts recommend a team approach for patient evaluations, both for enrollment, trial execution and follow-up. Two best practices to control for enrollment variations are for the principal investigator to review candidate patients with a central trial eligibility committee and to use a central echocardiographic core laboratory for transthoracic echocardiographic evaluations to determine patients' anatomical and severity qualities vs. entry criteria.

Each site should have a core team that includes a heart failure/valve cardiologist, an interventional cardiologist, cardiovascular surgeons and imaging specialists. IQVIA MedTech has found it beneficial to expand this team to include geriatricians and other specialties such as heart failure experts, stroke neurologists, electrophysiologists, anesthesiologists and behavioral specialists. In particular, IQVIA MedTech recommends EPD sponsors strive to characterize changes in a patient's neurocognition by using trial staff with neuropsychological experience.

In addition to precise endpoints and assessment protocols, sponsors also need to provide extensive training to maximize reproducibility and minimize variation between staff and sites. Such attention to detail and conduct are necessary to look objectively for subtle changes that TAVR might cause and for which EPD might protect in a patient's memory, concentration, executive function, psychomotor speed and the ability to manually organize and move spatial information (visuoconstructional ability).

A site team's capabilities require not only medical specialty expertise but the demonstrated ability to collaborate across disciplines to manage patients. A committed, organized and multidisciplinary interventional and surgical heart team can help a sponsor achieve the best patient outcomes, both in study settings as well as in post-approval commercial use of the devices. A CRO partner can identify gaps and propose solutions for staffing a trial's requisite endovascular expertise, as well as helping ready and supervise the heart valve teams, both at the site and study levels.

Experienced multidisciplinary TAVR teams usually reside at large-volume tertiary health care centers or those that routinely can convert their catheterization laboratories to surgical operating facilities, should a patient need it. A team's experience with the device implantation route can be a factor for site selection, given the different EPD-specific methods employed. Flexible facilities usually can handle more than one percutaneous route and are more frequently found in U.S. sites, while stand-alone cardiology centers, usually in Europe, may have only experienced the femoral artery approach.

Even with experienced, qualified sites, sponsors must invest in significant training to ensure teams understand the product-specific operations of the TAVR and EPD, the surgical procedures and the complications and outcomes. Until sites individually and across the trial achieve consistency and continuity, a sponsor may find it advisable to use on-site field engineers or clinical safety specialists to help support procedures.

ENDPOINTS

EPD trial endpoints must cover many aspects of efficacy and safety. Many aspects of traditional interventional cardiology, and specifically TAVR, trial endpoints address such needs. To best understand complications, sponsors of EPD trials should ensure their protocols include standardized definitions and criteria for the known and probable clinical, neurological and cognitive symptoms of overall health, stroke and brain lesions. Sponsors also must delineate imaging, other technology and functional testing and timing of their use for the study enrollment, procedure and near- and long-term follow-ups. Collection and documentation of postoperative complications, such as atrial fibrillation, are necessary for determining if TAVR or EPD had any contributing roles to post-procedure strokes. Moreover, these data can help establish if EPD devices influence not only new stroke or lesion rates but also their clinical significance. Additionally, sponsors should create protocols for the assessment of the EPDs after removal.

IQVIA MedTech also recommends that endpoints must be considered within the existing and anticipated regulatory requirements, whether for the internal review board of an individual site or a national marketing clearance criteria and how to address such conditions via a trial's design, conduct and evaluations. Most sponsors have active registries to address needs for analyses of any safety issues. Knowing the regulatory path for an investigational EPD also can yield efficiencies via trial protocols that address current and future data needs.

STROKE AND NEUROLOGICAL ASSESSMENT

In asking investigators to adopt their guidance, the AHA/ASA noted that in clinical research stroke definitions "should always reflect the goals of a given research study and should be carefully specified before initiating the trial."[13] The consensus affirmed the possible use of ischemic stroke as a trial's primary outcome, and secondary endpoints could capture "subtle neuropsychological findings in association with evidence of ischemia or imaged infarction without more

overt clinical sequelae."[13] Since the inclusion of clinically silent brain lesions in endpoints would represent a new field of data collection and analyses, the AHA/SAS cautioned that:

"Including such imaged events as strokes may unnecessarily inflate the assessment of risk of those procedures without a measurable clinical advantage to doing so. One way to address this problem is to define categories of stroke representing degrees of clinical activity, such as obvious symptoms and signs, subtle signs ..."[13]

In studies with long-term follow-up, as might be the case for EPDs, sponsors investigating the use in intermediate-risk TAVR populations, imaging technology is likely to change. AHA/ASA anticipated this evolution and recommended therefore that studies use two definitions for stroke: 1) the existence of clinical stroke symptoms or signs lasting 24 or more hours, and 2) the occurrence of focal symptoms of less than 24 hours but with positive imaging.[13]

NEUROLOGICAL TESTING

Sponsors should involve neurologists to assess patients during the trial and follow-up because their clinical experience can contribute to more accurate diagnosis of impairment. Of note, the five-year assessment of the PARTNER trial, which involved 699 TAVR patients, did not include a neurologist, leading the investigators to conclude that the results could raise "concerns of under-reporting of neurologic events; however, if neurologic events were under-diagnosed, it would probably occur equally in each treatment group."[19] Such assumptions may not be appropriate for smaller study populations and would be unacceptable for trials examining cerebral lesions and micro-embolisms.

In TAVR trials, sponsors have detected new neurologic deficits using the National Institutes of Health Stroke Scale (NIHSS), the Montreal Cognitive Assessment (MoCA), the Center for Epidemiologic Studies Depression Scale (CES-D) and Mini-Mental State Examination (MMSE). Some trials also used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a collection of 12 tests of language, attention, visual and constructional skills, immediate memory, and delayed memory, which can be repeated with elderly patients.

One team of experts recommended that elderly patients' assessments should focus on possible vascular impairments of cognition, such as executive function and processing speed. By combining results from neurocognitive tests with those of a patient's physical health, frailty, mood, activities of daily living and quality of life, investigators can develop a complete context in which to assess the clinical significance of any post-procedure lesions.

IMAGING

While there are additional modalities that can aid in the detection of stroke and provide further insight to procedural causes of microembolization, MRI with diffusion-weighted imaging (DWI) is considered the gold standard for detecting and quantifying brain ischemia related to cardiovascular procedures such as TAVR.[18]

TRANSCRANIAL DOPPLER SIGNAL DETECTION

The incidence of cerebral microembolization (CME) and postoperative neurological deficit (stroke, TIA) is significant, but a correlation between them remains elusive. Transcranial Doppler (TCD) is a non-invasive technique that is used for real-time intraoperative monitoring of intracranial blood flow and embolization. The ultimate goal of future studies using TCD is to correlate the volume of intraoperative CMEs detected by TCD to the severity of postoperative neurological impairment.

IQVIA MedTech and Medical Metrics recommend requiring the use of baseline and post-procedure MRI data for endpoints in EDP-related clinical research to locate, count and quantify volumes of lesions. Various

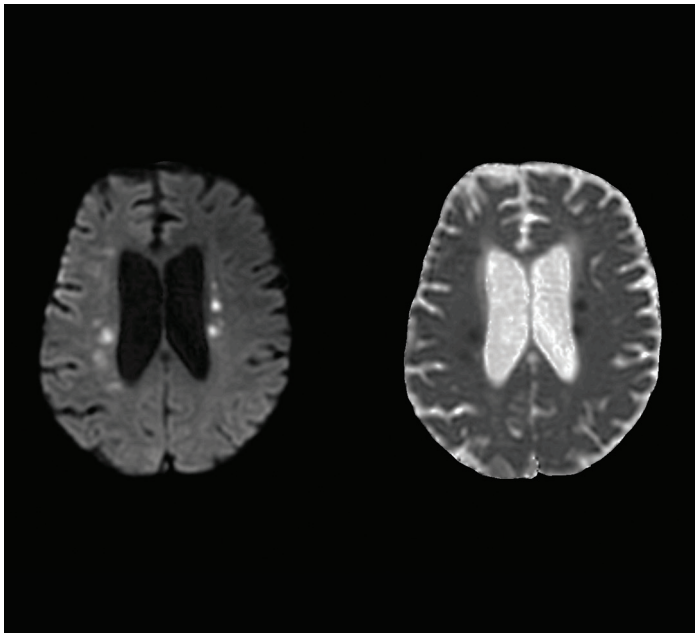
MRI sequences are utilized to accurately characterize not just the extent and distribution of acute ischemia but to also differentiate acute ischemia from existing lesions, such as white matter changes or leukoaraiosis related to chronic ischemic microangiopathy, and to identify areas of hemorrhage. It is also recommended that Apparent Diffusion Coefficient (ADC) maps be used, if available, in conjunction with DWI because DWI can be hyperintense from T_2 shine-through effect.

DWI is the most reliable imaging method for the early detection of acute ischemia, defining the extent of infarct core, and differentiating acute ischemia from other neurological conditions that can mimic stroke. DWI is highly sensitive and specific for detecting acute ischemia (90-100% range) and can show diffusion changes within minutes of symptom onset. Since most acute infarctions related to TAVR will be small, and can limit detection by partial volume effect, sensitivity for identifying small infarctions can be increased by scanning DWI in multiple orientations (e.g., axial, coronal and sagittal). If time permits, diffusion tensor imaging (DTI) can be used in lieu of DWI. DTI is more sensitive in detecting acute ischemia than DWI and also provides other parameters such as mean diffusivity and fractional anisotropy, which can be used to determine white matter tract integrity that can correlate with specific neurological test metrics. Various stroke studies have utilized perfusion imaging (DSC with contrast or ASL without contrast) to identify regions of low blood flow at risk (penumbra) surrounding the infarct core. However, perfusion defects for small embolic infarctions are most likely negligible unless there is occlusion in the proximal circle of Willis (e.g., ICA, M1-M2 MCA), which is rare for TAVR procedures.

DWI is highly sensitive and specific for detecting acute ischemia and can show diffusion changes within minutes of symptom onset.

Common MRI sequences for evaluating acute ischemia

SEQUENCE	APPLICATION
DWI	Provides information on water diffusion in tissue, which is reduced in acute ischemia. Most sensitive and specific sequence for identifying acute ischemia.
T_2 FLAIR	Provides structural information by suppressing signal from cerebral spinal fluid and increases conspicuity of fluid signal elsewhere in the brain. Helpful for differential diagnosis including increased signal with edema, gliosis, and white matter changes related to chronic ischemia.
T_2* GRE	Evaluates hemorrhage and calcification with decreased signal.
T_1 FSE	Provides structural information and helpful for differential diagnosis including increased signal with fat, subacute hemorrhage, and proteinaceous fluid.
T_2 FSE	Provides structural information and helpful for differential diagnosis similar to T_2 FLAIR with occasional higher sensitivity for lesions involving deep gray matter including basal ganglia, thalamus, and infratentorial structures.
DTI	Similar to DWI but a longer scan with multiple diffusion directions evaluated. Provides parameters such as mean diffusivity and fractional anisotropy along white matter tracts that can be followed for acute infarction. Higher SNR than DWI.
3D T_1 SPGR	High resolution structural scan similar to T_1 FSE with reformatting capabilities.

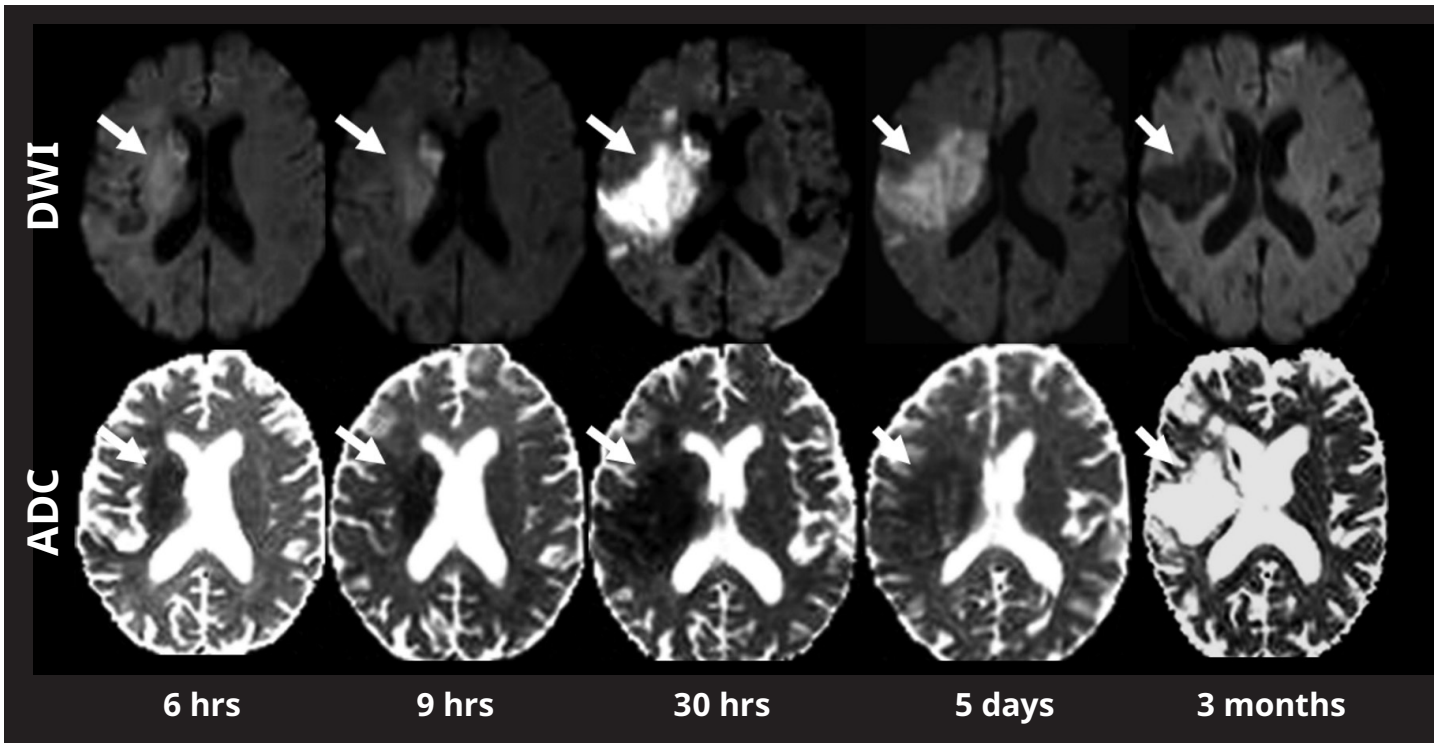


DWI (left) and ADC map (right) demonstrate multiple microinfarcts that are hyperintense on DWI and hypointense on ADC map. ADC is helpful in determining if the hyperintense lesions on DWI are acute infarctions (hypointense on ADC map) or chronic from T_2 shine-through (hyperintense on ADC map).

When designating MRI use in clinical trials, it is essential to utilize an experienced imaging core lab for centralized evaluation of the imaging. The objective is to assure consistent acquisition and interpretation of the imaging across all participating clinical trial sites. Medical Metrics and other core lab institutions establish standardized protocols for MRI acquisition and data transfer by the site, in addition to protocols on how reviewers will score and evaluate the images. For MRI acquisition standardization, sponsors should consider differences between field strengths because the related sensitivity differences can influence the ability to find small lesions. Signal-to-noise ratio (SNR) is directly proportional to magnetic field strength, measured in tesla (T), which determines the quality of its images. Most MRIs in clinical practice are 1.5T, yet 3.0T MRIs are readily found in academic medical centers and high-end specialty practices and gaining footholds in facilities replacing aging systems. Greater sensitivity and resolution in images and shorter scan times from 3.0T MRIs could be advantageous for new studies. However, one must also be aware of the conditions for which the implanted heart valve prosthesis is considered safe for the patient to have an MRI scan as determined by manufacturer testing.

While all of the heart valve prostheses listed in the present U.S. market are considered safe/conditional at 1.5T, only some are safe/conditional at 3.0T. For this reason, most of the early TAVR trials of embolic protection devices have used images gathered with 1.5T machines,[12] although recent trials have used 3.0T machines.[20, 21] Additionally, magnetic field strength differences are particularly important for sponsors planning to leverage historical reference device data in regulatory filings or meta-analyses, as using analogous MRI strengths will help evaluative comparisons.

Similarly, sponsors of trials that compare two interventional approaches should ensure both the standardization of imaging technology and the timing of its use with patients. The timing of MRIs is critical because the quantity and dimensions of lesions can change substantially during the first week after a patient undergoes TAVR.[21] This early change of lesion visualization is due to a rapid decrease in water diffusion that is markedly hyperintense on DWI.[22] Ideally, imaging should be performed within 24 hours pre-procedure, and 24 to 48 hours post-procedure. Early follow-up within 48 hours will minimize the heterogeneity of the detected lesion volumes that would occur within a larger time interval, such as two to seven days, and assure stronger causality that the infarct is related to the procedure. The etiology of cerebral injury is multifactorial, and embolic risk may persist for days after the procedure is complete.[21] As appropriate, additional imaging follow-up at five to seven days and/or 30 days may be performed to monitor how the infarctions evolve over time, confirm equivocal findings at an earlier time point and evaluate for complications such as hemorrhagic transformation and enlarging infarct.



Axial DWI images (upper row) and ADC maps (second row) demonstrate the temporal evolution of infarction (arrows). At 6 hours, the right MCA territory infarction is mildly hyperintense on DWI and hypointense on ADC maps due to cytotoxic edema. By 30 hours, there is marked DWI hyperintensity and ADC hypointensity due to increased cytotoxic edema at the ADC nadir.[22]

Sponsors can account for any influence on results by ensuring neurological tests and evaluations capture baseline variations among patients, such as stroke history and education levels, as well as post-treatment factors, such as delirium.

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