Cerebral Embolic Protection In Patients Undergoing Surgical Aortic Valve Replacement (SAVR)

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For the Cardiothoracic Surgical Trials Network (CTSN)

American College of Cardiology
Late Breaking Clinical Trials
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Disclosures

• Co-PI of Partner 3 Trial – Sponsor Edwards Lifesciences
• Co-PI COAPT Trial- Sponsor Abbott Vascular
• Executive Board Intrepid Trial- Sponsor Medtronic
Background

- ~50,000 patients undergo SAVR per year in the U.S.
- The incidence of clinical stroke when examined by a neurologist and postoperative DW MRI in SAVR patients:

Purpose

Determine the safety and effectiveness of 2 cerebral embolic protection devices in reducing ischemic CNS injury

The **CardioGard** embolic protection cannula

The **Embol-X** intra-aortic filtration device
CONSORT Diagram

Assessed for Eligibility (n=4225)

Excluded (n=3842)
- Did not meet inclusion criteria (n=3355)
- Refused to participate (n=460)
- Other (n=27)

Randomized (n=383)

Embol-X (n=133)

Shared Control (n=132)

CardioGard (n=118)

Primary Endpoint Analysis
- Embol-X (n=133)
- Control (n=132)

Primary Endpoint Analysis
- CardioGard (n=118)
- Control (n=120)*

*12 subjects were randomized to control prior to the start of randomization in the CardioGard arm
CTSN Clinical Sites-18
383 Patients

- Baylor Research Institute-70
- Mission Hospital-56
- University of Pennsylvania-50
- University of Virginia-34
- Emory University-34
- Hôpital Laval-27
- Montreal Heart Institute-23
- Dartmouth-Hitchcock Medical Center-20
- University of Southern California-17
- Duke University-12
- Montefiore – Einstein-12
- NIH Heart Center at Suburban Hospital-7
- Columbia University Medical Center-6
- Cleveland Clinic Foundation-4
- Toronto General Hospital-4
- University of Alberta-3
- Ohio State University -2
- University of Maryland-2
Trial Infrastructure

**Clinical and Data Coordinating Center**
- Annette Gelijns, PhD, Alan Moskowitz, MD, Michael Parides, PhD
- InCHOIR, Mount Sinai

**Network Chairs**
- Richard Weisel, MD
- University of Toronto
- Patrick O’Gara, MD
- Brigham and Women’s Hospital

**Funding**
- NHLBI- Marissa Miller, DVM
- NINDS- Claudia Moy, PhD
- CIHR

**Core Labs**
- **Magnetic Resonance Imaging**
  - University of Pennsylvania MRI Core Lab
    - Michel Bilello, PhD
- **Neurocognitive**
  - Duke Neurocognition Core Lab
    - Jeffrey Browndyke, PhD
- **Histopathology**
  - CVPath Institute
    - Renu Virmani, MD
Trial Endpoints

- **PRIMARY**
  - Freedom from clinical or radiographic CNS infarction at 7 (+- 3) days post procedure

- **SECONDARY**
  - Composite: 1) clinical ischemic stroke, 2) acute kidney injury (AKI), 3) death ≤30 days after surgery
  - Volume and number of radiographic brain lesions
  - Mortality at 30 days
  - Serious AEs and readmissions within 90 days
  - Delirium 7 days post-operatively
  - Neurocognition at 90 days
Trial Design & Analysis

- ITT comparison of proportion of pts with evidence of CNS injury, with imputation for missing data
- Assumed control rate of 50% incidence of post-operative CNS infarcts
- 90% power to show reduction of 17.5% (absolute)
- 495 patients, 165 per group
Actual Sample Size

- At interim analysis, randomization was halted due to low conditional power for achieving primary endpoint.
- 383 patients randomized (77% of intended enrollment) when halted.
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CardioGard (N=118)</th>
<th>Control (N=120)</th>
<th>Embol-X (N=133)</th>
<th>Control (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age</td>
<td>74.6 ± 6.8</td>
<td>73.4 ± 6.7</td>
<td>73.6 ± 6.6</td>
<td>73.6 ± 6.7</td>
</tr>
<tr>
<td>Male</td>
<td>69 (58.5)</td>
<td>77 (64.2)</td>
<td>81 (60.9)</td>
<td>86 (65.2)</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14 (11.9)</td>
<td>16 (13.3)</td>
<td>13 (9.8)</td>
<td>16 (12.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>48 (40.7)</td>
<td>36 (30.0)</td>
<td>36 (27.1)</td>
<td>37 (28.0)</td>
</tr>
<tr>
<td>MI</td>
<td>16 (13.6)</td>
<td>8 (6.7)</td>
<td>15 (11.3)</td>
<td>10 (7.6)</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>16 (13.6)</td>
<td>8 (6.7)</td>
<td>11 (8.3)</td>
<td>8 (6.1)</td>
</tr>
<tr>
<td><strong>Cognitive Impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one deficit</td>
<td>37/102 (36.3)</td>
<td>28/109 (25.7)</td>
<td>36/121 (29.8)</td>
<td>31/120 (25.8)</td>
</tr>
</tbody>
</table>

*Continuous variables are expressed as mean ± SD and categorical variables as count (%).*
## Surgical Characteristics

<table>
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<tr>
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<tr>
<td><strong>Surgical Procedure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated AVR</td>
<td>67 (56.8)</td>
<td>73 (60.8)</td>
<td>80 (60.2)</td>
<td>80 (60.6)</td>
</tr>
<tr>
<td>AVR &amp; CABG</td>
<td>51 (43.2)</td>
<td>47 (39.2)</td>
<td>53 (39.8)</td>
<td>52 (39.4)</td>
</tr>
<tr>
<td><strong>Concomitant procedures</strong></td>
<td>18 (15.3)</td>
<td>19 (15.8)</td>
<td>26 (19.5)</td>
<td>20 (15.2)</td>
</tr>
<tr>
<td>Duration of CPB– min</td>
<td>104.9± 39.6</td>
<td>102.2 ± 40.2</td>
<td>109.1 ± 42.4</td>
<td>101.7 ± 39.8</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean ± SD and categorical variables as count (%).
Debris Captured

- Debris captured in 75.8% of CardioGard subjects and 99.1% of Embol-X
- CardioGard filter
- Embol-X filter

6 mm
Percent of Embol-X Patients with at Least One Particle of a Given Size

- ≥ 0.15 mm: 99%
- ≥ 0.5 mm: 88%
- ≥ 1 mm: 61%
- ≥ 2 mm: 16%

Percent of Cardiogard Patients with at Least One Particle of a Given Size

- ≥ 0.15 mm: 68%
- ≥ 0.5 mm: 43%
- ≥ 1 mm: 14%
- ≥ 2 mm: 2%

Valve Tissue
Arterial Wall
Myocardium
Calcium Plaque
Thrombus

Automated measurement
Primary Endpoint*

Freedom From Clinical or Radiographic CNS infarction

OR of CNS Infarct:
1.06 (95% CI: 0.60,1.87)
P = 0.84

OR of CNS Infarct:
1.40 (95% CI: 0.81,2.40)
P = 0.22

*OR and P-value based on analysis of imputed data; bar chart based on observed data
FLAIR Scan (Linearly aligned to T1)
DWI Scan (Linearly aligned to T1)
Segmented DWI Lesion
ROI (region of interest) Segmentation
MRI Lesion Volume: Deciles of Observed Infarct Volume Distribution

**CardioGard:**
- Mean (sd): 178.5 (386.4)
- Median (IQR): 42 (0, 151)

**Control:**
- Mean (sd): 476.4 (2229.9)
- Median (IQR): 31 (0, 155)

p=0.28

**Embol-X:**
- Mean (sd): 321.3 (778.3)
- Median (IQR): 74 (0, 322)

**Control:**
- Mean (sd): 484.4 (2169.5)
- Median (IQR): 35 (0, 168)

p=0.49

**CardioGard:**
- Mean (sd): 178.5 (386.4)
- Median (IQR): 42 (0, 151)

**Control:**
- Mean (sd): 476.4 (2229.9)
- Median (IQR): 31 (0, 155)

P=0.18

**Embol-X:**
- Mean (sd): 321.3 (778.3)
- Median (IQR): 74 (0, 322)

**Control:**
- Mean (sd): 484.4 (2169.5)
- Median (IQR): 35 (0, 168)

p=0.49

P=0.59
Clinical Stroke

- Severe (>20)
- Moderate (5-15)
- Mild (0-4)

<table>
<thead>
<tr>
<th></th>
<th>≤7 Days</th>
<th>≤3 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>CardioGard</td>
<td>5.1%</td>
<td>6%</td>
</tr>
<tr>
<td>Control</td>
<td>5.8%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Embol-X</td>
<td>8.3%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Control</td>
<td>6.1%</td>
<td>5%</td>
</tr>
</tbody>
</table>

P-values:
- P=0.61
- P=0.49
- P=0.77
- P=0.99
Delirium at 7 Days

CardioGard vs. Control

P = 0.03

Embol-X vs Control

P = 0.07

% of Patients

Active
Control

CardioGard vs. Control
Embol-X vs Control
Composite Clinical Endpoint at 30 Days

Clinical ischemic stroke
Acute kidney injury
Death

CardioGard vs. Control
Emboli-X vs Control

% of Patients

P=0.61
P=0.08

Active
Control

CardioGard vs. Control
Emboli-X vs Control

CTS
CARDIOVASCULAR SURGICAL TRIALS NETWORK
AEs at 90 Days

Rate per 100-pt mths

- Bleeding
- Neurological Dysfunction
- AKI
- Cardiac Arrhythmias
- All Serious AEs

CardioGard vs Control

- P = 0.55
- P = 0.12
- P = 0.74
- P = 0.35

Embol-X vs Control

- P = 0.75
- P = 0.24
- P = 0.02
- P = 0.08

P < 0.01

All Serious AEs
Neurocognitive Decline at 90 Days

% of Patients w/ Decline

<table>
<thead>
<tr>
<th>Function</th>
<th>CardioGard</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Memory</td>
<td>Red</td>
<td>Blue</td>
<td>0.14</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Red</td>
<td>Blue</td>
<td>0.65</td>
</tr>
<tr>
<td>Overall Cognition</td>
<td>Red</td>
<td>Blue</td>
<td>0.82</td>
</tr>
</tbody>
</table>

% of Patients w/ Decline

<table>
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<th>Control</th>
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</thead>
<tbody>
<tr>
<td>Verbal Memory</td>
<td>Red</td>
<td>Blue</td>
<td>0.40</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Red</td>
<td>Blue</td>
<td>0.05</td>
</tr>
<tr>
<td>Overall Cognition</td>
<td>Red</td>
<td>Blue</td>
<td>0.54</td>
</tr>
</tbody>
</table>

P-values indicate statistical significance.
Limitations

- This trial was first experience with these devices in study sites
- MRI infarcts were diagnosed with both 1.5T and 3T scanners possibly creating heterogeneity
- Trial was underpowered for clinical stroke and other endpoints especially since stopped early
- One third of strokes occurred after day 3 and would not be expected to be impacted by protection devices
- 90 day follow up does not adequately assess long term neurocognitive outcomes
Summary

- In patients undergoing SAVR, the use of 2 different embolic protection devices...
  - Was NOT associated with an improvement in
    - Freedom from clinical or radiographic infarction
    - Clinical stroke
    - Overall volume of CNS infarcts by MRI
    - Neurocognitive outcomes at 90 days
  - Was associated with
    - Capture of embolic debris in most patients
    - A reduction in delirium
    - An observed difference in infarct size distribution with fewer large volume infarcts
    - An increase in AE’s in the Embol-X patients
Conclusions

• We were unable to demonstrate an increase in freedom from CNS infarction with 2 different devices compared with control
• Baseline cognitive impairment exists in 1/4 -1/3 of ”neurologically normal” patients undergoing SAVR
• A majority of patients undergoing SAVR have evidence of radiographic infarct by MRI.
• The association between clinical and radiographic findings in this study and long-term neurocognitive outcomes is the subject of ongoing investigation
Implications

- This is the first large multicenter trial to collect information on brain injury after SAVR
- The relationship between brain injury and long term neurocognitive outcomes will be further explored