Cerebral Protection during Percutaneous Structural Cardiac Interventions

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United Kingdom

Heart and Brain Workshop, Prague 2018
ESC Council on Valvular Heart Disease
Incidence of New Brain Lesions


Stroke is a rare but devastating complication of TAVI. 50% of events occur periprocedurally. Clinically ‘silent’ or non-detected strokes are frequent. New embolic lesions in the brain can be detected in up to 100% of patients following a TAVI procedure. Embolic events have been linked to neurocognitive decline.
Neurocognitive Decline and New Lesions

- Pre-existing and new lesions on DW-MRI after catheterization is related to cognitive decline.
- Patients with new ischemic lesions post CABG (20%) had a larger neurocognitive decline than the patients with stable.
- The link between new lesions on DW MRI in TAVI cohort yet to be established.

Lund et al, 2005  Restrepo et al Stroke 2002
TAVI is moving to Lower Risk Patient Groups

- Bicuspid Valves
- Lower Age
- Moderate AS
- Asymptomatic AS
- AS with Impaired LV
Moving to Low Risk Patients

LOW RISK & LEAFLET SUB-STUDY

- **Patient Population: Low Risk Cohort**
  - Determined by Heart Team to be low surgical risk

- **Primary Endpoint:**
  - Safety: Death, all stroke, life-threatening bleeding, major vascular complications, or AKI at 30 days
  - Efficacy: Death or major stroke at 2 years

- **Sample Size:** \(~1200\) Subjects

- **Follow-up Evaluations:**
  - 30-days, 6-month, and 1 Through 5 years

- **Number of Sites:** Up to 80 sites
Asymptomatic, Severe Aortic Stenosis

Screening / Stress Test
Inclusion/exclusion criteria, treadmill stress test

Asymptomatic
Negative stress test OR medical history

1:1 Randomization

Transfemoral TAVR

Primary Endpoint
2 year composite of all-cause mortality, all stroke, and unplanned cardiovascular hospitalization

Symptomatic
Positive stress test

Registry
Commercial AVR (TAVR or SAVR), Clinical Trial (e.g. PARTNER 3 Trial), etc.

Principal Investigator:
Philippe Généreux, MD,
Chair: Martin B. Leon, MD

NCT03042104
Asymptomatic Severe AS and 2D-TTE (PV $\geq 4$ m/s or AVA $\leq 1$ cm$^2$) Exclusion if patient is symptomatic, EF$<50\%$, concomitant surgical indications, bicuspid valve, or STS $>8$.

Treadmill Stress-Test

Stress-Test Normal
- CTA and Angiography
- TF- TAVR eligibility
- Early-TAVR Randomized Trial

Stress-Test Abnormal
- Early TAVR Registry

Randomization 1:1 Stratified by STS ($<3$ vs $\geq 3$)
- TF- TAVR
- Clinical Surveillance

Primary Endpoint (superiority): 2-year composite of all-cause mortality, all strokes, and repeat hospitalizations (CV)
TAVR UNLOAD Trial

Study Design
(600 patients, 1:1 Randomized)

TAVR UNLOAD Trial

Heart Failure
LVEF < 50%
NYHA ≥ 2
Optimal HF therapy (OHFT)
Moderate AS

Follow-up:
1 month
6 months
1 year
Clinical endpoints
Symptoms
Echo
QoL

Primary Endpoint
Hierarchical occurrence of:
- All-cause death
- Disabling stroke
- Hospitalizations for HF, aortic valve disease
- Change in KCCQ

TAVR + OHFT

OHFT Alone

Reduced AFTERLOAD
Improved LV systolic and diastolic function
Patient Perceptions and Expectations

- Staying alive: 7%
- Ability to do a specific activity: 48%
- Maintaining independence: 30%
- Reducing symptoms: 15%
CLINICAL QUESTIONS

1. Is (embolic) stroke during TAVI/R a relevant clinical problem?
2. Is there clinical/functional correlation of ‘silent’ microembolic events?
3. Can we improve outcomes with embolic protection devices?
Mechanisms of peri-procedural stroke

*Embolic*
- Wire and catheter manipulation
- BAV
- Device positioning in the root
- Valve deployment
- Post-dilatation

*Haemorrhagic*
- Bolus dose heparin
- Severe hypertension

*Global Ischaemia*
- Severe hypotension
- Rapid pacing
MRI imaging is "truly frightening" post TAVI...

- 68-100% of TAVI patients affected\textsuperscript{1-10}
- Most patients have multiple infarcts
- "Silent" infarcts associated with\textsuperscript{11-13}
  - 2-4-fold risk of future stroke
  - >3-fold risk of mortality
  - >2-fold risk of dementia
  - Cognitive decline
  - Dementia
Insight from Pivotal studies

Acute Manifestations: PARTNER A and B (30-Day Events)

PARTNER 2A
Disabling Stroke (ITT)

HR [95% CI] = 0.93 [0.65, 1.33]
P (log rank) = 0.702

Number at risk:

- TAVR: 1011, 918, 901, 870, 842, 825, 811, 801, 774
- Surgery: 1021, 838, 812, 783, 770, 747, 735, 717, 695

Disabling Stroke (%) vs Months from Procedure

- Surgery: 4.3%, 5.0%, 5.8%, 5.0%, 5.0%, 5.0%, 5.0%, 5.0%, 5.0%
- TAVR: 3.2%, 5.0%, 5.0%, 5.0%, 5.0%, 5.0%, 5.0%, 5.0%, 5.0%

Months from Procedure:
0, 3, 6, 9, 12, 15, 18, 21, 24
Major Stroke

CoreValve US Pivotal Trial

Surgical

Transcatheter

Major Stroke (%) vs Months Post-Procedure

No. at Risk

Surgical: 357, 333, 289, 263
Transcatheter: 390, 367, 344, 322
Major Stroke Rates: Better with TAVR but Consistent over time

TVT 30 day Stroke rates

% 30 Day Stroke

<table>
<thead>
<tr>
<th>Year</th>
<th>TAVR</th>
<th>SAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>2.4</td>
<td>5.6</td>
</tr>
<tr>
<td>2013</td>
<td>2.6</td>
<td>5.5</td>
</tr>
<tr>
<td>2014</td>
<td>2.6</td>
<td>6.1</td>
</tr>
<tr>
<td>2015</td>
<td>2.6</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Stroke is lower with TAVR than SAVR
National registry-FRANCE 2

• N 3191 pts undergoing TAVI
• 3.98% reported CVE
  – 55% major strokes
  – 14.5% minor strokes
  – 30.5 % TIA
• Predictors: advanced age, multiple valves

Tchetche et al. J Am Coll Cardiol Intv 2014;7: epub
### ALL Stroke Frequency with Contemporary TAVR Devices

Weighted average (n=4,795 pts) = ~3.5%

<table>
<thead>
<tr>
<th>Device/Study</th>
<th>30-Day All Stroke Frequency</th>
</tr>
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<tbody>
<tr>
<td>Evolut R</td>
<td>0.0%</td>
</tr>
<tr>
<td>Evolut R</td>
<td>3.0%</td>
</tr>
<tr>
<td>Evolut R</td>
<td>4.0%</td>
</tr>
<tr>
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<td>4.0%</td>
</tr>
<tr>
<td>Evolut R</td>
<td>5.5%</td>
</tr>
<tr>
<td>SAVI Registry</td>
<td>1.9%</td>
</tr>
<tr>
<td>CE Study</td>
<td>2.7%</td>
</tr>
<tr>
<td>FORWARD Interim Analysis</td>
<td>1.4%</td>
</tr>
<tr>
<td>US IFU</td>
<td>4.0%</td>
</tr>
<tr>
<td>CE Study</td>
<td>4.0%</td>
</tr>
<tr>
<td>CE Study</td>
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<td>S3 CE IR</td>
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<td>3.0%</td>
</tr>
<tr>
<td>S3 CE IR</td>
<td>6.8%</td>
</tr>
<tr>
<td>REPRISE II</td>
<td>7.0%</td>
</tr>
<tr>
<td>RE:SPOND</td>
<td>9.1%</td>
</tr>
<tr>
<td>DISCOVER</td>
<td>9.1%</td>
</tr>
<tr>
<td>Control Arm</td>
<td>9.1%</td>
</tr>
</tbody>
</table>

**Notes:**
- CE Study N=60
- FORWARD Interim Analysis N=300
- US IFU N=151
- SAVI Registry N=994
- CE Study N=222
- P2 S3 IR N=1,078
- P2 S3 HR/ER N=583
- S3 CE IR N=101
- S3 CE N=150
- REPRISE II N=250
- RE:SPOND N=1,014
- DISCOVER N=75
- Control Arm N=119

**ALL Stroke Frequency with Contemporary TAVR Devices**

- **Weighted average (n=4,795 pts) = ~3.5%**

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**Source:**
- CE Study
- FORWARD Interim Analysis
- US IFU
- SAVI Registry
- CE Study
- P2 S3 IR
- P2 S3 HR/ER
- S3 CE IR
- S3 CE
- REPRISE II
- RE:SPOND
- DISCOVER
- Control Arm

**Additional Notes:**
- All data represents weighted averages across various studies and registries.
- The data includes both pivotal and post-market studies.
- The weighted average is calculated based on the number of patients in each study or registry.
Timing of Strokes after TAVI

Insights Into Timing, Risk Factors, and Outcomes of Stroke and Transient Ischemic Attack After Transcatheter Aortic Valve Replacement in the PARTNER Trial (Placement of Aortic Transcatheter Valve) Study.

- 2621 patients from PARTNER (high and extreme risk);
- CEC adjudication
- Acute-phase (peri-procedural) stroke risk peaked at 2 days, with a low constant risk of 0.8% per year.

FRANCE 2: Timing of Stroke

50% periprocedural
Majority of major strokes on day 1

Time From Date of Valve Placement (in Calendar Days) | No. | Mean | SD | Median | Range
---|---|---|---|---|---
Overall | 131 | 22.9 | 59.5 | 2 | 0-422
Major stroke | 72 | 21.3 | 52.8 | 1 | 0-249
Minor stroke | 19 | 28.2 | 96.3 | 2 | 0-422
Transient ischemic attack | 40 | 23.1 | 48.8 | 2 | 0-188

Tchetche et al. J Am Coll Cardiol Intv 2014;7: epub
2nd generation devices and in intermediate risk patients—Stroke Remains Issue

Major Stroke Rates in Randomized TAVR Trials

1st Generation Devices

Current Generation Devices


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**Weighted average (n=8,987)**

- 1st Generation Devices:
  - SAPIEN: 6.7%
  - SAPIEN XT: 4.1%
  - CoreValve: 4.6%

- Current Generation Devices:
  - CoreValve: 5.5%
  - Evolut R: 4.0%

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**Weighted average (n=5,952)**

- Current Generation Devices:
  - SAPIEN 3: 3.4%
  - Lotus: 6.3%
  - Direct Flow: 4.7%
  - Control Arm: 8.9%

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Stroke Rates with Second Generation TAVR Valves


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

2.4% major stroke at 30-days

Stroke risk seem to be independent of operator experience

>53,000 TAVI patients from >350 US centres

No decline in rates with increasing experience

‘Self-reported’ rates almost certainly an underestimate
TVT Registry - TAVR in the U.S.

Relationship Between Procedure Volume and Outcome for Transcatheter Aortic Valve Replacement in U.S. Clinical Practice

Risk-Adjusted:
P for association = 0.1399
Major Stroke Increases Mortality 3-9 Fold

Kapadia et al, Circ Int 2016

Partner Trials

CoreValve High Risk Trial

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>15</th>
<th>10</th>
<th>5</th>
<th>2</th>
</tr>
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<tbody>
<tr>
<td>Major Stroke</td>
<td>15</td>
<td>10</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>No Major Stroke</td>
<td>37</td>
<td>368</td>
<td>329</td>
<td>217</td>
</tr>
</tbody>
</table>
The Dilemma: What is Cerebral Injury?

Patient level pooled analysis from the TriGuard Trials (N=142)

- VARC 2: Disabling stroke
- VARC 2: Stroke
- ASA/AHA: Stroke
- MOCA
- NIHSS or MoCA
- CNS Infarction DWI

Disability: 0%
Major stroke: 6%
Mild stroke: 19%
Cognitive decline: 35%
Covert Stroke: 39%

Lansky A, EuroPCR 2016
Classification, Application, and Assessment of Neurological Events

Lansky AJ et al. JACC 2017
Can we improve outcomes with embolic protection devices?

<table>
<thead>
<tr>
<th>Company and Product</th>
<th>Claret Medical Sentinel</th>
<th>Keystone TriGuard</th>
<th>Edwards Embrella</th>
<th>ICS Emblok</th>
<th>Transverse Point-Guard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EU Status</strong></td>
<td>CE Mark 97% market share</td>
<td>CE Mark 3% market share</td>
<td>CE Mark &lt;3% market share</td>
<td>FIM first clinical case March 15, 2017</td>
<td>Pre-clinical/prototype</td>
</tr>
<tr>
<td><strong>US Status</strong></td>
<td>IDE study completed Positive FDA Panel Feb 23, 2017</td>
<td>IDE trial underway</td>
<td>No IDE yet</td>
<td>No IDE yet</td>
<td>No IDE yet</td>
</tr>
<tr>
<td><strong>Access</strong></td>
<td>6 Fr Right Radial</td>
<td>9Fr TF</td>
<td>Right Radial</td>
<td>12Fr TF sheath</td>
<td>TF</td>
</tr>
<tr>
<td><strong>Debris</strong></td>
<td>Captures and removes</td>
<td>Deflects downstream</td>
<td>Deflects downstream</td>
<td>Captures and removes</td>
<td>Deflects downstream</td>
</tr>
<tr>
<td><strong>Placement and Interaction with TAVR devices</strong></td>
<td>Not in aortic arch</td>
<td>Sits in aortic arch. Devices must pass over and back across</td>
<td>Sits in aortic arch. Devices must pass over and back across</td>
<td>Sits in ascending aorta Devices must pass over and back across</td>
<td>Sits in aortic arch. Devices must pass over and back across</td>
</tr>
</tbody>
</table>
Current Devices

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

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

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

Transverse Medical POINTGUARD CEP Device

Maximum Filter Coverage

Balanced Filtration and Deflection

© Transverse Medical Inc.
Keystone Heart NEW TriGUARD 3 CEP Device

- Device Mesh
- Device Frame
- Device tail
- Curved nitinol tube (Shaft)
- Atraumatic Tip
- Connector
- 8Fr Crimper
CLARET

- Two independent filters capture & remove embolic material
- Polyurethane filter, pore size = 140 μm
- Standard R trans-radial sheath access (6F)
- One size accommodates most vessel sizes (brachiocephalic 9-15 mm and left common carotid [LCC] 6.5-10 mm)
- Deflectable compound-curve catheter facilitates cannulation of LCC
- Minimal profile in aortic arch (little interaction with other devices)
Claret data

It does seem effective in capturing debris..

MISTRAL-C trial of 65 patients randomised to Claret vs no protection

Debris found in all deployed devices

But only a modest effect on number and size of MRI lesions (with ~65% MRI follow up...

Some suggestion that neurocognitive decline ameliorated

Van Mieghem et al Eurointervention 2016;12:499-507
CLEAN-TAVI

100 patient, single-centre RCT

Randomised to Claret vs no Claret

Reduction in new MRI lesion volume and number

no data on neurocognitive improvement

Haussig et al JAMA 2016;316:592-601
Ulm Sentinel Study: Procedural Protection = Procedural Benefit

- 802 single center all-comer consecutive TAVR patients
- A propensity-matched analysis of 280 patients with Sentinel to 280 control patients

Predictor of Stroke at 7 days:
- No cerebral emboli protection (p=0.044)

Predictor of Stroke and Death at 7 deaths:
- No cerebral emboli protection (p=0.028)
- STS score (<8 vs. >8) (p=0.021)
TriGuard HDH Pooled Analysis

Primary Safety Endpoint of 30 day MACCE: 18.2% TG vs 24.1% Control, p=0.44

Lansky et al PCR 2016
Claret Randomised data
No difference in clinical stroke rates..

Despite a reduction in MRI lesion volume study failed to reach its primary end-point...

Favourable safety profile- ie no evidence of harm..

No difference in clinical stroke rates..

Kodali TCT 2016
SENTINEL US IDE Trial (N=363)
Primary Efficacy Endpoint (Superiority)

Median TLV in protected territories assessed by DW-MRI at Day 2-7 post-procedure

New Lesion Volumes in Protected Territories (mm$^3$)

- **Treatment (N=91):** Median 102.8
- **Control (N=98):** Median 178

**42.2% reduction** (95% CI: -3.2, 67.6)

$p = 0.33$

**HISTOPATHOLOGY**

Debris Capture by Type
Lessons Learned: Timing of Ascertainment Sentinel Trial

30 Day Stroke Diagnosis (Analyzed ITT)

<table>
<thead>
<tr>
<th></th>
<th>Device Arm (n=234)</th>
<th>Control Arm (n=111)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30-day Clinical Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any MACCE†</td>
<td>7.3%</td>
<td>9.9%</td>
<td>0.40</td>
</tr>
<tr>
<td>Death (all-cause)</td>
<td>1.3%</td>
<td>1.8%</td>
<td>0.65</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.6%</td>
<td>9.1%</td>
<td>0.25</td>
</tr>
<tr>
<td>Disabling</td>
<td>0.9%</td>
<td>0.9%</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-disabling</td>
<td>4.8%</td>
<td>8.2%</td>
<td>0.22</td>
</tr>
<tr>
<td>AKI (Stage 3)</td>
<td>0.4%</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td>TIA</td>
<td>0.4%</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Sentinel Access Site</td>
<td>0.4%</td>
<td>N/A</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Stroke Diagnosis ≤72 hours (Analyzed ITT)

*Fisher Exact Test

Days to Stroke

- **Day 1**: Sentinel 1.3%, Control 0.4%, p=0.40
- **Day 2**: Sentinel 0.9%, Control 0.4%
- **Day 3**: Sentinel 1.3%, Control 2.7%
- **Total**: Sentinel 4.5%, Control 8.2%, Reduction 63%

p=0.052*

30 Day Stroke Diagnosis (Analyzed ITT)

- **Device Arm (n=234)**
- **Control Arm (n=111)**
- **p-value**
Primary Safety Endpoint (NI):
All Cause Death, Stroke, AKI stage 3

30-Day MACCE

<table>
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<td>0.4%</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Sentinel Site Complications</strong></td>
<td>0.4%</td>
<td>N/A</td>
<td>0.53</td>
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</tbody>
</table>

Historical Performance
Goal 18.3%

Within Sentinel Trial
Obs. Diff = -2.6%

$p_{non-inferior} < 0.001$
Where to use without definitive/compelling evidence?

Selectively?

With mobile structures present on the AoV

Laminar LV thrombus in ‘no option’ patient

Large burden/mobile aortic atheroma..

?LA appendage clot/SEC
Or better for Everyone?

Would you take a chance and drive without a seatbelt?! You never know when you’ll need protection!?
Summary

- Stroke continues to be a clinically relevant problem in TAVI.
- ‘Silent’ cerebral infarcts are frequent and are shown to have an impact on cognitive function.
- While initial results with cerebral protection devices promising, so far failed to be validated in powered randomized trials.
- As TAVI moves to lower risk groups...
- Freedom from new brain lesions should be a gold standard after TAVI?