Cerebral Protection in Transcatheter Aortic Valve Replacement – The SENTINEL Study

Susheel Kodali, MD

Columbia University Medical Center
Cardiovascular Research Foundation
New York City
Disclosure Statement of Financial Interest  
TVT 2015; Chicago, IL  

Susheel K. 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.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tbody>
<tr>
<td>Honoraria</td>
<td>St. Jude Medical, Claret Medical</td>
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<td>Steering Committee</td>
<td>Edwards Lifesciences, Claret Medical</td>
</tr>
<tr>
<td>SAB</td>
<td>Thubrikar Aortic Valve, Inc, Dura Biotech, VS Medtech</td>
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### Stroke is not disappearing with new valves

<table>
<thead>
<tr>
<th>Study name</th>
<th>Outcome</th>
<th>Event rate</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
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<tbody>
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<td>DFM (DISCOVER)</td>
<td>Major Stroke</td>
<td>0.040</td>
<td>0.013</td>
<td>0.117</td>
<td>-5.393</td>
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<td>Portico (CE Trial)</td>
<td>Major Stroke</td>
<td>0.024</td>
<td>0.006</td>
<td>0.091</td>
<td>-5.171</td>
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<td>Sadra Lotus (REPRISE)</td>
<td>Major Stroke</td>
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<td>0.065</td>
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<td>0.094</td>
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<td>ACURATE TA (SAVI)</td>
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<td>SAPIEN 3 (Dvir)</td>
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<td>CENTERA (Binder)</td>
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<td>0.031</td>
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</table>

**2.8% major stroke**
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.)

![Graph showing 30-day stroke rates in recent TAVR RCTs](image1)

![Graph comparing rates of any new neurological deficit with positive imaging evidence of brain ischemia](image2)
Most cerebral damage in TAVR is unseen

Clinically apparent

Subtle and often undetected

Clinically unrecognized

… but can have far-reaching effects
• 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

Stroke, defined by AHA/ASA expert consensus, includes “silent” brain infarcts (imaging evidence alone)
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)

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

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 transcatheater aortic valve implantation. TIA indicates transient ischemic attack.

Multi-center cohort of 1,061 TAVI patients
- CVE most frequently occur day 0-1
- >50% are major strokes
- >95% of strokes are ischemic
Embolic events occur with device positioning and deployment.

Results - Transcranial Doppler Findings

- Medtronic CoreValve
- Edwards Sapien - TF
- Edwards Sapien - TA

Kahlert P,..., Eggebrecht H, Circulation 2012
New cerebral lesions are found in the vast majority of patients following TAVI

- 68-100% of TAVR patients affected
- Most patients have multiple infarcts
- "Silent" infarcts 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

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1. Sacco et al., Stroke 2013
2. Vermeer et al., Stroke 2003
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 TAVI delivery catheter and accessories during the TAVI procedure

CAUTION: Investigational device. Limited to investigational use by United States law.
Sentinel™ Cerebral Protection System animation
Claret Cerebral Protection System offers universal compatibility and protection

- Compatible with >90% of aortic arch and cerebral vessel anatomies
- Only 2% of the brain’s vascular regions remain unprotected when using the Sentinel*
- Has been used to protect >2000 patients worldwide to date

*Data on file – based on CLEAN-TAVI core lab analysis
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

Approx. 8 mm, captured in LCC

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

AK St Georg
Hamburg, Germany
ALSTER experience
SENTINEL-H Registry 2015

CAUTION: Investigational device. Limited to investigational use by United States law.
CLEAN-TAVI

Embolic debris captured during CLEAN-TAVI study using Claret Cerebral Protection Systems

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*

![Bar Chart](chart.png)

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

- **Any debris**: 88%
- **Thrombus**: 58%
- **Valve Tissue**: 50%
- **Arterial Wall**: 74%
- **Calcification**: 22%
- **Foreign material**: 4%

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

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**Note:**

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

CAUTION: Investigational device. Limited to investigational use by United States law.
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)
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.
What did CLEAN-TAVI show us?

- Embolic protection with the Claret device is safe and significantly reduces lesion number and volume
- Embolic protection may have benefit in improving neurologic and neurocognitive outcomes

**Strengths**
- Rigorous serial MRI at 4 time points
- 3T magnet strength for increased sensitivity
- Baseline subtraction MRI to reduce effect of existing lesions

**Limitations**
- Sample size not large enough for clinical endpoint
- Earlier generation device
- Neurologic testing limited (What is the right assessment?)
SENTINEL Study Design

Pivotal trial 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.

**Population**: Subjects with severe symptomatic calcified native aortic valve stenosis who meet the commercially-approved indications for TAVR with the Edwards Sapien THV/XT/S3 or Medtronic CoreValve/Evolut-R

N=296 subjects randomized 1:1:1 at sites in the U.S and Germany.

**US Co-PIs**:
Samir Kapadia, MD, Cleveland Clinic
Susheel Kodali, MD, Columbia U Med

**German Co-PI**:
Axel Linke, MD, Leipzig U

**SAFETY ARM**
TAVR with Sentinel

**TEST ARM**
TAVR with Sentinel

**CONTROL ARM**
TAVR only

- Safety Follow-up
- Histopathology
- Safety Follow-up
- MRI Assessments
- Neurological and Neurocognitive Tests

**Primary (superiority) Efficacy Endpoint**: Reduction in median total new lesion volume assessed by 3T DW-MR by baseline subtraction.

**Primary (non-inferiority) Safety Endpoint**: Occurrence of all MACCE at 30 days.

CAUTION: Investigational device. Limited to investigational use by United States law.
# SENTINEL Study: Leadership

## Co-Principal Investigators:

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susheel Kodali, MD</td>
<td>Co-director, NYP Columbia Heart Valve Center and Director of Interventional Cardiology Fellowship Program, Columbia University Medical Center</td>
</tr>
<tr>
<td>Samir Kapadia, MD</td>
<td>Director, Sones Cardiac Catheterization Laboratory and Director of Interventional Cardiology Fellowship Program, Cleveland Clinic</td>
</tr>
<tr>
<td>Axel Linke, MD</td>
<td>Klinik fuer Innere Medizin und Kardiologie, Herzzentrum Leipzig</td>
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## Clinical Steering Committee Chairman:

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Marty Leon, MD</td>
<td>Director, Center for Interventional Vascular Therapy, Columbia University Medical Center</td>
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## Study Medical Monitor:

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Roxana Mehran, MD</td>
<td>Professor of Medicine and Director of Interventional Cardiovascular Research and Clinical Trials, Mount Sinai School of Medicine</td>
</tr>
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</table>
Sentinel study – Core laboratories

• Magnetic Resonance Imaging Core Lab:
  - Buffalo Neuroimaging Analysis Center – Buffalo, NY
    - Dr. Robert Zivadinov

• Neurocognitive Core Lab:
  - Tananbaum Stroke Center, Neurological Institute, Columbia University Medical Center
    - Ronald Lazar, PhD

• Histopathology Core Lab:
  - CVPath Institute
    - Dr. Renu Virmani

• Sentinel CT Planning Center:
  - Cedars Sinai Medical Center
    - Dr. Hasan Jilaihawi
SENTINEL Study: US Investigational Sites

[Map showing locations of investigational sites across the United States.]
**Study Design: Primary Endpoints**

**Primary Efficacy Endpoint (Superiority):**
Reduction in median total new lesion volume in protected territories between the Imaging Arms (Test and Control Group) as assessed by DW-MRI at -7d post-procedure.

**Primary Safety Endpoint (Non-inferiority):**
Occurrence of Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 days compared to a historical performance goal.
MSCT Screening and Review Algorithm for the Trial

Director, Interventional Cardiology Imaging at Cedars-Sinai: Dr. Hasan Jilaihawi

- Reconstruction reports reviewed by 5 committee members: Drs. Linke, Van Mieghem, Schäfer, Kodali and Kapadia

- Arch type
- Vessel diameters, angles
- Angulation
- Viewing angle
- Atheroma, calcification
- General comments and considerations

- Universal 3D-pdf (can be manipulated)
- Angulation (tortuosity)
- Cross-sectional measurements
- Angio at optimal viewing angle
- Calcification

SENTINEL CT Planning Center Report Elements
Follow-up Imaging - Unique Challenges

- Smaller lesions (micro-emboli) vs. conventional strokes (macro-emboli)
- Highly affected by usually negligible artifacts
- No well-established imaging or analysis protocols
- Longitudinal match-up is much more challenging than with usual stroke analysis
- Additional confounding factors
  - Pre-existing pathology in aged population
  - High risk-factor population
  - New-onset atrial fibrillation (NOAF) can cause secondary emboli
Most Comprehensive Neuroimaging Methodology

Novel methodology with serial scan acquisition at baseline, 3-7 days and 30 days

- Baseline (B₀) mapping must be performed to eliminate over-estimation of existing lesions
  - Over 30% of TAVR patients have been shown to have lesions at baseline¹
- Serial co-registration must be performed based on the baseline (B₀) map, otherwise the analysis is not reliable

3-Tesla MR scanner standardization for optimal resolution across all study sites

- 3.0T is able to better resolve smaller lesions, allows shorter acquisition times, and has a higher signal-to-noise ratio than 1.5T MR scanners

Both diffusion-weighted (DW) and fluid-attenuated inversion recovery (FLAIR) MR sequences

- To assess both acute (DW) and chronic (FLAIR) lesions

Core lab analysis of all scans

- Buffalo Neuroimaging Analysis Center (BNAC), Buffalo, NY
  - Robert Zivadinov, MD, PhD
  - Mike Dwyer, PhD

¹ Data on file. CLEAN-TAVI MRI data, analysis by BNAC
Highly Specific/Sensitive Cognition Battery

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<th>Test Battery:</th>
<th>Laterality</th>
<th>Domain</th>
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<td>Neurocognitive Test</td>
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<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>
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<tr>
<td>Digit Span</td>
<td>Bi-hemispheral</td>
<td>Attention</td>
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<tr>
<td>Digit Symbol</td>
<td>Bi-hemispheral</td>
<td>Processing Speed</td>
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<tr>
<td>Controlled Oral Word Association</td>
<td>Left Hemisphere</td>
<td>Processing Speed</td>
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<tr>
<td>Hopkins Verbal Learning Test</td>
<td>Left Hemisphere</td>
<td>Verbal Memory</td>
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<td>Rey Complex Figure (Copy)</td>
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<td>Brief Visual Memory Test</td>
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<td>Mini Mental State Exam</td>
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<td>Geriatric Depression Scale</td>
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<td>Depression</td>
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- 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 core lab-trained and certified study neuropsychologist or technician under the direct supervision of a neuropsychologist.

- Dr. Ronald M. Lazar, Professor of Neuropsychology (in Neurology and Neurological Surgery) at the Columbia University Medical Center Director, Levine Cerebral Localization Laboratory Columbia University College of Physicians & Surgeons.
SENTINEL data types for correlations

**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

**Imaging**
- Number of lesions/group
- Total lesion volume/group
- Number of lesions/patient
- Total lesion volume/patient
- Serial 3.0T MRI with baseline subtraction
- Prevalence of large lesion volumes
- Ischemic & inflammatory imaging markers (DW-MRI and FLAIR-MRI)
- Cerebral territory mapping
- Cerebral vascular mapping

**Neurological & Cognitive**
- NIHSS
- mRS
- Neurocognitive test battery
- Baseline, discharge, and FU
Sentinel Study Status

- 15 centers active and enrolling
- 5 centers in Germany added to protocol
- Anticipate completion Q1 ‘16
- Protocol revisions just approved:
  - Use of any approved TAVR device
  - Expanded indications for TAVR
Claret clinical evidence program: studying more than 700 patients

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<th>Location</th>
<th># pts</th>
<th>Trial Type</th>
<th>Procedure (Valves)</th>
<th>Data Available</th>
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<tr>
<td>SENTINEL</td>
<td>Dr. Samir Kapadia &amp; Dr. Susheel Kodali</td>
<td>15+ centers in USA and Europe</td>
<td>296</td>
<td>Randomized</td>
<td>TAVR (Sapien XT, S3, and CoreValve Evolut R)</td>
<td>2015</td>
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<tr>
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<td>Prof. Christoph Naber</td>
<td>10 centers in Europe</td>
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