Cerebral Protection Devices

Samir Kapadia, MD
Professor of Medicine
Section head, Interventional Cardiology
Director, Cardiac Catheterization Laboratories
Cleveland Clinic
Conflict of Interest

- Co PI for Sentinel Trial
Outline

- Risk of Stroke During TAVR
  - Clinical
  - Silent Brain Infarction
- Timing and mechanism of Stroke
- Options of Neuroprotection
  - Devices
  - Available clinical data
  - On going trials
All Stroke: PARTNER A (ITT)

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>SAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>4.4</td>
<td>2.6</td>
</tr>
<tr>
<td>TF</td>
<td>3.7</td>
<td>1.7</td>
</tr>
<tr>
<td>TA</td>
<td>6.8</td>
<td>4.3</td>
</tr>
<tr>
<td>1 Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>4.6</td>
<td>2.3</td>
</tr>
<tr>
<td>TF</td>
<td>6</td>
<td>3.1</td>
</tr>
<tr>
<td>TA</td>
<td>9.3</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Smith et al, NEJM, June 2011
All Strokes at 30 Days
Edwards SAPIEN Valves

PARTNER I and II Trials

Neurologist evaluations (pre- and post)

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>Pre-Evaluation</th>
<th>Post-Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIB (TF)</td>
<td>6.7%</td>
<td></td>
</tr>
<tr>
<td>PIA (All)</td>
<td>5.6%</td>
<td></td>
</tr>
<tr>
<td>P2B (TF)</td>
<td>4.1%</td>
<td></td>
</tr>
<tr>
<td>P2B (TF)</td>
<td>4.3%</td>
<td></td>
</tr>
<tr>
<td>S3HR (All)</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>S3i (All)</td>
<td>2.6%</td>
<td></td>
</tr>
</tbody>
</table>
Stroke Risk With Second Generation TAVR valves

Meta-analysis of ~20 non-randomized, mostly FIM, valve-company sponsored studies

2.4% major stroke at 30-days

Timing of Neurological Event

Tay et al, J Am Coll Cardiol Intv 2011;4:1290 –7

Miller et al, 2012;143:832-43
Updated PARTNER Analysis

![Graph showing stroke percentage over time after TAVR]

- Patients at Risk
  - TF-TAVR: 1521, 1231, 929, 648, 468, 295, 201
  - TA-TAVR: 1100, 830, 554, 316, 191, 75, 45

Kapadia et al, submitted
Mortality After Stroke and TIA
TF TAVR – PARTNER Trial

Stroke

TIA

Survival (%)

Years after Stroke

Patients at Risk
86
32
15
8

Years after TIA

Patients at Risk
21
11
7
4

Cleveland Clinic
Mortality after Stroke: TAVR Patients

CoreValve High Risk Trial

<table>
<thead>
<tr>
<th>Months Post Procedure</th>
<th>Major Stroke No. at Risk</th>
<th>No Major Stroke No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>329</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>217</td>
</tr>
</tbody>
</table>

Log-rank P<0.0001
Silent brain infarcts seen with DW-MRI 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
DW-MRI imaging shows “silent infarcts” in TAVR

New lesions found in vast majority of diffusion-weighted MR images (DW-MRI) of the brain following TAVI
Do We See Embolic Material?

Fragments of aortic valve leaflet

- 86%
- 74%
- 63%
- 10%
- 0%
- 20%
- 40%
- 60%
- 80%
- 100%

Percent of Patients (%)
Embolic Protection Devices

**TriGuard Embolic Deflection Device (Keystone Heart)**
- Pore Size: 130 µm
- Delivery Sheath: 9F
- Access: Transfemoral
- Coverage: Brachiocephalic, left common carotid, left subclavian

**Sentinel Cerebral Protection System (Claret Medical)**
- Pore Size: 140 µm
- Delivery Sheath: 6F
- Access: Brachial or radial
- Coverage: Brachiocephalic, left common carotid

**Embrella Embolic Deflector System (Edwards Lifesciences)**
- Pore Size: 100 µm
- Delivery Sheath: 6F
- Access: Brachial
- Coverage: Brachiocephalic, left common carotid

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Embolic Protection Devices
Patients under investigation

Embrella
TriGuard
Claret
Claret US Pivotal

Patients Treated with EPD

Feasibility
Single-Arm Observational
Comparative, Randomized

Claret US Pivotal: 356
Claret: 198
TriGuard: 113
Embrella: 60

References:
1Nietlispach, et. al., J Am Coll Cardiol Intv 2010; 3: 1133-8;
3Rodes-Cabau, et al., J Am Coll Cardiol Intv 2014;7:1146-55;
4Naber, et al., EuroIntervention 2012; 8: 43-50;
5Van Mieghem, et al., J Am Coll Cardiol Intv 2015; 8: 718-24;
6Linke, et al., presented at TCT 2014;
7Van Mieghem, et al., presented at TCT 2015;
8Onsea, et al., EuroIntervention 2012;8:51-6;
9Baumbach, et al., EuroIntervention 2015;11:75-84;
10Lansky, et al., Eur Heart J 2015;36:2070-8
# Embolic Protection Devices

## Trial Designs

<table>
<thead>
<tr>
<th>CLEAN-TAVI</th>
<th>MISTRAL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=100</strong></td>
<td><strong>N=65</strong></td>
</tr>
<tr>
<td><strong>Purpose:</strong></td>
<td>Demonstrate reduction in brain lesions at day 2</td>
</tr>
<tr>
<td><strong>Device:</strong></td>
<td>Claret Montage</td>
</tr>
<tr>
<td><strong>Imaging:</strong></td>
<td>3-T MRI</td>
</tr>
<tr>
<td><strong>Follow-up:</strong></td>
<td>Baseline and day 2, 7, 30, 365</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PROTAVI-C</th>
<th>DEFLECT-III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=52</strong></td>
<td><strong>N=85</strong></td>
</tr>
<tr>
<td><strong>Purpose:</strong></td>
<td>Exploratory safety and efficacy</td>
</tr>
<tr>
<td><strong>Device:</strong></td>
<td>Edwards Embrella</td>
</tr>
<tr>
<td><strong>Imaging:</strong></td>
<td>MRI</td>
</tr>
<tr>
<td><strong>Follow-up:</strong></td>
<td>Baseline, day 7, day 30</td>
</tr>
</tbody>
</table>

| **Purpose:** | Demonstrate reduction in brain lesions at day 5 |
| **Device:** | Claret Sentinel |
| **Imaging:** | 3-T MRI, transcranial doppler |
| **Follow-up:** | Baseline and day 5 |

| **Purpose:** | Exploratory, benchmark event rates |
| **Device:** | Keystone TriGuard |
| **Imaging:** | 1.5-T MRI at day 4, no baseline |
| **Follow-up:** | Baseline, day 4, day 30 |
Montage (Claret)
CLEAN-TAVI | Safety 30-days

<table>
<thead>
<tr>
<th>CLEAN-TAVI (N=100)</th>
<th>Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montage (N=50)</td>
<td>Control (N=50)</td>
</tr>
<tr>
<td>Age</td>
<td>80 ± 5</td>
</tr>
<tr>
<td>Male</td>
<td>40%</td>
</tr>
<tr>
<td>STS</td>
<td>5.6 ± 3.3%</td>
</tr>
</tbody>
</table>

All-Cause Mortality: Montage (N=50) 0.0%, Control (N=50) 2.0%
Acute Kidney Injury: Montage (N=50) 2.0%, Control (N=50) 10.0%

Median Total New Lesion Volume (mm3)
P=0.0093

57% Reduction
CLEAN-TAVI: Effective protection

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 testing Claret dual-filter Cerebral Protection System
Sentinel (Claret)  
MISTRAL-C | Safety

### MISTRAL-C (N=65) | Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sentinel (N=32)</th>
<th>Control (N=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>81</td>
<td>82</td>
<td>0.60</td>
</tr>
<tr>
<td>Male</td>
<td>53%</td>
<td>51%</td>
<td>0.90</td>
</tr>
<tr>
<td>STS</td>
<td></td>
<td>4.8%</td>
<td></td>
</tr>
</tbody>
</table>

#### MISTRAL-C (N=65)

- All-Cause Mortality: Sentinel (3.0%) vs. Control (10.0%)
- Major Stroke: Sentinel (0.0%) vs. Control (7.0%)

#### Patients with Worsening Montreal Cognitive Assessment (relative to baseline)

<table>
<thead>
<tr>
<th>Year</th>
<th>Sentinel (N=32)</th>
<th>Control (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.0%</td>
<td>28.0%</td>
</tr>
<tr>
<td>2</td>
<td>4.0%</td>
<td>27.0%</td>
</tr>
</tbody>
</table>

#### Patients with Worsening MMSE (relative to baseline)

<table>
<thead>
<tr>
<th>Year</th>
<th>Sentinel (N=32)</th>
<th>Control (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.0%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>27.0%</td>
<td></td>
</tr>
</tbody>
</table>
# TriGuard (Keystone)
## DEFLECT III | Safety

### DEFLECT III (N=85) | Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TriGuard (N=46)</th>
<th>Control (N=39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>82.7 ± 6.5</td>
<td>82.5 ± 5.9</td>
<td>0.62</td>
</tr>
<tr>
<td>Male</td>
<td>40.9%</td>
<td>50.0%</td>
<td>0.41</td>
</tr>
<tr>
<td>STS</td>
<td>4.7%</td>
<td>7.4%</td>
<td>0.48</td>
</tr>
</tbody>
</table>

### DEFLECT III N=85

- **All-Cause Mortality**
  - TriGuard (N=42): 2.2%
  - Unprotected (N=32): 4.3%

- **Stroke**
  - TriGuard (N=42): 4.3%
  - Unprotected (N=32): 5.6%

- **Life-Threatening Bleeding**
  - TriGuard (N=42): 4.5%
  - Unprotected (N=32): 7.8%

- **AKI (2/3)**
  - TriGuard (N=42): 2.2%
  - Unprotected (N=32): 0.0%

- **Major Vascular Complications**
  - TriGuard (N=42): 17.4%
  - Unprotected (N=32): 20.7%

- **Volume (mm³)**
  - TriGuard (N=42): 34.8 mm³
  - Unprotected (N=32): 19.6 mm³

- **Patients with Worsening NIHSS (relative to baseline)**
  - TriGuard (N=42): 0.0%
  - Unprotected (N=32): 15.4%

- **Patients with Worsening Montreal Cognitive Assessment (relative to baseline)**
  - TriGuard (N=42): 25.0%
  - Unprotected (N=32): 37.1%
Embrella (Edwards) PROTAVI | Safety

### PROTAVI (N=52) | Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Embrella (N=41)</th>
<th>Control (N=11)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>83</td>
<td>84</td>
<td>0.72</td>
</tr>
<tr>
<td>Male</td>
<td>46.3%</td>
<td>72.7%</td>
<td>0.18</td>
</tr>
<tr>
<td>STS</td>
<td>5.4%</td>
<td>6.6%</td>
<td>0.93</td>
</tr>
</tbody>
</table>

### PROTAVI-C N=52

- All-Cause Mortality: Embrella (7.3%), Control (4.9%), P=0.003
- Stroke: Embrella (0.0%), Control (0.0%)
- Life-Threatening Bleeding: Embrella (7.3%), Control (7.3%)
- Renal Insufficiency: Embrella (0.0%), Control (0.0%)
- Major Vascular Complications: Embrella (12.2%), Control (9.1%)

\[^{1}\text{Rodes-Cabau, et al., J Am Coll Cardiol Intv 2014;7:1146-55}\]
## Embolic Protection Devices: Summary

<table>
<thead>
<tr>
<th>CLEAN-TAVI</th>
<th>MISTRAL-C</th>
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</thead>
<tbody>
<tr>
<td><strong>N=100</strong></td>
<td><strong>N=65</strong></td>
</tr>
</tbody>
</table>

### Purpose:
- **CLEAN-TAVI**
  - Demonstrate reduction in brain lesions at day 2
- **MISTRAL-C**
  - Demonstrate reduction in brain lesions at day 5

### Achieved:
- **CLEAN-TAVI**
  - Statistically better outcomes with EPD
  - Stage set for US IDE Trial (SENTINEL)
- **MISTRAL-C**
  - Better outcomes with EPD on Mini-Mental State Exam (MMSE), lost MRI statistical power with patients lost to MRI follow-up

<table>
<thead>
<tr>
<th>PROTAVI</th>
<th>DEFLECT-III</th>
</tr>
</thead>
<tbody>
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<td><strong>N=52</strong></td>
<td><strong>N=85</strong></td>
</tr>
</tbody>
</table>

### Purpose:
- **PROTAVI**
  - Exploratory safety and efficacy
- **DEFLECT-III**
  - Exploratory, benchmark event rates

### Achieved:
- **PROTAVI**
  - Better MRI outcomes with EPD
- **DEFLECT-III**
  - Better outcomes with EPD
  - Stage set for US IDE Trial (REFLECT)
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 SapienTHV/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

**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 Endpoints

• Efficacy
  – Reduction in median total new lesion volume in protected territories between the Imaging Arms (Test and Control Group) as assessed by DW-MRI at Day 4-7 post-procedure.

• Safety
  – Occurrence of all Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 days compared to a historical performance goal.
Male, 85 year old

**BMI:**
- **Ht:** 170.2 cm
- **Wt:** 71.305 kg

**ALL:** NKDA

**PMHx:**
- CAD/MI, CABG 2006 (L-LAD, V-Dg, PL, PDA)
- Colon cancer s/p hemicolecetomy

**Meds:**
- Kcl, captopril, heparin SC, Aspirin, Atorva

**Echo 1/22**
- EF 20-25%
- AS: 89/52, 0.38, 0.12, SVI 22.8

**CT - 1/26**
- CSA 480mm2
- Perimeter: 79mm
- Diam: 30x21mm

**Access:** TF XT  Size: #26
- Angles: L/Cra 20/23, R/Cau 20/20

**Coronary distance:** LM 14, RCA 15

**Angiogram (12/15/14)**
- LM: 90-95%
- LAD: 90%
- LCx: 80%
- RCA: 60-70 rPDA
- Patent L-LAD, V-DG, V-PL, V-rPDA

**Labs (02/02/15)**
- BUN/Cr: 31/1.25
- Hgb/Hct: 13/38
- Plt: 103
- INR: --

**Coronary distance (CT-1/26):**
- LM: 14
- RCA: 15
- CSA: 480mm2
- Perimeter: 79mm
- Diam: 30x21mm

**Meds:**
- Kcl, captopril, heparin SC, Aspirin, Atorva
6F Right Radial Arterial Access
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Event rate</th>
<th>Approach</th>
<th>Clinical predictors</th>
<th>Anatomical predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay et al 2011</td>
<td>253</td>
<td>9%</td>
<td>TA/TF</td>
<td>H/O stroke/TIA</td>
<td>Carotid stenosis*</td>
</tr>
<tr>
<td>Nuis et al 2012</td>
<td>214</td>
<td>9%</td>
<td>TF</td>
<td>New onset AF</td>
<td>Baseline AR &gt;3+</td>
</tr>
<tr>
<td>Amat Santos et al 2012</td>
<td>138</td>
<td>6.5%</td>
<td>TA/TF</td>
<td>New onset AF</td>
<td>None</td>
</tr>
<tr>
<td>Franco et al 2012</td>
<td>211</td>
<td>4.7%</td>
<td>TA/TF</td>
<td>None</td>
<td>Post-dilation</td>
</tr>
<tr>
<td>Miller et al 2012</td>
<td>344</td>
<td>9%</td>
<td>TA/TF</td>
<td>History of stroke</td>
<td>Smaller AVA</td>
</tr>
<tr>
<td>Non TF-TAVR candidate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabau et al 2011</td>
<td>60</td>
<td>68% (MRI)</td>
<td>TA/TF</td>
<td>Male, History of CAD</td>
<td>Higher AVG</td>
</tr>
<tr>
<td>Fairbairn et al 2012</td>
<td>31</td>
<td>77% (MRI)</td>
<td>TF</td>
<td>Age</td>
<td>Aortic atheroma</td>
</tr>
<tr>
<td>Nombela-Franco et al 2012</td>
<td>1061</td>
<td>5.1%</td>
<td>TA/TF</td>
<td>Balloon postdilatation, valve dislodgement, New onset AF, PVD, Prior CVA</td>
<td></td>
</tr>
</tbody>
</table>
Should We Use EPD in All Patients?

- Is the stroke risk high?
  - Subgroups?
- Do EPDs work?
  - Which device?
- Are EPDs safe?
  - Which device?
- Can we afford them?
  - Who are “we” (patient, physicians, hospitals, insurers)

- Higher than consumer expectation
- Preliminary data +ve; Trials ongoing
- Initial data convincing
- Depends how rich we feel we are
Conclusion

• Stroke after TAVR is an important problem.
• Stroke rate after TAVR may not be worse than stroke after SAVR but it is associated with mortality and morbidity.
• Risk of stroke is predominantly procedural.
• If TAVR stroke risk can be reduced further, it can be a differentiated feature from SAVR.
• Progress is rapid in the field of procedural neuroprotection.