Embolic Protection in TAVR

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Disclosure

Scientific Advisory Board Abbott Structural Heart
Stroke in TAVR

- Stroke is an issue (~3.5% average rate) in contemporary TAVR studies
- TAVR device trials tend to emphasize only the major/disabling stroke rates

Patient Perceptions and Expectations

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

Health Expectations

Patient-defined goals for the treatment of severe aortic stenosis: a qualitative analysis

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Consequences of Stroke

Peri-procedural Stroke after TAVR Increases 30d Mortality

- **Mortality after disabling stroke:**
  - 1-year mortality of 67% vs. 12% and 2-year mortality of 83% vs. 20%.\(^1\)

- **PHYSICAL FUNCTIONING:**
  - 40% moderate to severe permanent disability
  - 55%-75% of “fully recovered”: residual dysfunction at least one limb.\(^2\)\(^3\)

- **EFFECT OF STROKE / WHITE MATTER LESIONS in WORKING POPULATION**
  - 44% return to work
  - 33% significant financial strains
  - 79% report social isolation\(^4\)
  - even without physical impairment from stroke: impaired social cognition, occupational disability, and inability to maintain relationships with family and friends\(^5\)

- **References:**

\* Muralidharan et al. *Am J Cardiol* 2016
<table>
<thead>
<tr>
<th>Unmatched Cohorts</th>
<th>Matched Cohorts</th>
<th>P value</th>
<th>Unmatched Cohorts</th>
<th>Matched Cohorts</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>Unmatched Cohorts</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>TAVR Non-Stoke (N=30054)</strong></td>
<td></td>
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<tr>
<td><strong>TAVR-Stroke (N=776)</strong></td>
<td></td>
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<tr>
<td>Age- mean (SD), y</td>
<td>81 (8)</td>
<td>83 (7)</td>
<td>&lt;0.001</td>
<td>82 (8)</td>
<td>83 (7)</td>
</tr>
<tr>
<td>Female</td>
<td>47.5%</td>
<td>54.4%</td>
<td>&lt;0.001</td>
<td>51.7%</td>
<td>53.1%</td>
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<tr>
<td>Hypertension</td>
<td>79.3%</td>
<td>74.4%</td>
<td>&lt;0.001</td>
<td>74.9%</td>
<td>75.1%</td>
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<tr>
<td>Diabetes</td>
<td>34.5%</td>
<td>30.8%</td>
<td>0.031</td>
<td>28.9%</td>
<td>31.3%</td>
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<tr>
<td>Previous Stroke/TIA</td>
<td>10.7%</td>
<td>10.9%</td>
<td>0.886</td>
<td>14.5%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>46.3%</td>
<td>51.1%</td>
<td>0.008</td>
<td>51.6%</td>
<td>50.7%</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>11.7%</td>
<td>15.6%</td>
<td>&lt;0.001</td>
<td>13.9%</td>
<td>15%</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>29.7%</td>
<td>35.4%</td>
<td>0.001</td>
<td>37.8%</td>
<td>34.7%</td>
</tr>
<tr>
<td>Chronic Renal Disease</td>
<td>36.2%</td>
<td>33.3%</td>
<td>&lt;0.001</td>
<td>32.9%</td>
<td>33.7%</td>
</tr>
<tr>
<td>Transfemoral Access</td>
<td>76.9%</td>
<td>71.2%</td>
<td>0.001</td>
<td>74.4%</td>
<td>71.5%</td>
</tr>
<tr>
<td><strong>In Hospital Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4%</td>
<td>11.2%</td>
<td>&lt;0.001</td>
<td>4.1%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Non-home Discharge</td>
<td>28.6%</td>
<td>66.8%</td>
<td>&lt;0.001</td>
<td>29.8%</td>
<td>66.1%</td>
</tr>
<tr>
<td>Gastrostomy</td>
<td>1%</td>
<td>11%</td>
<td>&lt;0.001</td>
<td>0.7%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>1.2%</td>
<td>5.8%</td>
<td>&lt;0.001</td>
<td>2.4%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>2.7%</td>
<td>13.9%</td>
<td>&lt;0.001</td>
<td>1.7%</td>
<td>5.1%</td>
</tr>
<tr>
<td>LOS, mean (SD), d</td>
<td>8 (8)</td>
<td>15 (12)</td>
<td>&lt;0.001</td>
<td>9 (9)</td>
<td>15 (12)</td>
</tr>
<tr>
<td>Hospital Charges (Index Hospitalization) US$</td>
<td>222413 (146080)</td>
<td>313171 (211876)</td>
<td>&lt;0.001</td>
<td>220474 (140574)</td>
<td>302422 (199923)</td>
</tr>
<tr>
<td>30-Day Readmission</td>
<td>18.3%</td>
<td>23.2%</td>
<td>0.026</td>
<td>15.6%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Readmission Mortality</td>
<td>0.9%</td>
<td>2.1%</td>
<td>&lt;0.001</td>
<td>1.3%</td>
<td>3.1%</td>
</tr>
<tr>
<td>LOS of readmission</td>
<td>6 (7)</td>
<td>10 (24)</td>
<td>&lt;0.001</td>
<td>7 (7)</td>
<td>10 (22)</td>
</tr>
<tr>
<td>Hospital Charges (Readmission) US$</td>
<td>57526 (146080)</td>
<td>123179 (490062)</td>
<td>&lt;0.001</td>
<td>53596 (56534)</td>
<td>124363 (444760)</td>
</tr>
</tbody>
</table>

OUTCOMES OF ACUTE ISCHEMIC STROKE AFTER TAVR: POTENTIAL IMPACT OF EMBOLIC PROTECTION

Mohamad Adnan Alkhoul et al

Journal of the American College of Cardiology Volume 71, Issue 11 Supplement, March 2018
DOI: 10.1016/S0735-1097(18)31833-3
Neurologically adjudicated SURTAVI Trial, IR, CoreValve Trial

1204 propensity matched Partner trial patients 2007-2014
Stroke rates much higher with routine Neurologist adjudication 9-27% (AHA/ASA)

TVT Registry: Data from 42,988 commercial TAVR procedures at 395 US hospitals

- Unadjusted (orange) and risk-adjusted (blue) frequency of outcomes.
- The p value < 0.05 for linearity suggests a nonlinear relationship.
- The orange- and blue-colored bands represent 95% confidence limits, which are broader for stroke due to the low rate of site-reported stroke and the fewer hospital sites contributing cases.

Increasing TAVR experience generally associated with better outcomes.
Increasing site volume associated with lower inhospital risk-adjusted outcomes, including mortality, vascular complications, and bleeding but was not associated with stroke.


STS/ACC TVT Registry J Am Coll Cardiol 2017;70:29–41.
Diffusion Weighted MRI (DWMRI)

- Improves the sensitivity and specificity of defining new ischemic injuries
- Invaluable tool in diagnosing new ischemic stroke
- Use in longitudinal studies of populations for understanding of impact of covert infarcts on long term outcomes
- Use in patients undergoing CV procedures to understand the risk of “silent stroke”
Covert Infarct outside of TAVR

- Cognitive decline relates directly to loss of brain substance with progression of lesion burden (Schmidt et al, Annals of Neurology 2005)

- Cumulative burden of ischemic brain injury causes neuropsychological deficits and aggravates vascular dementia (Lancet Neurol 2006; 5: 364-372)

- Infarcts are associated with brain volume reduction, but, importantly, also with detectably lower cognition (Blum et al, Neurology, Nov 2012)
Silent Cerebral Infarcts

- In Covert Infarcts, size, location and number of infarcts are important prognostically in development of neurocognitive dysfunction.
- Additional silent infarcts in setting of prior infarcts increase neurocognitive dysfunction.

Silent brain infarcts and the risk of dementia and cognitive decline.

Education and the cognitive decline associated with MRI-defined brain infarct
First published August 7, 2006, DOI: https://doi.org/10.1212/01.wnl.0000228246.89109.98

Neuroimaging findings in midlife and risk of late-life dementia over 20 years of follow-up
Nancy A. West, B. Gwen Windham, David S. Knopman, Dean K. Shibata, Laura H. Coker, Thomas H. Mosley
Neurology February 26, 2019; 92 (9)
New cerebral lesions found in the vast majority of patients after TAVR

- 68-100% of TAVR patients affected
- Most patients have multiple infarcts
- "Silent" infarcts associated with\(^1,2,3\)
  - 2-4-fold risk of future stroke
  - >3-fold risk of mortality
  - >2-fold risk of dementia
  - Cognitive decline

1. Sacco et al., Stroke 2013
2. Vermeer et al., Stroke 2003
2-7 day DW-MRI Scans after TAVR

In stroke patients, lesion size, number, and location are ALL important.

Size | Number | Location

--- | --- | ---

3 Control Arm Stroke Patients

The total volume of ischemic brain infarction quantified after TAVI in imaging studies ranges from 1.5 cm$^3$ to 4.3 cm$^3$ of brain tissue, which equates to cell death of $\approx 2$ million neurons and $\approx 1$ billion synapses.
Equal Distribution of Cerebral Embolization to All Cerebral Vessels

Distribution of Embolic Lesions by DW MRI

Arnold et al. Embolic Cerebral Insults After TAVI Detected by MRI. JACC 2010.

Average number of new infarcts with TAVR 4.1
Effect of Cerebral Embolic Protection Devices on CNS Infarction in Surgical Aortic Valve Replacement: A Randomized Clinical Trial

Michael J. Mack, MD; Michael A. Acker, MD; Annetine C. Gelijns, PhD; et al

RANDOMIZED TRIAL: EMBOLEX FILTER VS CONTROL
CARDIOGUARD VS CONTROL

383 PATIENTS
NO DIFFERENCE IN CLINICAL STROKE RATE -5-7% ACROSS GROUPS
NO DIFFERENCE IN EMBOLIC RATES DWMRI

EMBOLEX 72%
CARDIOGUARD 68%
CONTROL 65%
Gross Images of the Filter and Debris Collected by the Cell Strainer. In each panel there is a gross image of the filter (top left) and debris collected by the cell strainer (top right), along with scanned images of H&E-stained slides (mid and bottom left) and scanned images of Movat pentachrome-stained slides (mid and bottom right). (A) This is an example of a large piece of valve tissue. (B) This is an example of myocardium and valve tissue. (C) This is an example of acute thrombus associated with tissue and some calcification. (D) This is an example of acute thrombus, valve and arterial wall tissue, and calcifications. (E) This is an example of a large piece of proteoglycan-rich arterial wall.
Sentinel Trial
Captured debris in the proximal filter in relation to valve type. Regarding the observed rate of acute thrombus, organizing thrombus, valve tissue, arterial wall, calcification, foreign material, myocardium, necrotic core, or any debris, there was no difference among the 3 valve types.
Similarly, captured debris in the distal filter in relation to valve type. Regarding the observed rate of acute thrombus, organizing thrombus, valve tissue, arterial wall, calcification, foreign material, myocardium, necrotic core, or any debris, there was no difference among the 3 valve types.
Significantly more larger particles captured with Sapien than self expanding from proximal filters. Smaller size particles evenly distributed across all valve platforms.
A) shows the number of particles with respect to implanted valve type captured in the proximal filter. (B) shows the number of particles with respect to implanted valve type captured for the distal filter. Number of particles in the proximal filter was significantly lower with the Boston Scientific Lotus valve compared with the Medtronic CoreValve Evolut R and Edwards SAPIEN 3 valve.
(A) shows the total area of captured debris with respect to implanted valve type of the proximal filter. Results for the distal filter are demonstrated in (B). Total tissue area was significantly smaller for the Boston Scientific Lotus valve compared with the other 2 valve types in the proximal filter. In contrast, for the distal filter there was no difference with respect to valve types for total tissue area.
Embolic Protection Devices

- Deflectors
- Capture
Capture Devices: Sentinel Device

- Claret Medical acquired by Boston Scientific for $250M July 2018
- 6 F right radial access, prox filter 9-15 mm, distal filter 6.5-10 mm
- Device delivered prior to any AV manipulation
- Pore size 140 microns
- FDA approved June 5, 2017, safety not efficacy endpoints were met
- Receives New Technology Add on Payment Oct 2018
Sentinel Trial

- RCT: Safety arm n=123, Device arm n=121, Imaging control arm n = 119
- Successful device deployment = 94% Added 13 minutes to procedure
- Protected territories: 42% reduction in device arm of total lesion volume (P =0.33) and a 33% reduction in number of lesions (P = 0.90)
- All territories: 5% reduction in total lesion volume (p= 0.81) and a 40% reduction in number of lesions (p= 0.77)
- No difference in neurocognitive scores from baseline to 30 or 90 day follow up
- If there were neurocognitive changes, correlated with median new lesion volume in protected areas
- Post hoc analysis valve type and prior infarct significant predictors
- PROTECT-TAVI – Ongoing study powered for efficacy
Sentinel trial

CENTRAL ILLUSTRATION: Primary Safety and Efficacy Endpoints

A. 30-day MACCE Rates

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Device Cohort</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate (%)</td>
<td>8±2.5</td>
<td>12±3.4</td>
</tr>
</tbody>
</table>

Historical Performance
Goal: 18.3%
(P noninferior <0.001)

Within SENTINEL Trial
\( p = 0.40 \)

B. New Lesion Volume on MRI

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Device</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protected New Volumes, mm³</td>
<td>102.83</td>
<td>177.98</td>
</tr>
</tbody>
</table>

\( p = 0.33 \)

Embolic Protection Devices
Triguard

- Keystone Heart acquired by Venus Medtech Dec 2018 ~$140M
- Contralateral 9F Femoral Access
- Single wire nitinol frame with mesh filter 130 micron pore size
- Deflect I and II trials: single arm studies, safety and performance
- Deflect III: Prospective, multicenter randomized and blinded trial, safety and efficacy with 85 patients
  - Safety endpoints no difference 89% successful deployment
  - Freedom from new DWI lesions 21.2% with device vs 11.5% without device
  - Improved cognitive function
  - CE mark approval
  - Low numbers to evaluate safety and 31% lost to DWI and 26% loss to neurocognitive testing
Triguard

- Reflect US Trial
- Evaluates second generation device, changes to filter and 8F access
- 285 patients randomized 2:1 to Triguard (190) versus unprotected TAVR (95)
- Trial has completed enrollment
- Data review is beginning this week
Cerebral Protection Devices in Development

**Point-Guard**
- Access: Contralateral Femoral
- Pore size: not available
- Innovation: contouring design of the deflector, able to adapt to any arch configuration
- Transverse Medical Inc

**Embolisher**
- Access: Ipsilateral Femoral
- Pore Size: not available
- Innovation: same access, detaching deflector
- Cardioptimus

**ProtEmbo**
- Access: left radial 6F
- Pore size: 60 microns
- Innovation: left radial access, full shield 60 microns
- Five patients to date
- Protembis
Emblok
Access: Contralateral Fem 11F
Pore size: 125 microns
Innovation: Capture and block up to 35 mm, integrated pigtail and filter
FIM March 2019
Innovative Cardiac Solutions

Captis
Access: Ipsilateral Femoral
Pore size: not defined
Innovation: deflects and captures, ipsilateral, disconnects
Preclinical
Filterlex

Emboliner
Access: Contralateral Femoral 9F
Pore size: 150 microns
Innovation: doubled nitinol mesh that allows for access of the embolic collection “tube”
FIM June 2018 Firstpass clinical trial EU
Embliner
Challenges within Embolic Protection

- Device interaction
- Porosity of device, thrombogenicity
- Access
- Embolic events related to device
- Procedural impact
Embolic Protection

- Clinical stroke is underestimated in TAVR patients and has a significant impact on short and long term patient and socioeconomic outcomes.
- Covert infarcts occur in the vast majority of patients undergoing TAVR and may impact future stroke risk, neurocognitive decline and risk of dementia.
- Cerebral embolic protection in TAVR and other CV interventions should improve overt and covert infarcts.
- Complete cerebral protection, device stability, freedom from interaction with TAVR device and ease of use will be critical for device implementation.
- Patients ask about protection every day.
Cerebral embolic protection systems for transcatheter aortic valve replacement
# Embolic Protection Devices

## Deflectors

<table>
<thead>
<tr>
<th>Device</th>
<th>Access Site</th>
<th>Access Size</th>
<th>Pore Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triguard Keystone Heart</td>
<td>Contralateral femoral</td>
<td>9F</td>
<td>130 micron</td>
</tr>
<tr>
<td>Embrella Edwards</td>
<td>Left Radial</td>
<td>6F</td>
<td>100 micron</td>
</tr>
<tr>
<td>Transverse Medical</td>
<td>Probably Femoral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protembus Protembus HG</td>
<td>Right Radial</td>
<td>6F</td>
<td>60 micron</td>
</tr>
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</table>

## Capture

<table>
<thead>
<tr>
<th>Device</th>
<th>Access Site</th>
<th>Access Size</th>
<th>Pore Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sentinel Boston Sci</td>
<td>Left Radial</td>
<td>6F</td>
<td>140 micron</td>
</tr>
<tr>
<td>Emblok ICS</td>
<td>Contralateral femoral</td>
<td>12F</td>
<td>125 micron</td>
</tr>
<tr>
<td>Emboliner</td>
<td>Contralateral femoral</td>
<td>12F</td>
<td></td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Embrella</td>
<td>Claret</td>
<td>TriGuard</td>
</tr>
<tr>
<td>----------------------</td>
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<td>--------------------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Edwards Lifesciences; Irvine, California, United States</td>
<td>Claret Medical, Inc.; Santa Rosa, California, United States</td>
<td>Keystone Heart Ltd., Herzliya, Israel</td>
</tr>
<tr>
<td>Structure</td>
<td>Oval shaped nitinol frame (length 59 mm, width 25.5 mm) Covered with a porous polyurethane membrane</td>
<td>Two oval coned mesh positioned within brachiocephalic (sized 9-15 mm diameter) and left common arteries (sized 6.5–10 mm in diameter)</td>
<td>Single-wire nitinol frame and mesh filter, maintained by stabilizers in the brachiocephalic artery and the inner curvature of the aortic arch.</td>
</tr>
<tr>
<td></td>
<td>Pore size: 100 μm</td>
<td>Pore size: 140 μm</td>
<td>Pore size: 130 μm</td>
</tr>
<tr>
<td>Delivery approach</td>
<td>Radial/brachial artery</td>
<td>Radial/brachial artery</td>
<td>Femoral</td>
</tr>
<tr>
<td>Sheath Size</td>
<td>Radial/brachial artery</td>
<td>Radial/brachial artery</td>
<td>9 French</td>
</tr>
<tr>
<td>Primary Mechanism</td>
<td>Deflection</td>
<td>Deflection</td>
<td>Deflection</td>
</tr>
<tr>
<td>Coverage</td>
<td>Brachiocephalic and the left common carotid arteries</td>
<td>Brachiocephalic and the left common carotid arteries</td>
<td>Brachiocephalic, left common carotid, and left subclavian arteries</td>
</tr>
<tr>
<td>Most relevant study</td>
<td>PROTAVI-C (41)</td>
<td>SENTINEL (43)</td>
<td>DEFLECT III (44)</td>
</tr>
<tr>
<td>Methods</td>
<td>Prospective, non-randomized study. Device n = 54 Control n = 12</td>
<td>RCT Safety arm n = 123 Device arm n = 121</td>
<td>RCT Device n = 46 Control n = 39</td>
</tr>
<tr>
<td>Patient and</td>
<td>52% male, median age 83 years. Only balloon expandable TAVR (Edwards Sapien XT) Only Transfemoral TAVR Successful device positioning in 100%</td>
<td>48% male, median 83 years Balloon expandable TAVR in 70% Transfemoral TAVR in 95% Successful device positioning in 94%</td>
<td>46% male, mean age 82 years Balloon expandable TAVR in 64% Transfemoral TAVR in 97% Successful device positioning in 89%</td>
</tr>
<tr>
<td>procedural</td>
<td></td>
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<tr>
<td>characteristics</td>
<td></td>
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<tr>
<td>Outcomes</td>
<td>DW-MRI:</td>
<td>DW-MRI:</td>
<td>DW-MRI:</td>
</tr>
<tr>
<td></td>
<td>- Non-significant increase in lesion numbers (8 vs. 4, P = 0.41) in device group.</td>
<td>- 42% reduction in device arm of total lesion volume (P = 0.33)</td>
<td>- Device related greater freedom from new cerebral DWI lesions (21.2 vs. 11.5%).</td>
</tr>
<tr>
<td></td>
<td>- Significantly lower lesion volumes (40% smaller, P = 0.003) in device group.</td>
<td>- 33% reduction in number (P = 0.90).</td>
<td>- 44% reduction of median lesion size</td>
</tr>
<tr>
<td></td>
<td>TCD:</td>
<td>All territories:</td>
<td>Neurocognitive:</td>
</tr>
<tr>
<td></td>
<td>- Higher procedural HITS rates in device group.</td>
<td>- 5% reduction of total lesion volume (P = 0.81), 40% in number (P = 0.77).</td>
<td>- Reduction worsening in National Institutes of Health Stroke Scale score from baseline (2.6 vs. 3.5).</td>
</tr>
</tbody>
</table>
Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial

Stephan Haussig, MD1; Norman Mangner, MD1; Michael G. Dwyer, MD2; et al

Table 3. Brain Lesion Characteristics as Determined by Magnetic Resonance Imaging

<table>
<thead>
<tr>
<th></th>
<th>2 Days Filter (n = 49)</th>
<th>Control (n = 45)</th>
<th>Difference (95% CI)a</th>
<th>P Value</th>
<th>7 Days Filter (n = 45)</th>
<th>Control (n = 43)</th>
<th>Difference (95% CI)a</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potentially Protected Areas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of new lesions, median (IQR)</td>
<td>4.00 (3.00-7.25)b</td>
<td>10.00 (6.75-17.00)b</td>
<td>5.00 (2.00-8.00)b</td>
<td>&lt;.001</td>
<td>3.00 (1.00-5.25)</td>
<td>7.00 (3.00-13.50)</td>
<td>3.00 (1.00-5.00)</td>
<td>.003</td>
</tr>
<tr>
<td>Volume of new lesions, median (95% CI), mm³</td>
<td>242 (159-353)</td>
<td>527 (364-830)</td>
<td>234 (91-406)</td>
<td>.001</td>
<td>101 (60-174)</td>
<td>292 (181-515)</td>
<td>160 (57-281)</td>
<td>.002</td>
</tr>
<tr>
<td><strong>Partially Protected Areas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of new lesions, median (IQR)</td>
<td>2.00 (1.00-3.25)</td>
<td>4.00 (2.00-7.00)</td>
<td>2.00 (0.00-3.00)</td>
<td>.008</td>
<td>1.00 (0.00-3.00)</td>
<td>3.00 (1.00-5.00)</td>
<td>1.00 (0.00-2.00)</td>
<td>.02</td>
</tr>
<tr>
<td>Volume of new lesions, median (95% CI), mm³</td>
<td>113 (72-164)</td>
<td>247 (147-399)</td>
<td>98 (18-194)</td>
<td>.01</td>
<td>37 (11-70)</td>
<td>129 (67-227)</td>
<td>72 (3-129)</td>
<td>.008</td>
</tr>
<tr>
<td><strong>Entire Brain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of new lesions, median (IQR)</td>
<td>8.00 (5.00-12.00)</td>
<td>16.00 (9.75-24.25)</td>
<td>6.00 (3.00-10.00)</td>
<td>.002</td>
<td>5.00 (2.75-8.00)</td>
<td>10.00 (3.00-18.00)</td>
<td>4.00 (1.00-8.00)</td>
<td>.009</td>
</tr>
<tr>
<td>Volume of new lesions, median (95% CI), mm³</td>
<td>466 (349-711)</td>
<td>800 (594-1407)</td>
<td>311 (66-580)</td>
<td>.02</td>
<td>205 (115-338)</td>
<td>472 (385-909)</td>
<td>240 (51-393)</td>
<td>.009</td>
</tr>
</tbody>
</table>

Abbreviations: DWMRI, diffusion-weighted magnetic resonance imaging; IQR, interquartile range; TAVI, transcatheter aortic valve implantation.  

a Differences calculated as independent samples Hodges-Lehmann median difference estimates.  
b The primary end point was numerical reduction in positive postprocedure DWMRI-perfused brain lesions relative to baseline at 2 days following TAVI in potentially protected territories. The 1.5T scanner was used in patients who were intermittently pacemaker-dependent with a temporary lead in place and who were not approved for 3.0T MRI.
### Table 2. Procedural TAVI and Filter Deployment Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Filter Group (n = 50)</th>
<th>Control Group (n = 50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-area product -cGycm²</td>
<td>18 803 (15 884-21 722)</td>
<td>17 772 (15 269-20 276)</td>
<td>.82</td>
</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>17.4 (14.8-19.9)</td>
<td>14.4 (12.4-16.3)</td>
<td>.02</td>
</tr>
<tr>
<td>Amount of contrast medium, mL</td>
<td>128 (119-136)</td>
<td>131 (121-141)</td>
<td>.59</td>
</tr>
<tr>
<td><strong>Time, min</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From insertion of sheath into radial artery to insertion of device</td>
<td>21.1 (19.3-22.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>From insertion of device to device in final position</td>
<td>7.1 (5.5-8.7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>From device in final position to retraction of device</td>
<td>23.9 (21.3-26.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total time from insertion to retraction of device</td>
<td>31.0 (27.9-34.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Procedural time, min</td>
<td>72.1 (65.7-78.5)</td>
<td>54.1 (50.0-58.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Device success, No. (%)</td>
<td>46 (92)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Procedural success, No. (%)</td>
<td>45 (90)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Thoracotomy, No. (%)</td>
<td>3 (6)</td>
<td>0</td>
<td>.24</td>
</tr>
</tbody>
</table>

**Abbreviations:** NA, not applicable; TAVI, transcatheter aortic valve implantation.

a Data are reported mean (95% CI) unless otherwise stated.

b Difference, 2.7 (95% CI, 0.4-4.8).

c Difference, 15.0 (95% CI, 10.0-20.0).

d Device success was defined as successful positioning and deployment of both filters in correct anatomical position.

e Procedural success was defined as successful positioning and deployment of both filters in correct anatomical position, correct positioning of both filters during TAVI, and successful retrieval of both filters after TAVI.

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**Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial**


Stephan Haussig, MD¹; Norman Mangner, MD¹; Michael G. Dwyer, MD²; et al
Stroke After Transcatheter Aortic Valve Replacement: Incidence, Risk Factors, Prognosis, and Preventive Strategies

![Graph showing the incidence of stroke after transcatheter aortic valve replacement over different time periods.](https://via.placeholder.com/150)

Acute Events: N/A
Sub-acute Events: N/A
Late events: N/A

0-2 days: 45.04%
3-10 days: 28.12%
11-30 days: 10.54%
1 mo-1 year: 10.65%
TF TAVR new cerebral DW MRI lesions

Percent of TAVR Patients with new MRI lesions

- Fairbanks 2012: 77.7%
- Kohler 2010: 84%
- Ghan 2010: 73%
- Astavil 2010: 92%
- Rhodes 2011: 69%
- Uddin 2014: 82%
- Clean TAVI 2016: 98%
- Protavi C 2017: 100%

Average of 4.1 new lesions per patient
Six studies provided a total of 366 patients; 177 in the EPD and 189 in the control group. 4 different EPD's were used. There was no difference in stroke rate between EPD and control groups (6.6% vs. 5.9%, p>0.05). There was no difference in number of patients who developed new DW-MRI brain lesions (82% vs. 87.8%, p>0.05). Secondary outcomes analysis disclosed no difference on the number of lesions/patient or mortality. There was a significant 10.73 μl (4.73-16.72) less lesion volume/patient in the EPD group compared to the control group (p<0.05).
**CENTRAL ILLUSTRATION: Primary Safety and Efficacy Endpoints**

### A. 30-day MACCE Rates

- **Historical Performance**
  - Goal: 18.3%
  - (P noninferior <0.001)

- **Within SENTINEL Trial**
  -  \( p = 0.40 \)

### B. New Lesion Volume on MRI

- **Device**
  - 102.83
- **Control**
  - 177.98

\( p = 0.33 \)


Samir R. Kapadia et al. JACC 2017;69:367-377
Silent Embolic Events on DW-MRI after TAVR

- Affect 58-100% of patients
- Multiple infarcts (≤36, $\bar{x} = 4.6$)
- Associated with:
  - Neurocognitive decline
  - >2 fold risk of dementia
  - >3 fold risk of stroke

% of Subjects with New Lesions

- Arnold: 68%
- Astucci: 93%
- Fairbairn: 77%
- Ghanem: 72%
- Kahlert: 84%
- Knipp: 58%
- Rodes-Cabau: 68%
- Uddin: 82%
- CLEAN TAVI: 98%
- PROTAVI: 100%

References:
- Restrepo et al. Stroke 2002;33:2909
- Schwarz et al. Am Heart J 2011;162:736
- Vermeer et al. NEJM 2003;348:1215
- Vermeer et al. Stroke 2003;34:1126
- Arnold et al. JACC Cardiovasc Interv 2010;3:1126
- Fairbairn et al. Heart 2012;98:18
- Kahlert et al. Circ. 2010;121:870
- Linke et al. TCT 2014
- Rodes-Cabau et al. JACC Cardiovasc Interv 2014;7:1245
Stroke After Transcatheter Aortic Valve Replacement: Incidence, Risk Factors, Prognosis, and Preventive Strategies

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute episode of a focal or global neurological deficit with at least 1 of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting 1 side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke</td>
</tr>
<tr>
<td>Stroke: duration of a focal or global neurological deficit ≥ 24 h; OR &lt; 24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death</td>
</tr>
<tr>
<td>TIA: duration of a focal or global neurological deficit &lt; 24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct</td>
</tr>
<tr>
<td>No other readily identifiable nonstroke cause for the clinical presentation (eg, brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist*</td>
</tr>
<tr>
<td>Confirmation of the diagnosis by at least 1 of the following: Neurologist or neurosurgical specialist Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue</td>
</tr>
<tr>
<td>Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage</td>
</tr>
<tr>
<td>A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke definitions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disabling stroke: an mRS score of 2 or more at 90 days and an increase in at least 1 mRS category from an individual’s prestroke baseline</td>
</tr>
<tr>
<td>Non-disabling stroke: an mRS score of &lt; 2 at 90 days or one that does not result in an increase in at least 1 mRS category from an individual’s prestroke baseline</td>
</tr>
</tbody>
</table>

*Adapted from Kappetein et al., 2013* | mRS, Modified Rankin Scale. *Patients with nonlocal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction-based upon neuroimaging studies (CT scan or Brain MRI).* *Modified Rankin Scale assessments should be made by qualified individuals according to a certification process.*
Pooled effect estimates for the risk of death or stroke according to the use of cerebral embolic protection versus not during TAVR in all RCT to date
In this clinical event meta-analysis including the totality of RCT on this subject to date, EP was associated with a nonsignificant trend towards lower risk for death or stroke, which might correspond to a 3.5% absolute risk reduction and NNT of \(~28\) (i.e., for every \(~28\) patients assigned to an EP device, 1 death or stroke event may be averted). These findings suggest that EP may be a clinically relevant adjunctive strategy in patients undergoing TAVR. It is plausible that the magnitude of the benefit may be accentuated in patients at high risk for cerebrovascular complications. Additionally, because subclinical ischemic brain injury is associated with both cognitive and functional neurological impairment over time, prevention of subclinical embolization may be particularly important when treating younger and lower risk patients with severe aortic stenosis.

Gennaro Giustino et al. JACC 2017;69:465-466
% Reduction in New Lesion Volumes in Protected Territories (mm²)

SENTINEL IDE²
(n = 363)

42% Control
(n = 98)

Treatment
(n = 91)

CLEAN TAVI⁴
(n = 100)

41% Control
(n = 50)

Treatment
(n = 50)

MISTREX-CT²
(n = 65)

52% Control
(n = 33)

Treatment
(n = 32)

SENTINEL CPS (Treatment) & Without SENTINEL CPS (Control)
Median ± 95% Confidence Interval