The Compelling Saga of Strokes after TAVR and SAVR Diagnostic Considerations and NeuroARC

Alexandra Lansky, MD

Professor of Medicine, Section of Cardiology

Yale School of Medicine

Disclosures

Speaker's name: Alexandra Lansky

☑ **I have the following potential conflicts of interest to report:**

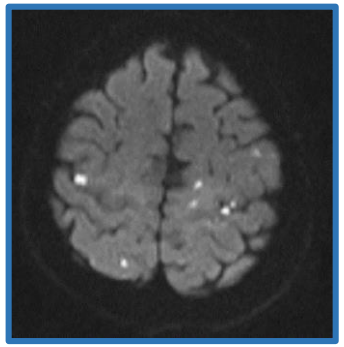
Grants/research support: Keystone Heart

Honoraria: Keystone Heart

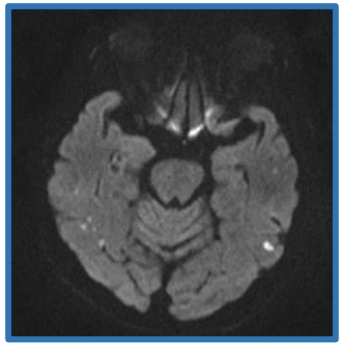
After TAVR all Patients have Brain Injury

Brain Injury

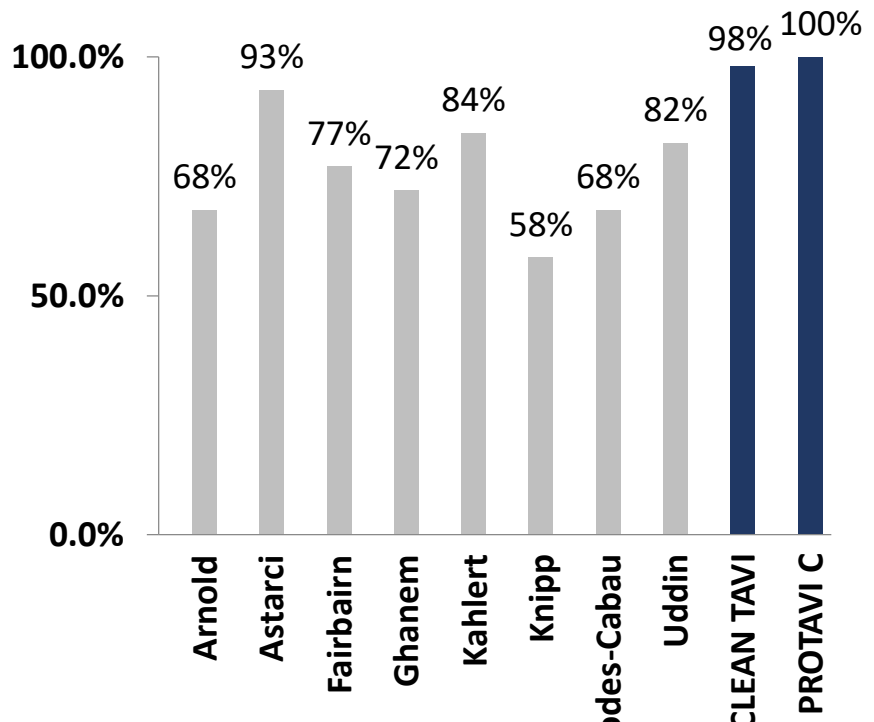
- "Silent" infarcts are associated with adverse neurological and cognitive consequences:
  - Impaired mobility
  - Physical decline
  - Depression
  - Cognitive dysfunction
  - Dementia
  - Alzheimer disease



- ***After TAVR silent brain injury is associated with:***
  - ***Neurocognitive decline***
  - ***>2 fold risk of dementia***
  - ***>3 fold risk of stroke***



% of Subjects with New Lesions



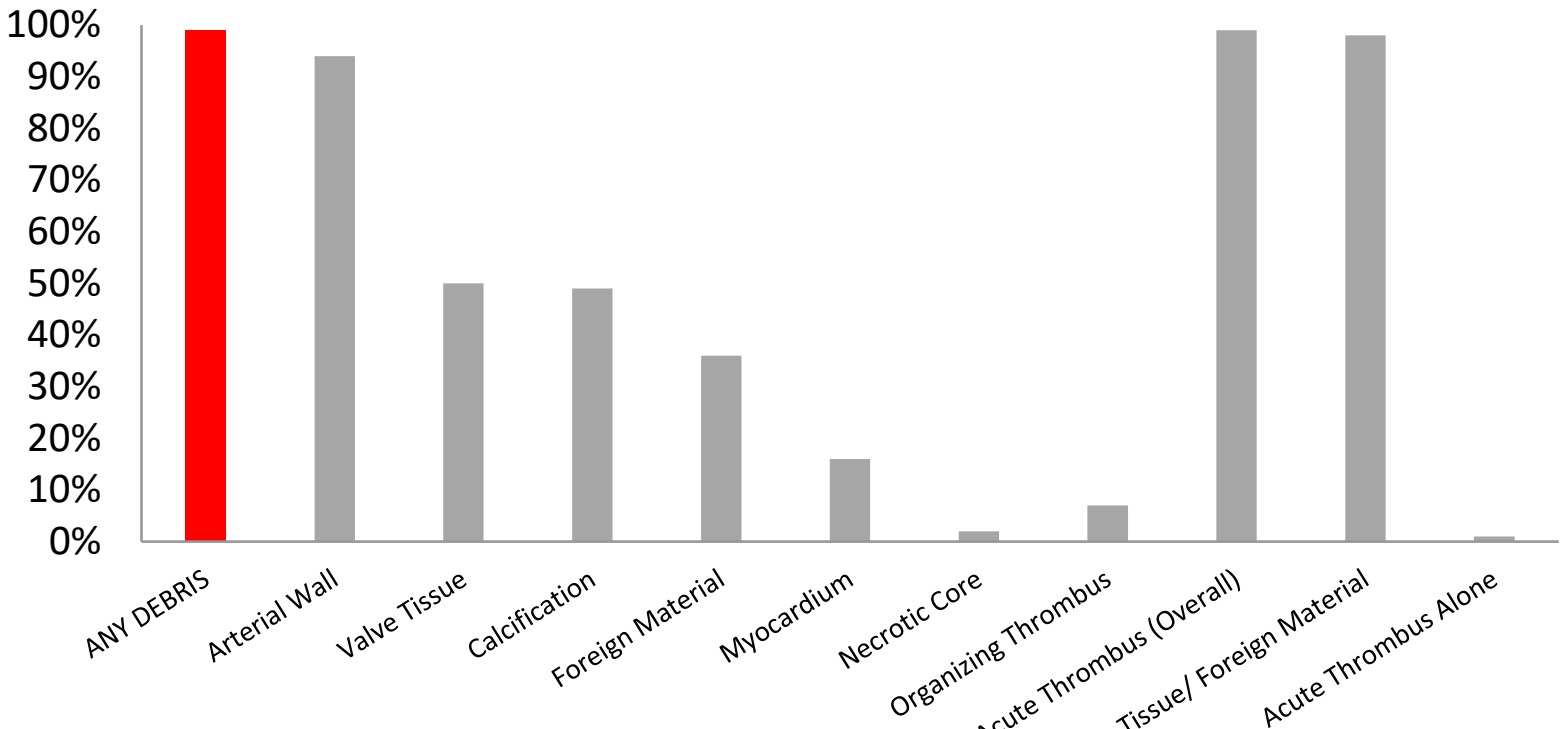
Multiple infarcts (≤36, $\bar{x}$ = 4.6)
Total lesion Volume: 1.5cm²-4.3cm²

Sources: Restrepo et al. *Stroke* 2002;33:2909, Lund et al. *Eur Heart J*. 2005;26:1269, Schwarz et al. *Am Heart J* 2011;162:756, Knipp et al. *Ann Thorac Surg* 2008;85:872, Vermeer et al. *NEJM 2003*; 348:1215, Vermeer et al. *Stroke* 2003; 34:1126, Arnold et al. *JACC Cardiovasc Interv*. 2010;3:1126, Astarci et al. *J Heart Valve Dis*. 2013;22:79, Fairbairn et al. *Heart* 2012;98:18, Ghanem et al. *EuroIntervention*. 2013;8:1296, Kahlert et al. *Circ*. 2010;121:870, Knipp et al. *Interact Cardiovasc Thorac Surg*. 2013;16:116, Linke et al. TCT 2014, Rodes-Cabau et al. *JACC Cardiovasc Interv* 2014;7:1146.

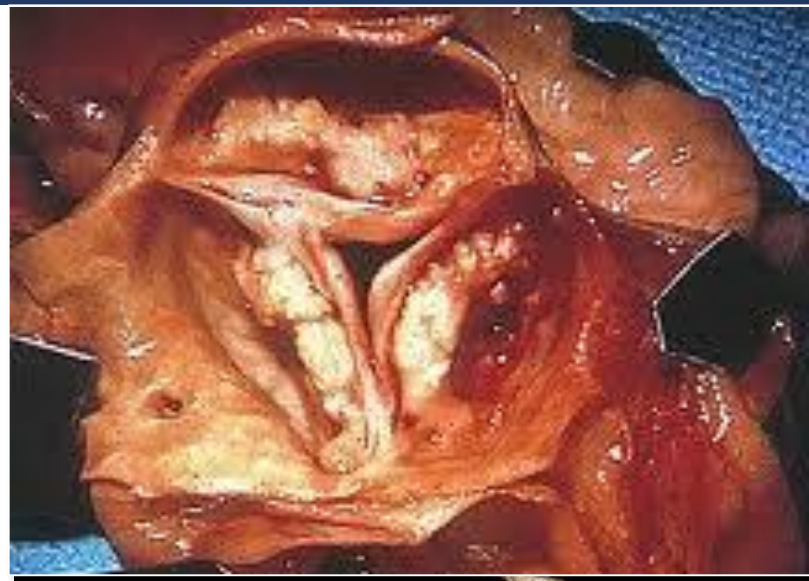
Embolic Brain Injury During TAVR: SENTINEL Trial

HISTOPATHOLOGY

Debris Capture by Type



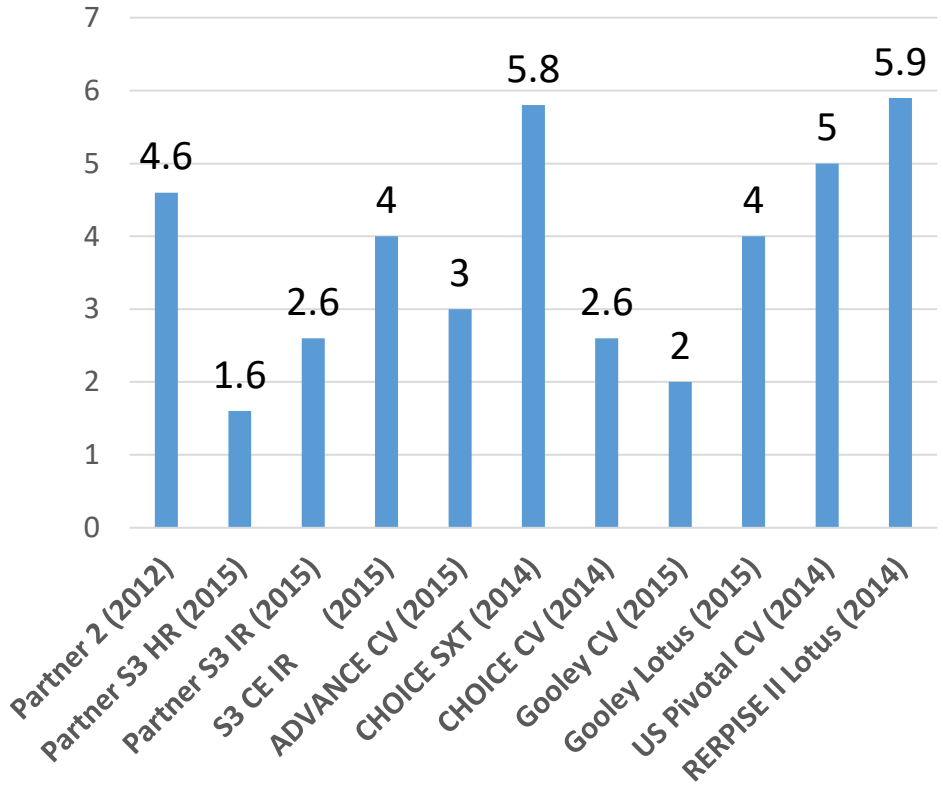
- >80% debris 150-500 micron
- <5% debris >1000 microns
- Up to 2000 microns



Stroke Rates in AVR Studies

Severe Stroke

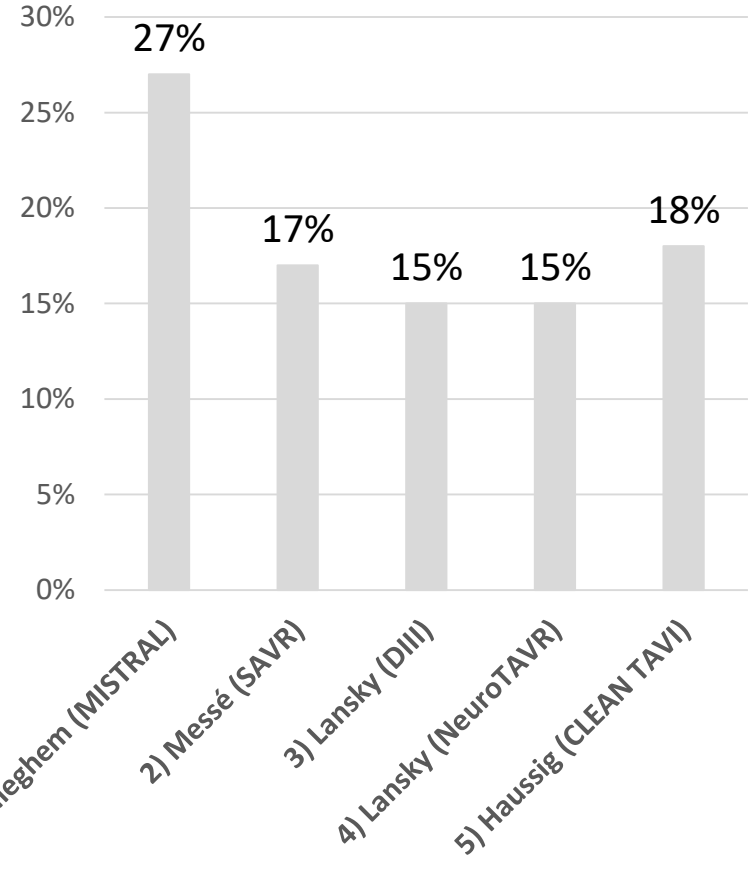
Major and disabling stroke rates range from 1.6%-5.9%



Mild, Moderate and Severe Stroke

Stroke rate is 15-27% by current AHA/ASA definitions

Neurologist identified deficits with new brain MRI lesions



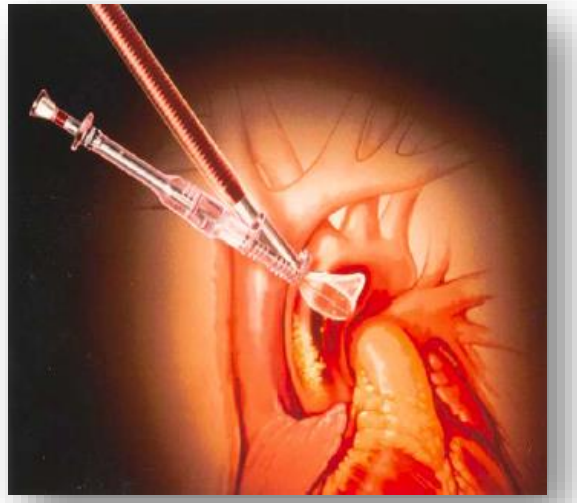
[1]Van Mieghem NM, EuroIntervention. 2016;12:499. [2]Messe S, Circulation. 2014;129:2253. [3]Lansky AJ, Eur Heart J. 2015; 36:2070.
[4]Lansky AJ, AJC 2016. [5]Haussig S, JAMA. 2016;316:592.

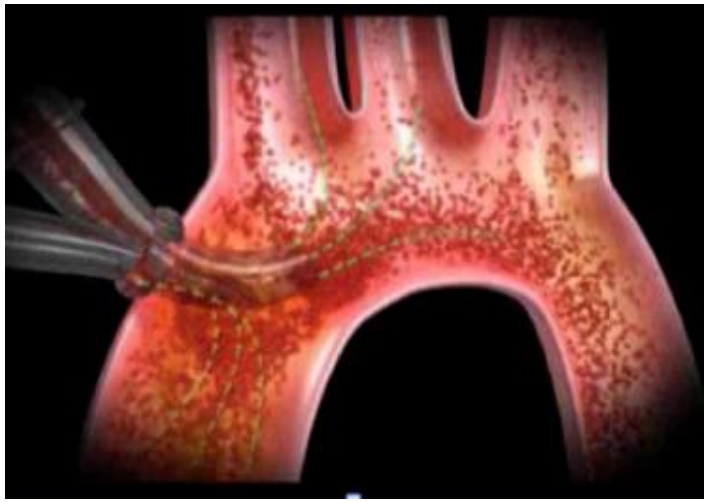
Cerebral Protection: A Legacy of Failed Trials

Trial design considerations

1. Variation in stroke definitions
   - VARC
   - ASA/AHA
   - Severe stroke vs all stroke

2. Uncertainty in DW MRI Endpoint
   - Frequency (CTSN) vs Volumes (Sentinel)
   - Variability of the measure
   - Clinical relevance

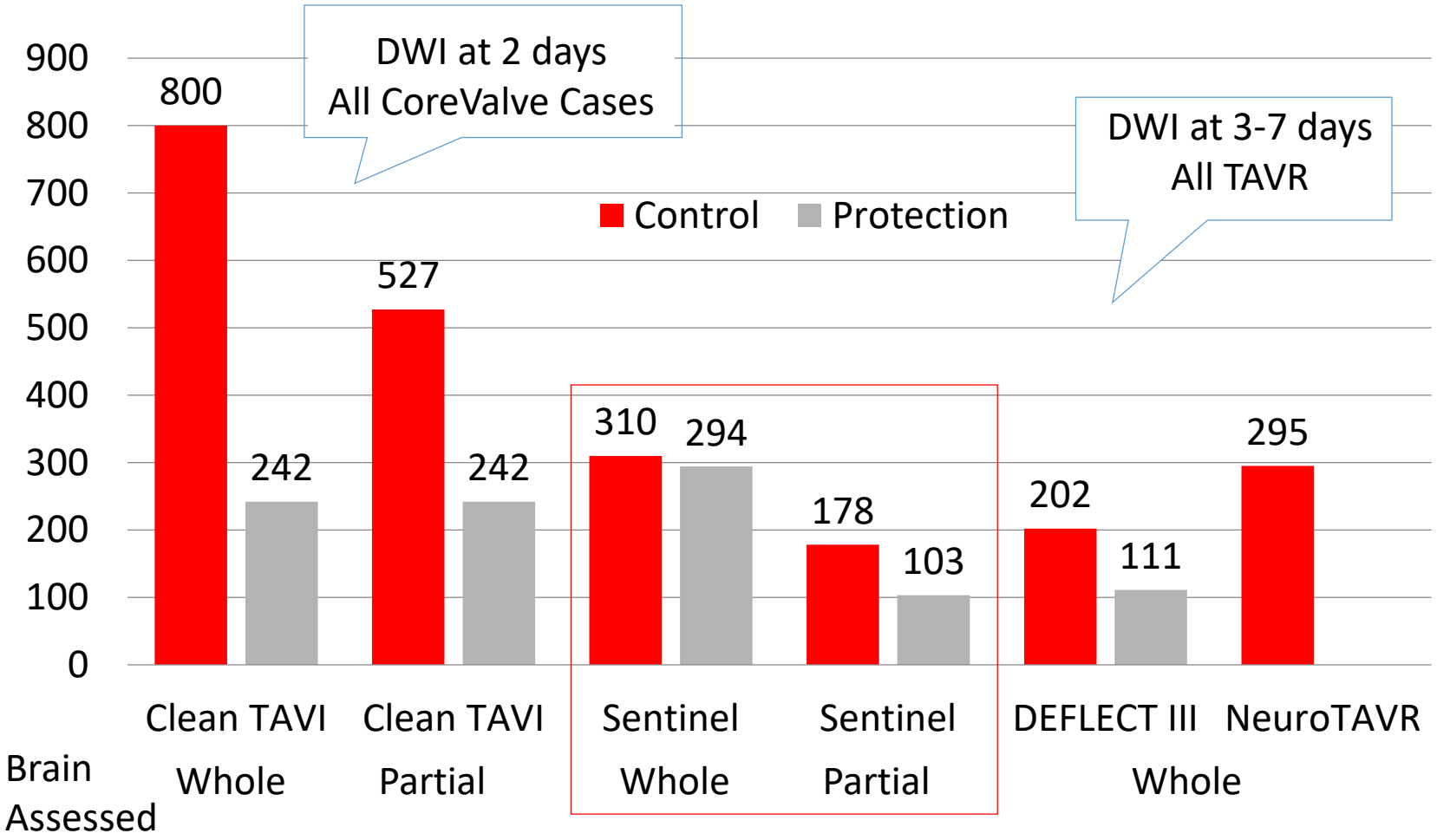




Device performance considerations

- Is the device effective?
- Is the device safe?

Sentinel trial: Why was the trial Underpowered? Variability in TLV



[5]Haussig S, JAMA. 2016;316:592.
Lansky AJ, Eur Heart J. 2015; 36:2070.; Lansky AJ, AJC 2016 .

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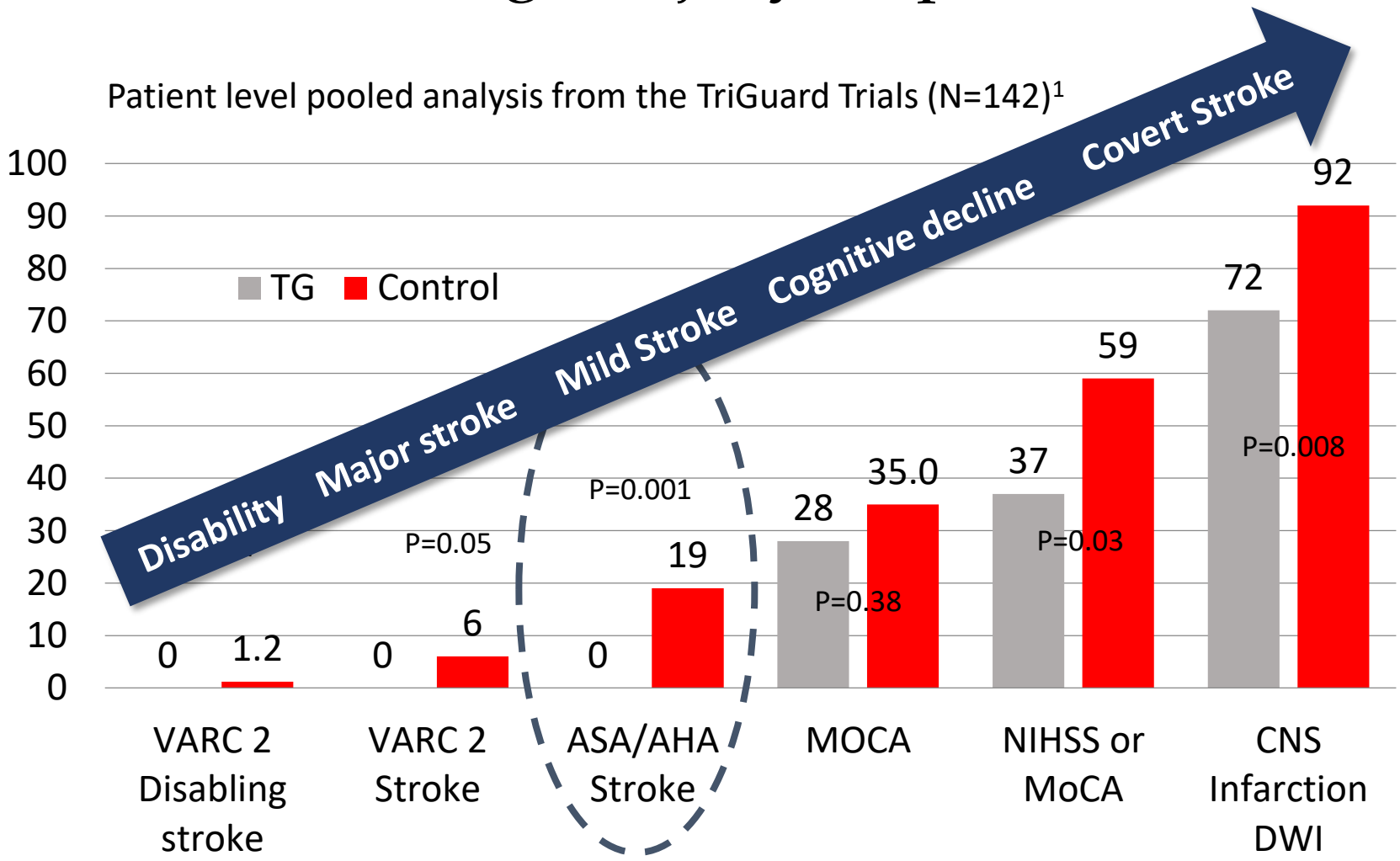
Factors contributing to TLV variability

- MRI timing (signal intensity attenuation)
- 3 vs 1.5 Tesla system
- Wide variation in TLV (SD is wide)
- Not a normal distribution
- TAVR system used
- Loss to FU (bias)
- For Sentinel: 140 pts per group would have been required to demonstrate superiority at 80% power (Sentinel had 98 control and 91 claret)

TriGuard Pooled analysis: Variability in Neurologic Injury

Incidence of Neurlogic Injury Depends on Definition



Lansky et al PCR 2016

Proposed Standardized Neurologic Endpoints in Cardiovascular Clinical Trials [NeuroARC]

Framework on how to assess, measure and classify neurologic endpoints associated with cardiovascular procedures

International Multi Stakeholder Consensus

Interventional/Structural/ CT Surgery	Neurology/Neuroradiology/ Neuropsychology/NINDS	FDA/ARC/Pathology
Andreas Baumbach	Kevin Abrams	**FDA**
John Forrest	Michel Bilello	Andrew Farb
David Holmes	Adam Brickman	Nicole Ibrahim
Susheel Kodali	Jeffrey Browndyke	John Laschinger
Alexandra Lansky	Karen Furie	Carlos Pena
Axel Linke	David Greer	Bram Zuckerman
Raj Makkar	Daryl Gress	**Academic Research Consortium (ARC)**
Jeffrey Moses	Ronald Lazar	Donald Cutlip
Cody Pietras	Steven Messé	Gerrit-Anne van Es
Jeffrey Popma	Claudia Moy	Mitch Krucoff
Bernard Prendergast	Nils Petersen	Roxana Mehran
Joachim Schofer	Ola Selnes	**Pathology and Regulatory**
Arie P. Kappetein	Michael Dwyer	Semih Oktay
Michael Mack	Szilard Voros	Renu Virmani
	Bart van der Worp	

NeuroARC applies to all CV trials

Neurologic evaluation and endpoints should be tailored to the procedure/device category

CATEGORY I **Primary** Procedural Safety Measure	CATEGORY II Primary Procedural Efficacy Measure	CATEGORY III **Primary** Procedural Safety, Long-term Efficacy Measure
Devices with inherent iatrogenic embolic risk • Surgical cardiac procedures (valve replacement, CABG, dissection, aneurysm repair) • Adjunctive pharmacology	**Devices designed to prevent iatrogenic or spontaneous acute neurologic injury** • Neuroprotection device • Cerebral temperature management devices	**Devices with inherent iatrogenic embolic risk and designed for prevention of spontaneous long-term risk** • Atrial Fibrillation Ablation • PFO or LAA closure devices

NeuroARC

Definitions and Classification Relevant to Patients, Comprehensive, Practical

Lansky A, Messe S, Baumbach A et al.; JACC 2017 and EHJ 2017

Type 1: Overt CNS Injury (Acutely Symptomatic)		
Type 1a	**Ischemic Stroke**	Focal or multi-focal vascular territory Symptoms ≥24 hours or until death or Symptoms <24 hours with neuroimaging confirmation
Subtype 1aH: Ischemic Stroke with Hemorrhagic conversion		**Class A**: Petechial Hemorrhage **Class B**: Confluent Hemorrhage (with space occupying effect)
Type 1.b	**Intracerebral Hemorrhage**	Symptoms (focal or global) caused by an intraparenchymal or intraventricular bleed
Type 1.c	**Subarachnoid Hemorrage**	Symptoms (focal or global) caused by a subarachnoid bleed
Type 1.d	**Stroke, not otherwise specified**	Symptoms ≥24 hours or until death, without imaging
Type 1.e	**Hypoxic-Ischemic Injury**	Global neurologic symptoms due to diffuse brain injury attributable to hypotension and/or hypoxia
Type 2: Covert CNS Injury (Acutely Asymptomatic brain injury detected by NeuroImaging)		
Type 2.a	**Covert CNS Infarction**	Acutely asymptomatic focal or multi-focal ischemia, based on neuroimaging
Subtype 2aH: Ischemic Stroke with Hemorrhagic conversion		**Class A**: Petechial Hemorrhage **Class B**: Confluent Hemorrhage (with space occupying effect)
Type 2.b	**Covert Cerebral Hemorrhage**	Neuroimaging or Acutely asymptomatic CNS hemorrhage on neuroimaging that is not caused by trauma
Type 3: Neurologic Dysfunction without CNS Injury (Acutely Symptomatic)		
Type 3.a	**Transient Ischemic Attack (TIA)**	Symptoms <24 hours with no evidence of acute infarction by neuroimaging
Type 3.b	**Delirium without CNS injury**	Transient non-focal (global) neurologic signs or symptoms (variable duration) without evidence of cell death by pathology or neuroimaging

NeuroARC Definitions and Classification Consistent with Historical Definitions

COMPOSITES	
CNS Infarction (overt and covert) (ASA/AHA definition*)	Any brain, spinal cord, or retinal infarction based on imaging, pathology, or clinical symptoms fitting a vascular territory and persisting for ≥24 hours; (includes Types 1a, 1.a.H, 1d, 1e, 2a, 2.a.H)
CNS Hemorrhage (overt and covert)	Any brain, spinal cord, or retinal hemorrhage based on imaging or pathology, not caused by trauma; (includes Type 1.c, 2.b)
VARC 2 Stroke**	All Type 1 overt stroke

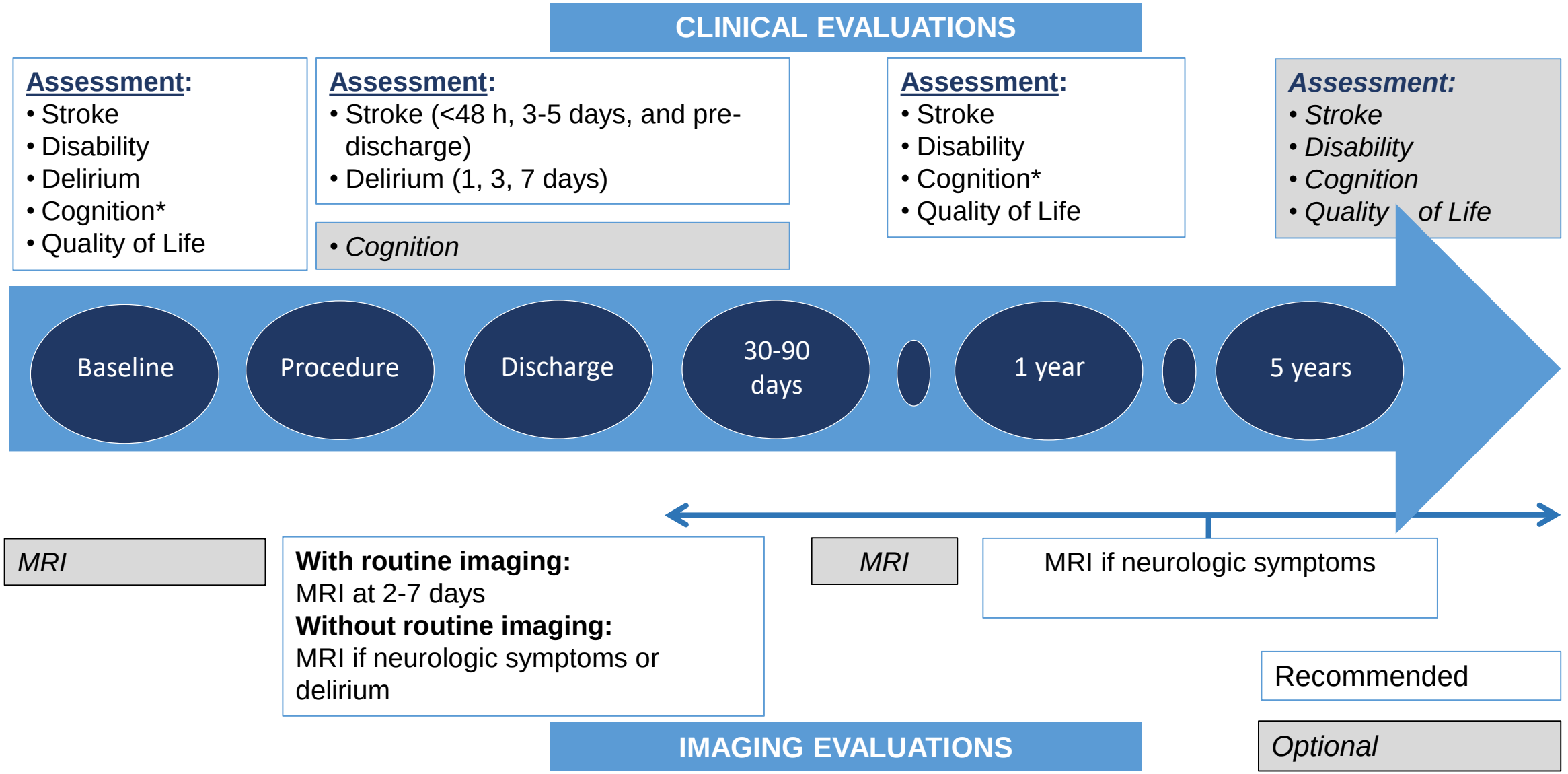
*Sacco, RL AHA ASA Statement: Stroke 2013;44:2064-89 **Kappetein, AP VARC2 update: JTCVS 2013;145;6-23

NeuroARC Stroke Severity and Disability: Clinically Relevant

CLASSIFICATION OF ACUTE SEVERITY, RECOVERY, AND LONG TERM DISABILITY	
Acute Severity	**Mild neurologic dysfunction:** NIHSS 0-5 **Moderate neurologic dysfunction:** NIHSS 6-14 **Severe neurologic dysfunction:** NIHSS ≥15
Long-Term Stroke Disability	**Fatal Stroke**: Cause of death is attributable to the stroke. **Disabling stroke**: A modified Rankin Score (mRS) ≥2 at 90 days with an increase of at least 1 point compared to the pre-stroke baseline. **Non-disabling stroke**: An mRS score <2 at 90 days, or ≥2 without an increase of at least 1 compared to the pre-stroke baseline. **Stroke with complete recovery**: An mRS score at 90 days of 0 OR a return to the patient's pre-stroke baseline mRS

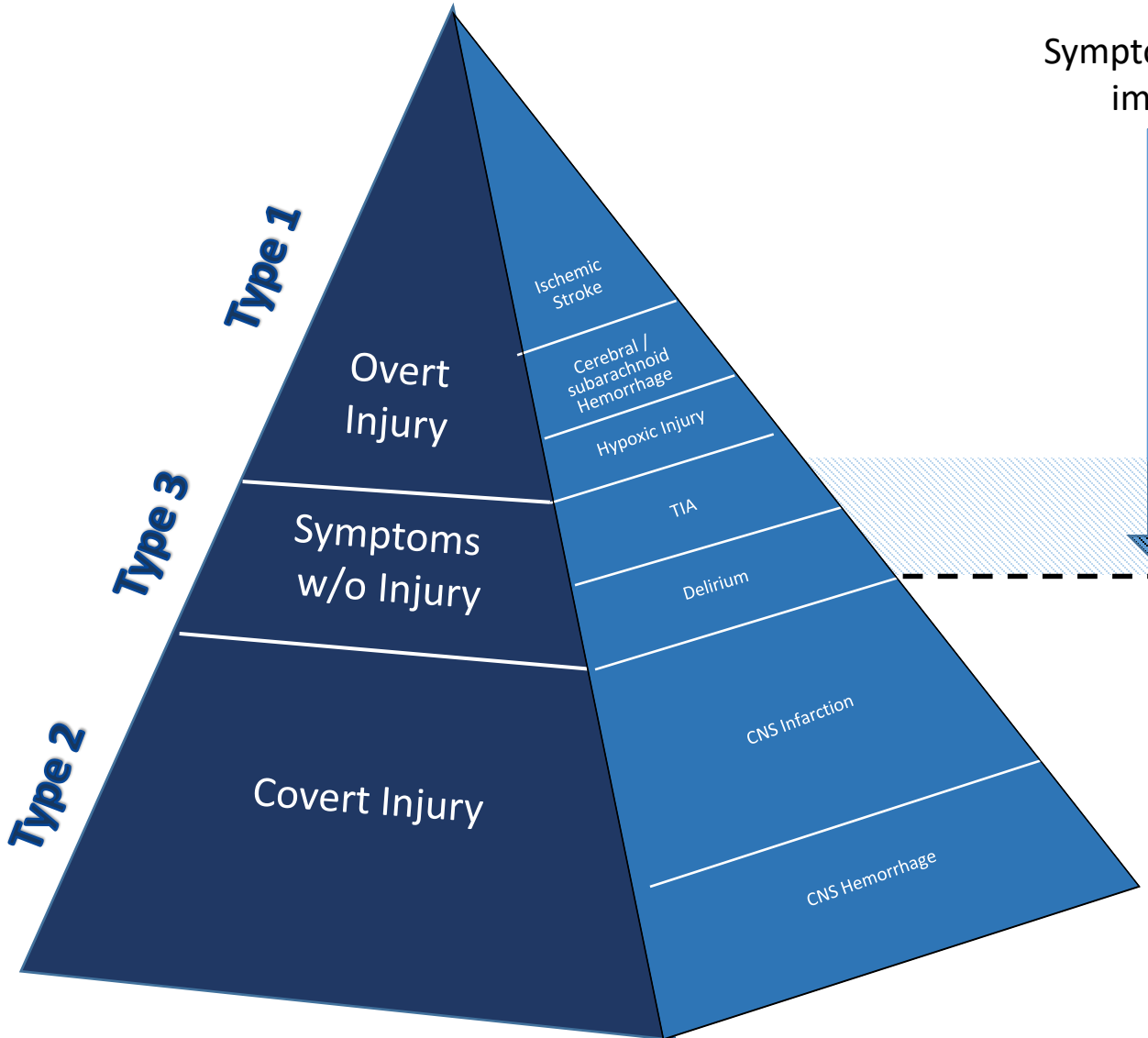
Disability is assessed in subjects with overt CNS injury (Type 1) at 90±14 days after the stroke event.

NeuroARC Recommended Assessments: Clinical, Functional, Anatomic Correlations



CLASSIFICATION

APPLICATION AND ASSESSMENT



Safety Trials

Symptom driven imaging

DWI +

Serial neurologic + delirium assessments

Serial cognitive screening

DWI -

Effectiveness trials

Protocol required Imaging

DWI +

Serial neurologic + delirium assessment

Serial detailed cognitive assessments

DWI -

DWI +

Evaluate for Subclinical dysfunction
Long-term cognitive changes and quality of life

Key Messages

Stroke is unpredictable and devastating after SAVR/TAVR

- 1.6-6% are major or disabling
- >15% are clinically detectable (minor-major)
- >95% have CNS infarction

NeuroARC provides recommendations for the assessment of neurologic endpoints in CV trials

- Device/procedure specific
- Differentiate requirements for safety and efficacy measures
- Provide increased sensitivity of clinically relevant measures
- Provide MRI endpoint selection and considerations to reduce measurement variability