The Compelling Saga of Strokes after TAVR

Search for Meaningful Measures of Clinical Efficacy: NeuroARC and Beyond

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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

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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, $\bar{x} = 4.6$)
- Total lesion Volume: 1.5cm$^2$-4.3cm$^2$

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

Incidence of New Brain Lesions by DWMRI

Mechanism of Embolic Brain Injury During CV Procedures (simulation)

- Tracers: 22% / 78%
- r = 625 micron: 81% / 19%
- r = 2 mm: 94% / 6%

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?
Patient level pooled analysis from the TriGuard Trials (N=142)¹

Incidence of Neurologic 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**

<table>
<thead>
<tr>
<th>Interventional/Structural/CT Surgery</th>
<th>Neurology/Neuroradiology/Neuropsychology/NINDS</th>
<th>FDA/ARC/Pathology</th>
</tr>
</thead>
</table>
| 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  
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  Bram Zuckerman  
  **Academic Research Consortium (ARC)**  
  Donald Cutlip  
  Gerrit-Anne van Es  
  Mitch Krucoff  
  Roxana Mehran  
  **Pathology and Regulatory**  
  Semih Oktay  
  Renu Virmani |
NeuroARC Consensus

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

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

<table>
<thead>
<tr>
<th>Type 2.a</th>
<th>Covert CNS Infarction</th>
<th>Acutely asymptomatic focal or multi-focal ischemia, based on neuroimaging</th>
</tr>
</thead>
</table>
| 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)

<table>
<thead>
<tr>
<th>Type 3.a</th>
<th>Transient Ischemic Attack (TIA)</th>
<th>Symptoms &lt;24 hours with no evidence of acute infarction by neuroimaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 3.b</td>
<td>Delirium without CNS injury</td>
<td>Transient non-focal (global) neurologic signs or symptoms (variable duration) without evidence of cell death by pathology or neuroimaging</td>
</tr>
</tbody>
</table>
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

Covert Injury

Type 2

CNS Hemorrhage

CNS Infarction

Delirium

TIA

Hypoxic Injury

Cerebral/subarachnoid Hemorrhage

Ischemic Stroke

Overt Injury

Type 3

Symptoms w/o Injury

Type 1
# NeuroARC Definitions and Classification
Consistent with Historical Definitions

<table>
<thead>
<tr>
<th>COMPOSITES</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>CNS Infarction (overt and covert) (ASA/AHA definition</em>)</em>*</td>
</tr>
<tr>
<td>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)</td>
</tr>
<tr>
<td><strong>CNS Hemorrhage (overt and covert)</strong></td>
</tr>
<tr>
<td>Any brain, spinal cord, or retinal hemorrhage based on imaging or pathology, not caused by trauma; (includes Type 1.c, 2.b)</td>
</tr>
<tr>
<td><strong>VARC 2 Stroke</strong></td>
</tr>
<tr>
<td>All Type 1 overt stroke</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Acute Severity</th>
<th>Long-Term Stroke Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild neurologic dysfunction:</strong> NIHSS 0-5</td>
<td><strong>Fatal Stroke:</strong> Cause of death is attributable to the stroke.</td>
</tr>
<tr>
<td><strong>Moderate neurologic dysfunction:</strong> NIHSS 6-14</td>
<td><strong>Disabling stroke:</strong> A modified Rankin Score (mRS) ≥2 at 90 days with an increase of at least 1 point compared to the pre-stroke baseline.</td>
</tr>
<tr>
<td><strong>Severe neurologic dysfunction:</strong> NIHSS ≥15</td>
<td><strong>Non-disabling stroke:</strong> An mRS score &lt;2 at 90 days, or ≥2 without an increase of at least 1 compared to the pre-stroke baseline.</td>
</tr>
</tbody>
</table>

**Stroke with complete recovery:** An mRS score at 90 days of 0 OR a return to the patient’s pre-stroke baseline mRS
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
- Quality of Life

**Assessment:**
- Stroke
- Disability
- Cognition*
- Quality of Life

**Baseline**
**Procedures**
**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

**IMAGING EVALUATIONS**

**MRI**

MRI if neurologic symptoms

**Recommended**

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

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

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Lessons Learned: Timing of Ascertainment Sentinel Trial

30 Day Stroke Diagnosis (Analyzed ITT)

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

Stroke Diagnosis ≤72 hours (Analyzed ITT)

- **Device Arm** (n=234): 5.6% of patients experienced a stroke within 72 hours.
- **Control Arm** (n=111): 9.1% of patients experienced a stroke within 72 hours.

The p-value for the difference is 0.25, indicating a statistically significant reduction in stroke diagnosis within 72 hours for the Device Arm compared to the Control Arm.

Other clinical outcomes include:
- **Any MACCE**: 4.5% in the Device Arm vs. 9.9% in the Control Arm (p=0.40)
- **Death (all-cause)**: 0.9% vs. 0% (p=0.65)
- **Disabling Stroke**: 1.3% vs. 0% (p=1.00)
- **Non-disabling Stroke**: 2.7% vs. 0% (p=0.22)
- **AKI (Stage 3)**: 0.9% vs. 0% (p=1.00)
- **TIA**: 0.4% vs. 0% (p=1.00)

**Sentinel Access Site Complications**: 0.4% in the Device Arm vs. N/A in the Control Arm (p=0.53)

*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)

Wöhrle 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

VARC 2
Disabling stroke
VARC 2 Stroke
NIHSS + MRI lesion

Rates are non-cumulative

NeuroTAVR: N=44

<table>
<thead>
<tr>
<th></th>
<th>Discharge</th>
<th>30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>VARC 2 Stroke</td>
<td>2,3</td>
<td>2,4</td>
</tr>
<tr>
<td>VARC 2 Stroke</td>
<td>6,8</td>
<td></td>
</tr>
<tr>
<td>NIHSS + MRI lesion</td>
<td>7,3</td>
<td>14,8</td>
</tr>
</tbody>
</table>

Procedural Aortic Valve Implantation (TAVI)

Stordecky, 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

Amanda L. 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 Brown dyke; 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

Eur Heart J ehx037. DOI: https://doi.org/10.1093/eurheartj/ehx037
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