Sentinel Dual Filter Device: Technology Overview and Status of the CLEAN-TAVI Randomized Trial

Martin B. Leon, MD

Columbia University Medical Center
Cardiovascular Research Foundation
New York City

Monday, September 15, 2014
Disclosure Statement of Financial Interest
TCT 2014; Washington, DC; Sept 13-17, 2014

Martin B. Leon, MD

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

<table>
<thead>
<tr>
<th>Affiliation / Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant / Research Support</td>
<td>Abbott, Boston Scientific, Edwards Lifescience, Medtronic</td>
</tr>
<tr>
<td>Consulting Fees / Honoraria</td>
<td>Meril Lifescience, Micell</td>
</tr>
<tr>
<td>Shareholder / Equity</td>
<td>Claret, Elixir, GDS, Medinol, Mitralign, Valve Medical</td>
</tr>
</tbody>
</table>
Sentinel Cerebral Protection

Technology Overview
# Cerebral Embolic Protection Devices

<table>
<thead>
<tr>
<th><strong>TriGuard™ Cerebral</strong></th>
<th><strong>Embrella™</strong></th>
<th><strong>Claret Sentinel™</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Deflector</td>
<td>Deflector</td>
<td>Dual Filter</td>
</tr>
<tr>
<td>Femoral Access</td>
<td>Radial Access</td>
<td>Radial Access</td>
</tr>
<tr>
<td>9F Sheath (7F Delivery)</td>
<td>6F Shuttle Sheath</td>
<td>6F Radial Sheath</td>
</tr>
<tr>
<td>240 micron pore size</td>
<td>100 micron pore size</td>
<td>140 micron pore size</td>
</tr>
<tr>
<td>Aortic arch position</td>
<td>Aortic arch position</td>
<td>Brachiocephalic and LCC</td>
</tr>
</tbody>
</table>

Embolic debris “deflection” or Filtration, “capture & remove”
Claret Sentinel Animation
Claret Sentinel
Cerebral Protection System (CPS)

- Dual, independent filter (proximal and distal) embolic protection device with visible embolic capture
- The 3rd generation of the first commercially available CE Marked embolic protection device
- Universal size and shape
- Deflectable compound-curve sheath to facilitate cannulation of LCC
- Easy-to-use handle design
Claret Sentinel
Cerebral Protection System (CPS)

Proximal Filter
(Innominate Artery)
9–15 mm

Distal Filter
(LCC Artery)
6.5–10 mm

Minimal device “footprint” in the ascending aorta to avoid interaction with TAVR equipment
Montage to Sentinel CPS Changes

- **Control Handle**
  - Replaced with ergonomic, intuitive and easy-to-use injection molded handle

- **Proximal Filter**
  - Filter frame strut angle modified to improve filter apposition with vessel wall
  - Greatly reduced filter deployment force at handle actuator for improved ease of deployment in tortuous anatomy

- **Distal Filter**
  - Vessel size range increase from 8-10mm to 6.5-10mm
Embolic Material after TAVR
40 TAVR pts treated with the dual filter system

Prevalence of Cases with Any Debris (n=40)

- 75% (30/40)

Distribution of Debris Captured (n=30)

- 70% (21/30) Thrombus
- 43% (n=13) Thrombus with other materials
- 70% (21/30) Collagenous tissue
- 43% (n=13) Collagenous tissue

- 27% (n=8) Thrombus alone
- 27% (n=8) Valve tissue

- 17% (5/30) Calcium
- 13% (4/30) Foreign material

Van Mieghem NM et al. Circulation 2013
Histopathology of Embolic Debris Captured During Transcatheter Aortic Valve Replacement
Nicolas M. Van Mieghem, Marguerite E. I. Schipper, Elena Ladich, Elham Faqiri, Robert van der Boon, Abas Randjgari, Carl Schultz, Adriaan Moelker, Robert-Jan van Geuns, Fumiyuki Otsuka, Patrick W. Serruys, Renu Virmani and Peter P. de Jaegere
Sentinel Cerebral Protection

CLEAN-TAVI Study
Background

- Stroke remains a major TAVR complication, which increases mortality by 3 fold
- Recent TAVR and SAVR studies demonstrated high stroke rates with neurologist performing NIHSS assessment.


Eggebrecht H et al, EuroIntervention 2012, 8: 129-138
• 196 patients with open surgical AVR at two sites, enrollment over 4 years (DeNOVO study)
• Pre and post-op neurological assessments and post-op MRI studies
• Clinical strokes 17%, TIA 2%, in-hospital mortality 5%
• Mod-severe strokes (NIHSS ≥ 10) in 4% and strongly associated with increased in-hospital mortality (38% vs. 4%, p = 0.005)
• In stroke-free pts (n=109), silent MRI infarcts in 59% (no △ mortality or LOS)
**Study Flow Chart**

**Design**

- **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
Study Endpoints

• **Primary Endpoint:**
  - Numerical reduction in positive post procedure Diffusion Weighted MRI (DW-MRI) perfused brain lesions relative to baseline at **2 days** in protected territories

• **Secondary Endpoints:**
  - Serial volumetric and numerical reduction in positive post DW-MRI perfused brain lesions at 2, 7, 30, 360 days
  - Serial neurological assessment by a neurologist
  - Serial neurocognitive assessment
  - Peri-procedural Transcranial Doppler assessment
Study Hypothesis

Reduction in number of cerebral emboli by 50 % at 2 days after TAVR by the use of the Claret Montage™ dual filter in patients undergoing transfemoral TAVR using the Medtronic CoreValve™

Sample size analysis: power 0.9, alpha 0.05, SD 2.0, drop-out 16%, n=100 patients
MRI Methodology

Unique challenges:
• Numerous, small, widely distributed lesions
• Lots of pre-existing pathology in aged population

Image acquisition:
• Improved sensitivity with 3-Tesla scanner
• High-resolution T1-weighted anatomical image
• Diffusion-weighted imaging (DWI) for ischemic lesions

Analysis approach:
• Sub-millimeter longitudinal co-registration for precise lesion tracking of lesion serially over time
• Subtraction imaging technique relative to baseline to focus analysis only on relevant new pathology
• Precise analysis based on 28 pre-specified vascular territories on the right and left hemispheres (one unprotected vascular territory)

Linke et al., CLEAN-TAVI
Cerebrovascular Territories

Anterior cerebral a.
Anterior choroidal a.
Middle cerebral a.
Posterior cerebral a.
Superior cerebellar a.
Anterior inferior cerebellar a.

Anterior cerebral and anterior communicating aa.
(perforating branches)
Middle cerebral a.
(perforating branches)
Posterior cerebral and posterior communicating aa.
(perforating branches)

Posterior inferior cerebellar artery
Inclusion and Exclusion Criteria

- **Inclusion criteria:**
  Symptomatic and relevant aortic stenosis with indication for transfemoral aortic valve replacement (TAVR) using Medtronic CoreValve™ (MCV)

- **Exclusion criteria:**
  - Patient unsuitable to undergo TAVR with MCV
  - Pacemaker
  - Stroke within the last 12 month
  - > 70 % stenosis of carotid artery
  - Relevant stenosis of brachiocephalic trunk or subclavian artery
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control Group (N = 50)</th>
<th>Filter Group (N = 50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr</td>
<td>79 ± 4</td>
<td>80 ± 5</td>
<td>0.466</td>
</tr>
<tr>
<td>Female sex – no. (%)</td>
<td>27 (54)</td>
<td>30 (60)</td>
<td>0.545</td>
</tr>
<tr>
<td>STS PROM, mean estimate – %</td>
<td>5.2 ± 2.7</td>
<td>5.6 ± 3.3</td>
<td>0.847</td>
</tr>
<tr>
<td>Logistic EuroSCORE – %</td>
<td>14.6 ± 8.6</td>
<td>16.3 ± 10.1</td>
<td>0.478</td>
</tr>
<tr>
<td>Diabetes mellitus – no. (%)</td>
<td>25 (50)</td>
<td>20 (40)</td>
<td>0.315</td>
</tr>
<tr>
<td>History of hypertension – no. (%)</td>
<td>47 (94)</td>
<td>44 (88)</td>
<td>0.295</td>
</tr>
<tr>
<td>Peripheral vascular disease – no. (%)</td>
<td>4 (8)</td>
<td>2 (4)</td>
<td>0.400</td>
</tr>
<tr>
<td>Cardiac risk factor:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Coronary artery disease – no. (%)</td>
<td>26 (52)</td>
<td>25 (50)</td>
<td>0.841</td>
</tr>
<tr>
<td>-Congestive heart failure – no. (%)</td>
<td>47 (94)</td>
<td>45 (90)</td>
<td>0.461</td>
</tr>
<tr>
<td>-Prior atrial fibrillation or atrial flutter – no. (%)</td>
<td>18 (36)</td>
<td>16 (32)</td>
<td>0.673</td>
</tr>
</tbody>
</table>
Procedural Results

- **Device Success 48/50 (96%)**
  - Unsuccessful distal filter deployment due to LCC tortuosity, n=1
  - Unsuccessful deployment of both filters due to SC tortuosity, n=1

- **Procedural Success 47/50 (94%)**
  - Accidental dislocation of a correctly deployed filter by pigtail, n=1

<table>
<thead>
<tr>
<th>Procedural Outcomes</th>
<th>Control Group (N = 50)</th>
<th>Filter Group (N = 50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury – no. (%)</td>
<td>5 (10)</td>
<td>1 (2)</td>
<td>0.226</td>
</tr>
<tr>
<td>Thoracotomy – no. (%)</td>
<td>0 (0)</td>
<td>3 (6)</td>
<td>0.242</td>
</tr>
<tr>
<td>New-onset or worsening atrial fibrillation – no. (%)</td>
<td>7 (14)</td>
<td>7 (14)</td>
<td>1.000</td>
</tr>
<tr>
<td>Death at 30 days – no. (%)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Fluoroscopy time – min.</td>
<td>14.3 ± 6.5</td>
<td>17.0 ± 9.1</td>
<td>0.028</td>
</tr>
<tr>
<td>Amount of contrast medium - ml</td>
<td>131 ± 33</td>
<td>125 ± 29</td>
<td>0.613</td>
</tr>
<tr>
<td>Lesions positive at 2 days – no. (%)</td>
<td>44/45 (98)</td>
<td>47/48 (98)</td>
<td>N.S.</td>
</tr>
</tbody>
</table>
Total Lesion Number at 2 & 7 days

**Protected regions**
- 60% p=0.009
- 57% p=0.0023

**All regions**
- 50% p=0.0023
- 50% p=0.0123

The boxes identify the 25%-75% CI, the black lines and number represents the median.

Linke et al., CLEAN-TAVI
Total Lesion Volume at 2 & 7 days

Protected regions

- 53 %
P = 0.0023

- 65 %
P = 0.002

All regions

- 41 %
P = 0.0243

- 53 %
P = 0.0127

The boxes identify the 25%-75% CI, the black lines and number represents the median.

Linke et al., CLEAN-TAVI
Neurological Outcome

<table>
<thead>
<tr>
<th>intention-to-treat</th>
<th>cumulative</th>
<th>2 days (No, %)</th>
<th>7 days (No, %)</th>
<th>30 days (No, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any symptom</td>
<td>17 (34 %)</td>
<td>14 (28 %)</td>
<td>5 (10 %)</td>
<td>6 (12 %)</td>
</tr>
<tr>
<td>- Ataxia</td>
<td>16 (32 %)</td>
<td>12 (24 %)</td>
<td>4 (8 %)</td>
<td>5 (10 %)</td>
</tr>
<tr>
<td><strong>Filter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any symptom</td>
<td>14 (28 %)</td>
<td>8 (16 %)</td>
<td>8 (16 %)</td>
<td>6 (12 %)</td>
</tr>
<tr>
<td>- Ataxia</td>
<td>12 (24 %)</td>
<td>6 (12 %)</td>
<td>7 (14 %)</td>
<td>6 (12 %)</td>
</tr>
</tbody>
</table>

RR 1.379 (0.927 to 2.050), OR 2.042, p=0.175
RR 1.439 (0.963 to 2.149), OR 2.316, p=0.118
Neurological Outcome

<table>
<thead>
<tr>
<th></th>
<th>per protocol</th>
<th>cumulative</th>
<th>2 days (No, %)</th>
<th>7 days (No, %)</th>
<th>30 days (No, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any symptom</td>
<td></td>
<td>17 (34 %)</td>
<td>14 (28 %)</td>
<td>5 (10 %)</td>
<td>6 (12 %)</td>
</tr>
<tr>
<td>- Ataxia</td>
<td></td>
<td>16 (32 %)</td>
<td>12 (24 %)</td>
<td>4 (8 %)</td>
<td>5 (10 %)</td>
</tr>
<tr>
<td>Filter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any symptom</td>
<td></td>
<td>11 (24 %)</td>
<td>6 (13 %)</td>
<td>6 (13 %)</td>
<td>4 (12 %)</td>
</tr>
<tr>
<td>- Ataxia</td>
<td></td>
<td>9 (20 %)</td>
<td>4 (9 %)</td>
<td>5 (11 %)</td>
<td>4 (12 %)</td>
</tr>
<tr>
<td>n=45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR 1.458 (1.006 to 2.114), OR 2.5, p=0.08
RR 1.559 (1.083 to 2.214), OR 3.2, p<0.05
Mechanistic Outcomes Summary

In patients with severe aortic stenosis who are at increased surgical risk, the use of Claret Medical Montage™ dual filter cerebral protection system during TAVR significantly reduces the number and volume of cerebral lesions as determined by DW-MRI subtraction at 2 and 7 days after TAVR.

Linke et al., CLEAN-TAVI
Neurological Outcomes Summary

• The ‘Intent-to-Treat’ analysis at 2 days post TAVI shows that neurological deficit was observed in 34% of the patients when evaluated by a NIHSS trained specialist.

• The Filter group in ‘Per Protocol’ analysis at 2 days post TAVI shows a significantly lower ataxia rate (24% vs 9%) than the control group, which supports the notion that the filter has the potential to improve neurological outcome.

Linke et al., CLEAN-TAVI
Conclusion

- In accordance with recent SAVR* study results, when neurological and MRI assessments are used prospectively, procedure-related cerebral lesions and stroke symptoms are more frequently associated with TAVR than previously thought.

- Larger outcomes studies are necessary in order to validate the observed beneficial effects of routine cerebral protection during TAVR in improving acute neurological outcome and reducing stroke rate.

*Messe SR et al, Circulation 2014;129:2253-2261
Linke et al., CLEAN-TAVI
Sentinel Cerebral Protection

Final Thoughts
The Dilemma: What is Cerebral Injury?

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Stroke/ TIA</th>
<th>MCI / VD</th>
<th>Cerebral Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>VARC</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Assessment</td>
<td>Heart-Team</td>
<td>+ NEURO / PSY</td>
<td>+ MRI</td>
</tr>
<tr>
<td>Victim(s)</td>
<td>Patient / Relatives / Society</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* mild cognitive impairment / vascular dementia
Cerebral Protection in TAVR

Final Thoughts

• Despite improvements in case selection, TAVR devices, procedural techniques, and adjunctive pharmacology… embolic strokes are still a devastating complication after TAVR!

• Moreover, with rigorous neurologic scrutiny and systematic neuro-imaging, clinical and silent stroke frequency after TAVR remains a frequent event.

• Embolic debris removal studies and early clinical evidence suggests that cerebral protection devices during TAVR may be beneficial.
Cerebral Protection in TAVR

**Final Thoughts**

- The CLEAN-TAVI randomized trial provides further strong evidence that DW-MRI lesion number and total volume are significantly reduced after Sentinel cerebral protection during CoreValve TAVR!

- *If additional studies confirm consistent reductions in neuro-imaging stroke lesions, especially if correlated with improvement in clinical neurological endpoints, then cerebral protection with TAVR will become the standard-of-care in the future!*