Cerebral protection devices are still meaningful and necessary

Eberhard Grube MD, FACC, FSCAI
University Hospital, Dept of Medicine II, Bonn, Germany
Stanford University, Palo Alto, California, USA
<table>
<thead>
<tr>
<th>Physician Name</th>
<th>Company/Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eberhard Grube, MD</td>
<td>Medtronic, CoreValve: C, SB, AB, OF</td>
</tr>
<tr>
<td></td>
<td>Direct Flow: C, SB, AB</td>
</tr>
<tr>
<td></td>
<td>Mitralign: AB, SB, E</td>
</tr>
<tr>
<td></td>
<td>Boston Scientific: C, SB, AB</td>
</tr>
<tr>
<td></td>
<td>Biosensors: E, SB, C, AB</td>
</tr>
<tr>
<td></td>
<td>Cordis: AB</td>
</tr>
<tr>
<td></td>
<td>Abbott Vascular: AB</td>
</tr>
<tr>
<td></td>
<td>InSeal Medical: AB, E</td>
</tr>
<tr>
<td></td>
<td>Valtech: E, SB,</td>
</tr>
<tr>
<td></td>
<td>Claret: SB</td>
</tr>
<tr>
<td></td>
<td>Keystone: AB</td>
</tr>
<tr>
<td></td>
<td>Shockwave: E, AB</td>
</tr>
</tbody>
</table>
Stroke incidence and mortality after TAVI
Meta-analysis of 10,037 published patients

Stroke remains a major TAVI complication...

Table 3. Incidence of stroke.

<table>
<thead>
<tr>
<th></th>
<th>Number of publications with available data (n)</th>
<th>Overall number of patients with available data (n)</th>
<th>Number of events (n)</th>
<th>Weighted mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural stroke (&lt;24h)</td>
<td>24</td>
<td>3041</td>
<td>47</td>
<td>1.5±1.4%</td>
</tr>
<tr>
<td>30-day stroke/TIA</td>
<td>53</td>
<td>10037</td>
<td>334</td>
<td>3.3±1.8%</td>
</tr>
<tr>
<td>30-day major stroke</td>
<td>42</td>
<td>5514</td>
<td>158</td>
<td>2.9±1.8%</td>
</tr>
<tr>
<td>30-day minor stroke/TIA</td>
<td>42</td>
<td>5514</td>
<td>53</td>
<td>1.0±1.3%</td>
</tr>
<tr>
<td>30-day overall mortality</td>
<td>52</td>
<td>10022</td>
<td>812</td>
<td>8.1±3.9%</td>
</tr>
<tr>
<td>30-day mortality in patients suffering stroke</td>
<td>29</td>
<td>4430</td>
<td>41</td>
<td>25.5±21.9%</td>
</tr>
<tr>
<td>30-day mortality in patients without stroke</td>
<td>29</td>
<td>4430</td>
<td>312</td>
<td>6.9±4.2%</td>
</tr>
<tr>
<td>6-month stroke</td>
<td>9</td>
<td>669</td>
<td>29</td>
<td>4.3±1.6%</td>
</tr>
<tr>
<td>12-month stroke</td>
<td>7</td>
<td>1507</td>
<td>78</td>
<td>5.2±3.4%</td>
</tr>
</tbody>
</table>

...which increases 30-day mortality >3 fold

*EuroIntervention* 2012;8:129-138 publish online ahead of print March 2012
Risk of stroke after transcatheater aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients
TAVI stroke is mostly periprocedural

Timing of Cerebrovascular Events (CVE) in FRANCE-2 Registry (n=3,191)
- CVE most frequently occur day 0-1
- >50% are major strokes
- Median time to major stroke is 1 day

Tchétché et al. J Am Coll Cardiol Intv 2014; 7(10)

Multi-center cohort of 1,061 TAVI patients
- CVE most frequently occur day 0-1
- >50% are major strokes
- >95% of strokes are ischemic

Nombela-Franco et al., Circulation 2012;126:3041-53

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**Figure 1** Timing of Cerebrovascular Events

Number of days elapsed from the index procedure before the occurrence of a cerebrovascular event.

**Figure 2**. Timing of cerebrovascular events (CVEs) within 30 days after transcatheter aortic valve implantation. TIA indicates transient ischemic attack.
Procedural stroke risk factors

- Presence and location of arch atheroma
- Micro-embolization of calcification and thrombus on valve
- Catheter handling and device placement technique
- Secondary maneuvers
- Procedural duration
- Optimal anti-coagulation and anti-aggregation
- Arrhythmia management

A
Latest Stroke Data from Studies Presented at EuroPCR 2015

<table>
<thead>
<tr>
<th>Study</th>
<th>Valve</th>
<th>Patients</th>
<th>FU</th>
<th>NE rate %</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corevalve Evolut R CE Mark</td>
<td>Corevalve Evolut</td>
<td>60</td>
<td>30 days</td>
<td>0.0%</td>
<td>Varc 2</td>
</tr>
<tr>
<td>Respond CE</td>
<td>Boston Lotus</td>
<td>250</td>
<td>30 days</td>
<td>3.3%</td>
<td>Varc 2</td>
</tr>
<tr>
<td>Advance 2</td>
<td>Corevalve Basic</td>
<td>200</td>
<td>30 days</td>
<td>2.1%</td>
<td>Varc 2</td>
</tr>
<tr>
<td>Discover Registry</td>
<td>Direct Flow</td>
<td>250</td>
<td>30 days</td>
<td>2.0%</td>
<td>N/A</td>
</tr>
<tr>
<td>Italian DFM Registry</td>
<td>Direct Flow</td>
<td>136</td>
<td>30 days</td>
<td>0.7%</td>
<td>N/A</td>
</tr>
<tr>
<td>Biovalve</td>
<td>Biotronik</td>
<td>13</td>
<td>30 days</td>
<td>0.0%</td>
<td>Varc 2</td>
</tr>
<tr>
<td>Portico CE Trial</td>
<td>Portico</td>
<td>102</td>
<td>30 days</td>
<td>3.9%</td>
<td>N/A</td>
</tr>
<tr>
<td>Sapien 3 CE</td>
<td>Sapien 3</td>
<td>96</td>
<td>30 days</td>
<td>1.1%</td>
<td>Varc 2</td>
</tr>
<tr>
<td>Sapien 3 CE (Intermediate Risk)</td>
<td>Sapien 3</td>
<td>101</td>
<td>30 days</td>
<td>4.0%</td>
<td>Varc 2</td>
</tr>
</tbody>
</table>
Under-reporting remains an issue and 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>
</tbody>
</table>

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.

Emboli distribution to cerebral circulation is not in concordance with volumetric flow assumptions
Cardiogenic emboli moves preferentially to right hemisphere

Diffusion-weighted MRI shows new lesions

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
DW-MRI imaging shows “silent lesions” in TAVI

New lesions found in vast majority of diffusion-weighted MR images (DW-MRI) of the brain following TAVI
Silent brain infarcts increase the risk of clinical infarction by 2 to 4 times in population-based studies.

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
Cerebral protection reduces periprocedural strokes during carotid angioplasty & stenting


### Pooled Analysis for Total Stroke Rate Within 30 Days After Protected and Unprotected Carotid Stenting in 134 Studies*

<table>
<thead>
<tr>
<th></th>
<th>With Protection (n=82)</th>
<th>Without Protection (n=76)</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Procedures</td>
<td>Total Strokes</td>
<td>Procedures</td>
<td>Total Strokes</td>
</tr>
<tr>
<td>All patients</td>
<td>12,263</td>
<td>324 (2.6%)</td>
<td>11198</td>
<td>474 (4.2%)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>2427</td>
<td>91 (3.8%)</td>
<td>3149</td>
<td>176 (5.6%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2460</td>
<td>41 (1.7%)</td>
<td>2032</td>
<td>56 (2.8%)</td>
</tr>
</tbody>
</table>

RR: relative risk, CI: confidence interval.
* 24 studies included data on both protected and unprotected CAS. Of all studies, only 67 studies reported outcomes on symptomatic patients (34 with protected and 39 with unprotected stenting), while 56 reported outcomes on asymptomatic patients (28 with protected and 30 with unprotected stenting).
† P<0.05.

Why should this be different in TAVR?

# Embolic Protection Devices

<table>
<thead>
<tr>
<th>Claret Sentinel™ Cerebral Protection System</th>
<th>Edwards Embrella™ Embolic Deflector</th>
<th>TriGuard™ Cerebral Protection Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filter capture</td>
<td>Deflector</td>
<td>Deflector</td>
</tr>
<tr>
<td>6F (radial)</td>
<td>6F (radial)</td>
<td>9F (femoral)</td>
</tr>
<tr>
<td>140 micron pore size</td>
<td>100 micron pore size</td>
<td>130 x 250 micron pore size</td>
</tr>
<tr>
<td>Brachiocephalic and LCC</td>
<td>Aortic arch position</td>
<td>Aortic arch position</td>
</tr>
<tr>
<td>CE marked and commercialized</td>
<td>CE marked</td>
<td>CE marked</td>
</tr>
</tbody>
</table>

CAUTION: Investigational device. Limited to investigational use by United States law.
Examples of debris captured with Claret CPS

University of Virginia
Charlottesville, VA, USA
SENTINEL trial 2015

Institute Dante Pazzanese de Cardiologia
São Paulo, Brazil
TCT Live Case 2013

CAUTION: Investigational device. Limited to investigational use by United States law.
Embolic debris captured by valve type during TAVI procedures at AK St Georg (Hamburg)

- 52 cases of TAVI using Claret Medical Cerebral Protection System performed at AK St Georg (Hamburg)

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sapien/XT</td>
<td>27</td>
<td>(52%)</td>
</tr>
<tr>
<td>S3</td>
<td>11</td>
<td>(21%)</td>
</tr>
<tr>
<td>CoreValve</td>
<td>9</td>
<td>(17%)</td>
</tr>
<tr>
<td>Jena</td>
<td>2</td>
<td>(4%)</td>
</tr>
<tr>
<td>Portico</td>
<td>2</td>
<td>(4%)</td>
</tr>
<tr>
<td>Centera</td>
<td>1</td>
<td>(2%)</td>
</tr>
</tbody>
</table>

- Filter contents subsequently analyzed by CVPath Institute
  - Debris captured in 96% of patients

Note: percentages reflect percent of patients in each group in which each particular tissue type was captured. Some filters captured several types of debris, so percentages will not add to 100%


CAUTION: Investigational device. Limited to investigational use. Not available for sale.
CLEAN-TAVI: First RCT of Cerebral Protection in TAVI

100 higher-risk patients with aortic stenosis undergoing TAVR with CoreValve were randomized 1:1 to TAVR with the Claret Montage™ Cerebral Protection System filters or TAVR without filters. MRI, neurological and neurocognitive assessments were compared with baseline and between groups.

Study Flow Chart

- **DESIGN:** Prospective, 1:1 randomized controlled, double-blind study
- **OBJECTIVE:** To evaluate the impact of the use of Claret Montage™ on the number of cerebral lesions in higher-risk patients with aortic stenosis undergoing TAVR with the Medtronic CV
- **PRINCIPAL INVESTIGATOR**
  Axel Linke, MD
  University of Leipzig, Heart Center, Germany

100 patients enrolled between April 2013 and June 2014 at the University of Leipzig

MRI, Neurological & Neurocognitive Assessments, TCD, Histopathology

- Control Group (C)
  TAVR without Filter (n=50)
  - 2 day MRI (n=45)
  - 7 day MRI (n=43)
  - 30 day MRI (n=38)

- Filter Group (F)
  TAVR with Filter (N=50)
  - 2 day MRI (n=48)
  - 7 day MRI (n=44)
  - 30 day MRI (n=40)

Linke et al., CLEAN-TAVI

CAUTION: Investigational device. Limited to investigational use by United States law.
CLEAN-TAVI shows the problem and the promise

The Problem

Representative slices from each of the orthogonal planes showing new lesions from control group (unprotected, no filters) of CLEAN-TAVI randomized trial.

The Promise

Claret Montage Cerebral Protection System significantly reduces new cerebral lesion number and volume at 2 & 7 days, as measured by DW-MRI, and reduces ataxia at 2d

<table>
<thead>
<tr>
<th>Per Protocol</th>
<th>at 2 days No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
</tr>
<tr>
<td>(n=50)</td>
<td>any symptom</td>
</tr>
<tr>
<td></td>
<td>- ataxia</td>
</tr>
<tr>
<td><strong>Filter</strong></td>
<td></td>
</tr>
<tr>
<td>(n=45)</td>
<td>any symptom</td>
</tr>
<tr>
<td></td>
<td>- ataxia</td>
</tr>
</tbody>
</table>

RR 1.559 (1.083 to 2.244), OR 3.2, p<0.05
CLEAN-TAVI shows the promise of protection

The Problem
Control group (no filters)

The Promise
Test group (filters)

Representative slices from each of the orthogonal planes showing new lesions at 2d from each arm of CLEAN-TAVI randomized trial of cerebral embolic protection in TAVI using Claret dual-filter Cerebral Protection Systems

Claret Montage Cerebral Protection System significantly reduces new cerebral lesion number and volume at 2 & 7 days, as measured by DW-MRI

1. CLEAN-TAVI (manuscript in review)
Pivotal study confirming the therapeutic importance of embolic debris capture and removal during TAVR

**Objective:** Assess the safety and efficacy of the Claret Medical Sentinel Cerebral Protection System in reducing the volume and number of new ischemic lesions in the brain and their potential impact on neurocognitive function.

**Primary Investigators:**
- Samir Kapadia, MD
  *Cleveland Clinic*
- Susheel Kodali, MD
  *Columbia University Medical Ctr*

**Population:** Subjects with severe symptomatic calcified native aortic valve stenosis who meet the commercially-approved indications for TAVR with the Edwards Sapien THV or XT, or Medtronic CoreValve.

**N=296 subjects randomized 1:1:1 at 15 sites in the U.S.**

**Primary Efficacy Endpoint:** Reduction in median total new lesion volume as assessed by DW-MRI.

**Primary Safety Endpoint:** Occurrence of all MAE at 30 days.
SENTINEL MRI methodology

• 3-Tesla MR scanner standardization for optimal resolution across all study sites
  – 3.0T is able to resolve smaller lesions, allows shorter acquisition times, and has a higher signal-to-noise ratio than 1.5T MR scanners

• Diffusion-weighted (DW) and fluid-attenuated inversion recovery (FLAIR) MR sequences
  – To assess both acute (DW) and chronic (FLAIR) lesions

• Novel methodology with serial scan acquisition
  – Baseline mapping must be performed to eliminate over-estimation of existing lesions.
  – Serial co-registration must be performed based on the baseline, otherwise the analysis is not reliable

• Core lab analysis of all scans
  – Buffalo Neuroimaging Analysis Center, Buffalo, NY
Composite images of CLEAN-TAVI MRIs

Embolic Lesion Burden of 78 Cases (from both arms of trial) with Scans at all Time Points in CLEAN-TAVI Study

- Baseline FLAIR Scan
- 2-Day DWI Scan
- 7-Day DWI Scan
- 30-Day FLAIR Scan

Blinded analysis of first 78 patients
DEFLECT III: Pilot RCT using TriGuard deflection device

Final 30-day results of the DEFLECT III trial: a prospective randomised evaluation of the novel embolic protection DEFLECTion device during TAVI
DEFLECT III: DW-MRI Results

- Trend to lower lesion burden

CAUTION: Investigational device. Limited to investigational use by United States law.
Trend towards improved neurological and neurocognitive outcomes

- Blunt instruments (NIHSS and MoCA) show trends towards improved neurological and neurocognitive outcomes with protection.

- Larger trials and more comprehensive neurocognitive batteries (e.g. RECON) will further elucidate benefit.
Conclusions

- Stroke remains a devastating complication of TAVR, even with new devices
- Clinical stroke is often under-diagnosed
- Periprocedural subclinical cerebral infarcts are common and increase future risk of events
- Cerebral protection devices show promise in reducing cerebral ischemic burden and improving outcomes for TAVI patients
- Large multicenter randomized trials with detailed MR imaging and neurocognitive assessments will further elucidate potential