14:20 Stroke Michael, *Thomas Modine*
TAVI complication session: Stroke

Dr. Thomas Modine MD, PhD, MBA
Eurovalve 2016, Bruxelles
Disclosure

- Medtronic – Consultant, Proctor, advisory board and study investigator
- Boston scientific: Consultant, Proctor, steering committee
- Edwards: consultant
- GE: Consultant
- Directflow: consultant
- CardiaQ: study investigator
- Tendyne: study co-PI
- Twelve: study investigator
- Cephea: consultant
- Micrport: consultant and proctor
Hippocrates

Apoplexy = to strike down

“It is impossible to remove a strong attack of apoplexy, and not easy to remove a weak attack.”

Some patients recover, because they believe in doctors

~ Hippocrates ~

Thaler, TCT 2015
The brain is our most sensitive indicator of subtle organ injury.
Stroke is bad!

But how common is it?
Mortality and Major Stroke
PARTNER 1B TAVI patients

Leon, TCT 2010
Mortality after Stroke: TAVR Patients
CoreValve High Risk Trial

No. at Risk

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

Log-rank $P<0.0001$

Adams, ACC 2014
Transcatheter Aortic-Valve Implantation — At What Price?

Hartzell V. Schaff, M.D.

In 2000, Bonhoeffer et al. described transvenous placement of a pulmonary-valve prosthesis and speculated that similar technology might be used in other cardiac valves, including the aortic position. Two years later, the first transcatheter insertion of an aortic-valve prosthesis was performed by Cribier et al. Transcatheter aortic-valve patients who are eligible for transfemoral insertion and may decrease vascular injury. But the increased risk of stroke associated with transcatheter replacement, as compared with surgical replacement, is a special concern. Smith and colleagues report a 5.5% risk of stroke or transient ischemic attack within 30 days after
Strokes (ITT)- TAVR vs SAVR

PARTNER 1A

HR [95% CI] = 1.09 [0.62, 1.91]
p (log rank) = 0.763

No. at Risk

<table>
<thead>
<tr>
<th>TAVR</th>
<th>348</th>
<th>287</th>
<th>250</th>
<th>228</th>
<th>211</th>
<th>176</th>
<th>139</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR</td>
<td>351</td>
<td>246</td>
<td>230</td>
<td>217</td>
<td>197</td>
<td>169</td>
<td>139</td>
</tr>
</tbody>
</table>

Leon, TCT 2013
Corevalve US Pivotal Trial - All Stroke

- Surgical
- Transcatheter

Months Post-Procedure:
0 1 2 3 4 5 6 7 8 9 10 11 12

All Stroke (%):
0 5 10 15 20

No. at Risk:
Surgical: 357 322 274 249
Transcatheter: 390 363 334 314

Log-rank P=0.10

Adams, ACC 2014
Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients

53 studies, 10,037 patients

TF CoreValve (1.4±1.5%); TF Edwards (2.1±3.0%)

<table>
<thead>
<tr>
<th></th>
<th>Medtronic/CoreValve transarterial</th>
<th>Edwards SAPIEN transarterial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of publications with available data (n)</td>
<td>Overall number of patients with available data (n)</td>
</tr>
<tr>
<td>Patient age (years)</td>
<td>18</td>
<td>3236</td>
</tr>
<tr>
<td>Female gender</td>
<td>16</td>
<td>2798</td>
</tr>
<tr>
<td>Logistic EuroSCORE (%)</td>
<td>18</td>
<td>3236</td>
</tr>
<tr>
<td>Procedural stroke (&lt;24h)</td>
<td>9</td>
<td>1872</td>
</tr>
<tr>
<td>30-day stroke/TIA</td>
<td>18</td>
<td>3236</td>
</tr>
<tr>
<td>30-day major stroke</td>
<td>14</td>
<td>1795</td>
</tr>
<tr>
<td>30-day minor stroke/TIA</td>
<td>14</td>
<td>1795</td>
</tr>
<tr>
<td>30-day overall mortality</td>
<td>18</td>
<td>3236</td>
</tr>
</tbody>
</table>

Procedural stroke (<24 hr.) 1.5±1.4%

30-day stroke/TIA 3.3±1.8%

1-year stroke/TIA 5.2±3.4%

<table>
<thead>
<tr>
<th></th>
<th>Number of publications with available data (n)</th>
<th>Overall number of patients with available data (n)</th>
<th>Number of events (n)</th>
<th>Weighted mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural stroke (&lt;24h)</td>
<td>24</td>
<td>3041</td>
<td>47</td>
<td>1.5±1.4%</td>
</tr>
<tr>
<td>30-day stroke/TIA</td>
<td>53</td>
<td>10037</td>
<td>334</td>
<td>3.3±1.8%</td>
</tr>
<tr>
<td>30-day major stroke</td>
<td>42</td>
<td>5514</td>
<td>158</td>
<td>2.9±1.8%</td>
</tr>
<tr>
<td>30-day minor stroke/TIA</td>
<td>42</td>
<td>5514</td>
<td>53</td>
<td>1.0±1.3%</td>
</tr>
<tr>
<td>30-day overall mortality</td>
<td>52</td>
<td>10022</td>
<td>812</td>
<td>8.1±3.9%</td>
</tr>
<tr>
<td>30-day mortality in patients suffering stroke</td>
<td>29</td>
<td>4430</td>
<td>41</td>
<td>25.5±21.9%</td>
</tr>
<tr>
<td>30-day mortality in patients without stroke</td>
<td>29</td>
<td>4430</td>
<td>312</td>
<td>6.9±4.2%</td>
</tr>
<tr>
<td>6-month stroke</td>
<td>9</td>
<td>669</td>
<td>29</td>
<td>4.3±1.6%</td>
</tr>
<tr>
<td>12-month stroke</td>
<td>7</td>
<td>1507</td>
<td>78</td>
<td>5.2±3.4%</td>
</tr>
</tbody>
</table>

Eggbrecht et al. EuroIntervention 2012
30-day stroke rate

All Strokes at 30 Days- device iterations (All clinically apparent strokes)

Edwards SAPIEN Valves

**PARTNER I and II Trials**

Neurologist evaluations (pre- and post)

<table>
<thead>
<tr>
<th>Device</th>
<th>SAPIEN</th>
<th>SAPIEN XT</th>
<th>SAPIEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1B (TF)</td>
<td>6.7%</td>
<td>4.1%</td>
<td>2.6%</td>
</tr>
<tr>
<td>P1A (Overall)</td>
<td>5.6%</td>
<td></td>
<td>1.5%</td>
</tr>
<tr>
<td>P2B (TF)</td>
<td>4.1%</td>
<td>4.3%</td>
<td>2.6%</td>
</tr>
<tr>
<td>S3HR (Overall)</td>
<td>1.5%</td>
<td></td>
<td>2.6%</td>
</tr>
<tr>
<td>S3i (Overall)</td>
<td>2.6%</td>
<td></td>
<td>1.5%</td>
</tr>
</tbody>
</table>

Kodali, ACC 2015
Neurologist evaluation results in the greater detection of (non major) stroke

Historically:

Results:
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

Daneault et al, JACC 2011;58: 2143-50
Stroke is bad!
Stroke redefined- “not so silent” infarction

• “Silent” infarcts associated with
  – Impaired mobility
  – Physical decline
  – Depression
  – Cognitive dysfunction
  – Dementia
  – Parkinson’s
  – Alzheimer’s
Stroke Timing post TAVI

Figure 1. Timing of Cerebrovascular Events

Number of days elapsed from the index procedure before the occurrence of a cerebrovascular event.

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

D. Tchetché et al. JACC CV Int. 2014;7:1138-1145

Multi-center cohort of 1,061 TAVI patients
- CVE most frequently occur day 0-1
- >50% are major strokes
- >95% of strokes are ischemic

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

Figure 2. Timing of cerebrovascular events (CVEs) within 30 days after transcatheter aortic valve implantation. TIA indicates transient ischemic attack.
ADVANCE | Type and Timing of Stroke

996 patients implanted

- Procedure to Day 2: 12 strokes
  - Ischemic: 11
  - Hemorrhagic: 1
  - Undetermined: 0

- Day 2 - 1 Month: 15 strokes
  - Ischemic: 14
  - Hemorrhagic: 0
  - Undetermined: 1

- 1 Month - 1 Year: 9 strokes
  - Ischemic: 6
  - Hemorrhagic: 2
  - Undetermined: 1

Legend:
- Blue: Ischemic
- Pink: Hemorrhagic
- Green: Undetermined
Substrates for thromboembolism in TAVI

- Presence and location of arch atheroma
- Micro-embolization of native valve calcification
- Catheter handling and device placement technique
- Secondary manoeuvres (post-dil/VinV)
- Procedural duration
- Pro-thrombotic/hypercoagulable state
- Arrhythmia (AF)
- Rapid RV pacing (cerebral hypoperfusion)
- Subclinical prosthetic leaflet thrombosis
Reduced leaflet motion with possible subclinical leaflet thrombus

Makkar, Fontana, Jilaihawi et al, NEJM 2015
### Subclinical leaflet thrombus
Unclear connection to stroke/TIA

<table>
<thead>
<tr>
<th>Registries</th>
<th>Normal Leaflet Motion</th>
<th>Reduced Leaflet Motion</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in study</td>
<td>115</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Stroke/TIA¶</td>
<td>1</td>
<td>3</td>
<td>0.007</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>0</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>TIA</td>
<td>0</td>
<td>3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Makkar, Fontana, Jilaihawi et al, NEJM 2015
Therapeutic actions
## Predictors for Cerebrovascular Events with TAVI

<table>
<thead>
<tr>
<th>Time Window</th>
<th>Incidence</th>
<th>Variable</th>
<th>Model</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute &lt;24h</strong></td>
<td>29 (2.7%)</td>
<td>Balloon postdilatation</td>
<td>OR: 2.46</td>
<td>CI: 1.07 to 5.67</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valve dislodgment/embolization</td>
<td>OR: 4.36</td>
<td>CI: 1.21 to 15.69</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>Subacute 24h&gt;30 Days</strong></td>
<td>25 (2.4%)</td>
<td>New onset AF</td>
<td>OR: 2.76</td>
<td>1.11 to 6.83</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Late &gt;30 Days</strong></td>
<td>35 (3.3%)</td>
<td>Chronic AF</td>
<td>HR: 2.84</td>
<td>1.46 to 5.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PAD</td>
<td>HR: 2.02</td>
<td>1.02 to 3.97</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior CVA</td>
<td>HR: 2.04</td>
<td>1.01 to 4.15</td>
<td></td>
</tr>
</tbody>
</table>
### Predictors for Tissue Embolization (collected debris with Claret)

<table>
<thead>
<tr>
<th>Independent Predictors of Tissue Embolization</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balloon-expandable THV</td>
<td>7.315</td>
<td>1.398-38.289</td>
<td>p=0.018</td>
</tr>
<tr>
<td>Cover index</td>
<td>1.141</td>
<td>1.014-1.283</td>
<td>p=0.028</td>
</tr>
<tr>
<td>Balloon post-dilation</td>
<td>2.67</td>
<td>0.675-10.073</td>
<td>p=0.17</td>
</tr>
</tbody>
</table>

Device for cardiac surgery stroke prevention: Embol-X

Adverse Neurologic Events

- Control: n=278
- EMBOL-X System: n=304

All Outcomes: p=0.001

Complication Rate %

- Stroke
- TIA
- Delirium
- Coma
- Memory Deficit

Single center, Non-randomized
Neurologic assessment, physicians blinded to treatment group

Schmitz et al, JCTVS 2003
Embolic material collected during TAVR with the Claret device

Why Sentinel IDE Matters?

One preventable stroke is too many.

Captured during TCT 2013 Live Case: Courtesy of Dr. Alex Abizaid
Institute Dante Pazzanese de Cardiologia, São Paulo, Brazil
Cerebral embolic debris captured in TAVI patients (n=81)

Note: percentages reflect percent of patients in the series in which each particular tissue type was captured. Some filters captured several types of debris, so percentages will not add to 100%
# Cerebral Embolic Protection

<table>
<thead>
<tr>
<th>TriGuard Cerebral Deflector</th>
<th>Embrella Deflector</th>
<th>Claret Sentinel Filter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deflector</strong></td>
<td><strong>Deflector</strong></td>
<td><strong>Filter</strong></td>
</tr>
<tr>
<td>3 Vessels Covered</td>
<td>2 Vessel Coverage</td>
<td>2 Vessel Coverage</td>
</tr>
<tr>
<td>Femoral Access</td>
<td>Radial Access</td>
<td>Radial Access</td>
</tr>
<tr>
<td>Nitinol® Mesh</td>
<td>Polymer based Mesh</td>
<td>Polymer based Filter</td>
</tr>
<tr>
<td>130μm Pore Size</td>
<td>100 μm Pore Size</td>
<td>140 μm Pore Size</td>
</tr>
<tr>
<td>EU Feasibility</td>
<td>CE approved</td>
<td>CE approved</td>
</tr>
<tr>
<td>9F Sheath (Mullins)</td>
<td>6F Shuttle Sheath</td>
<td>6F Radial Sheath</td>
</tr>
</tbody>
</table>
Randomized EPD Data

CLEAN TAVI, n=100

MISTRAL-C, n=65

SENTINEL (ongoing)

DEFLECT III, n=85
CLEAN-TAVI Study
Randomized study of CoreValve implantation with (n=50) and without (n=50) embolic protection (Total N = 100)

<table>
<thead>
<tr>
<th>Control</th>
<th>Any symptom</th>
<th>Control</th>
<th>Any symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia</td>
<td>17 (34 %)</td>
<td>Ataxia</td>
<td>16 (32 %)</td>
</tr>
<tr>
<td></td>
<td>14 (28 %)</td>
<td></td>
<td>12 (24 %)</td>
</tr>
<tr>
<td></td>
<td>5 (10 %)</td>
<td></td>
<td>4 (8 %)</td>
</tr>
<tr>
<td></td>
<td>6 (12 %)</td>
<td></td>
<td>5 (10 %)</td>
</tr>
<tr>
<td>Filter</td>
<td>11 (24 %)</td>
<td>Filter</td>
<td>9 (20 %)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>6 (13 %)</td>
<td>Ataxia</td>
<td>4 (9 %)</td>
</tr>
<tr>
<td></td>
<td>6 (13 %)</td>
<td></td>
<td>5 (11 %)</td>
</tr>
<tr>
<td></td>
<td>4 (12 %)</td>
<td></td>
<td>4 (12 %)</td>
</tr>
</tbody>
</table>

RR 1.458 (1.006 to 2.114), OR 2.5, p=0.08
RR 1.559 (1.083 to 2.214), OR 3.2, p<0.05
There were 2 clinical strokes in each arm.

In the TriGuard arm, the single disabling stroke occurred in a patient who did not have full cerebral protection during the procedure; an additional non-disabling stroke occurred in a subject who appeared to have full coverage.

Association of warfarin therapy with clinical events after bioprosthetic AVR: STS database

25,656 patients undergoing bioprosthetic AVR at 797 hospitals in the STS database

Warfarin plus aspirin associated with a reduced risk of death and embolic events, compared to aspirin alone

Brennan M. et al. JACC 2012
**GALILEO** (Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement (TAVR) to optimize clinical outcomes will compare rivaroxaban-based)

1520 patients after successful TAVI procedure

- **Rivaroxaban 10 mg OD and Aspirin 75-100mg OD**
  - Drop of aspirin
  - **Rivaroxaban 10 mg OD**

- **Clopidogrel 75 mg OD Aspirin 75-100 mg OD**
  - Drop of clopidogrel
  - **Aspirin 75-100 mg OD**

*Primary end-point is* death, MI, stroke, non-CNS systemic emboli, symptomatic valve thrombosis, deep vein thrombosis or pulmonary embolism, major bleedings over 720 days of treatment exposure.
Primary end-point is a composite of death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombus, episode of deep vein thrombosis or pulmonary embolism, major bleedings over one year follow-up.

*2.5mg bid if creatinine clearance 15-29mL/min or if two of the following criteria: age≥80 years, weight≤60kg or creatinine≥1,5mg/dL (133µMol).
**Stroke diagnosis in the cath lab with dyna CT**

<table>
<thead>
<tr>
<th>00 min</th>
<th>Arrival at hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min</td>
<td>Neurological exam</td>
</tr>
<tr>
<td>30 min</td>
<td>Angio suite Imaging</td>
</tr>
<tr>
<td>45 min</td>
<td>Angio suite, treatment</td>
</tr>
</tbody>
</table>

**1h saved = 20% better chance for good outcome (mRS ≤ 2)**

- Hemorrhagic or ischemic?
- Clot location? Collaterals?
- To treat or not to treat?

Law, TCT 2015
What about when a stroke has already occurred? Endovascular treatment for acute ischemic stroke

(Stroke 2015 46:909-914)
MR CLEAN study

• Usual care vs. Usual care + intra-arterial therapy (<6h from onset)
• Anterior circulation large vessel occlusion
• ~90% received IV tPA
• TICI 2b or 3 in 59%

Berkhemer et al, NEJM 2015 372: 11-20
Post-TAVR Stroke: Conclusions I

• The incidence of presumed embolic phenomena on detailed neuroimaging (MRI) after TAVR is high (consistently $\geq 50\%$) but translates to low rates of clinical stroke

• The incidence of routinely detected stroke after surgical and transcatheter aortic valve replacement appears to be low and the reported rates are overall similar ($\approx 2\text{-}5\%$), mostly peri-procedural

• Major stroke rates are declining to $\approx 1\text{-}2\%$ or less in contemporary TAVR practice even with neurology assessment
Post-TAVR Stroke: Conclusions II

• Peri-procedural stroke
  – In high and extreme risk groups, cost-benefit analysis will be important if use of neuro-protection is to be widespread? Stratification of likelihood of stroke by anatomy
  – In intermediate and low risk groups, the impact of so-called “sub-clinical strokes” merits further study and may support use of neuro-protection
  – In all groups, the ability to treat post TAVR strokes with intra-arterial therapy is of enormous interest