Sentinel ‘Filter Science’: Preventing irreversible cerebral infarction during contemporary TAVI procedures

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University Heart Center Hamburg, Germany
Disclosure Statement of Financial Interest

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 vascular, Medtronic, St. Jude Medical, Edwards Lifesciences, Symetis SA</td>
</tr>
<tr>
<td>Consulting Fees/Honoraria</td>
<td>• Abbott vascular, Cardiokinetix, Medtronic, St. Jude Medical, Edwards Lifesciences, Boston Scientific, Symetis SA, Biotronik, NVT, Claret, Mitralix</td>
</tr>
<tr>
<td>Major Stock Shareholder/Equity</td>
<td>• None</td>
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<tr>
<td>Royalty Income</td>
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</tr>
<tr>
<td>Ownership/Founder</td>
<td>• None</td>
</tr>
<tr>
<td>Intellectual Property Rights</td>
<td>• None</td>
</tr>
<tr>
<td>Other Financial Benefit</td>
<td>• None</td>
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</table>
Background
Stroke incidence and mortality after TAVR
Meta-analysis of 10,037 published patients

Stroke remains a major TAVR complication…

…which increases 30-day mortality >3 fold

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>
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

Multi-center cohort of 1,061 TAVR patients
- CVE most frequently occur day 0-1
- >50% are major strokes
- >95% of strokes are ischemic
Clinical stroke may be under-reported, and as high as 15-28%

- AHA/ASA consensus definition of stroke includes imaging evidence of a CNS infarction with or without acute neurological dysfunction
- Most studies do not use routine imaging or routine proactive discharge exams by neurologists
- Studies using **routine discharge exam by neurologists** report much higher clinical stroke rates (Messe, et al, e.g.)

Lansky, A. The Neuro-TAVI Trial, presented at London Valves 2015

Kappetein et al. EHJ (2012) 33, 2403-2418
Sacco et al, Stroke. 2013; 44:2064-2089
New cerebral lesions are found in vast majority of patients following TAVR

- 68-100% of TAVR patients affected
- Most patients have multiple infarcts
- “Silent” infarcts are associated with\(^1\,2\,3\)
  - 2-4-fold risk of future stroke
  - >3-fold risk of mortality
  - >2-fold risk of dementia
  - Cognitive decline
  - Dementia

% of TAVR patients with new cerebral lesions on DW-MRI

1. Sacco et al., Stroke 2013
2. Vermeer et al., Stroke 2003
### Predictors for Cerebral Embolization with TAVI

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Variable</th>
<th>Risk</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute &lt;24h</td>
<td>Balloon postdilation</td>
<td>OR: 2.46</td>
<td>CI: 1.07 to 5.67</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>Valve dislodgement/embolization</td>
<td>OR: 4.36</td>
<td>CI: 1.21 to 15.69</td>
<td>0.024</td>
</tr>
<tr>
<td>Subacute 24h&gt;&lt;30 Days</td>
<td>New onset AF</td>
<td>OR: 2.76</td>
<td>1.11 to 6.83</td>
<td>0.028</td>
</tr>
<tr>
<td>Late &gt;30 Days</td>
<td>Chronic AF</td>
<td>HR: 2.84</td>
<td>1.46 to 5.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PAD</td>
<td>HR: 2.02</td>
<td>1.02 to 3.97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior CVA</td>
<td>HR: 2.04</td>
<td>1.01 to 4.15</td>
<td></td>
</tr>
</tbody>
</table>

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

### Predictors for Tissue Embolization

<table>
<thead>
<tr>
<th>Independent Predictors of Tissue Embolization</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balloon-expandable THV</td>
<td>7.315</td>
<td>1.398-38.289</td>
<td>p=0.018</td>
</tr>
<tr>
<td>Cover index</td>
<td>1.141</td>
<td>1.014-1.283</td>
<td>p=0.028</td>
</tr>
<tr>
<td>Balloon post-dilation</td>
<td>2.67</td>
<td>0.675-10.073</td>
<td>p=0.17</td>
</tr>
</tbody>
</table>

Van Mieghem: JACC Vol 8. No 5. 2015
Technology
Claret Sentinel™ Cerebral Protection System (CPS)

- The only dual, independent filter (proximal and distal) cerebral embolic protection device with visible embolic debris capture and removal
- The 3rd generation of the 1st commercially available CE Marked embolic protection device
- Universal size and shape
- Deflectable compound curve sheath facilitates cannulation of LCC
- Right transradial 6F sheath access using a standard 0.014” guidewire
- Filters are out of the way of TAVR delivery catheter and accessories during the TAVR procedure
- Ease of use with deployment in less than 3 minutes

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

Cedars-Sinai, Los Angeles, CA, USA, SENTINEL trial 2015

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

Henry Ford Hospital
Detroit, MI
SENTINEL trial 2015

CAUTION: Investigational device. Limited to investigational use by United States law.
Embolic debris captured in 97% of TAVR procedures at AK St Georg

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

- Using Sapien S3/XT, CoreValve/ EvolutR, etc. valves

Filter contents subsequently analyzed by CVPath Institute

- Debris captured in 97% of patients

Cerebral embolic debris captured in TAVR patients (n=109)

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

Cerebral embolic debris found in 100% of patients in MISTRAL-C

Van Mieghem NM, MISTRAL C, presented at TCT 2015
CLEAN-TAVI: First prospective, randomized trial of cerebral embolic protection in TAVR

Axel Linke¹, Stephan Haussig¹, Michael G Dwyer², Norman Mangner¹, Lukas Lehmkuhl¹, Christian Lücke¹, Felix Woitek¹, David M Holzhey¹, Friedrich W Mohr¹, Matthias Gutberlet¹, Robert Zivadinov², Gerhard Schuler¹

¹University of Leipzig, Heart Center, Leipzig, Germany,
²University of Buffalo, Buffalo, NY, US

Linke A., et al. CLEAN-TAVI presented at TCT 2014
CLEAN-TAVI shows Claret filters significantly reduce lesion number and volume.

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

CLEAN-TAVI (manuscript in review)
CLEAN-TAVI lesion probability map

- Entire brain analysis by Buffalo Neuro Imagining Core lab based on CLEAN-TAVI full cohort.
- **Yellow** areas are where the control, unprotected, population was more likely to have lesions (p<0.05)
- **Blue** areas are where the test (filter), protected, population was more likely to have lesions (p<0.05)
Claret filter reduces new cerebral lesion volume in TAVR

3D renderings of new lesions on DW-MRI at 7-days post-procedure for the median patients by lesion volume from each arm of CLEAN-TAVI

Using filters reduces new lesion volume by 267mm³ on average (57%), or about the size of an 8mm sphere

Analysis by Buffalo Neuroimaging Analysis Center

CLEAN-TAVI (manuscript in review)
CLEAN-TAVI shows the promise of protection

The Problem

Control group (no filters)

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

CLEAN-TAVI (manuscript in review)
Embolic debris captured in 88% of patients during CLEAN-TAVI study

50 cases of TAVI using Claret Cerebral Protection System performed at Univ. of Leipzig - Herzzentrum
- Filter arm of CLEAN-TAVI randomized trial
- All using Medtronic CoreValve

Filter contents subsequently analyzed by CVPath Institute
- **Debris captured in 88% of patients**

Cerebral embolic debris captured in CLEAN-TAVI patients (n=50)

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any debris</td>
<td>88%</td>
</tr>
<tr>
<td>Thrombus</td>
<td>58%</td>
</tr>
<tr>
<td>Valve Tissue</td>
<td>50%</td>
</tr>
<tr>
<td>Arterial Wall</td>
<td>74%</td>
</tr>
<tr>
<td>Calcification</td>
<td>22%</td>
</tr>
<tr>
<td>Foreign material</td>
<td>4%</td>
</tr>
</tbody>
</table>

Thrombus was found in combination with other materials in 87% of filters which contained thrombus

1. Unpublished data. CVPath Institute data on file at Claret Medical. CLEAN-TAVI presented by Linke A at TCT 2014
Most damage is unseen…

Clinically apparent

Subtle and often undetected

Clinically unrecognized

….but can have far-reaching effects
MISTRAL-C showed 52% reduction in total new lesion volume when Claret CPS is used

- Assessments conducted 5 days post-TAVR
- Patients underwent highly sensitive 3-Tesla brain MRI
- Patients implanted with balloon or self expandable TAVR valves

van Mieghem NM, MISTRAL-C as presented at TCT
When Sentinel CPS is used, significantly fewer patients show worsening neurocognitive changes

Mental cognition deterioration battery:

- Mini mental state examination (MMSE),
- Montreal Cognitive Assessment,
- Depression scale of the Center for Epidemiological Studies (CES-D),
- NIHSS

van Mieghem NM, MISTRAL-C as presented at TCT 2015
Claret CPS shows promise in other endovascular procedures

Data presented at TCT 2015 from small POC studies showed embolic debris captured during MitraClip\(^1\), LAA\(^2\) and Valve in Valve\(^3\) procedures.

1. AK St Georg (Hamburg) and University Hospital RWTH (Aachen). CVPath Institute data on file at Claret Medical
2. AK St Georg (Hamburg). CVPath Institute data on file at Claret Medical
Embolic debris captured during **MitraClip** procedures by Claret Medical Cerebral Protection Systems

14 cases of MitraClip TMVR using Claret Medical Cerebral Protection System.
- Performed at AK St Georg (Hamburg) and University Hospital RWTH (Aachen)

Filter contents subsequently analyzed at CVPath Institute
- **Debris captured in 93% of patients**
- Debris includes thrombus, despite short procedures and high ACT, valve or artery tissue, and foreign material.
- Debris characterization differs from TAVR, as expected, in not including calcification.

<table>
<thead>
<tr>
<th>Any debris</th>
<th>Thrombus</th>
<th>Tissue</th>
<th>Calcification</th>
<th>Foreign material</th>
</tr>
</thead>
<tbody>
<tr>
<td>93%</td>
<td>79%</td>
<td>57%</td>
<td>0%</td>
<td>79%</td>
</tr>
</tbody>
</table>

- Thrombus was found in combination with other materials in 85% of filters which contained thrombus

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1. AK St Georg (Hamburg) and University Hospital RWTH (Aachen). CVPath Institute data on file at Claret Medical
Embolic debris captured during **LAA closure** procedures by Claret Medical Cerebral Protection Systems

5 cases of LAA closure (Watchman and Amplatzer) using Claret Cerebral Protection Systems

Filter contents subsequently analyzed at CVPath Institute

- **Debris captured in 100% of patients**
- Debris includes acute thrombus and organizing thrombus, as well as endocardium and intimal tissue
- Debris differs from TAVR, as expected, in not including calcification or valve tissue

### Cerebral embolic debris captured in LAA occlusion cases (n=5)

<table>
<thead>
<tr>
<th>Debris Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any debris</td>
<td>100%</td>
</tr>
<tr>
<td>Acute thrombus</td>
<td>60%</td>
</tr>
<tr>
<td>Organizing thrombus</td>
<td>80%</td>
</tr>
<tr>
<td>Tissue</td>
<td>40%</td>
</tr>
<tr>
<td>Calcification</td>
<td>0%</td>
</tr>
<tr>
<td>Foreign material</td>
<td>0%</td>
</tr>
</tbody>
</table>

Note: percentages reflect percent of patients in the series in which each particular tissue type was captured. Some filters captured several types of debris, so percentages will not add to 100%.
9 cases of ViV TAVI using Claret Cerebral Protection System performed at AK St Georg (Hamburg)
- TAVR valves used included CoreValve/EvolutR, Portico, Sapien XT, and Lotus

Filter contents subsequently analyzed by CVPath Institute
- Debris captured in 100% of patients

Cerebral embolic debris captured in ViV TAVR patients (n=9)

Silent Ischemia in TEVAR

19 stable TEVAR patients studied
- Talent, Medtronic, 4 patients
- Valiant, Medtronic, 7 patients
- Relay, Bolton Medical, 7 patients
- Gore Tag, W. L. Gore & Associates, 1 patient

12/19 patients (63%) had new lesions post-procedure
- Lesions were usually multiple (1 to 6 lesions per patient) and ranged in size between 15 mm$^3$ and 300 mm$^3$;
- 16 lesions in the left hemisphere, 13 lesions in the right hemisphere.
Embollic debris captured during TEVAR procedures by Claret Medical Cerebral Protection Systems

5 cases of TEVAR using Claret Medical Cerebral Protection System at University Hospital Essen
- Including Gore TAG, Medtronic Valiant Captivia, and Bolton Relay NBS

Filter contents subsequently analyzed by team of Dr Virmani at CVPath Institute
- Debris was captured in 100% of patients
- Debris includes arterial wall tissue, valve tissue, calcification, foreign material, and acute and organizing thrombus

<table>
<thead>
<tr>
<th>Procedure and Center</th>
<th># of patients</th>
<th>Any debris</th>
<th>Acute Thrombus</th>
<th>Organizing Thrombus</th>
<th>Valve Tissue</th>
<th>Arterial Wall</th>
<th>Calcification</th>
<th>Foreign Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEVAR¹ Univ. Hosp. Essen</td>
<td>n=5</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>25%</td>
<td>100%</td>
<td>25%</td>
<td>100%</td>
</tr>
</tbody>
</table>

- University Hospital Essen. CVPath Institute data on file at Claret Medical
- Courtesy of Dr P/ Kahlert and Dr Janosi – Essen, Germany
Debris Anywhere (but, especially in the Brain) is Not Benign…

Thank You!