Why Cerebral Protection after TAVR Will Become the Standard of Care

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Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Physician Name</th>
<th>Company/Relationship</th>
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<tbody>
<tr>
<td>Eberhard Grube, MD</td>
<td>Medtronic, CoreValve: C, SB, AB, OF</td>
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<tr>
<td></td>
<td>Direct Flow: C, SB, AB</td>
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<td></td>
<td>Mitralign: AB, SB, E</td>
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<td>Boston Scientific: C, SB, AB</td>
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<td>Biosensors: E, SB, C, AB</td>
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<td></td>
<td>Cordis: AB</td>
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<td>Abbott Vascular: AB</td>
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<td>InSeal Medical: AB, E</td>
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<td>Valtech: E, SB</td>
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<td>Claret: SB</td>
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<td>Keystone: AB</td>
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Key:
- G – Grant and or Research Support
- E – Equity Interests
- S – Salary, AB – Advisory Board
- C – Consulting fees, Honoraria
- R – Royalty Income I – Intellectual Property Rights
- SB – Speaker’s Bureau
- O – Ownership
- OF – Other Financial Benefits
Let Me Lay out my Position in Advance.

1. I am a TRUE believer in TAVR and its role in treating AS in defined patient groups

2. However, TAVR undoubtedly causes embolic showers to the Brain, which cause lesions: some ‘silent’, some more clinically obvious

3. Many TAVR studies under-report Stroke & few employ independent neurologists

4. Percentages do not always tell the whole story and Stroke is truly devastating

5. If cerebral protection can reduce or eliminate lesions in the brain, then it should become routine practice
Stroke Remains a Real Risk

### Clinical Outcome at 30 Days (I)

<table>
<thead>
<tr>
<th></th>
<th>Balloon-expandable (n=121)</th>
<th>Self-expandable (n=117)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>5/121 (4.1%)</td>
<td>6/117 (5.1%)</td>
<td>0.77</td>
</tr>
<tr>
<td>From CV causes</td>
<td>5/121 (4.1%)</td>
<td>5/117 (4.3%)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>7/121 (5.8%)</td>
<td>3/117 (2.6%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Major</td>
<td>3/121 (2.5%)</td>
<td>3/117 (2.6%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Minor</td>
<td>4/121 (3.3%)</td>
<td>0/117 (0.0%)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>1/121 (0.8%)</td>
<td>0/117 (0.0%)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life threatening</td>
<td>10/121 (8.3%)</td>
<td>14/117 (12.0%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Major</td>
<td>23/121 (19.0%)</td>
<td>17/117 (14.5%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Minor</td>
<td>11/121 (9.1%)</td>
<td>9/117 (7.7%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Major or minor</td>
<td>34/121 (28.1%)</td>
<td>26/117 (22.2%)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Vascular complications</strong></td>
<td>17/121 (14.0%)</td>
<td>15/117 (12.8%)</td>
<td>0.78</td>
</tr>
<tr>
<td>All</td>
<td>12/121 (9.9%)</td>
<td>13/117 (11.1%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Major</td>
<td>5/121 (4.1%)</td>
<td>2/117 (1.7%)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*Published online March 30, 2014*
CoreValve High Risk Pivotal RCT from ACC 2014

All Stroke

Major Stroke

No. at Risk
Surgical 357 322
Transcatheter 390 363

Log-rank P = 0.59

No. at Risk
Surgical 357 333 289 263
Transcatheter 390 367 344 322
Stroke Has a Significant Impact on Mortality

Meta-analysis of 10,037 published patients

H. Eggebrecht et al, EuroIntervention 2012, 8: 129-138
Many Strokes Occur Periprocedurally

ADVANCE Registry: Stroke Timing

Results - Transcranial Doppler Findings

P. Kahlert et al, Circulation 2012;126:1245-1255
Diffusion Weighted MRI Study

Example of an 82-year-old patient two days after successful TAVR:

Before TAVR

Two days after TAVR

Treating Physician:
Philipp Kahlert, MD
West German Heart Center Essen
University Duisburg-Essen
TCT 2013 Live TAVR Case: Dr. Alex Abizaid, Brazil

“...this would have definitely stroked the patient...”

Approx. 8 mm
Clinical Need—Stroke, Silent and Apparent

A closer look at the patients reveals a looming risk: >70% of TAVR patients have ischemic brain lesions when examined by DW-MRI.
DW-MRI Imaging of “Silent Lesions” Following TAVR

Can these really all be benign?
Larger total DWI lesion volumes are associated with significantly higher risk of clinically evident stroke \((p<0.001)\)

**Clinical Presentation**
- Hemispheric ischaemic stroke
- No focal deficit

**Claret Can Capture & Remove Embolic Material Before it reaches the Brain**

*Bonati et al., Lancet Neurol 2010; 9: 353–62*
### TAVR Expanding to Healthier Patients

<table>
<thead>
<tr>
<th>SURTAVI</th>
<th>PARTNER IIa</th>
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<tbody>
<tr>
<td>≥4 and ≤10</td>
<td>≥4 and ≤10</td>
</tr>
<tr>
<td>&gt;22</td>
<td>&gt;32</td>
</tr>
<tr>
<td>AVA ≤ 1.0 cm²&lt;br&gt;Indexed AVA &lt; 0.6 cm²/m²</td>
<td>AVA ≤ 0.8 cm²&lt;br&gt;Indexed AVA &lt; 0.5 cm²/m²</td>
</tr>
<tr>
<td>Discharge, 30 days, 3 months, 6 months, 12 months, 18 months, 24 months, annually for 5 years</td>
<td>Discharge, 30 days, 6 months, 1 year, annually for 5 years</td>
</tr>
<tr>
<td>All-cause death + disabling stroke @ 2 yrs (~2600 pts)</td>
<td>Primary endpoint (sample size)</td>
</tr>
<tr>
<td>Global - US, EU, Canada (up to 115 centers)</td>
<td>Geography</td>
</tr>
</tbody>
</table>
New Expanded AHA/ASA Consensus Definition of Stroke, May 2013

• “Silent brain infarcts increase the risk of clinical infarction by 2 to 4 times in population-based studies”

• “…silent infarcts are associated with risk of Alzheimer disease as well as of vascular dementia.”

Several studies have shown that patients with silent brain infarcts had a 5 times higher stroke incidence than those without.
Silent infarcts are well recognized to be associated with several adverse neurological and cognitive consequences:

- Impaired mobility
- Physical decline
- Depression
- Cognitive dysfunction
- Dementia
- Parkinson’s disease
- Alzheimer disease

An Updated Definition of Stroke for the 21st Century: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association, Stroke. published online May 7, 2013
“Not So Silent” Lesions and Disabling Stroke

Silent Brain Infarcts and White Matter Lesions Increase Stroke Risk in the General Population
The Rotterdam Scan Study
Sarah E. Vermeer, MD; Monika Hoffkane, MD; Ewoud J. van Dijk, MD; Albert Hofman, MD; Peter J. Koudstaal, MD; Monique M.B. Breteler, MD

Background and Purpose—Silent brain infarcts and white matter lesions are associated with an increased risk of subsequent stroke in minor stroke patients. In healthy elderly people, silent brain infarcts and white matter lesions are common, but little is known about their relevance. We examined the risk of stroke associated with these lesions in the general population.

Methods—The Rotterdam Scan Study is a population-based prospective cohort study among 1077 elderly people. The presence of silent brain infarcts and white matter lesions was scored on cerebral MRI scans obtained from 1995 to 1996. Participants were followed for stroke for an average of 4.2 years. We estimated the risk of stroke in relation to presence of brain lesions with Cox proportional hazards regression analysis.

Results—Fifty-seven participants (6%) experienced a stroke during follow-up. Patients with silent brain infarcts had a 3.5 times higher stroke incidence than those without. The presence of silent brain infarcts increased the risk of stroke (HR 3.5, 95% CI 2.3 to 6.8). People in the upper tertile of the white matter lesion distribution had an increased stroke risk compared with those in the lower tertile (adjusted hazard ratio 4.7, 95% CI 2.0 to 11.2) and for subcortical lesions 3.6, 95% CI 1.4 to 9.2). Silent brain infarcts and severe white matter lesions increased the stroke risk independently of each other.

Conclusion—Elderly people with silent brain infarcts and white matter lesions are at a strongly increased risk of stroke, which could not be explained by the major stroke risk factors.

Conclusion – “Elderly people with silent brain infarcts and white matter lesions are at a strongly increased risk of stroke, which could not be explained by the major stroke risk factors”

Silent Brain Infarcts and White Matter Lesions Increase Stroke Risk in the General Population: The Rotterdam Scan Study
Sarah E. Vermeer, MD et al; Stroke. 2003;34:1126-1129

Population based cohort study of 1077 elderly people followed for 4+ years

14.3% with silent brain infarcts developed a stroke during follow up period

Presence of silent brain infarcts increased risk of stroke by >3 fold
Second Generation ‘Repositionable’ TAVR Devices Still Require Finesse

Safety: Death & Stroke at 30 Days

REPRISE II (N=120)

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients (N=119)*</th>
</tr>
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<tbody>
<tr>
<td>All-cause mortality (primary safety endpoint)</td>
<td>4.2% (5)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>4.2% (5)</td>
</tr>
<tr>
<td>All stroke†</td>
<td>5.9% (7)</td>
</tr>
<tr>
<td>* Disabling stroke</td>
<td>1.7% (2)</td>
</tr>
<tr>
<td>* Non-disabling stroke</td>
<td>4.2% (5)</td>
</tr>
</tbody>
</table>

* All patients were assessed by a neurologist before and after TAVR
† One patient withdrew consent

All patients were assessed by a neurologist before and after TAVR

Dr. Ian Meredith, TCT 2013
Under Reporting Remains an Issue & is Even Seen in Surgical AVR

**Stroke After Aortic Valve Surgery**

196 patients aged 65 years or older were evaluated by neurologists for clinical stroke and silent infarct before and after aortic valve replacement.

<table>
<thead>
<tr>
<th>In-Hospital Mortality</th>
<th>Clinical Stroke (n = 34)</th>
<th>No Clinical Stroke (n = 162)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NIHSS Scores</td>
<td>9%</td>
<td>4%</td>
<td>NS</td>
</tr>
<tr>
<td>NIHSS Score &gt; 10</td>
<td>38%</td>
<td>4%</td>
<td>.005</td>
</tr>
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Clinical stroke was identified in 17% of patients. The same cohort had a stroke rate of 6.6% reported in the Society for Thoracic Surgery database.

**Conclusion:** Clinical stroke after AVR occurs more often than previously thought and can be associated with higher risk of in-hospital mortality.

Future Reporting Must be Consistent

Valve Academic Research Consortium (VARC) 2: Updated Definitions

**Updated Stroke Definitions**

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<tr>
<th></th>
<th>Non Disabling</th>
<th>Disabling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Modified Rankin score &lt; 2 at 30 and 90 days*</td>
<td>Modified Rankin score ≥ 2 at 30 and 90 days AND an increase in the modified Rankin score of ≥ 1</td>
</tr>
<tr>
<td></td>
<td>OR an increase in the modified Rankin score of ≤ 1</td>
<td></td>
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</table>

Supercedes original VARC® stratification of TIA, minor and major strokes. Ischemic or hemorrhagic stroke classified per proposed FDA consensus panel definitions.

*Modified Rankin score assessments should be made by qualified individuals according to a certification process. If there is discordance between 30- and 90-day scores, a final determination will be adjudicated by the neurology members of the clinical events committee.

**References**


Studies must encourage Independent Neurologist pre & post assessment to ensure correct reporting
Neuro Cognition Testing Post-TAVR is Complex and Needs Specific Battery of Assays

- Heart Disease & Neurocognition
  - CABG
  - Atrial Fibrillation
  - Cardiac Arrest
  - Heart Failure
  - TAVR

- Embolism
- Perfusion Failure
- Both?
Cerebral Protection Reduces Periprocedural Strokes During Carotid Angioplasty & Stenting


Why should this be different in TAVR?

The Answers Are Coming Soon

1:1 Blinded RCT
N=100
CoreValve with & without Claret Montage
Principal Investigator
Axel Linke, MD
Leipzig Heart Center (Leipzig, Germany)

Primary Endpoint
Serial volumetric signature in positive post-procedure DW-MR perfused brain lesions at 2, 7, 30, and 360 days post-procedure relative to baseline

Secondary Endpoints
-Neurocognitive Tests
NIHSS, MMS, MoCA, Barthel @ 2, 7, 30, & 360 days
Modified Rankin @ index & 90 days
-Correlation of captured debris with MR lesions
-Correlation of TCD with DW-MR lesions
-Histopathology of captured debris in the 2 filters

Expected Completion
-Enrollment Q4 2013-Q1 2014
-30-day data Q1 2014

CLEAN TAVI Study to be Presented at TCT 2014
Devices Are Shown to be Effective in Extracting Debris

So why would you NOT use them routinely?

Van Mieghem et al, Circulation 2013;127:2194-2201
Debris analysis by Dr. Renu Virmani, CVPath Institute of Histopathology
Accepted Wisdoms are Sometimes Flawed...

In-Stent Restenosis is NOT Benign

In-Stent Restenosis is not simply a benign clinical entity: It presents as ACS in 40% of cases

Rathod KS, Jones DA, Rathod VS, Akhtar M, Guttmann O, Pain T, Behar J, Jain A, Mathur A, Knight C and Wragg A
Department of Cardiology, Barts and the London NHS Trust, London, United Kingdom

Neither are ‘silent’ lesions in the brain

Abu-Own et al: doi:10.1136/heartjnl-2011-300198.36
My Conclusion

- Devices are Improving
- Procedural Techniques are improving
- Patient Selection is Improving
- Adjunctive pharma therapy is improving

*BUT*: Embolic Stroke still remains an issue in TAVR and is truly devastating!!!

*Cerebral Protection will (and should) become Standard of Care*