Disclosure Statement of Financial Interest

Susheel Kodali, 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.

**Affiliation/Financial Relationship**  
- Grant/Research Support  
- Steering Committee  
- SAB (Equity)

**Company**  
- Edwards Lifesciences  
- Edwards Lifesciences, Claret Medical, Meril  
- Thubrikar Aortic Valve, Inc
**Methods:**
- Meta-analysis from 53 studies in 10,037 pts treated with TAVI (TA, TF, or TS) published from Jan, 2004 to Nov, 2011
- Mean age $81.5 \pm 1.8$ yrs and mean logES $24.8 \pm 5.6\%$

**Results:**
- Procedural stroke (<24 hrs) $1.5 \pm 1.4\%$; 30-day stroke/TIA $3.3 \pm 1.8\%$; most major strokes $2.9 \pm 1.8\%$; 1-year stroke/TIA increased to $5.2 \pm 3.4\%$
- Different stroke rates with different approaches and valve prostheses; lowest with TA-ES $2.7 \pm 1.4\%$ vs. TF-ES $4.4 \pm 2.2\%$ (30-day stroke/TIA)
- Mortality at 30 days + stroke = 25.5% vs. - stroke = 6.9% (>3.5X)

**Overall stroke/TIA:** $3.3\%$
METHODS:
• Meta-analysis from 53 studies in 10,037 pts treated with TAVI (TA, TF, or TS) published from Jan, 2004 to Nov, 2011
• Mean age 81.5 ± 1.8 yrs and mean logES 24.8 ± 5.6%

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30-day mortality bar chart:
- All patients: 25.5%
- Patients with stroke: 8.1%
- Patients without stroke: 6.9%
Neurologic Event Rates Decreasing

If major stroke rates are ~1%, is there a need for embolic protection?

Neurologist evaluations (pre- and post)

<table>
<thead>
<tr>
<th>Device</th>
<th>Count</th>
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<tbody>
<tr>
<td>P1B (TF)</td>
<td>179</td>
</tr>
<tr>
<td>P1A (All)</td>
<td>344</td>
</tr>
<tr>
<td>P2B (TF)</td>
<td>276</td>
</tr>
<tr>
<td>P2B XT (TF)</td>
<td>284</td>
</tr>
<tr>
<td>S3HR (All)</td>
<td>583</td>
</tr>
<tr>
<td>S3i (All)</td>
<td>1076</td>
</tr>
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</table>

Cardiovascular Research Foundation: A Passion for Innovation
Clinical Need – Stroke, Silent and Apparent

>70% of TAVR patients have ischemic brain lesions when examined by DW-MRI

Silent and Apparent Cerebral Ischemia After Percutaneous Transfemoral Aortic Valve Implantation

A Diffusion-Weighted Magnetic Resonance Imaging Study

Philipp Kahlert, MD,* Stephan C. Knipp, MD,* Marc Schlamann, MD; Matthias Thielmann, MD; Fadi Al-Rashid, MS; Marcel Weber, MD; Uwe Johansson, MD; Daniel Wenth, MD; Heinz G. Jakob, MD; Michael Forsting, MD; Stefan Sack, MD, FESC; Raimund Erbel, MD, FESC; Holger Eggert, MD, FESC

Background—The risk of stroke after transfemoral aortic valve implantation (TAVI) due to dislodgement and subsequent embolization of debris from aortic arch atheroma or from the calcified valve itself ranges between 2% and 10%. The rate of clinically silent cerebral ischemia is unknown but may be even higher.

Methods and Results—Thirty-two patients who underwent TAVI with the use of a balloon-expandable (n=22) or self-expandable (n=10) stent valve prosthesis were included in this descriptive study and compared with a historical control group of 21 patients undergoing open surgical aortic valve replacement. Peri-procedural apparent and silent cerebral ischemia was assessed by neurological testing and serial cerebral diffusion-weighted magnetic resonance imaging at baseline, at 3.4 (2.5 to 4.4) days after the procedure, and at 3 months. TAVI was successful in all patients. After the procedure, new foci of restricted diffusion on cerebral diffusion-weighted magnetic resonance imaging were found in 27 of 32 TAVI patients (84%) and were more frequent than after open surgery (10 of 21 patients [48%]; P=0.011). These lesions were usually multiple (1 to 19 per patient) and dispersed in both hemispheres in a pattern suggesting cerebral embolization. Volumes of these lesions were significantly smaller after TAVI than after surgery (77 [59 to 94] versus 224 [111 to 338] mm³; P=0.001). There were neither measurable impairments of neurocognitive function nor apparent neurological events during the in-hospital period among TAVI patients, but there was 1 stroke (5%) in the surgical patient group. On 3-month follow-up diffusion-weighted magnetic resonance imaging, there were no new foci of restricted diffusion, and there was no residual signal change associated with the majority (80%) of the foci detected in the peri-procedural period.

Conclusions—Clinically silent new foci of restricted diffusion on cerebral magnetic resonance imaging were detected in almost all patients (84%) undergoing TAVI. Although typically multiple, these foci were not associated with apparent neurological events or measurable deterioration of neurocognitive function during the 3-month follow-up. Further work needs to be directed to determine the clinical significance of these findings in a larger patient population. (Circulation. 2011;123:870–878.)
Clinical Need – Stroke, Silent and Apparent

>70% of TAVR patients have ischemic brain lesions when examined by DW-MRI

**Stroke**

Silent and Apparent Cerebral Ischemia After Percutaneous Transfemoral Aortic Valve Implantation
A Diffusion-Wighted Magnetic Resonance Imaging Study

Philipp Kahler, MD; Stephan C. Knipp, MD; Marc Schlamann, MD; Matthias Thielmann, MD; Fadi Al-Rashid, MS; Marcel Weber, MD; Uwe Johansson, MD; Daniel Wendi, MD; Heinz G. Jakob, MD; Michael Forsting, MD; Stefan Sack, MD, FESC; Raimund Erbel, MD, FESC; Holger Eggertshögl, MD, FESC

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Conclusions—Clinically silent new foci of restricted diffusion on cerebral magnetic resonance imaging were found in almost all patients (84%) undergoing TAVI. Although typically multiple, these foci endured without new neurological events or measurable deterioration of neurocognitive function during follow-up. Further research needs to be directed to determine the clinical significance of these findings in a larger patient population.
Diffusion-Weighted MRI Study

Philipp Kahlert, MD
West German Heart Center Essen

Pre-TAVI

Post-TAVI

Embolic phenomenon
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

Several studies have shown that patients with silent brain infarcts had a 5 times higher stroke incidence than those without.
## 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>130 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”
Overview of Sentinel™ Cerebral Protection System (CPS)

- 6F right radial access over
- Articulating distal sheath (ADS) with anatomical compound bend facilitates placement
- Universal sizing and independently adjustable filters accommodate a wide range of vascular anatomy
- Unobtrusive to aortic arch
- 140µm diameter pore filters capture and remove embolic debris

Profile: 6F (Right arm access only)

Full device length: ~148 cm
Working length to ADS tip: 95 cm

CAUTION: Investigational device. Limited to investigational use by United States law.
Sentinel CPS – Articulating Distal Sheath (ADS)

Designed to accommodate a wide variety of patient anatomy:

- Compound curve with back bend for optimal filter placement and apposition
- Translation, rotation, and articulation of sheath allows multi-plane tip deflection for cannulation of LCC
Sentinel CPS - Articulating Distal Sheath (ADS)

- Minimal intrusion into aortic arch
- Low risk of interference with TAVR catheter or accessories
- Compatible with complex aortic arch & take-off anatomies
Sentinel™ Cerebral Protection System animation
Embolic Material after TAVR
Embolic Material after TAVR
40 TAVR pts treated with the dual filter system
40 TAVR pts treated with the dual filter system

Van Mieghem NM et al. Circulation 2013
**Design**

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

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

MRI, Neurocogn. Assessment, Frailty, Echo

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

**Filter Group**
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
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.
Total Lesion Volume at 2 & 7 days

Protected regions

All regions

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 (No, %)</th>
<th>2 days (No, %)</th>
<th>7 days (No, %)</th>
<th>30 days (No, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C</strong>ontrol</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>F</strong>ilter</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>
SENTINEL Study Design

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

SAFETY ARM
TAVR with Sentinel

TEST ARM
TAVR with Sentinel

CONTROL ARM
TAVR only

Histopathology

Safety Follow-up

Safety Follow-up

MRI Assessments

Neurological and Neurocognitive Tests

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

Primary Safety Endpoint: Occurrence of all MAE at 30
TriGard™ Embolic Deflection Device

- Nitinol mesh filter with pore size of 130μm designed to deflect cerebral emboli while allowing maximal blood flow
- Positioning across all 3 cerebral vessels is maintained by stabilizers
- Delivered via 9 Fr sheath from femoral artery
Keystone Embolic Deflection Device
**Design:** Multicenter prospective single-blind randomized controlled trial at 13 sites (EU/IL)

**Objective:** To evaluate the safety, efficacy and performance of TriGuard protection compared with unprotected TAVR.

**Sample Size:** Exploratory study with no formal hypothesis testing (86 patients to set benchmark for pivotal trial).

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Lansky et al., ACC 2015
### DW-MRI Results – Single and Max Lesion Volume

Average # of new lesions/pt: 4.5 vs 4.0 for TG and Controls

Protection has lower SLV and MLV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SLV (mm^3)</th>
<th>MLV (mm^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention to Treat</td>
<td>28.0</td>
<td>34.5</td>
</tr>
<tr>
<td>Per Treatment</td>
<td>19.6</td>
<td>33.2</td>
</tr>
</tbody>
</table>

**Better**

Lansky et al., ACC 2015
Is Complete Coverage Crucial?

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

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!

• Clinical and silent stroke frequency after TAVR remains a frequent event.

• Early clinical evidence suggests that cerebral protection devices during TAVR may be beneficial.
Cerebral Protection in TAVR

Final Thoughts

• The CLEAN-TAVI and DEFLECT III randomized trials provide further evidence that DW-MRI lesion number and total volume are significantly reduced with embolic protection

• *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!*