

Progress in Cerebral Embolic Protection

The Search for Meaningful Measures of Clinical 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

Cerebral Protection: A Legacy of Failed Trials

Trial design considerations

1. Variation in stroke definitions

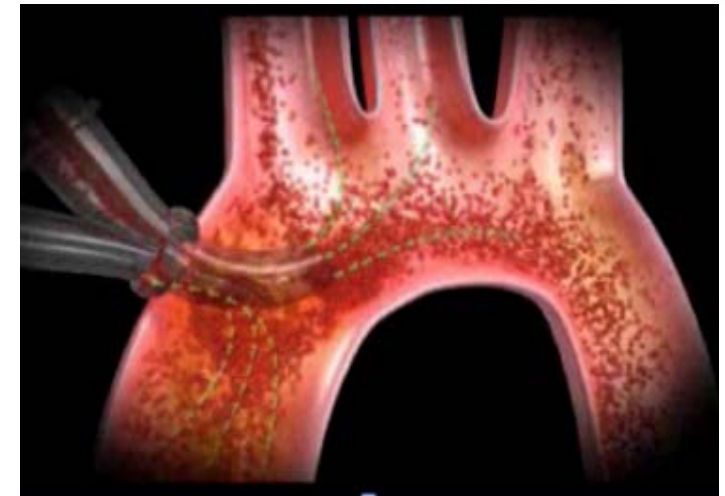
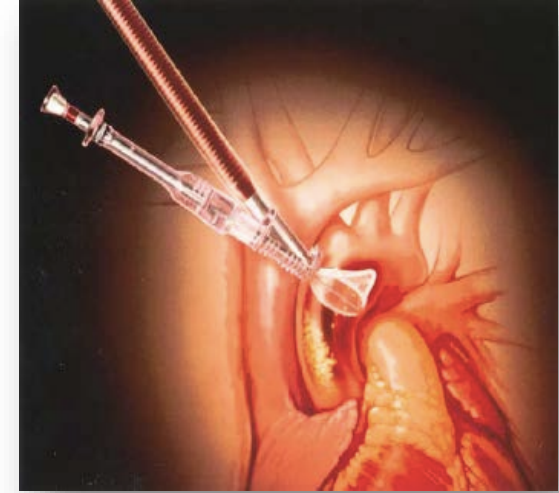
- VARC
- ASA/AHA
- Severe stroke vs all stroke
- Timing of ascertainment

2. Uncertainty in DW MRI Endpoints

- Frequency (CTSN) vs Volumes (Sentinel)
- Variability of the measure
- Clinical relevance

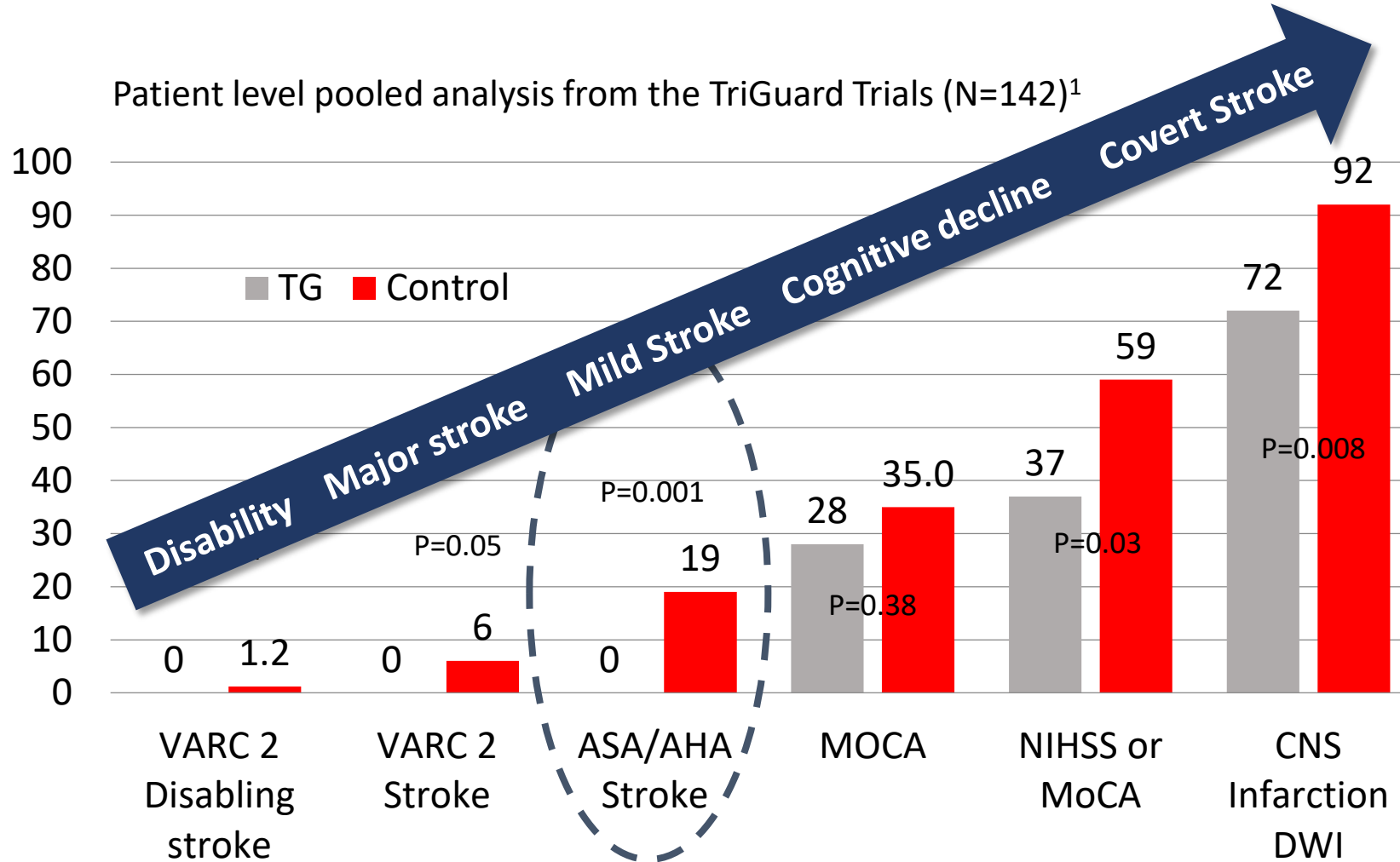
Device performance considerations

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



TriGuard Pooled analysis: Variability in Measures of Neurologic Injury

Incidence of Neurologic Injury Depends on Definition



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

NeuroARC applies to all CV trials

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

CATEGORY I <u>Primary Procedural Safety Measure</u>	CATEGORY II <u>Primary Procedural Efficacy Measure</u>	CATEGORY III <u>Primary Procedural Safety, Long-term Efficacy Measure</u>
<p>Devices with inherent iatrogenic embolic risk</p> <ul style="list-style-type: none">• Surgical cardiac procedures (valve replacement, CABG, dissection, aneurysm repair)• Adjunctive pharmacology	<p>Devices designed to prevent iatrogenic or spontaneous acute neurologic injury</p> <ul style="list-style-type: none">• Neuroprotection device• Cerebral temperature management devices	<p>Devices with inherent iatrogenic embolic risk and designed for prevention of spontaneous long-term risk</p> <ul style="list-style-type: none">• Atrial Fibrillation Ablation• PFO or LAA closure devices

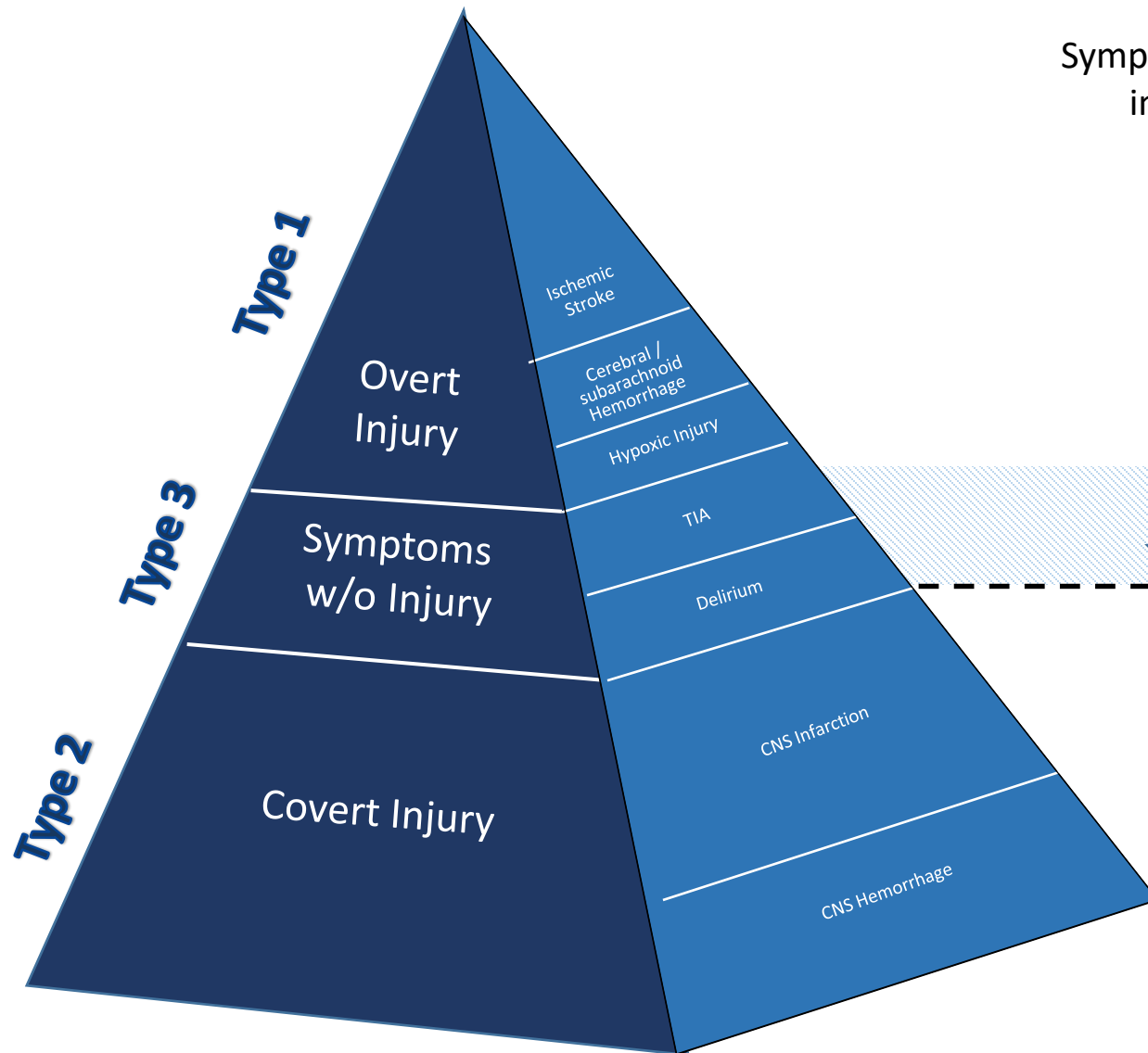
NeuroARC

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

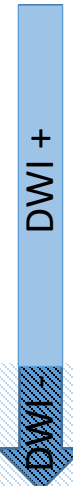
CLASSIFICATION

APPLICATION AND ASSESSMENT



Safety Trials

Symptom driven
imaging

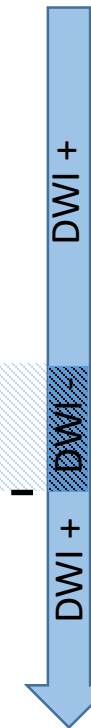


Serial neurologic +
delirium
assessments

Serial cognitive
screening

Effectiveness trials

Protocol required
Imaging



Serial neurologic +
delirium
assessment

Serial detailed
cognitive
assessments

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

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

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

CLINICAL EVALUATIONS

Assessment:

- Stroke
- Disability
- Delirium
- Cognition*
- Quality of Life

Assessment:

- Stroke (<48 h, 3-5 days, and pre-discharge)
- Delirium (1, 3, 7 days)
- Cognition

Assessment:

- Stroke
- Disability
- Cognition*
- Quality of Life

Assessment:

- Stroke
- Disability
- Cognition
- Quality of Life

Baseline

Procedure

Discharge

30-90
days

1 year

5 years

MRI

With routine imaging:

MRI at 2-7 days

Without routine imaging:

MRI if neurologic symptoms or delirium

MRI

MRI if neurologic symptoms

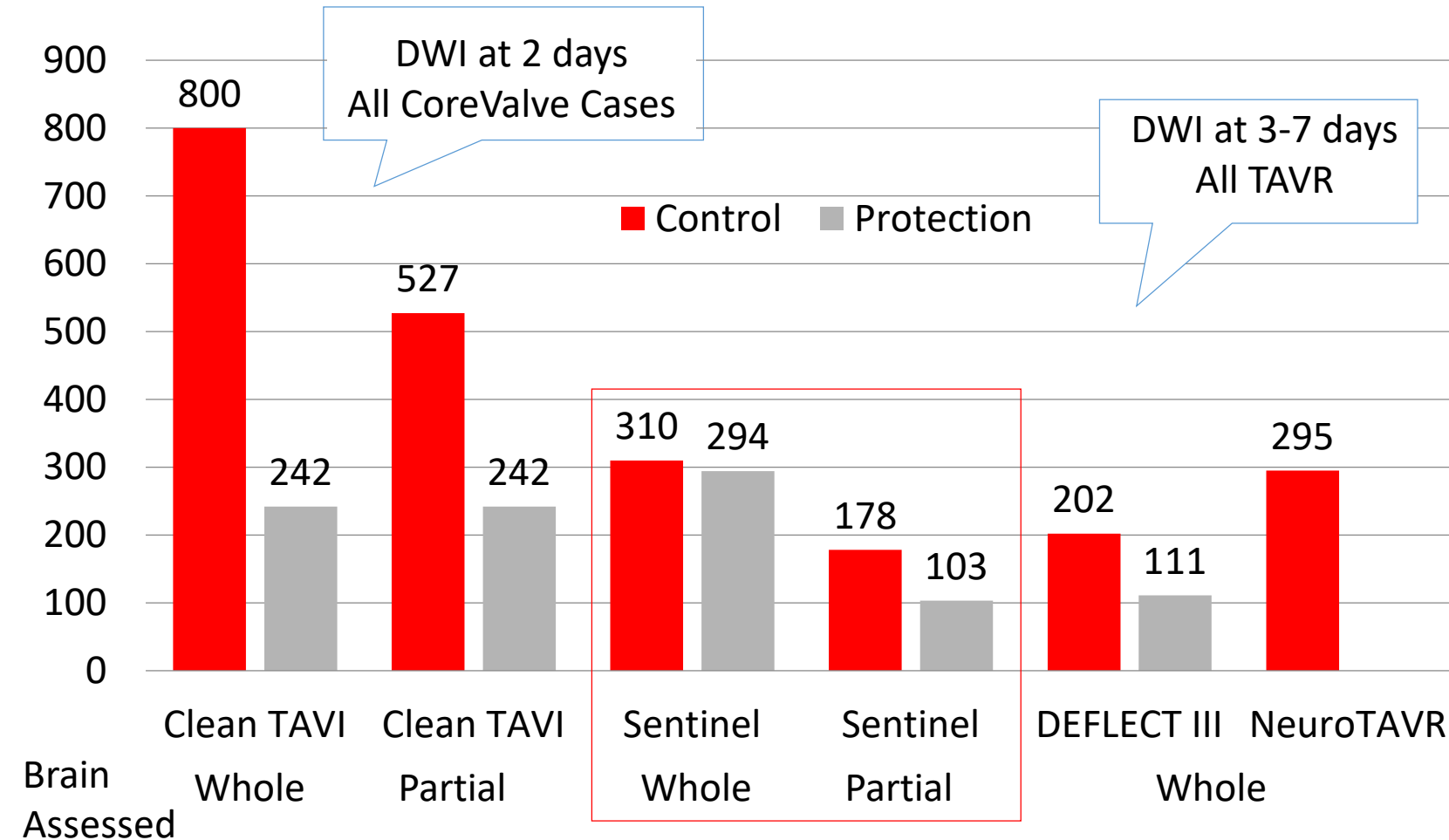
Recommended

Optional

IMAGING EVALUATIONS

Sentinel trial: Why was the trial Underpowered?

Variability in TLV: Timing is Important



⁵Haussig S, JAMA. 2016;316:592.

Lansky AJ, Eur Heart J. 2015; 36:2070.; Lansky AJ, AJC 2016 .

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?

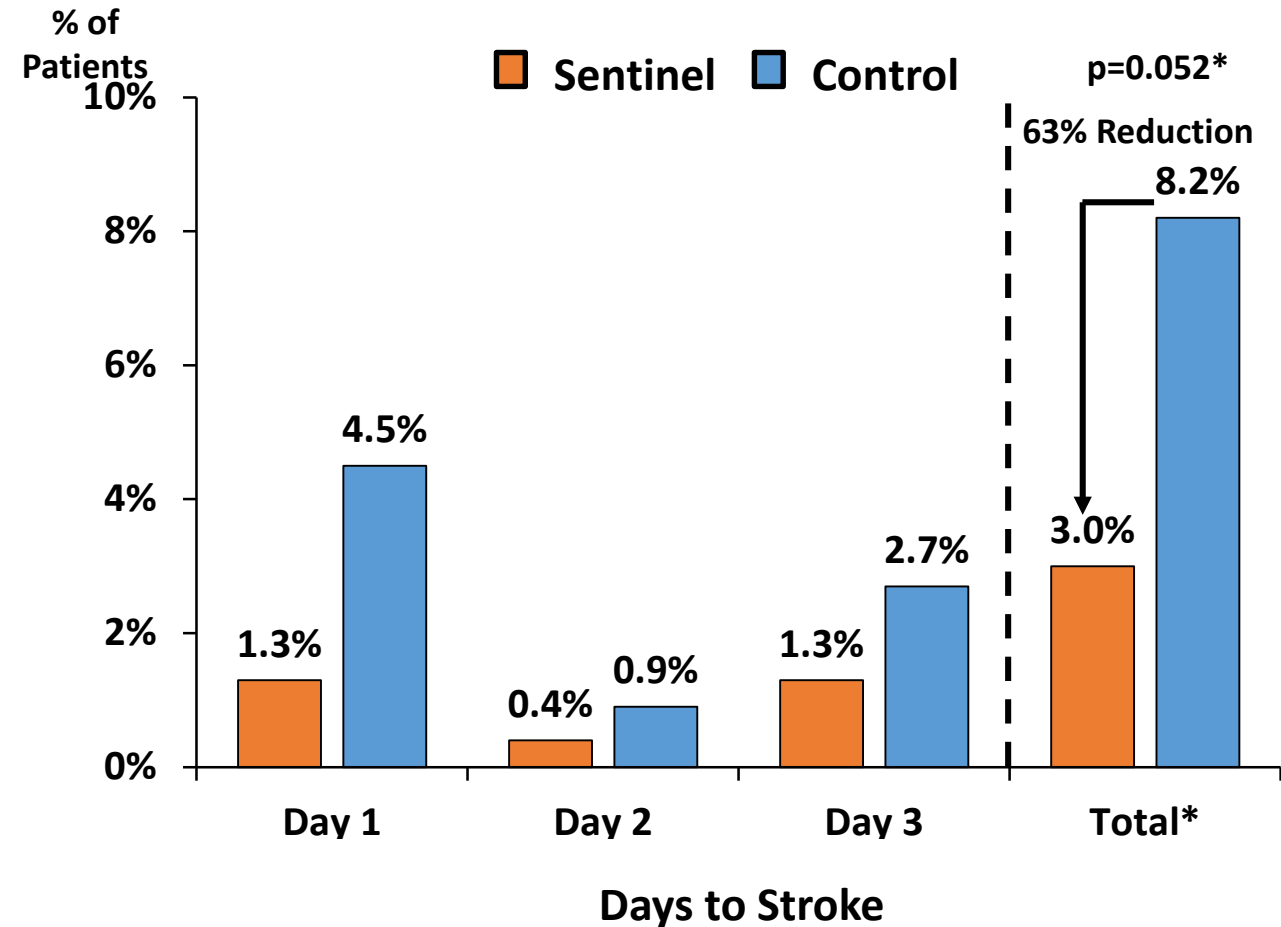
- **Size vs Location vs number:**
- correlates of acute symptoms vs
- Correlates of late symptoms

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

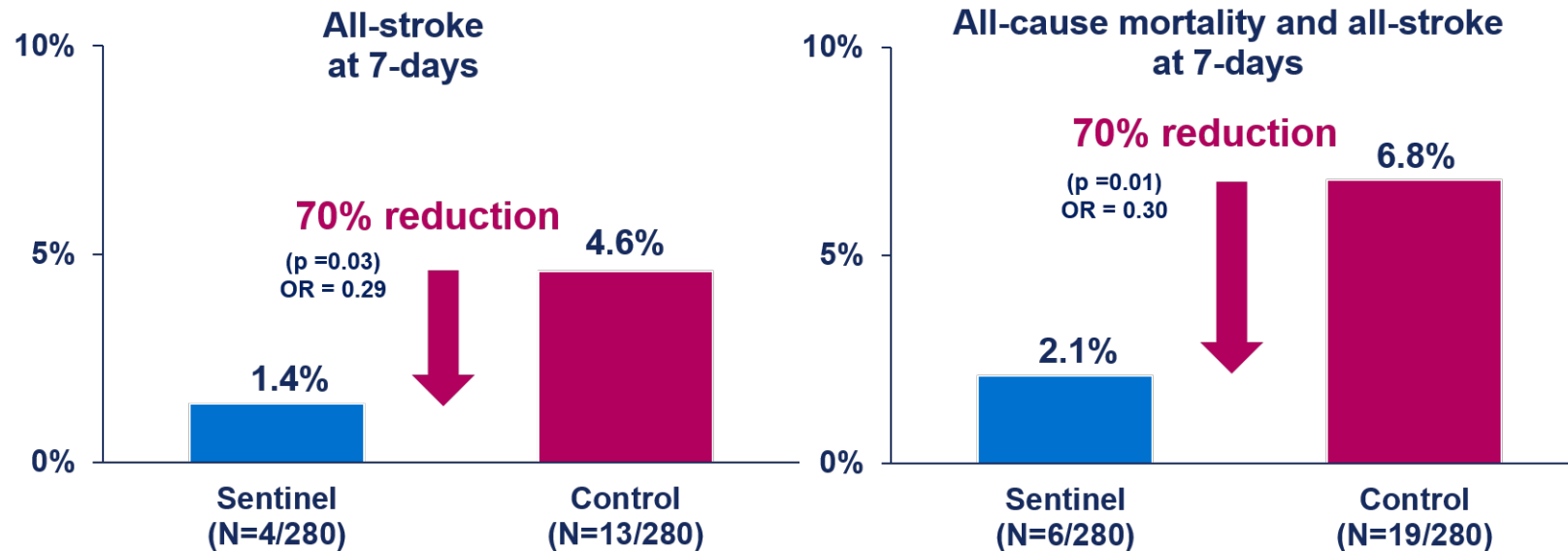
Stroke Diagnosis ≤72 hours (Analyzed ITT)



*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:

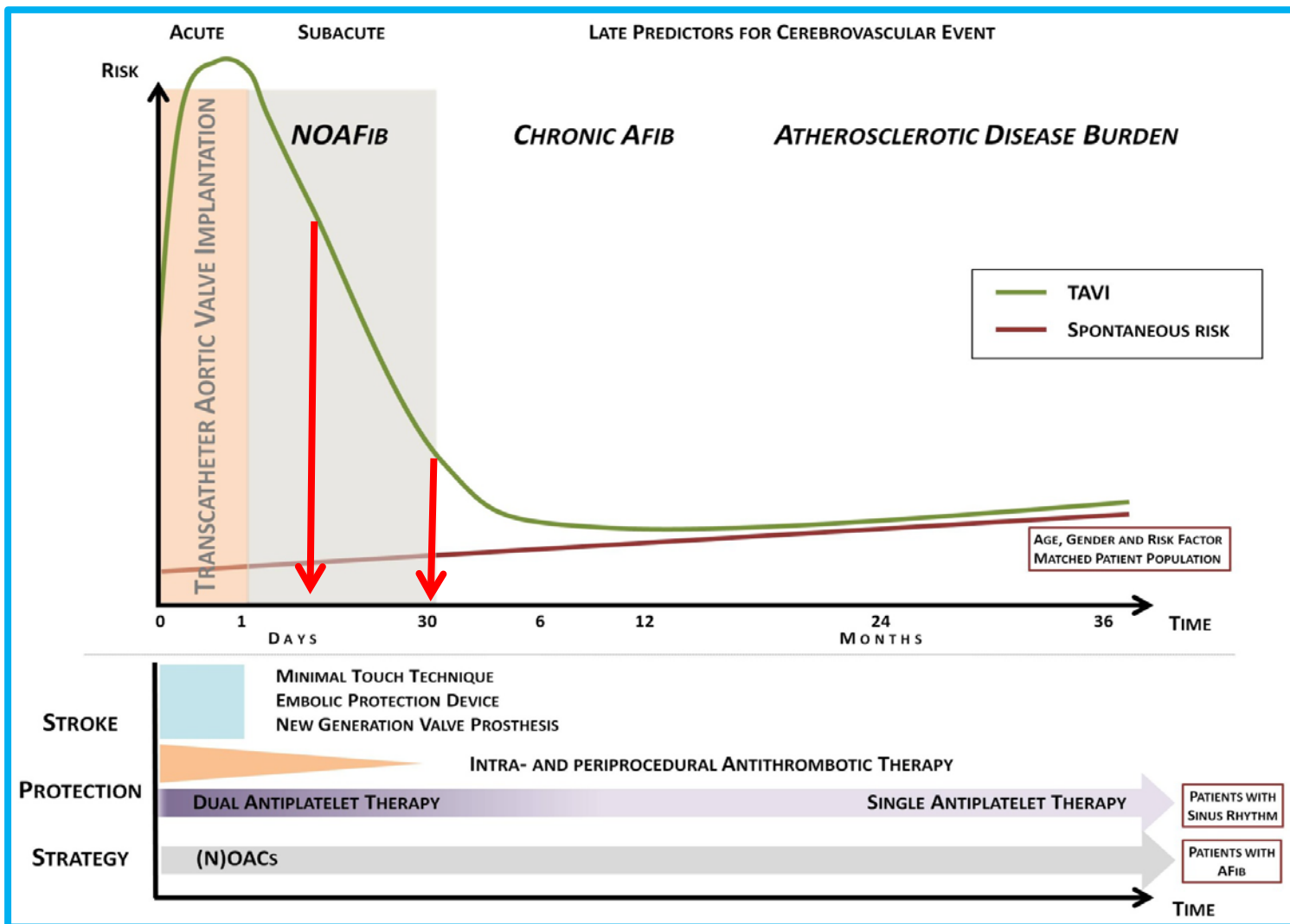
- No cerebral emboli protection (p=0.044)

Predictor of Stroke and Death at 7 deaths:

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

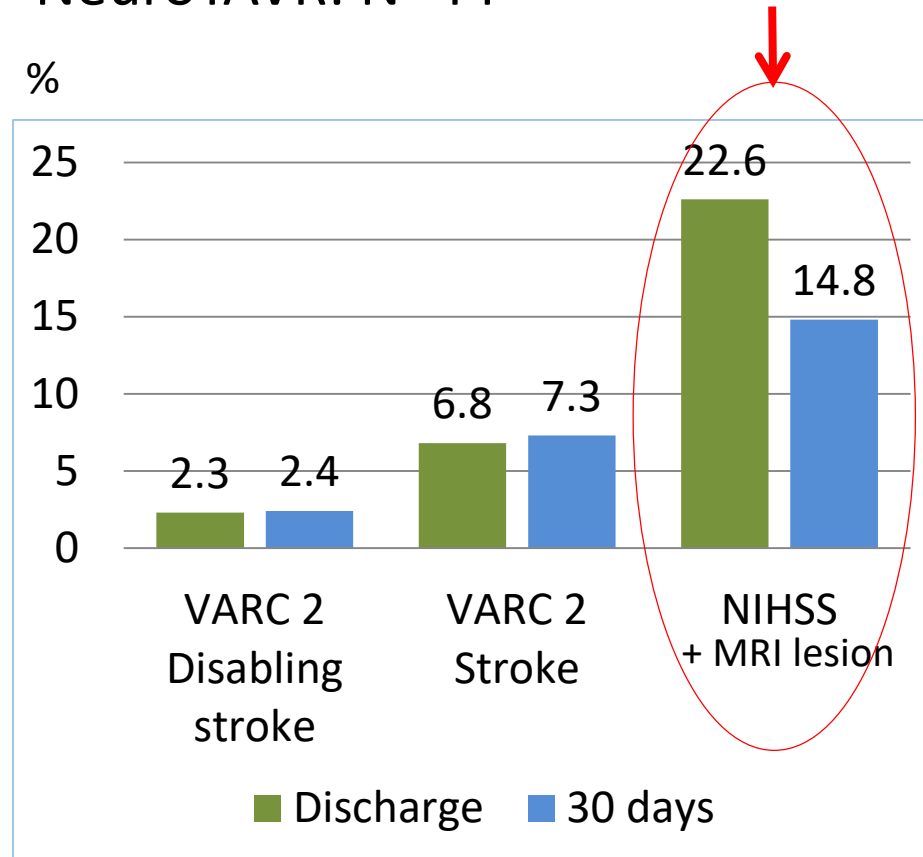
Procedural vs Spontaneous Stroke Risk:

Neuro ARC is more sensitive; Earlier is more Specific to the procedure



STORTECKY, WINDECKER. CIRCULATION 2012;126:2921-4

NeuroTAVR: N=44



LANSKY. AJC 2016

For more information Simultaneous publications in EHJ and JACC



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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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