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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials

An Academic Research Consortium Initiative

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ABSTRACT

Surgical and catheter-based cardiovascular procedures and adjunctive pharmacology have an inherent risk of neurological complications. The current diversity of neurological endpoint definitions and ascertainment methods in clinical trials has led to uncertainties in the neurological risk attributable to cardiovascular procedures and inconsistent evaluation of therapies intended to prevent or mitigate neurological injury. Benefit-risk assessment of such procedures should be on the basis of an evaluation of well-defined neurological outcomes that are ascertained with consistent methods and capture the full spectrum of neurovascular injury and its clinical effect. The Neurologic Academic Research Consortium is an international collaboration intended to establish consensus on the definition, classification, and assessment of neurological endpoints applicable to clinical trials of a broad range of cardiovascular interventions. Systematic application of the proposed definitions and assessments will improve our ability to evaluate the risks of cardiovascular procedures and the safety and effectiveness of preventive therapies. (J Am Coll Cardiol 2017;69:679–91) © 2017 The Authors. Published by Elsevier Inc. on behalf of the American College of Cardiology Foundation. All rights reserved.

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ABBREVIATIONS AND ACRONYMS

CNS = central nervous system

DWI = diffusion-weighted imaging

MRI = magnetic resonance imaging

mRS = modified Rankin scale

NeuroARC = Neurologic Academic Research Consortium

Stroke is among the most feared complications of surgical and transcatheter cardiovascular interventions, affecting both benefit-risk evaluations and health care costs (1-6). The primary mechanism of procedure-related stroke is focal or multifocal embolization during cardiovascular instrumentation or surgical manipulation; diffuse cerebral hypoperfusion from sustained or profound procedural hypotension (i.e., global hypoxic ischemic injury) is a less common cause. The ongoing risk of spontaneous stroke beyond the periprocedural time frame may be more dependent on patient-related risk factors, although late device-related complications are also a concern (7,8). Clinical manifestations of periprocedural stroke are highly variable and substantially under-reported, and systematic evaluations by neurologists commonly uncover more subtle, but nonetheless clinically significant, neurological deficits (6,9-12). Routine neuroimaging has revealed that "silent" ischemic cerebral infarcts are common after a wide range of procedures (9,13), although their clinical significance and association with subsequent cognitive decline and future stroke remains incompletely characterized (14,15). Because such infarcts are estimated to affect 600,000 patients annually in the United States alone (16), a better understanding of their clinical implications, and the role of imaging and cognitive measures in device and procedural evaluations, is necessary. The Neurologic Academic Research Consortium (NeuroARC) is an international collaboration convened to propose sensitive but pragmatic definitions and assessments for neurological injury relevant to cardiovascular interventions.

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TABLE 1 Neurological Endpoint Definitions and Classification

		NeuroARC Neurological Event Definitions
Type 1		**Overt CNS Injury: Acutely Symptomatic Brain or Spinal Cord Injury**
Type 1.a	Ischemic stroke	Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that: 1. Persist for ≥24 h or until death, with pathology or neuroimaging evidence that demonstrates either: a. CNS infarction in the corresponding vascular territory (with or without hemorrhage); *or* b. Absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected *or* 2. Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. *Note:* When CNS infarction location does not match the transient symptoms, the event would be classified as covert CNS infarction (Type 2a) and a TIA (Type 3a), but not as an ischemic stroke. Signs and symptoms consistent with stroke typically include an acute onset of 1 of the following: focal weakness and/or numbness; impaired language production or comprehension; homonymous hemianopia or quadrantanopsia; diplopia; altitudinal monocular blindness; hemispatial neglect; dysarthria; vertigo; or ataxia.
Subtype 1.a.H	Ischemic stroke with hemorrhagic conversion	Ischemic stroke includes hemorrhagic conversions. These should be subclassified as Class A or B when ischemic stroke is the primary mechanism and pathology or neuroimaging confirms a hemorrhagic conversion. Class A: Petechial hemorrhage: Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect Class B: Confluent hemorrhage: Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect
Type 1.b	Symptomatic intracerebral hemorrhage	Rapidly developing neurological signs or symptoms (focal or global) caused by an intraparenchymal, intraventricular, spinal cord, or retinal collection of blood, not caused by trauma
Type 1.c	Symptomatic subarachnoid hemorrhage	Rapidly developing neurological signs or symptoms (focal or global) and/or headache caused by bleeding into the subarachnoid space, not caused by trauma
Type 1.d	Stroke, not otherwise specified	An episode of acute focal neurological signs or symptoms and/or headache presumed to be caused by CNS ischemia or CNS hemorrhage, persisting ≥24 h or until death, but without sufficient evidence to be classified (i.e., no neuroimaging performed)
Type 1.e	Symptomatic hypoxic-ischemic injury	Nonfocal (global) neurological signs or symptoms due to diffuse brain, spinal cord, or retinal cell death (confirmed by pathology or neuroimaging) in a nonvascular distribution, attributable to hypotension and/or hypoxia
Type 2		**Covert CNS Injury: Acutely Asymptomatic Brain or Spinal Cord Injury Detected by Neuroimaging**
Type 2.a	Covert CNS infarction	Brain, spinal cord, or retinal cell death attributable to focal or multifocal ischemia, on the basis of neuroimaging or pathological evidence of CNS infarction, without a history of acute neurological symptoms consistent with the lesion location
Subtype 2.a.H	Covert CNS infarction with hemorrhagic conversion	Covert CNS infarction includes hemorrhagic conversions. These should be subclassified as Class A or B when CNS infarction is the primary mechanism and neuroimaging or pathology confirms a hemorrhagic conversion. Class A: Petechial hemorrhage petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect Class B: Confluent hemorrhage: confluent hemorrhage originating from within the infarcted area with a space-occupying effect
Type 2.b	Covert CNS hemorrhage	Neuroimaging or pathological evidence of CNS hemorrhage within the brain parenchyma, subarachnoid space, ventricular system, spinal cord, or retina on neuroimaging that is not caused by trauma, without a history of acute neurological symptoms consistent with the bleeding location
Type 3		**Neurological Dysfunction (Acutely Symptomatic) Without CNS Injury**
Type 3.a	TIA	Transient focal neurological signs or symptoms (lasting <24 h) presumed to be due to focal brain, spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging)
Type 3.b	Delirium without CNS injury	Transient nonfocal (global) neurological signs or symptoms (variable duration) without evidence of cell death by neuroimaging or pathology
		Composite Neurological Endpoints*
CNS infarction		Any brain, spinal cord, or retinal infarction on the basis of imaging, pathology, *or* clinical symptoms persisting for ≥24 h (includes Types 1.a, 1.a.H, 1.d, 1.e, 2.a, 2.a.H)
CNS hemorrhage		Any brain, spinal cord, or retinal hemorrhage on the basis of imaging or pathology, not caused by trauma (includes Type 1.b, 1.c, 2.b)

*Neurological endpoints are not mutually exclusive; an individual subject may have >1 event. Valve Academic Research Consortium–defined stroke includes all Type 1 events (stroke and symptomatic hypoxic-ischemic injury). American Stroke Association–defined stroke includes Type 1.a–d events (overt [focal only] CNS injury), and Type 2.a and 2.a.H (covert CNS infarction).

CNS = central nervous system; mRS = modified Rankin Scale; NeuroARC = Neurologic Academic Research Consortium; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack.

NeuroARC COMPOSITION AND GOALS

In accordance with the Academic Research Consortium mission statement (17), we convened diverse stakeholders, including physician and scientific leaders in interventional and structural cardiology, electrophysiology, cardiac surgery, neurology, neuroradiology, and neuropsychology; clinical trialists representing academic research organizations from the United States and Europe; and representatives from the U.S. Food and Drug Administration and the medical device industry (Online Appendix). In-person meetings were held on October 11, 2015, in San Francisco, California, and on January 30, 2016, in New York, New York. Following the initial meeting, writing groups were established to capture the consensus on specific topics. The resulting draft was presented to and refined by the entire group at the second meeting, and the final document was subsequently adopted by general agreement. The accompanying Online Appendix provides additional details and practical considerations for the implementation of these recommendations in clinical trials.

The goals of NeuroARC are to establish consensus on: 1) definitions for reproducible endpoints reflecting neurological and cognitive outcomes relevant to a range of cardiovascular procedures; 2) classification of neurological events (type, acute severity, timing, and associated long-term disability); and 3) ascertainment methods for consistent event identification, adjudication, and reporting. Basic principles included: 1) emphasis on definitions that reflect clinically meaningful patient outcomes; 2) classification of the full spectrum of neurovascular injury, while discriminating between degrees of clinical effect; and 3) identification of practical assessment methodologies, while maintaining consistency with prior initiatives defining neurological endpoints (18–20). NeuroARC endorses incorporating the proposed definitions into the National Institute of Neurological Disorders and Stroke Common Data Element project (21) to increase data quality and to enable pooling of data across trials to enhance scientific, clinical, and regulatory insights.

SCOPE AND CHALLENGES OF NEUROLOGICAL ENDPOINT STANDARDIZATION

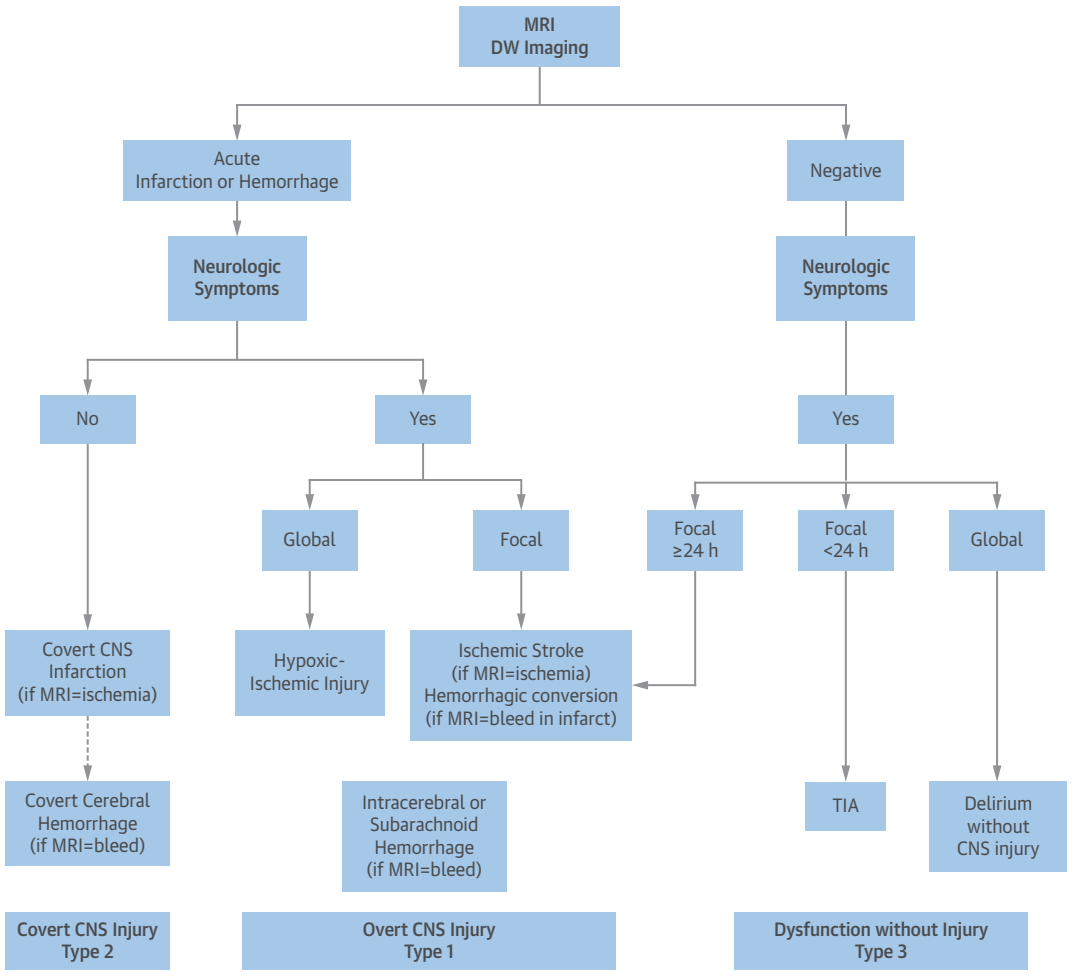
The NeuroARC recommendations apply to trials of a range of surgical and catheter-based cardiovascular interventions (and adjunctive pharmacotherapies) involving the heart, ascending aorta, and great vessels, or requiring the use of temporary or long-term mechanical circulatory or cardiopulmonary support (including cardiopulmonary bypass), for which neurological benefits and risks are important considerations. Given the diversity of relevant interventions and devices, these recommendations should be viewed as a framework to inform the application of relevant endpoints and assessments, rather than a mandate for the design of specific trials. NeuroARC recommendations are not intended to address acute stroke interventions, which have distinct therapeutic considerations.

Our ability to interpret the risks associated with procedure-related neurovascular injury is challenged by existing gaps in clinical evidence; in particular, the lack of a conclusive link between acute procedure-related subclinical brain lesions and long-term neurological or cognitive outcomes. We use the term *covert central nervous system (CNS) infarction* to acknowledge that these events are not necessarily free of clinical consequences, and that detection of neurological or cognitive sequelae is heavily dependent on the nature, sensitivity, and timing of outcome assessments. Because diffusion-weighted imaging (DWI) magnetic resonance imaging brain lesions are frequent after cardiovascular procedures and represent mostly permanent brain damage, and because large population-based studies demonstrate associations with cognitive decline, clinical stroke, and mortality (15,22,23), NeuroARC aims to define the full spectrum of neurovascular injury with the assumption that standardized data acquisition will accelerate differentiation between clinically meaningful and incidental findings. With these challenges in mind, the NeuroARC consensus is intended to be a living document, and will be reviewed every 2 years to determine whether evolving evidence warrants revision.

DEFINITION AND CLASSIFICATION OF NEUROLOGICAL INJURY

Brain injury related to cardiovascular procedures spans a spectrum from overt stroke to covert injury, and can be classified according to clinical signs and symptoms and neuroimaging. NeuroARC recommends classification on the basis of symptoms and evidence of CNS injury, including overt (acutely symptomatic) CNS injury (Type 1), covert (acutely asymptomatic) CNS injury (Type 2), and neurological dysfunction (acutely symptomatic) without CNS injury (Type 3). **Table 1** summarizes the proposed NeuroARC definition and classification of neurovascular events.

FIGURE 1 **Imaging-Driven Diagnosis of Stroke and CNS Infarction (for Studies With Routine Neuroimaging)**



Note: Assessment of the consistency of signs and symptoms with lesion distribution is a matter of clinical judgment and, in clinical trials, should be adjudicated by an independent Clinical Events Committee. CNS = central nervous system; DW = diffusion-weighted; MRI = magnetic resonance imaging; TIA = transient ischemic attack.

CNS INFARCTION AND THE ROLE OF IMAGING

With advances in neuroimaging and the widespread availability of magnetic resonance imaging (MRI), the accepted definitions of stroke and transient ischemic attack (TIA) have evolved considerably, shifting toward tissue-based, rather than symptom-based criteria (20,24). The American Heart Association/American Stroke Association recently proposed a new framework to define stroke that emphasizes CNS infarction, defined as "brain, spinal cord, or retinal cell death attributable to focal arterial ischemia, based on: 1) pathological, neuroimaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2) clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution with symptoms persisting ≥24 h or until death, and other etiologies excluded" (20). Thus, CNS infarction may be identified by neuroimaging alone, and its effect may be further characterized by the associated neurological and cognitive symptoms and by disability. NeuroARC recommends an approach that maintains historical consistency with the well-established symptom-based definitions of stroke, while enhancing the reporting of cerebral injury with the more sensitive tissue-based diagnostic criteria (**Table 1**, **Figure 1**).

TABLE 2 Recommended Endpoints and Assessments by Device or Procedure Category

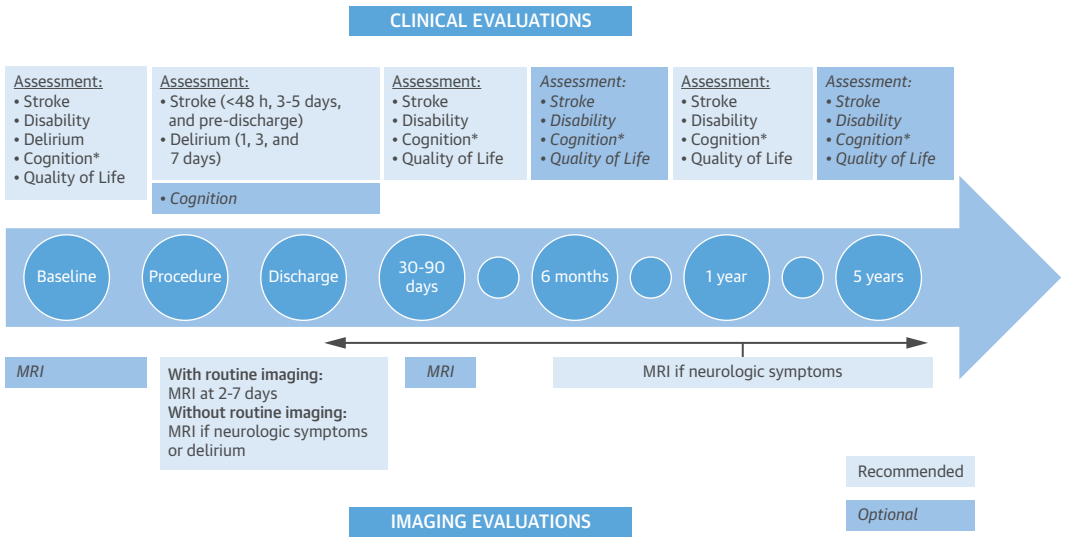
	Category I: Neurological Injury as Procedural and Long-Term Safety Measure	Category II: Neurological Injury as Procedural Efficacy Measure	Category III: Neurological Injury as Procedural Safety and Long-Term Efficacy Measure
Device/procedure type	Devices or procedures with inherent iatrogenic embolic risk, for example: • Surgical cardiac or ascending aorta procedures (valve replacement, CABG, ascending aorta, and aortic arch replacement) • Transcatheter cardiac procedures (TAVR, MVR, LV devices for heart failure) • Thoracic endovascular aortic repair	Devices or procedures designed to prevent iatrogenic or spontaneous acute neurological injury, for example: • Neuroprotection devices • Cerebral temperature management devices	Devices or procedures with inherent iatrogenic embolic risk and designed for prevention of spontaneous long-term risk, for example: • Atrial fibrillation ablation • PFO or LAA closure • Carotid interventions • Adjunctive pharmacotherapy trials
Suggested endpoints	Early and long-term safety endpoints • Overt CNS injury (Type 1) • CNS infarction and CNS hemorrhage • Neurological dysfunction (Type 3) • Cognitive change (overall) Optional early safety endpoints • MRI total lesion volume • Covert CNS injury (Type 2)	Early efficacy endpoints • Overt and covert CNS injury (Type 1 and 2) • CNS infarction and CNS hemorrhage • Neurological dysfunction (Type 3) • MRI total lesion volume • Cognitive change (overall and domain-specific)	Early safety and long-term efficacy endpoints • Overt CNS injury (Type 1) • CNS infarction and CNS hemorrhage • Neurological dysfunction (Type 3) • Cognitive change (overall and domain-specific) Optional early safety endpoints • MRI total lesion volume • Covert CNS injury (Type 2)
Clinical assessments	Neurological and functional impairment • NIHSS • QVSFS or ACAS TIA/stroke questionnaire • CAM (3D or ICU) • mRS • Barthel Index Cognitive • Cognitive Screening (e.g., MoCA) • Comprehensive Battery (Table 6) optional Quality of life • NeuroQol *or* EQ-5D • Incremental cost-effectiveness ratio	Neurological and functional impairment • NIHSS • CAM (3D or ICU) • mRS • Barthel Index Cognitive • Cognitive screening (e.g., MoCA) • Comprehensive battery (Table 6) Quality of life • NeuroQol *or* EQ-5D • Incremental cost-effectiveness ratio	Neurological and functional impairment • NIHSS • QVSFS or ACAS TIA/stroke questionnaire • CAM (3D or ICU) • mRS • Barthel Index Cognitive • Cognitive screening (e.g., MoCA) • Comprehensive battery (Table 6) Quality of life • NeuroQol *or* EQ-5D • Incremental cost-effectiveness ratio
Neuroimaging	• MRI is preferred and recommended in all patients with a suspected neurovascular event or acute delirium. • If MRI cannot be performed and a head CT is obtained to rule out hemorrhage, it can be used as an alternative to confirm CNS infarction • Post-procedure MRI should be considered in a subset of patients • TCD optional in early device evaluation	• MRI should be obtained post-procedure in all eligible patients; baseline MRI is optional for subtraction • CT scan is suboptimal for efficacy trial endpoints, but if clinically indicated (i.e., a sudden major neurological change), an immediate head CT should be obtained to rule out hemorrhage • TCD optional in early device evaluation	• MRI is preferred and recommended in all patients with a suspected neurovascular event or acute delirium • If MRI cannot be performed and a head CT is obtained to rule out hemorrhage, it can be used as an alternative to confirm CNS infarction • Post-procedure MRI should be considered in a subset of patients • TCD optional in early device evaluation

3D = 3-min diagnostic; ACAS = asymptomatic carotid atherosclerosis study; CABG = coronary artery bypass graft surgery; CAM = confusion assessment method; CT = computed tomography; ICU = intensive care unit; LAA = left atrial appendage; LV = left ventricular; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; MVR = mitral valve replacement; NIHSS = National Institutes of Health Stroke Scale; PFO = patent foramen ovale; QVSFS = Questionnaire for Verifying Stroke Free Status; TAVR = transcatheter aortic valve replacement; TCD = transcranial Doppler ultrasound; other abbreviations as in Table 1.

STROKE VERSUS GLOBAL HYPOXIC-ISCHEMIC INJURY

Stroke is the acute onset of symptoms consistent with focal or multifocal CNS injury caused by vascular blockage resulting in ischemia or vascular rupture resulting in hemorrhage, and is distinct from global hypoxic-ischemic injury. Stroke may be widespread, although it always occurs in specific vascular territories, whereas global hypoxic-ischemic insult causes diffuse neuronal injury that does not respect arterial or venous boundaries, and is often most severe in the more metabolically active grey matter (including the basal ganglia, thalamus, cerebral cortex, cerebellum, and hippocampus) (25). Although ischemic stroke and hypoxic-ischemic injury are not mutually exclusive and may co-occur, the prognoses of stroke and global ischemic injury are wholly distinct: mortality rates are <13% with ischemic stroke (26) compared with up to 80% following severe global hypoxic-ischemic injury (27). The distinction between focal or multifocal stroke and global hypoxic-ischemic injury is critical in cardiovascular clinical trials where procedural factors (prolonged hypotension or hypoxemia)

FIGURE 2 Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: Recommended Timing of Clinical and Imaging Evaluations



This figure provides recommended and optional assessments for each time point; appropriate follow-up duration will vary with device/procedure type and the goals of the study. *Cognitive screening (e.g., Montreal Cognitive Assessment) is recommended for all trial categories. Comprehensive cognitive assessment is recommended for studies with neurological outcomes as efficacy endpoints (Categories II and III in Table 2), and optional for safety studies (Category I in Table 2). MRI = magnetic resonance imaging.

may occur, or where "showers" of multifocal emboli may mimic global injury. Devices and procedures designed to prevent embolic complications (e.g., neuroprotection devices) can only be expected to have a beneficial effect on focal or multifocal ischemic injury. Therefore, NeuroARC recommends separate reporting of stroke and global hypoxic-ischemic injury. Although multifactorial, delirium (global neurological dysfunction) without CNS injury should also be adjudicated and reported due to its prognostic implications (28,29).

CEREBRAL HEMORRHAGE. CNS bleeding varies from clinically silent microbleeds to catastrophic hemorrhages, and requires clear definition, classification, and reporting in the context of cardiovascular trials (in which the use of adjunctive anticoagulant and antiplatelet therapy is common). CNS hemorrhage should be classified as a stroke when it is not caused by trauma, is associated with rapidly developing neurological signs or symptoms, and has been confirmed by imaging; major types include intracerebral hemorrhage and subarachnoid hemorrhage. For hemorrhagic conversion of an infarct, NeuroARC recommends a simplified American Stroke Association classification on the basis of the presence or absence of space-occupying effect (20). Class A hemorrhagic conversions of ischemic stroke or covert infarction represent minor isolated or confluent petechiae without mass effect; Class B hemorrhagic conversions are more significant confluent bleeds or hematomas resulting in mass effect (Table 1). In contrast to the American Heart Association/American Stroke Association, NeuroARC proposes to classify both Class A and B bleeds within ischemic stroke ("ischemic stroke with hemorrhagic conversion") or covert infarction ("covert infarction with hemorrhagic conversion") on the basis of presentation, as the goal is to identify the primary mechanism of injury.

OVERVIEW OF NEUROLOGICAL INJURY ASSESSMENT IN CLINICAL TRIALS

ASSESSMENT METHODOLOGY BY DEVICE OR PROCEDURE CATEGORY. Given the diversity of cardiovascular interventions, a single approach to neurological injury assessment for every type of clinical investigation is impossible. We propose a framework to categorize applicable procedures and devices in Table 2, and suggest corresponding assessments. Category I includes cardiovascular procedures associated with a risk of acute or long-term neurological events, for which neurological

TABLE 3 Neurological Endpoint Severity, Disability, and Timing Classification

Classification of Acute Severity, Recovery, and Long-Term Disability	
Acute severity	Mild neurological dysfunction: NIHSS 0–5 Moderate neurological dysfunction: NIHSS 6–14 Severe neurological dysfunction: NIHSS ≥15 *Note:* Severity assessment should be performed at the time of diagnosis of any overt and covert CNS injury (Types 1 and 2) to ensure accurate classification
Stroke recovery	Stroke with complete recovery: mRS score at 30–90 days of 0 *or* a return to the patient's pre-stroke baseline mRS score, in the absence of any ongoing new symptoms due to the stroke.
Stroke disability	Fatal stroke: death resulting from a stroke where the cause of death is attributable to the stroke. Disabling stroke: mRS score ≥2 at 30–90 days, with an increase of at least 1 point compared with the pre-stroke baseline. Nondisabling stroke: mRS score <2 at 30–90 days, or ≥2 without an increase of at least 1 point compared with the pre-stroke baseline. *Note:* Disability assessment applies only to subjects with overt CNS injury (Type 1), and should be performed at 90 ± 14 days after the stroke event.
Classification of Neurological Event Timing	
Periprocedural	≤30 days post-intervention
Late	>30 days post-intervention *Note:* Event timing should be reported separately for all patients with CNS infarction, and for patients with overt CNS injury.

Abbreviations as in Table 1.

outcomes are primarily a safety measure (e.g., surgical aortic valve replacement, transcatheter aortic valve replacement, or coronary artery bypass graft). Category II consists of devices or therapies intended to reduce the risk of procedure-related stroke, for which neurological outcomes are primarily a measure of effectiveness (e.g., embolic protection devices or adjunctive neuroprotective medications). Finally, Category III includes devices or procedures associated with a procedural stroke risk, but performed specifically to reduce the long-term risk of stroke; these studies are concerned with neurological outcomes as both safety and effectiveness measures (e.g., patent foramen ovale closure, left atrial appendage closure, or carotid artery revascularization).

TABLE 4 MRI Endpoint Reporting Recommendations

Primary Endpoint	Total Lesion Volume (mm^3) (Median, IQR, Min and Max)
Other endpoints	• Incidence (%): Proportion of patients with new post-procedure DWI lesions • Number of lesions • Single lesion volume (mm^3): (median, IQR) • Maximum lesion volume (mm^3): (median, IQR)
Analysis considerations	• Endpoints should be reported for the overall population, the population of patients with overt CNS injury, and those with covert CNS injury

DWI = diffusion-weighted imaging; IQR = interquartile range; other abbreviations as in Tables 1 and 2.

DIAGNOSTIC ALGORITHMS FOR APPROPRIATE INCORPORATION OF IMAGING. Unlike spontaneous stroke detection driven by clinical symptoms, trials evaluating neuroprotection devices or adjunctive medications (Category II) require protocol-driven post-procedure neuroimaging (Figure 1) to increase sensitivity for CNS infarction, and therefore, the power of the study to detect a treatment effect. The clinical relevance of a treatment effect driven by subclinical events is subject to interpretation in the context of the totality of trial data (including non-stroke complications) and evolving evidence on the clinical implications of covert CNS infarction. For studies not specifically focusing on perioperative neuroprotection, acquisition of brain imaging should be required in all patients with neurological signs or symptoms or acute delirium that might indicate a neurological event.

TIMING OF ASSESSMENTS. Serial assessments should be performed in all patients within prespecified timeframes to add consistency to results and provide documentation not only of the timing of injury, but also of reversibility or progression over time (Figure 2). Clinical events most often occur in the periprocedural period, and decrease with time (9). Therefore, neurological and delirium assessments should be performed early (1, 3, and 7 days post-procedure or pre-discharge) and trigger brain imaging and neurological evaluation, as necessary. Because the effects of neurological events may change over time, we recommend neurological screening and disability and quality-of-life assessments at 30 to 90 days in all studies, with longer-term follow-up on the basis of trial design (30). Disability with modified Rankin Scale (mRS) should always be assessed 90 ± 14 days after any stroke event (rather than after enrollment).

CLINICAL ASSESSMENT FOR STROKE AND NEUROLOGICAL DYSFUNCTION

POST-PROCEDURAL NEUROLOGICAL ASSESSMENT AND STROKE SEVERITY DETERMINATION. Neurovascular event rates vary substantially, depending on whether outcomes are ascertained passively or actively (using standardized assessments at prespecified time points) (9,31). Active stroke detection in the perioperative period can be confounded by recent exposure to anesthesia, patient discomfort, analgesic medications, ventilatory support, and various post-procedural complications. In this context, delirium is the presenting symptom of acute stroke in 13% to 48% of patients, and is associated with worse outcomes and higher mortality (32).

For this reason, new neurological changes or delirium should trigger neuroimaging in all categories of cardiovascular trials. **Table 3** includes recommendations for the classification of acute stroke severity and timing in relation to the index procedure. Although the procedure-related risk window may vary by procedure, within 30 days is a generally accepted timeframe to attribute complications to the procedure. Serial assessment of neurological change using established instruments, such as the National Institutes of Health Stroke Scale, and of delirium, using the Confusion Assessment Methods (3-min diagnostic or intensive care unit), are recommended to add consistency to study results, both within and across trials (Online Appendix).

LONG-TERM STROKE ASCERTAINMENT AND DISABILITY DETERMINATION

For long-term stroke screening, NeuroARC recommends the use of standardized instruments, including the National Institutes of Health Stroke Scale, as well as validated structured interviews querying for interval stroke symptoms, such as the Questionnaire for Verifying Stroke-Free Status (33) or the ACAS (Asymptomatic Carotid Atherosclerosis Study) transient ischemic attack/stroke algorithm (34). A patient response indicating a potential stroke symptom should trigger neuroimaging and a formal neurological assessment. Functional impairment and disability from stroke can be reliably assessed using validated tools, such as the mRS (35). For cardiovascular procedures, it is important to distinguish "fatal" from "disabling" and "nondisabling" strokes, as well as to identify patients having "stroke with complete recovery" (defined in **Table 3**). An important caveat is that the mRS does not formally differentiate between disability due to neurological symptoms and other comorbidities that may influence dependence (such as activity-limiting angina, dyspnea, or orthopedic conditions). Additional disability and quality of life scales are detailed in the Online Appendix.

MRI FOR THE DETECTION AND QUANTIFICATION OF CNS INFARCTION

MRI is the imaging modality of choice for detection and quantification of brain ischemia related to cardiovascular procedures and is recommended in trials, even if head computed tomography was obtained. At a minimum, NeuroARC recommends an early postprocedural MRI in efficacy trials (category II), and a MRI should be performed following symptoms suggestive of neurological injury in all trial categories. An independent central core laboratory is recommended to enhance consistency with validated qualitative and quantitative analysis methodologies, standardized acquisition protocols, and site training. Suggested reporting of MRI data is summarized in **Table 4**, and the Online Appendix discusses additional considerations for pre-procedure and late follow-up MRI assessments and reporting.

TABLE 5 Cognitive Endpoint Reporting Recommendations

Outcome Measures
Continuous measures • Score (mean ± SD): reported at all time points (baseline, post-procedure [optional], 30–90 days, 6–12 months) Categorical change (definition applies to all tests in **Table 5**) • Early: 30–90 day evaluation • Long-term: 12-month and annual evaluation • Cognitive decline (%): ≥0.5 SD decrease compared with baseline • Cognitive improvement (%): >0.5 SD increase compared with baseline • Cognitive unchanged (%): change in score within ± 0.5 SD compared with baseline
Analysis Considerations
• Cognitive screening (e.g., MoCA) is recommended for all studies • Comprehensive cognitive battery (**Table 6**) is recommended for efficacy endpoint trials (Categories II and III) and optional for safety endpoint trials (Category I) • Results should be reported overall and by domain when possible • For studies with routine neuroimaging, cognitive endpoints should be reported for the overall population, for subjects with and without CNS infarction, and for the subset of patients with overt CNS injury (Type 1) • For studies without routine neuroimaging, cognitive endpoints should be reported for the overall population, and for subjects with and without diagnosed stroke

Abbreviations as in **Tables 1 and 2**.

DWI: RELEVANCE AND INTERPRETATION. DWI allows detection of ischemic injury from several minutes to days after an ischemic event, and is highly sensitive to acute and subacute ischemic insults when performed within 12 h of symptom onset (sensitivity 0.99). The image contrast in DWI is sensitive to the random motion of water molecules, and becomes hyperintense as cytotoxic edema restricts local water diffusion, representing tissue damage resulting from ischemia (36–38). Although the observed diffusion defects may resolve with time, virtually all DWI lesions represent permanent neuronal cell death and signify irreversible brain injury (39–41). False negative rates for DWI drop substantially after 35 h (42), and observed lesion volume is maximal at 5 to 7 days (43). Because DWI lesions may begin to reverse intensity and/or shift through isointensity between 1 and 3 weeks, longer delays should be avoided. Therefore, 2 to 7 days is the recommended time window for acute or subacute imaging following cardiovascular procedures (**Figure 2**). Because measures of DWI visible lesion volumes may change rapidly over time, consistent timing of image acquisition in randomized trials is essential to avoid systematic bias.

TABLE 6 Cognitive Domains, Their Descriptions, and Representative Tests

Domain	Description	Representative Tests
Overall cognitive status	A "thumbnail" sketch of global cognitive abilities	• MoCA (53) • SLUMS (54)
Pre-morbid intellectual status estimation	Nonphonemic word pronunciation knowledge, or knowledge of general word meaning. A stable predictor of pre-morbid intellectual and educational status.	• WRAT-4 Reading Subtest (55) • WTAR (56) • WAIS-4 Vocabulary (57)
Attention	The ability to direct cognitive and perceptual resources to relevant stimuli and ignore irrelevant stimuli. Includes selective, sustained, and divided attention.	• Trailmaking Test Part A (58) • Digit Symbol-Coding (57) • Digit Span Test (57) • Conners' Continuous Performance Test-2nd or 3rd Revision (59) • RBANS-Attention (60)
Memory	The ability to learn, store, and retrieve information.	• HVLT-R (61) • CVLT-II (62) • BVMT-R (63) • RBANS-Immediate and Delayed Memory (60)
Language	Language refers to both receptive and expressive communication through oral and written channels	• Category fluency • Controlled Oral Word Association Test (64) • RBANS-Language (60)
Executive function	A broad category that refers to higher-order cognitive functioning, and to the ability to organize information, plan, conceptualize, reason, maintain working memory, inhibit, and change cognitive set.	• Trailmaking Test Part B (58) • WAIS-4 Similarities (57) • WAIS-4 Matrix Reasoning (57) • Ruff Figural Fluency Test (65) • Stroop Color-Word Association Test (66) • Complex Figure Test (67)
Visuospatial function	The ability to process visual information and higher-order spatial skills.	• Complex Figure Test (67) • Hooper Visual Organization Test (68) • BVMT-R Copy (63) • RBANS-Visuospatial/ Constructional (60)

BVMT-R = Brief Visual Memory Test-Revised; CVLT-II = California Verbal Learning Test, 2nd Edition; HVLT-R = Hopkins Verbal Learning Test-Revised; MoCA = Montreal Cognitive Assessment; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SLUMS = Saint Louis University mental status examination; WAIS-IV = Wechsler Adult Intelligence Scale-Fourth Edition; WRAT-4 = Wide Range Achievement Test Fourth Edition; WTAR = Wechsler Test of Adult Reading.

T_2-WEIGHTED FLUID-ATTENUATED INVERSION RECOVERY AND HEMORRHAGE SENSITIVE MRI SEQUENCES. T_2-weighted fluid-attenuated inversion recovery detects nonspecific injury after the acute phase and lesions that remain apparent throughout the chronic phase. Although DWI lesions represent irreversible infarction in 98% of cases (41), chronic lesion burden cannot be fully predicted from acute DWI lesions, as these may increase or decrease in size, resolve, or remain unchanged. The evolution of acute DWI lesions over time is important to consider, as lesions may reverse while damage remains (44). Moreover, whereas final T_2 lesion volume is often approximately one-half that of initial DWI (43), this discrepancy does not necessarily reflect tissue salvage. As post-procedure DWI lesions are often at the threshold of detection, lesions may remain invisible on T_2, despite existing damage, and some DWI lesions do not cavitate, but collapse entirely, leaving little trace on MRI, despite the loss of tissue (45). T_1 may be more sensitive to whether infarcts are cavitated in the chronic phase, particularly in the posterior circulation. In addition, susceptibility-weighted imaging or gradient echo T_2 (T_2*) are recommended in MRI imaging protocols to detect microbleeds and hemorrhage, as well as metallic microemboli that may occur with cardiovascular procedures (46).

ROLE OF TRANSCRANIAL DOPPLER IN CARDIOVASCULAR CLINICAL TRIALS

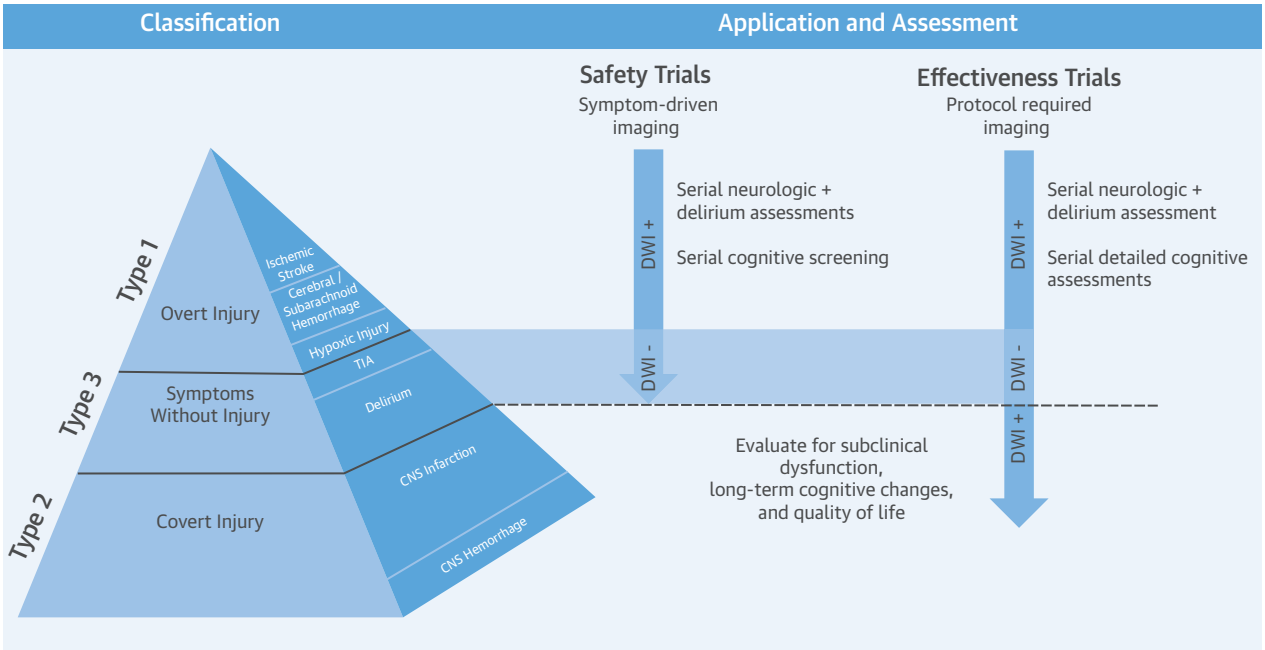
Transcranial Doppler can provide mechanistic insight into procedural cerebral embolization. The Online Appendix provides a summary of evidence and recommendations.

ASSESSMENT OF COGNITIVE OUTCOMES

ROLE OF COGNITIVE EVALUATION IN CARDIOVASCULAR CLINICAL TRIALS. Cognitive decline is an important, and potentially disabling consequence of surgical and interventional procedures. Although spontaneous covert CNS infarction has been associated with cognitive decline in long-term population-based studies (15), generalizability to short-term, procedure-related ischemic injury remains to be proven. Increasing appreciation of the potential cognitive consequences of cardiovascular disease and associated interventions has led to new scrutiny of iatrogenic and patient-specific factors that may influence clinical outcomes (47) and quality of life (48). Although extended cognitive evaluations are not integral to current neurological event definitions, they have provided valuable information in the context of acquired and developmental conditions (49,50). Their sensitivity to subtle decrements in function could prove useful in the evaluation of neuroprotective strategies and neurological outcomes in general. NeuroARC strongly recommends cognitive screening (e.g., Montreal Cognitive Assessment) for all cardiovascular trials, and a comprehensive cognitive assessment strategy for studies with neurological outcomes as efficacy endpoints.

NEUROPSYCHOLOGICAL TESTING CONSIDERATIONS. In selecting the appropriate neuropsychological tests for a cardiovascular trial, the following fundamental principles apply. First, appropriate cognitive domains must be selected on the basis of the patients and goals of the study, and the likely pathology underlying possible ischemic injury. In general,

CENTRAL ILLUSTRATION **Neurologic Academic Research Consortium Consensus: Classification, Application, and Assessment of Neurological Events in Clinical Trials**



Lansky, A.J. et al. J Am Coll Cardiol. 2017;69(6):679–91.

+ = positive infarct; − = no infarct; CNS = central nervous system; DWI = diffusion-weighted imaging; TIA = transient ischemic attack.

perioperative multifocal cerebrovascular injury (as observed in study patients undergoing cardiovascular procedures) predominantly affects processing speed and executive function (51), and frequently affects memory, language, and visuospatial function (52). Second, the complexity and length of the test(s) should be tailored to the study population (45 min of testing is generally tolerated).

Principal challenges to the incorporation of neuropsychological assessments into cardiovascular trials include the management of "noise" in the context of relatively subtle, but meaningful changes, and the complexity and heterogeneity of the target patients. **Table 5** provides recommendation for the selection and reporting of cognitive outcome measures, and **Table 6** lists common cognitive domains, their definitions, and representative tests. Additional considerations for test selection, administration, and interpretation are detailed in the Online Appendix. Evaluation with a battery of neuropsychological assessments provides far greater sensitivity and specificity than a single brief global cognitive screening instrument (e.g., Montreal Cognitive Assessment [53]) designed to detect frank cognitive impairment.

CONCLUSIONS

The NeuroARC recommendations provide a framework for characterization of the clinical consequences of iatrogenic and spontaneous neurological injury following cardiovascular procedures and interventions (**Central Illustration**). NeuroARC encourages investigators to incorporate standard definitions and consistent clinical, neuroimaging, and cognitive assessments into their clinical study designs to inform anatomic, physiological, clinical, and functional correlations. Tissue-based identification of CNS infarctions and their clinical correlates will enable more informed benefit-risk assessments for cardiovascular procedures, and facilitate the evaluation of novel approaches to prevent or mitigate brain injury, with the ultimate goal of improving patient outcomes.

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KEY WORDS cardiovascular, methodology, neurological definitions, outcomes, stroke, trials

APPENDIX For a list of study participants and supplemental Methods, please see the online version of this article.