The Compelling Saga of Strokes after TAVR

Search for Meaningful Measures of Clincial Efficacy: NeuroARC and Beyond

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Potential conflicts of interest

Speaker's name: Alexandra Lansky

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

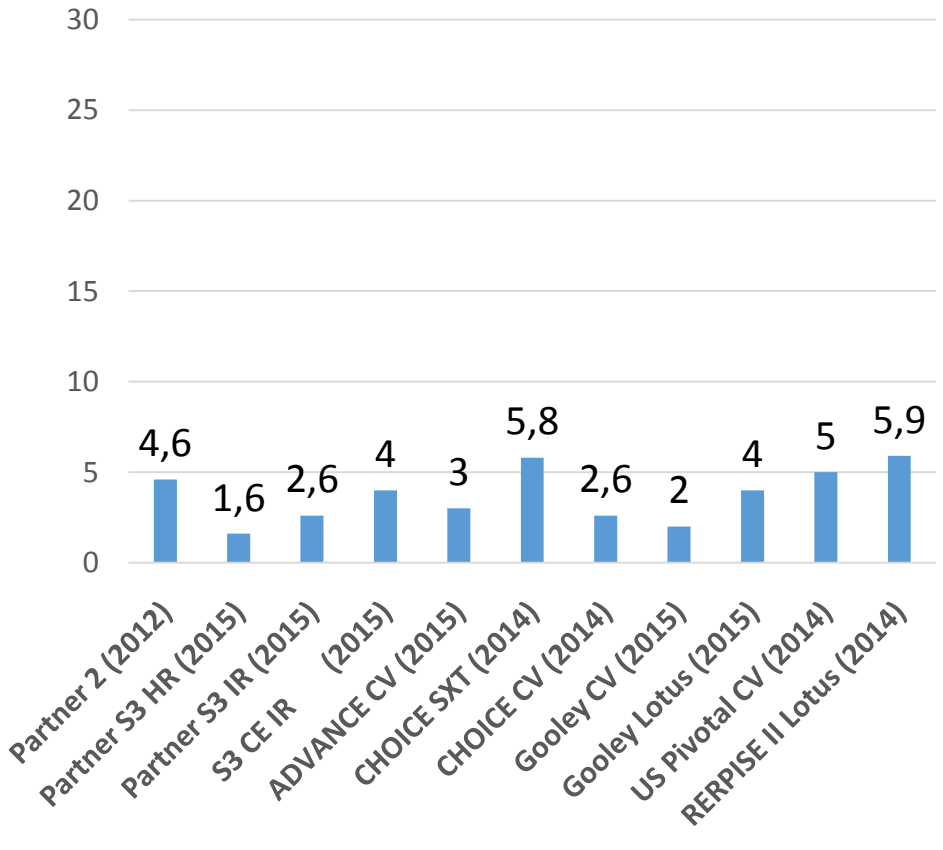
Grants/research support: Keystone Heart

Honoraria: Keystone Heart

Stroke Rates in AVR Studies Vary based on Stroke Severity

Severe Stroke

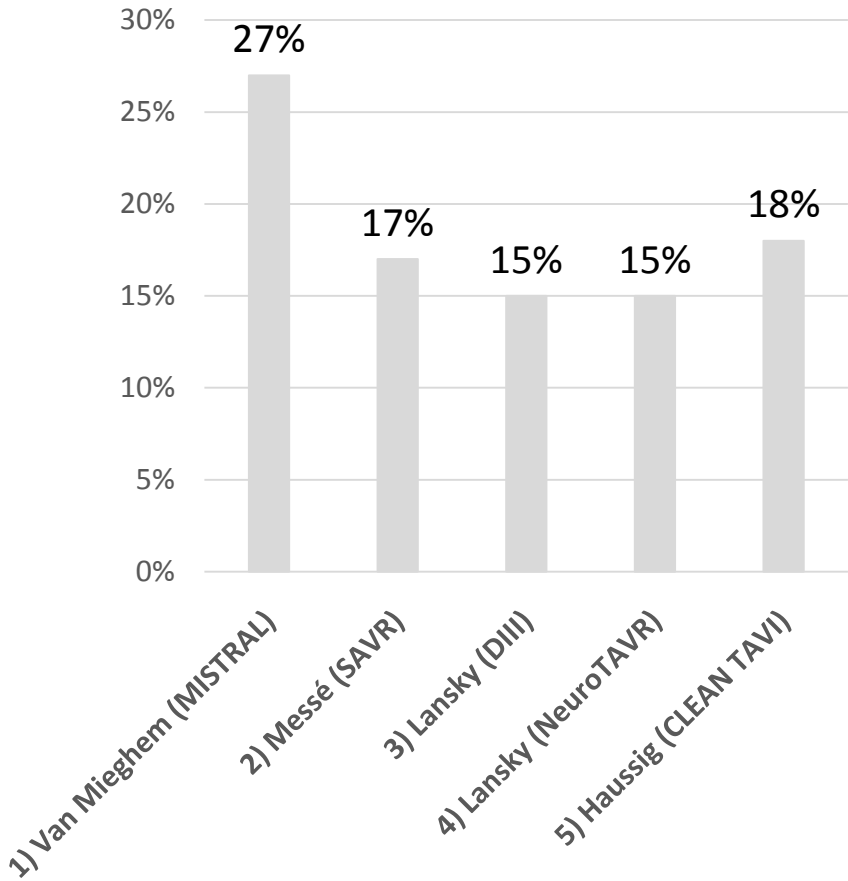
Major and disabling stroke rates range from 1.6%-5.9%



Mild, Moderate and Severe Stroke

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

Neurologist identified deficits with new brain MRI lesions

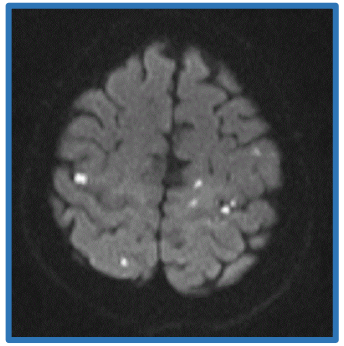


[1]Van Mieghem NM, EuroIntervention. 2016;12:499. [2]Messe S, Circulation. 2014;129:2253. [3]Lansky AJ, Eur Heart J. 2015; 36:2070.
[4]Lansky AJ, AJC 2016. [5]Haussig S, JAMA. 2016;316:592.

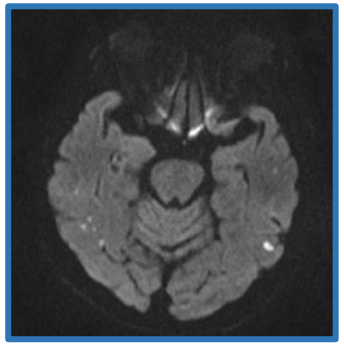
After TAVR most Patients have Brain Infarcts

Brain Injury

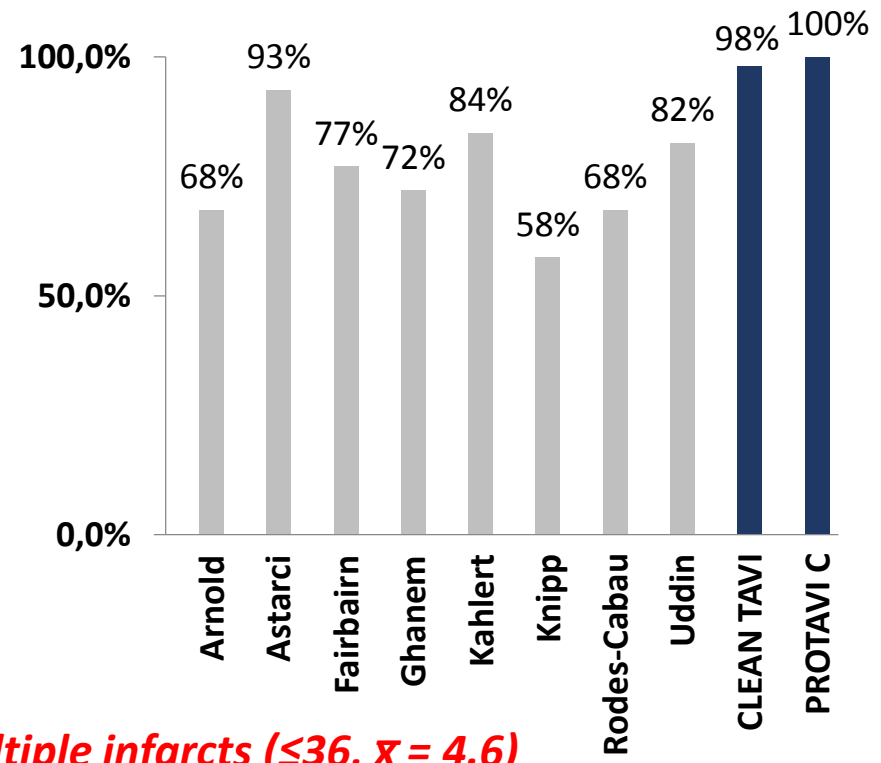
- "Silent" infarcts are associated with adverse neurological and cognitive consequences:
  - Impaired mobility
  - Physical decline
  - Depression
  - Cognitive dysfunction
  - Dementia
  - Alzheimer disease



- ***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



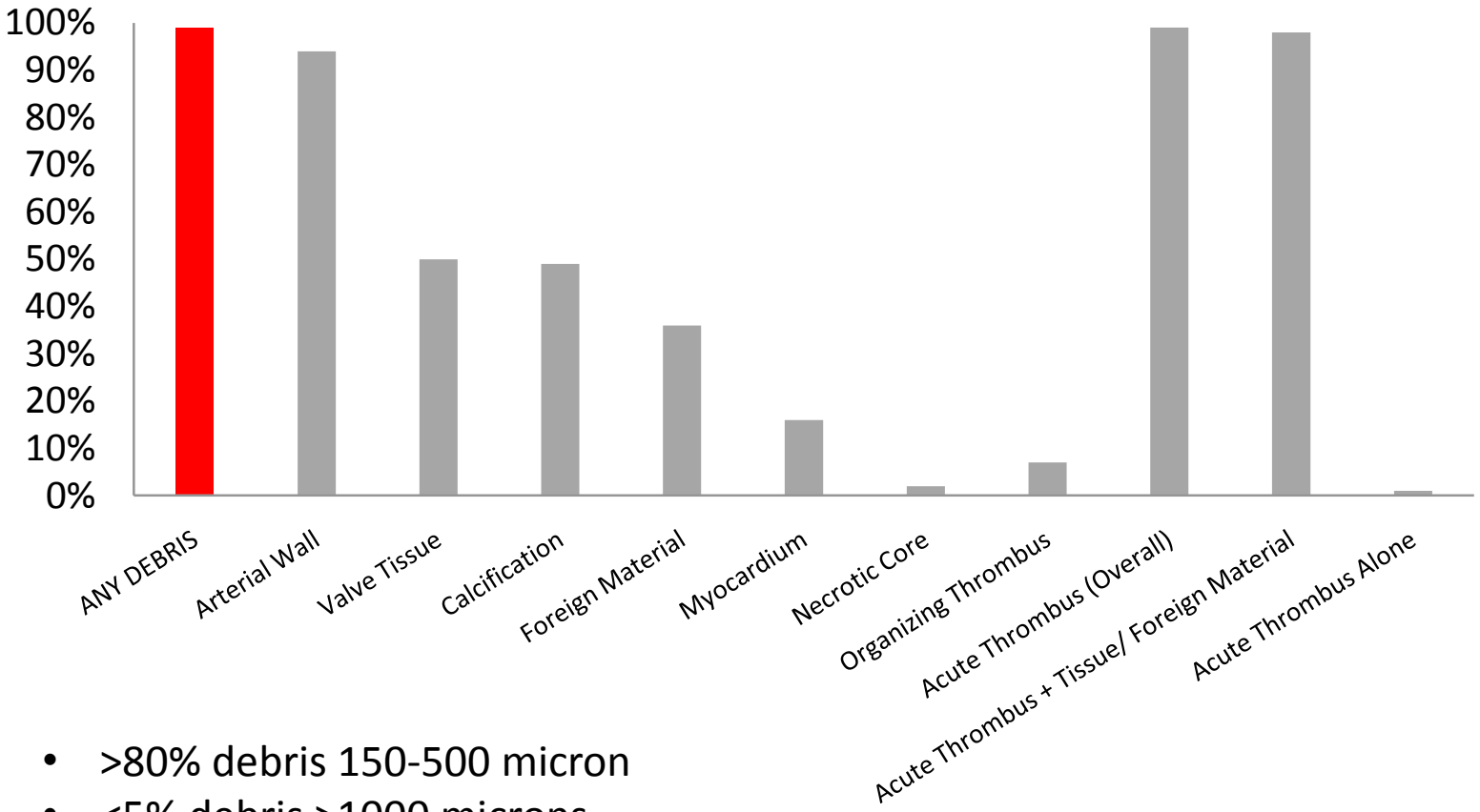
Multiple infarcts (≤36, x̄ = 4.6)
Total lesion Volume: 1.5cm^2-4.3cm^2

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.

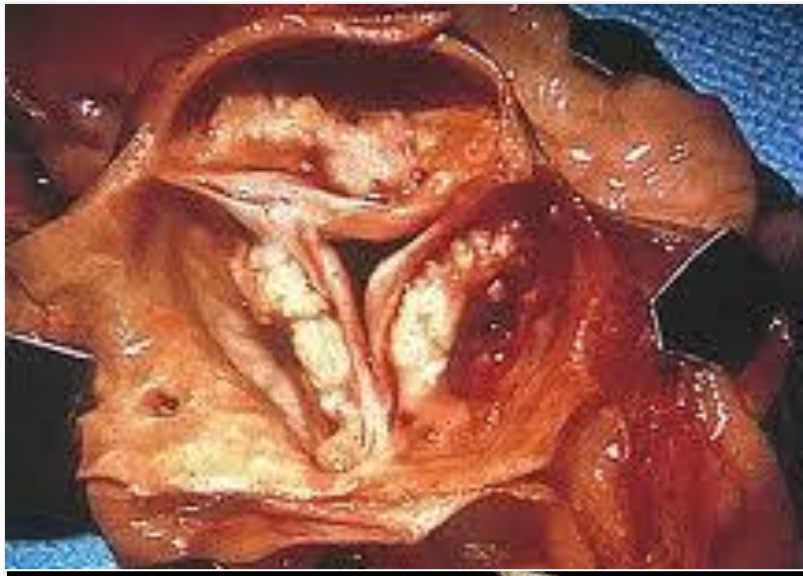
Embolic Brain Injury During TAVR: SENTINEL Trial

HISTOPATHOLOGY

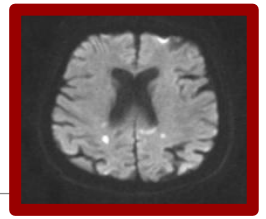
Debris Capture by Type

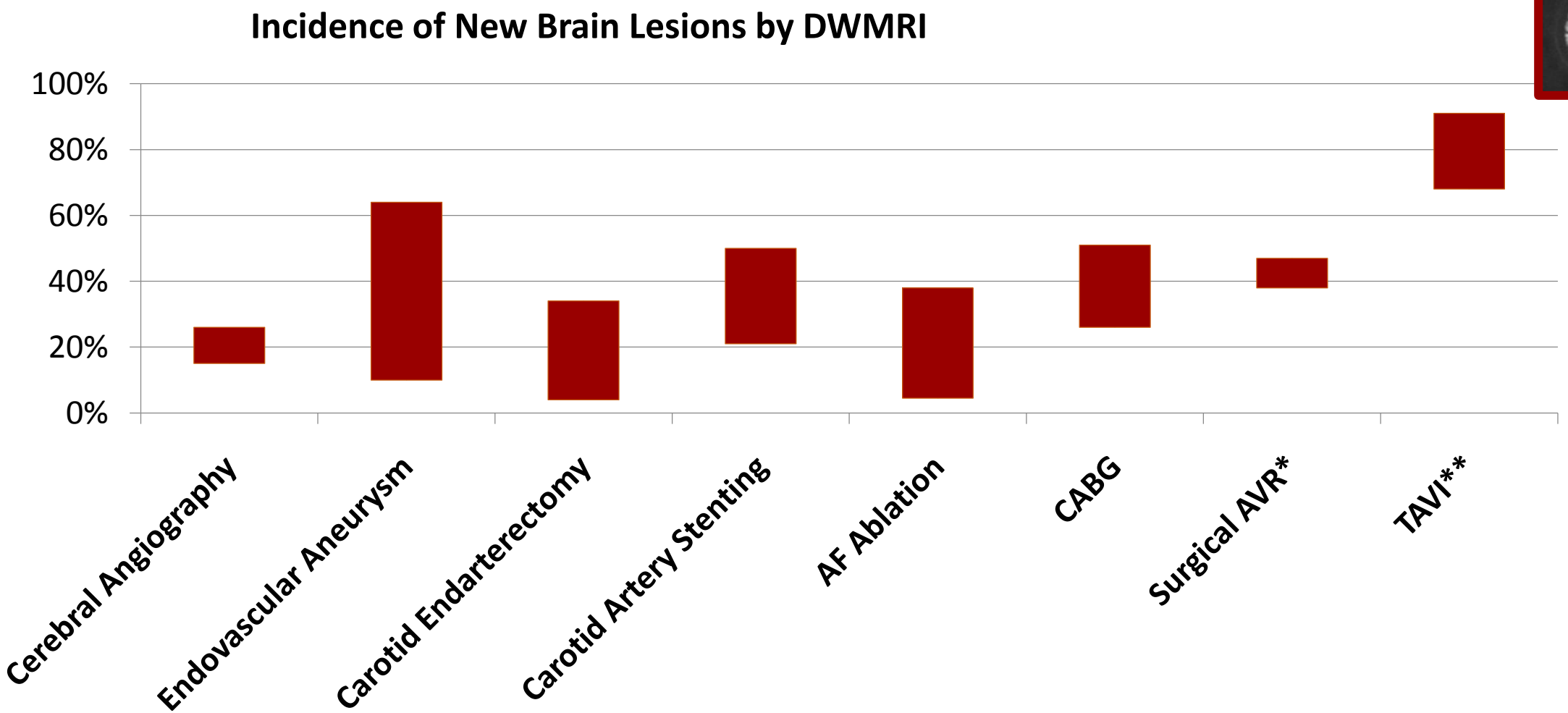


- >80% debris 150-500 micron
- <5% debris >1000 microns
- Up to 2000 microns



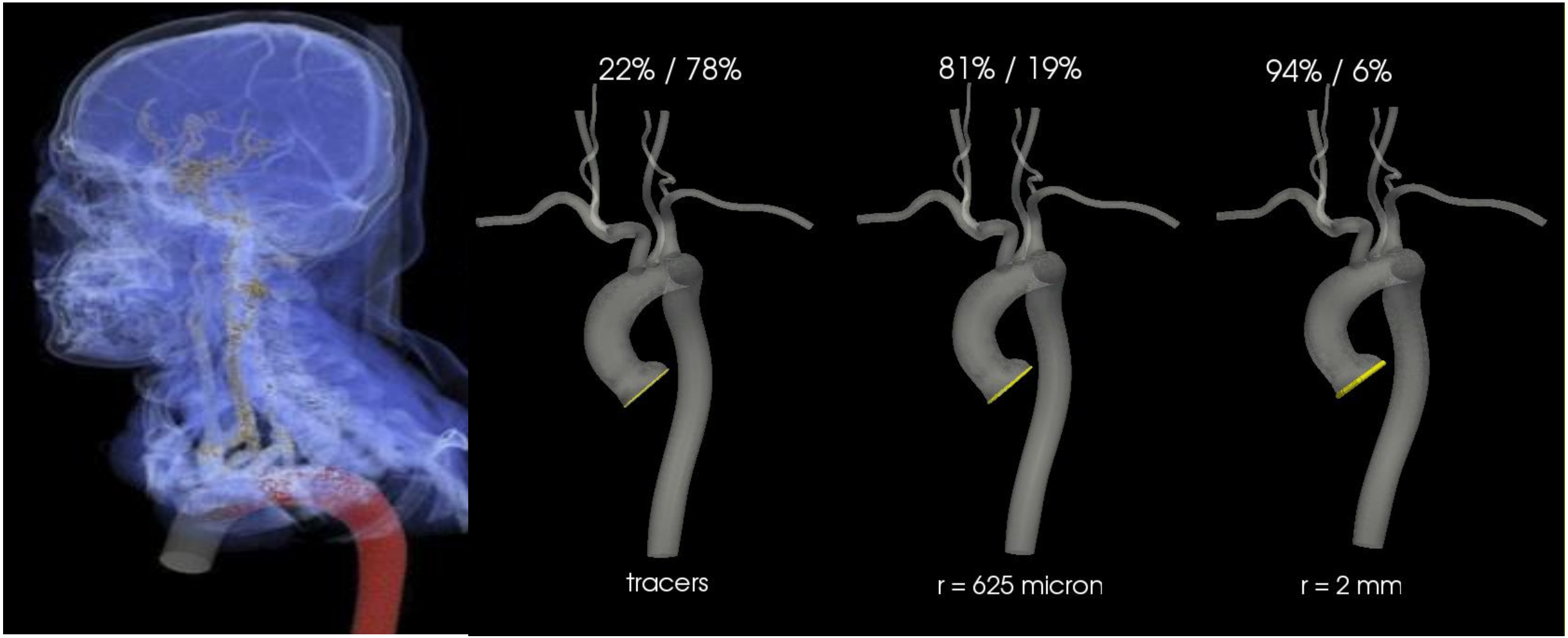
All CV Procedures cause Iatrogenic Embolization





*Knipp 2005, Stolz 2004. **Astarci 2011, Ghanem 2010, Kahlert 2010, Rodés-Cabau 2011.

Mechanism of Embolic Brain Injury During CV Procedures (simulation)

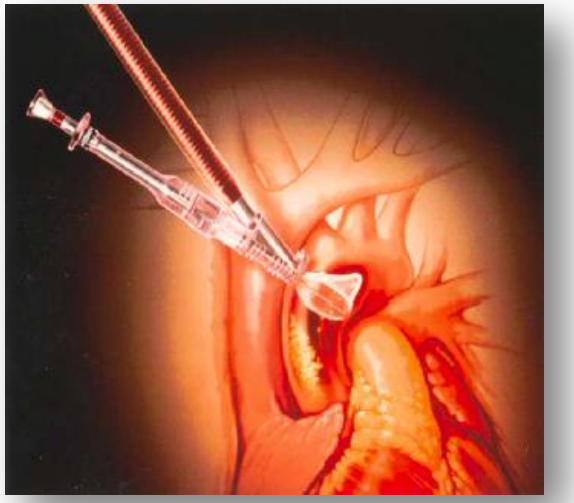


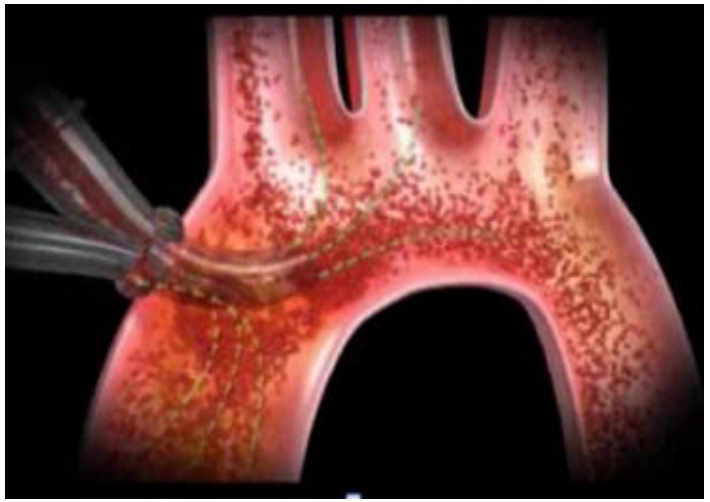
c/o Robert Schwartz

Cerebral Protection: A Legacy of Failed Trials

Trial design considerations

1. Variation in stroke definitions
   - VARC
   - ASA/AHA
   - Severe stroke vs all stroke
   - Timing of ascertainment
2. Uncertainty in DW MRI Endpoints
   - Frequency (CTSN) vs Volumes (Sentinel)
   - Variability of the measure
   - Clinical relevance



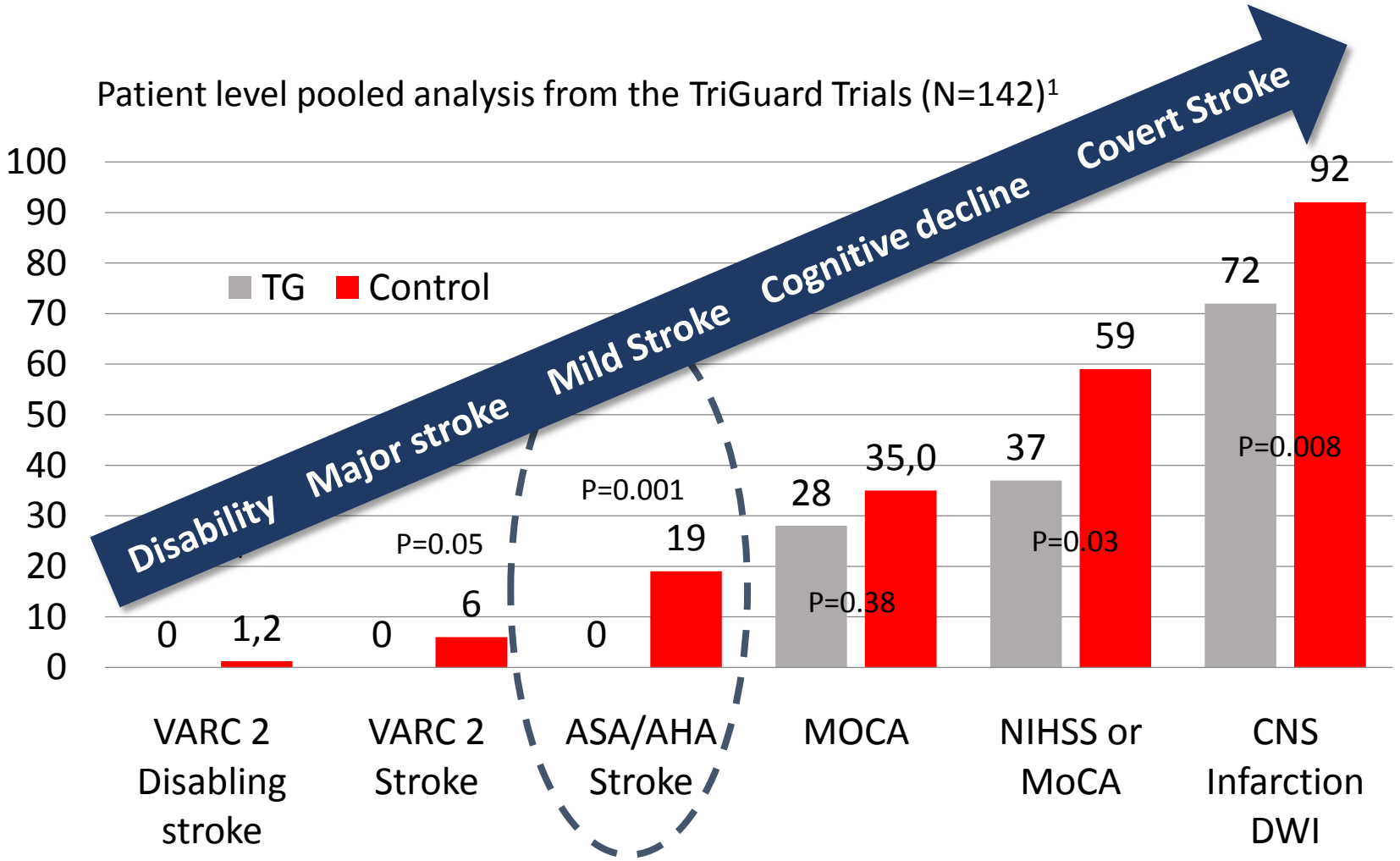


Device performance considerations

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

TriGuard Pooled analysis: Variability in Measures of 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 Concensus

2 Full day In Person Meetings:

October 2015 in San Francisco and January 2016, Yale Club in New York

International Multi Stakeholder Consensus

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

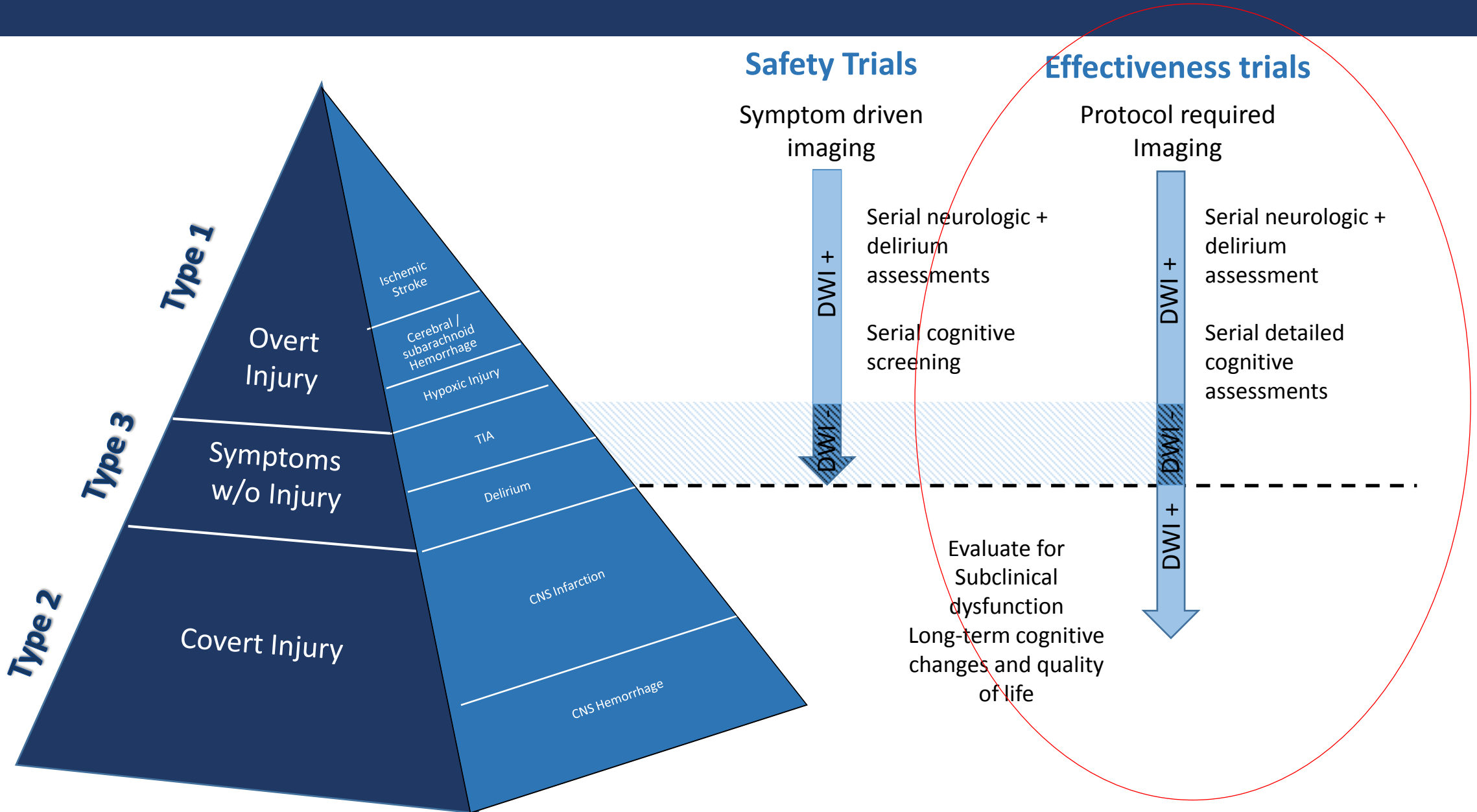
Definitions and Classification Relevant to Patients, Comprehensive, Practical

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 Hemorrhage**	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

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

CLASSIFICATION

APPLICATION AND ASSESSMENT



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

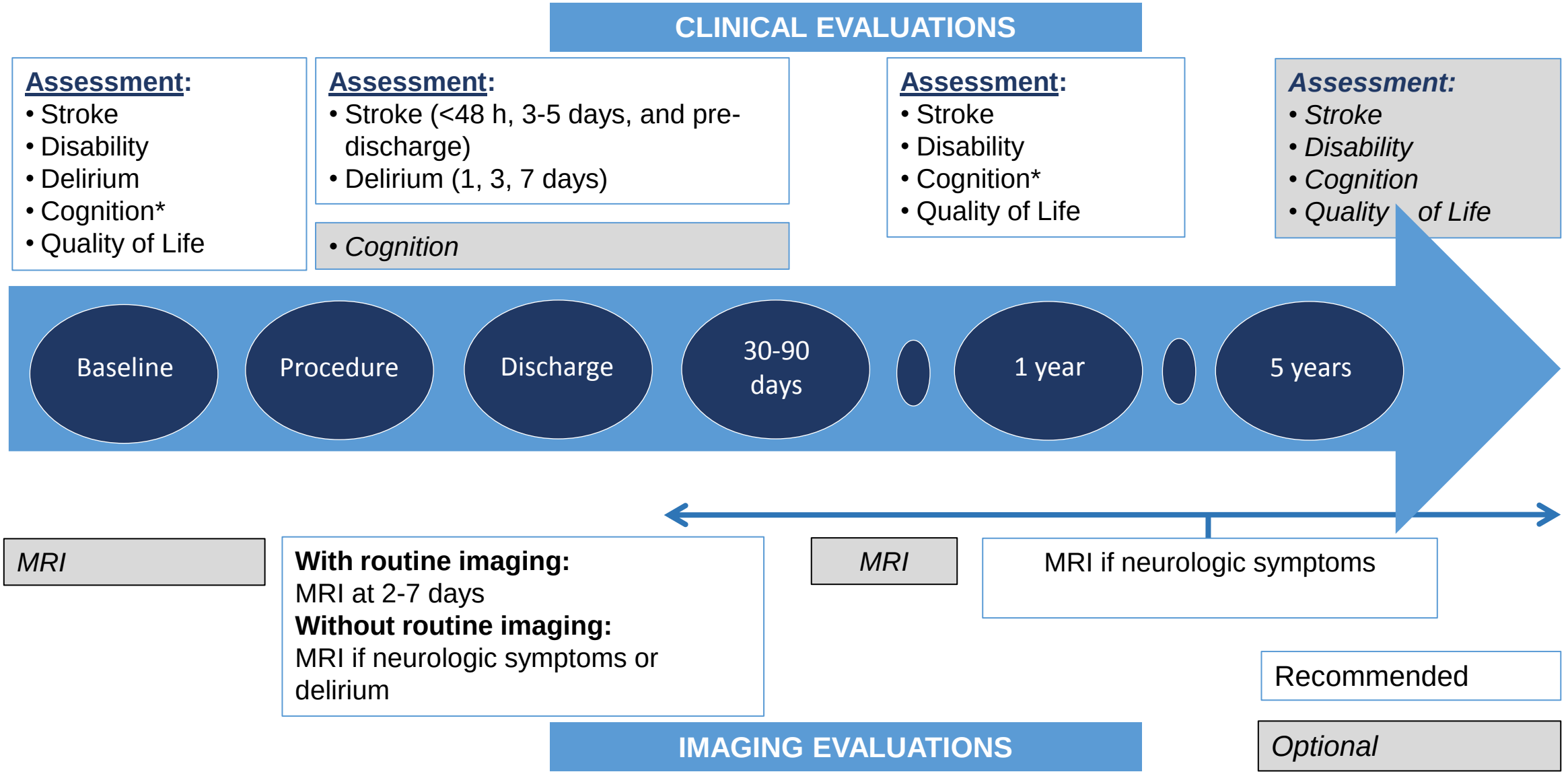
NeuroARC Stroke Severity and Disability: Clinically Relevant

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

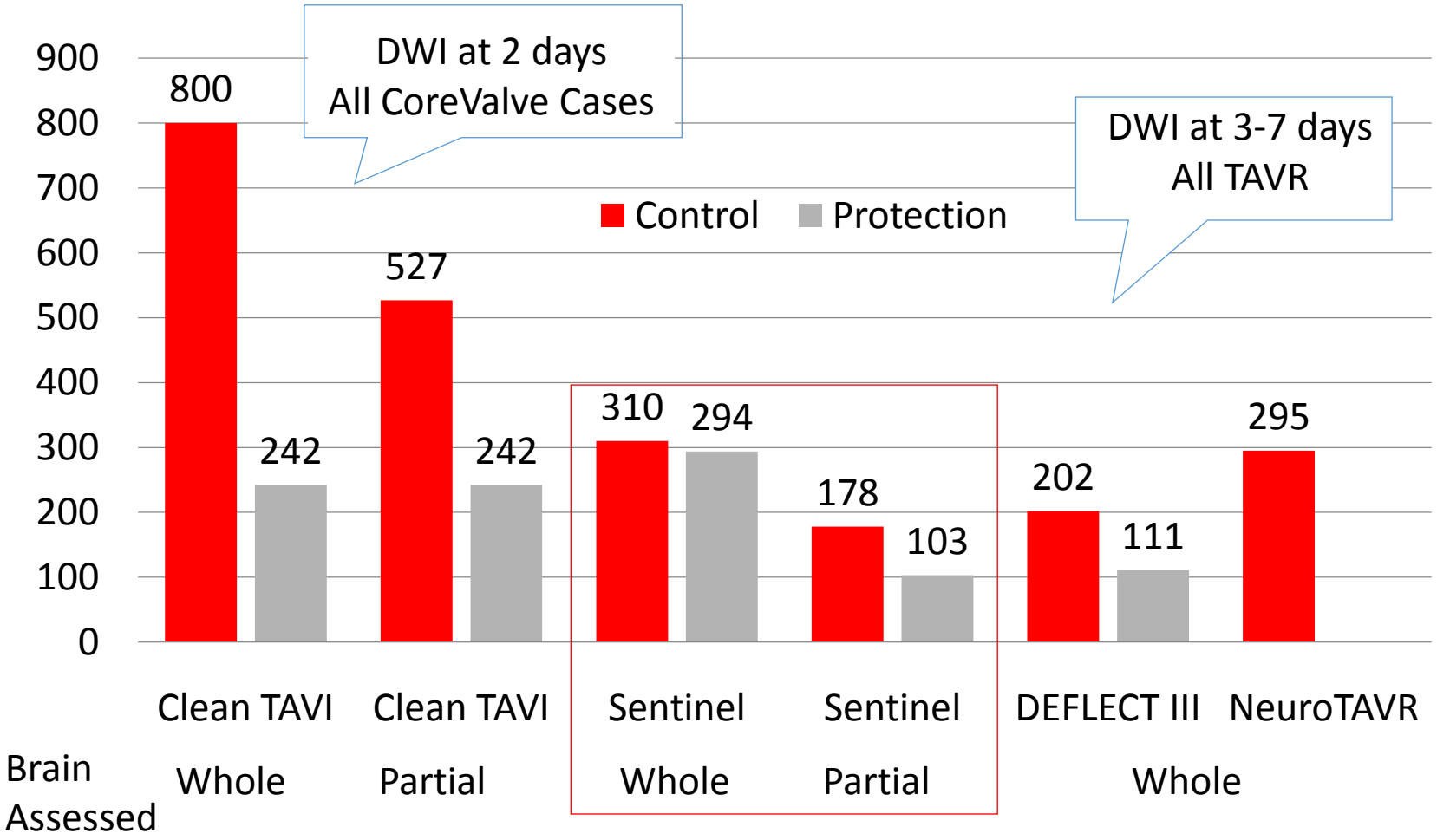
Disability is assessed in subjects with overt CNS injury (Type 1)

at 90±14 days after the stroke event.

NeuroARC Recommended Assessments: Clinical, Functional, Anatomic Correlations



Sentinel trial: Why was the trial Underpowered? Variability in TLV: Timing is Important



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

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Key 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)

Is TLV the right endpoint?

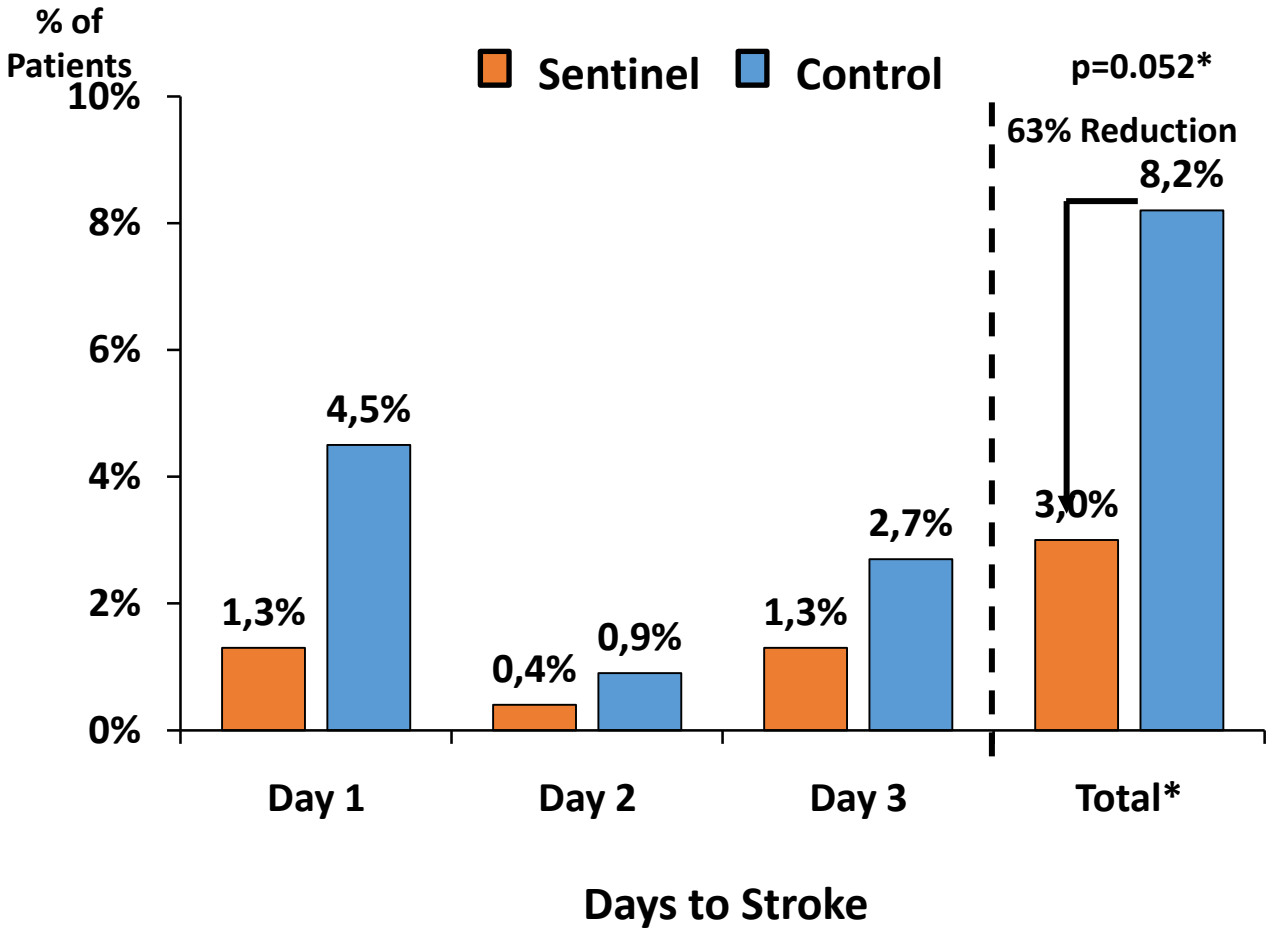
- **Size vs Location vs number**:
- corrolates of acute symtoms vs
- Corrolates of late symtpoms

Lessons Learned : Timing of Ascertainment Sentinel Trial

30 Day Stroke Diagnosis (Analyzed ITT)

	Device Arm (n=234)	Control Arm (n=111)	p-value
30-day Clinical Outcomes			
Any MACCE†	7.3%	9.9%	0.40
Death (all-cause)	1.3%	1.8%	0.65
Stroke	5.6%	9.1%	0.25
Disabling	0.9%	0.9%	1.00
Non-disabling	4.8%	8.2%	0.22
AKI (Stage 3)	0.4%	0%	1.00
TIA	0.4%	0%	1.00
Sentinel Access Site Complications	0.4%	N/A	0.53

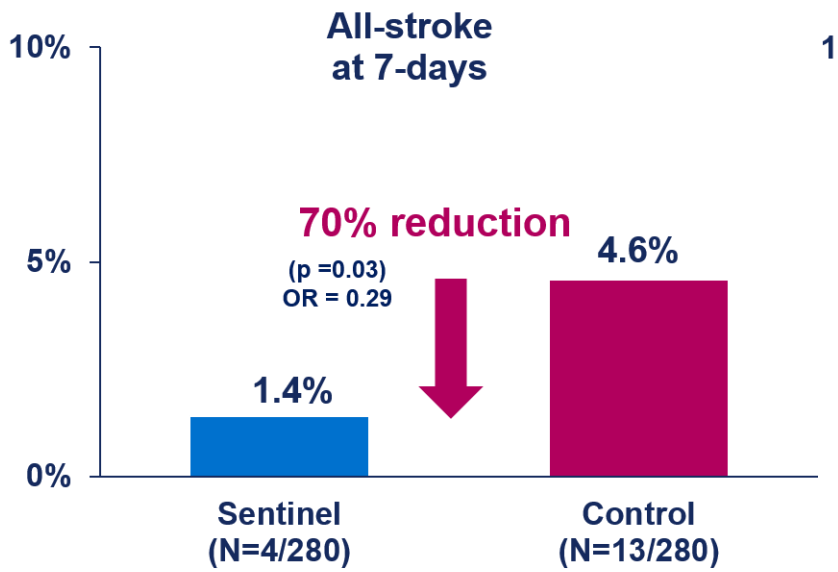
Stroke Diagnosis ≤72 hours (Analyzed ITT)

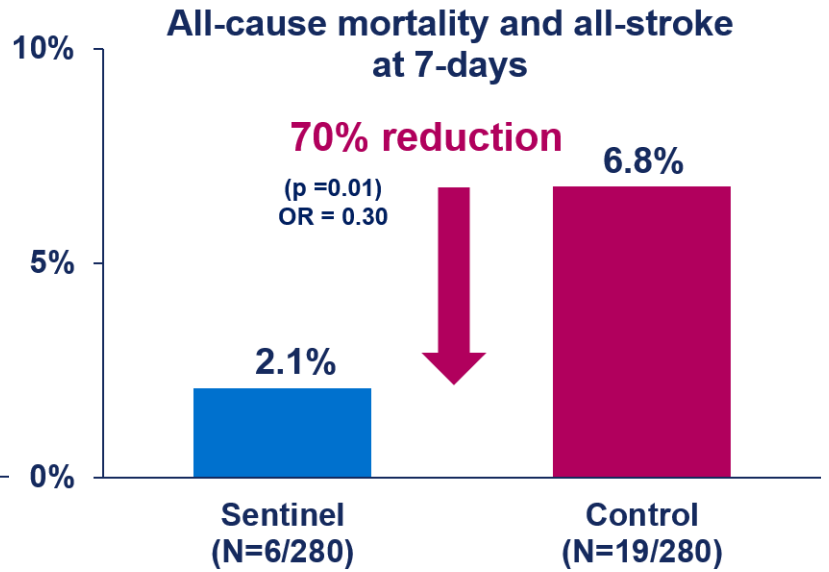


*Fisher Exact Test

Ulm Sentinel Study: Procedural Protection=Procedural Benefit

- 802 single center all-comer consecutive TAVR patients
- A propensity-matched analysis of 280 patients with Sentinel to 280 control patients





Predictor of Stroke at 7 days:

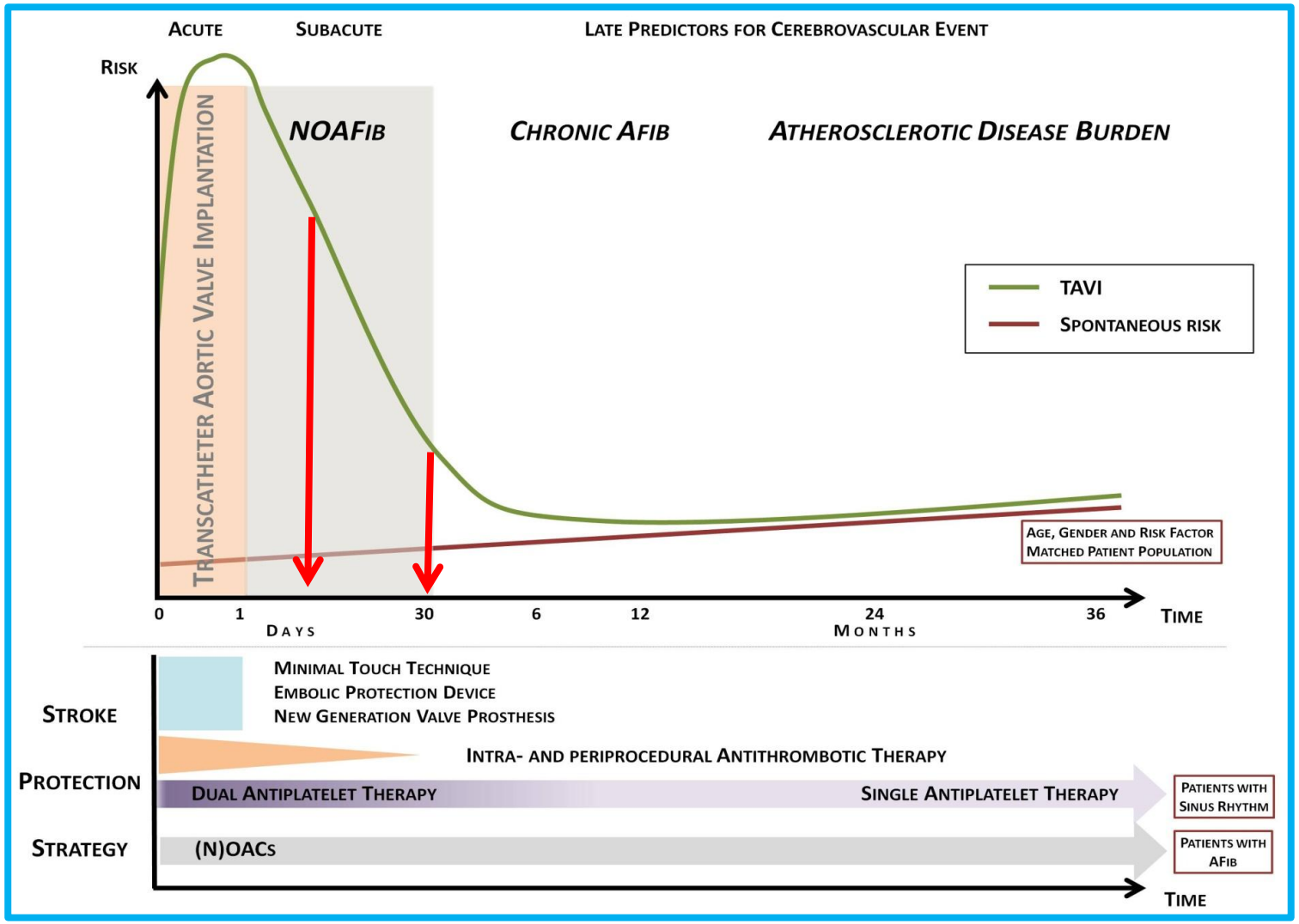
- No cerebral emboli protection (p=0.044)

Predictor of Stroke and Death at 7 deaths:

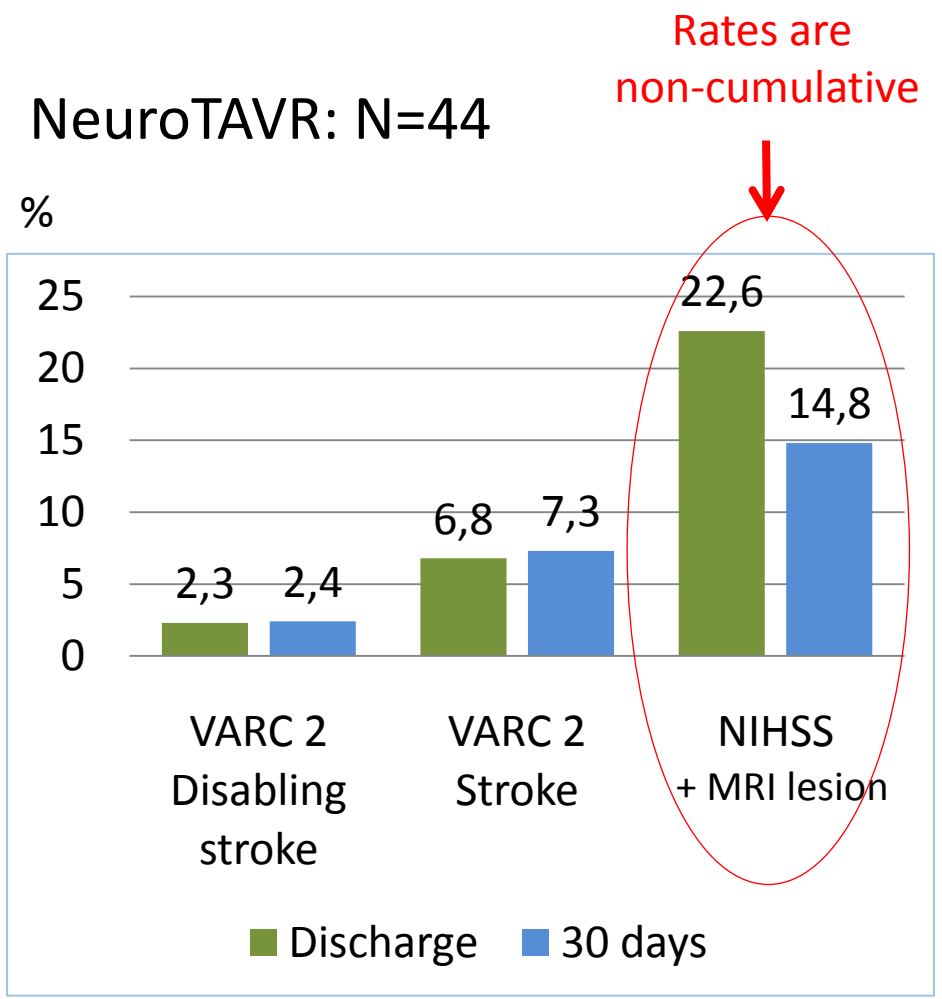
- No cerebral emboli protection (p=0.028)
- STS score (<8 vs. ≥8) (p=0.021)

Wörhle J, Seeger J, et al. DGK Mannheim 2017; CSI-Ulm-TAVR Study clinicaltrials.gov NCT02162069

Procedural vs Spontaneous Stroke Risk:
Neuro ARC is more sensitive; Earlier is more Specific to the procedure



Stortecky, Windecker. Circulation 2012;126:2921-4



Lansky. AJC 2016

For more information
Simultaneous publications in EHJ and JACC

Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative

Alexandra J. Lansky; Steven R. Messé; Adam M. Brickman; Michael Dwyer; H. Bart van der Worp; Ronald M. Lazar; Cody G. Pietras; Kevin J. Abrams; Eugene McFadden; Nils H. Petersen; Jeffrey Browndyke; Bernard Prendergast; Vivian G. Ng; Donald E. Cutlip; Samir Kapadia; Mitchell W. Krucoff; Axel Linke; Claudia Scala Moy; Joachim Schofer; Gerrit-Anne van Es; Renu Virmani; Jeffrey Popma; Michael K. Parides; Susheel Kodali; Michel Bilello; Robert Zivadinov; Joseph Akar; Karen L. Furie; Daryl Gress; Szilard Voros; Jeffrey Moses; David Greer; John K. Forrest; David Holmes; Arie P. Kappetein; Michael Mack; Andreas Baumbach

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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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