Cerebral Protection In Transcatheter Aortic Valve Replacement – The SENTINEL Study

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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

**Company**
- Edwards Lifesciences
- Edwards Lifesciences, Claret Medical (National Co-PI), Meril
- Thubrikar Aortic Valve, Inc
Introduction

• Although frequency has decreased slightly, cerebrovascular events continue to be a concern with transcatheter AVR
• Approximately 2/3 of patients have evidence of embolic events on DW-MRI imaging following TAVR
• These “silent infarcts” have been shown to result in a higher risk of stroke and in addition have been shown to have neurological and cognitive consequences
• Embolic protection with either filters or deflectors have been shown to reduce volume of debris
Stroke Rates

Neurologic Events

<table>
<thead>
<tr>
<th>30 Day Stroke Rate (%)</th>
<th>B (Sapien)</th>
<th>A (Sapien)</th>
<th>Sapien XT</th>
<th>Sapien</th>
<th>Extreme Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARTNER I</td>
<td>6.7%</td>
<td>4.7%</td>
<td>4.3%</td>
<td>4.1%</td>
<td>4.0%</td>
<td>4.9%</td>
</tr>
<tr>
<td>PARTNER II</td>
<td>PARTNER II</td>
<td>PARTNER II</td>
<td>PARTNER II</td>
<td>PARTNER II</td>
<td>PARTNER II</td>
<td>PARTNER II</td>
</tr>
<tr>
<td>CoreValve US Pivotal</td>
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<td>CoreValve US Pivotal</td>
</tr>
</tbody>
</table>
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
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.
Claret Medical Inc. 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
- Articulating sheath with compound curve to facilitate cannulation of LCC
- 6Fr Right Radial or Brachial Artery access
- Elastomeric membrane, 140 micron pore size

CAUTION: Investigational device. Limited to investigational use by U.S. law
CLEAN-TAVI Study Design Overview

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

Enrollment Completed
June 2014
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

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

<table>
<thead>
<tr>
<th>per protocol</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>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>11 (24 %)</td>
<td>6 (13 %)</td>
<td>6 (13 %)</td>
<td>4 (12 %)</td>
</tr>
<tr>
<td>- ataxia</td>
<td>9 (20 %)</td>
<td>4 (9 %)</td>
<td>5 (11 %)</td>
<td>4 (12 %)</td>
</tr>
</tbody>
</table>

n=45

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
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.
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.
The SENTINEL IDE Study

• **Pivotal study** confirming the therapeutic importance of embolic debris capture and removal during TAVR

• **Study 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

• **Study Population:** Subjects with severe symptomatic calcified native aortic valve stenosis who meet the commercially approved indications for TAVR with the Edwards SAPIEN THV or SAPIEN XT
SENTINEL Study Hypothesis

• The Sentinel System will be a safe and effective method for capturing and removing embolic material (thrombus/debris) during TAVR in order to reduce the ischemic burden in the brain
SENTINEL Study – Key Study Personnel

• Co-Principal Investigators:
  
  Susheel Kodali, MD  Director, NYP Columbia Heart Valve Center and Director of Interventional Cardiology Fellowship Program, Columbia University Medical Center

  Samir Kapadia, MD  Director, Sones Cardiac Catheterization Laboratory and Director of Interventional Cardiology Fellowship Program, Cleveland Clinic

• Clinical Steering Committee Chairman:
  
  Martin Leon, MD  Director, Center for Interventional Vascular Therapy, Columbia University Medical Center

• Study Medical Monitor:
  
  Roxana Mehran, MD  Professor of Medicine and Director of Interventional Cardiovascular Research and Clinical Trials, Mount Sinai School of Medicine
Study Design – Design Detail

- **Total Enrollment:**
  - **Roll-In Phase:** 3-5 subjects per site
  - **Randomized:** 284 subjects

- **Inclusion/Exclusion Criteria:** Based on PARTNER I (SAPIEN) and II (SAPIEN XT)
Study Design – Endpoint Detail

Randomize 1:1:1 (n=284 maximum) @ 15 sites

- **Randomization:**
  - 1:1:1, Safety Arm : Test Arm : Control Arm

- **Primary Efficacy Endpoint (Superiority):**
  - Reduction in median total new lesion volume as assessed by DW-MRI at Day 4-7 post-procedure

- **Primary Safety Endpoint (Non-Inferiority):**
  - Occurrence of all MACCE at 30 days
Study Design – Assessment Detail

• **Efficacy:**
  – MRI (DW-MRI at 0 and 4-7 days, FLAIR-MRI at 30 days
  – Neurocognitive
  – Histopathology

• **Safety:**
  – 30 and 90 day MACCE on all study subjects
MRI Methodology

• 3-Tesla MR scanner standardization for optimal resolution across all study sites
• DW and FLAIR
• Novel methodology with serial scan acquisition at baseline, 4-7 days and 30 days
• Core lab analysis of all scans
  – Buffalo Neuroimaging Analysis Center, Buffalo NY
Schedule of Assessments

Baseline
- MR Imaging
- Histopathology
- Safety
- Neurological
- Neurocognitive

TAVR with Sentinel™
- DWI/FLAIR
- Histology
- MACCE
- NIHSS mRS
- BATTERY

Discharge*
- DWI/FLAIR
- MACCE
- NIHSS mRS

Follow-Up (30 day)
- DWI/FLAIR
- MACCE
- NIHSS

Follow-Up (90 day)
- DWI/FLAIR
- MACCE
- mRS

*Subject discharge could be earlier than 7 days
**For subjects with post-procedural stroke
### Neurocognitive Assessment Battery

<table>
<thead>
<tr>
<th>Test Battery</th>
<th>Laterality</th>
<th>Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trails A</td>
<td>Bi-hemispheral</td>
<td>Attention</td>
</tr>
<tr>
<td>Trails B</td>
<td>Bi-hemispheral</td>
<td>Executive Function</td>
</tr>
<tr>
<td>Digit Span</td>
<td>Bi-hemispheral</td>
<td>Attention</td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>Bi-hemispheral</td>
<td>Processing Speed</td>
</tr>
<tr>
<td>Controlled Oral Word Association</td>
<td>Left Hemisphere</td>
<td>Processing Speed</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test</td>
<td>Left Hemisphere</td>
<td>Verbal Memory</td>
</tr>
<tr>
<td>Rey Complex Figure (Copy)</td>
<td>Right Hemisphere</td>
<td>Executive Function</td>
</tr>
<tr>
<td>Brief Visual Memory Test</td>
<td>Right Hemisphere</td>
<td>Visual Memory</td>
</tr>
<tr>
<td>Mini Mental State Exam</td>
<td>--</td>
<td>Mental Status</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td>--</td>
<td>Depression</td>
</tr>
</tbody>
</table>

- The proposed battery and its variants have been validated and used in both NIH-funded (NHLBI, NINDS) and industry-sponsored studies, assessing neurocognitive sequelae in end-stage heart failure and LVAD support, carotid artery disease, and recently piloted in the PARTNER II study.

- Assessments will be by corelab trained and certified study neuropsychologist or technician under the direct supervision of a neuropsychologist.
Secondary Endpoints
(for labeling with statistical inference)

1. Difference in Day 4-7 DW-MRI median number of new lesions

2. Difference in Day 4-7 DW-MRI median total new lesion volume

3. Difference in mean change in neurocognitive battery composite z-score from baseline to 90 days

4. Difference in Day 30 FLAIR-MRI median total new lesion volume
### Study Design – Other Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Safety Arm</th>
<th>Test (Efficacy)</th>
<th>Control (Efficacy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sentinel System acute delivery &amp; retrieval success</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>In-hospital MACCE</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Correlation of lesion volume metrics (DW-MRI and FLAIR-MRI) with change in neurocognitive battery composite score</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neurocognitive assessments at multiple time points</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Captured debris histopathology</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological (NIHSS and mRS) assessments at multiple time points</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Occurrence of major vascular complications at index and 30 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Occurrence of other Serious Adverse Events</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Sentinel Study – Core Laboratories

- **Magnetic Resonance Imaging Corelab:**
  Buffalo Neuroimaging Analysis Center – Buffalo, NY
  - Dr. Robert Zivadinov

- **Neurocognitive Corelab:**
  Tananbaum Stroke Center, Neurological Institute
  Columbia University Medical Center
  - Ronald Lazar, PhD

- **Histopathology Corelab:**
  CVPath Institute
  - Dr. Renu Virmani

- **Sentinel Planning Center:**
  Cedars Sinai Medical Center
  - Dr. Hasan Jilaihawi
## Data Types for Correlations

### Imaging
- Number of lesions/group
- Total lesion volume/group
- Number of lesions/patient
- Total lesion volume/patient
- Baseline, 2-7 day, & 30 day
- Prevalence of large lesion volumes
- Territory analysis
- Ischemic & inflammatory imaging markers (DW-MRI and FLAIR-MRI)

### Histopathology
- Presence of debris in Proximal Filter
- Presence of debris in Distal Filter
- Type of debris in Proximal Filter
- Type of debris in Distal Filter
- Size of debris in Proximal Filter
- Size of debris in Distal Filter

### Neurological & Cognitive
- NIHSS
- mRS
- Neurocognitive test battery
- Baseline, 30 day, & 90 day

### Safety Measures
- MACCE
- Major vascular complications
- Device acute delivery & retrieval success
Sentinel Study Status

• First subject enrollment planned for September
  – Columbia University Medical Center
Thank You!

Captured during TCT 2013 Live Case: Courtesy of Dr. Alex Abizaid
Institute Dante Pazzanese de Cardiologia, São Paulo, Brazil