Is Cerebral Embolic Protection Needed for TAVR?

The Evidence: Observations From DEFLECT 3, CLEAN-TAVI, and the SENTINEL Clinical Trials

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Section head, Interventional Cardiology
Director, Cardiac Catheterization Laboratories
Cleveland Clinic
Disclosure

• Co PI for Sentinel Trial
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

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>TF-TAVR</th>
<th>TA-TAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>1521</td>
<td>1100</td>
</tr>
<tr>
<td>0.5</td>
<td>1231</td>
<td>830</td>
</tr>
<tr>
<td>1.0</td>
<td>929</td>
<td>554</td>
</tr>
<tr>
<td>1.5</td>
<td>648</td>
<td>316</td>
</tr>
<tr>
<td>2.0</td>
<td>468</td>
<td>191</td>
</tr>
<tr>
<td>2.5</td>
<td>295</td>
<td>75</td>
</tr>
<tr>
<td>3.0</td>
<td>201</td>
<td>45</td>
</tr>
</tbody>
</table>

Kapadia et al, Circ Int 2016
Mortality After Stroke and TIA
TF TAVR – PARTNER Trial

Kapadia et al, Circ Int 2016
Mortality after Stroke: TAVR Patients CoreValve High Risk Trial

Log-rank $P<0.0001$

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Months Post Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Stroke</td>
<td>15 10 5 2</td>
</tr>
<tr>
<td>No Major Stroke</td>
<td>376 368 329 217</td>
</tr>
</tbody>
</table>

All-Cause Mortality, %

- Major Stroke
- No Major Stroke
Silent Infarction in TAVR

- Meta-analysis of 26 prospective studies reporting DW-MRI outcomes after unprotected TAVI
- Pooled analysis shows silent cerebral injury occurs in 77.5% patients

Do We See Embolic Material?

- Fragments of aortic valve leaflet

<table>
<thead>
<tr>
<th>Percent of Patients (%)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>86%</td>
<td>74%</td>
<td>63%</td>
<td>10%</td>
</tr>
</tbody>
</table>

1 Van Mieghem, et al., J Am Coll Cardiol Intv 2015; 8: 718-24
Embolic Protection Devices

TriGuard Embolic Deflection Device (Keystone Heart)\(^1\)
- Pore Size: 130 µm
- Delivery Sheath: 9F
- Access: Transfemoral
- Coverage: Brachiocephalic, left common carotid, left subclavian

Sentinel Cerebral Protection System (Claret Medical)\(^2\)
- Pore Size: 140 µm
- Delivery Sheath: 6F
- Access: Brachial or radial
- Coverage: Brachiocephalic, left common carotid

Embrella Embolic Deflector System (Edwards Lifesciences)\(^3\)
- Pore Size: 100 µm
- Delivery Sheath: 6F
- Access: Brachial
- Coverage: Brachiocephalic, left common carotid

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\(^1\) Lansky, et. al., presented at TCT 2015; \(^2\) Van Mieghem, et al., presented at TCT 2015; \(^3\) Rodes-Cabau, et al., J Am Coll Cardiol Intv 2014;7:1146-55
Embolic Protection Devices
Patients under investigation

- Claret US Pivotal: 363
- Claret: 198
- TriGuard: 113
- Embrella: 60

Feasibility
Single-Arm Observational
Comparative, Randomized

### Embolic Protection Devices Trial Designs

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

<table>
<thead>
<tr>
<th>Purpose:</th>
<th>Demonstrate reduction in brain lesions at day 2</th>
<th>Demonstrate reduction in brain lesions at day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device:</td>
<td>Claret Montage</td>
<td>Claret Sentinel</td>
</tr>
<tr>
<td>Imaging:</td>
<td>3-T MRI</td>
<td>3-T MRI, transcranial doppler</td>
</tr>
<tr>
<td>Follow-up:</td>
<td>Baseline and day 2, 7, 30, 365</td>
<td>Baseline and day 5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Purpose:</th>
<th>Exploratory safety and efficacy</th>
<th>Exploratory, benchmark event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device:</td>
<td>Edwards Embrella</td>
<td>Keystone TriGuard</td>
</tr>
<tr>
<td>Imaging:</td>
<td>MRI</td>
<td>1.5-T MRI at day 4, no baseline</td>
</tr>
<tr>
<td>Follow-up:</td>
<td>Baseline, day 7, day 30</td>
<td>Baseline, day 4, day 30</td>
</tr>
</tbody>
</table>
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>

CLEAN-TAVI shows Claret filters significantly reduce lesion number and volume

- **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%

Number of New Lesions

- **Claret CPS**
  - Median number of new lesions: 1

- **Control**
  - Median number of new lesions: 10

**p = .001** 60% Reduction

New Lesion Volume

- **Claret CPS**
  - Median lesion volume: 242

- **Control**
  - Median lesion volume: 527

**p = .001** 54% Reduction

Claret Montage Cerebral Protection System significantly reduces new cerebral lesion number and volume at 2 days in potentially protected areas, as measured by DW-MRI

CLEAN-TAVI: Effective protection

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 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>
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</table>

MISTRAL-C N=65

Patients with Worsening Montreal Cognitive Assessment (relative to baseline)

Patients with Worsening MMSE (relative to baseline)
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**: 2.2% (TriGuard) vs 5.1% (Control), 0.07
- **Stroke**: 4.3% (TriGuard) vs 5.6% (Control), 0.56
- **Life-Threatening Bleeding**: 4.5% (TriGuard) vs 7.8% (Control), 0.15
- **AKI (2/3)**: 2.2% (TriGuard) vs 0.0% (Control), 0.53
- **Major Vascular Complications**: 17.4% (TriGuard) vs 20.7% (Control), 0.46

**Volume (mm³)**

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

**Patients with Worsening NIHSS** (relative to baseline)
- 15.4% (TriGuard) vs 25.0% (Unprotected), 0.16

**Patients with Worsening Montreal Cognitive Assessment** (relative to baseline)
- 37.1% (TriGuard) vs 26.3% (Unprotected), 0.21
Embrella (Edwards)
PROTAVI | Safety

<table>
<thead>
<tr>
<th>PROTAVI (N=52)</th>
<th>Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Embrella (N=41)</td>
</tr>
<tr>
<td>Age</td>
<td>83</td>
</tr>
<tr>
<td>Male</td>
<td>46.3%</td>
</tr>
<tr>
<td>STS</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

PROTAVI-C
N=52

- **All-Cause Mortality**: Embrella (N=41) = 7.3%, Unprotected (N=11) = 4.9%
- **Stroke**: Embrella (N=41) = 0.0%, Unprotected (N=11) = 0.0%
- **Life-Threatening Bleeding**: Embrella (N=41) = 7.3%, Unprotected (N=11) = 0.0%
- **Renal Insufficiency**: Embrella (N=41) = 7.3%, Unprotected (N=11) = 0.0%
- **Major Vascular Complications**: Embrella (N=41) = 12.2%, Unprotected (N=11) = 9.1%

All-Cause Mortality: \( \cdot p=0.003 \)

\(^1\) Rodes-Cabau, et al., *J Am Coll Cardiol Intv* 2014;7:1146-55
### Embolic Protection Devices: Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>Achieved</th>
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<tbody>
<tr>
<td><strong>CLEAN-TAVI</strong></td>
<td>Demonstrate reduction in brain lesions at day 2</td>
<td>• Statistically better outcomes with EPD</td>
</tr>
<tr>
<td>N=100</td>
<td></td>
<td>• Stage set for US IDE Trial (SENTINEL)</td>
</tr>
<tr>
<td><strong>PROTAVI</strong></td>
<td>Exploratory safety and efficacy</td>
<td>• Better MRI outcomes with EPD</td>
</tr>
<tr>
<td>N=52</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MISTRAL-C</strong></td>
<td>Demonstrate reduction in brain lesions at day 5</td>
<td>• Better outcomes with EPD on Mini-Mental State Exam (MMSE), lost MRI statistical power with patients lost to MRI follow-up</td>
</tr>
<tr>
<td>N=65</td>
<td></td>
<td></td>
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<tr>
<td><strong>DEFLECT-III</strong></td>
<td>Exploratory, benchmark event rates</td>
<td>• Better outcomes with EPD</td>
</tr>
<tr>
<td>N=85</td>
<td></td>
<td>• Stage set for US IDE Trial (REFLECT)</td>
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## Meta Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Study Population</th>
<th>Approach</th>
<th>Device</th>
<th>EPD type</th>
<th>Timing of DW-MRI (days)</th>
<th>Age (y) EPD</th>
<th>Age (y) No EPD</th>
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<tbody>
<tr>
<td>Wendt et al. 2015</td>
<td>RCT</td>
<td>N=384 (n=198)</td>
<td>30</td>
<td>SAPIEN XT</td>
<td>EMBOL-X</td>
<td>6.5 ± 2.6†</td>
<td>81.0 ± 5.0</td>
<td>82.1 ± 4.1</td>
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<tr>
<td></td>
<td></td>
<td>EPD (n=186)</td>
<td>14</td>
<td>SAPIEN/XT/3, 26 CoreValve, 3 others</td>
<td>TriGuard HDH</td>
<td>4.0 ± 2.0</td>
<td>82.5 ± 6.5</td>
<td>82.3 ± 6.0</td>
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<td>Lansky et al. 2015</td>
<td>RCT</td>
<td>N=384 (n=198)</td>
<td>85</td>
<td>SAPIEN XT</td>
<td>EMBOL-X</td>
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<tr>
<td>Linke et al. 2014**</td>
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<td>100</td>
<td>SAPIEN XT</td>
<td>EMBOL-X</td>
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<td></td>
<td></td>
<td>EPD (n=186)</td>
<td>50</td>
<td>SAPIEN/XT/3, 26 CoreValve, 3 others</td>
<td>TriGuard HDH</td>
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<td>82.5 ± 6.5</td>
<td>82.3 ± 6.0</td>
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<tr>
<td>Van Mieghem et al. 2015**</td>
<td>RCT</td>
<td>N=384 (n=198)</td>
<td>65</td>
<td>SAPIEN XT</td>
<td>EMBOL-X</td>
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<td>82.5 ± 6.5</td>
<td>82.3 ± 6.0</td>
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<tr>
<td>Rodés-Cabau et al. 2014</td>
<td>Prospective</td>
<td>N=384 (n=198)</td>
<td>52</td>
<td>SAPIEN XT</td>
<td>EMBOL-X</td>
<td>6.5 ± 2.6†</td>
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<td>82.3 ± 6.0</td>
</tr>
<tr>
<td>Samim et al. 2015</td>
<td>Consecutive patients</td>
<td>N=384 (n=198)</td>
<td>52</td>
<td>SAPIEN XT</td>
<td>EMBOL-X</td>
<td>6.5 ± 2.6†</td>
<td>81.0 ± 5.0</td>
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<td>4.0 ± 2.0</td>
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<td>82.3 ± 6.0</td>
</tr>
</tbody>
</table>

### Primary endpoints
- Number of new lesions per patient
- Total lesion volume

### Secondary endpoints
- Number of patients with new lesions
- Single lesion volume
Meta-Analysis

Giustino et al, J Am Coll Cardiol Intv 2016;9:2124–33
Patients with Severe Symptomatic Aortic Stenosis Undergoing TAVR

Patients Randomized (1:1:1) n=363

Safety Cohort

SAFETY ARM TAVR with Sentinel (n=123)

TEST ARM TAVR with Sentinel (n=121)

CONTROL ARM TAVR Only (n=119)

Imaging Cohort

Clinical Follow-Up

Serial MRIs (Baseline, Day 2-7 & Day 30)

Serial Neurocognitive Workup (Baseline, Day 30 & Day 90)

Histopathology & Morphometry

Tomorrow @ 9:00 AM
Susheel Kodali
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

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 hemicolecctomy

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: 30 x 21 mm

CSA 482 cm²
Perimeter: 81.5 mm
Diam: 31 x 22 mm

Access: TF XT Size: #26
Angles: L/Cra 20/23, R/Cau 20/20
Coronary distance: LM 14, RCA 15

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

Angiogram (12/15/14)
LM: 90-95%
LAD: 90%
LCx: 80%
RCA: 60-70 rPDA
Patent L-LAD, V-DG, V-PL, V-rPDA
6F Right Radial Arterial Access
## Predictors of Stroke, Neuro events or MRI findings

<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 Non TF-TAVR candidate</td>
<td>Smaller AVA</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 TAVR?

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

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

• Stroke after TAVR is an important problem.
• Stroke rate after TAVR is not worse than stroke after SAVR but it is associated with increased 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.
• Sentinel Data will be presented tomorrow in LBCT session (9:00 AM, Susheel Kodali).