Catheter-Based Approach for Prevention of Stroke in 2018: PFO, LAA closure and cerebral protection

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Disclosure Statement of Financial Interest
Saibal Kar, MD, FACC

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

**Affiliation/Financial Relationship**
- Grant/Research Support
- Consulting Fees/Honoraria
- Other Financial Benefit

**Company**
- Abbott Vascular, Boston Scientific, Edwards Lifesciences, WL Gore, Mitralign
- Abbott Vascular, Boston Scientific, WL Gore
- Valcare
Cardioembolic stroke

- Atrial fibrillation
- Valvular heart disease
- Cardiomyopathy
- Tumors
- Endocarditis
- Paradoxical embolism through a PFO
Cardioembolic stroke

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- Tumors
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- Paradoxical embolism through a PFO
Patent Foramen Ovale (PFO)
Normal variant presented in 20% of population

On Valsalva, PRA > PLA

Fig. 6.69 Patent foramen ovale. Heart held against the light (viewed from the right ventricle).
PFO Anatomy

Atrial septal aneurysm: (ASA) = Hypermobile Septum primum

Size of PFO is determined by the number of bubbles crossing from right to left during agitated saline injection in the right side.
Bubble study
Transesophageal Echo with bubble study

- Interatrial septum
- Left atrium
- Right atrium
Transcranial Doppler with bubble study
Pathophysiology of PFO and Ischemic Stroke

Blood clot passing through the PFO as a paradoxical embolism or originating in the PFO becoming an embolism
PFO Syndromes: Isolated or Combined

Migraine

Stroke

Hypoxemia

Courtesy Dr John Carroll
Recurrent Cerebrovascular Events Associated with PFO, Atrial Septal Aneurysm, or Both

- 581 patients with cryptogenic CVA
- ASA 300 mg/day
- 4 year F/U

Mas, et al. NEJM Dec 13, 2001
## PFO Stroke Trials

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</table>
Techniques of Closure
PFO Occluder in Clinical Trial

STARFlex (NMT Med)

Helex Septal Occluder (Gore)

PFO occluder (AGA Med)

Gore Septal Occluder (Gore)
Initial data from the CLOSURE I, RESPECT, and PC trial

• Non statistically significant reduction of stroke
• No safety issues with device
Clinical Data

- RESPECT trial long term data
- REDUCE trial
- CLOSE Trial
**Device Description:**
- Self-expandable double disc device lined with thin polyester fabric
- Linked together by a short connecting waist
- Nitinol wire mesh
- Recapturable, repositionable
- Self-centering
- Distal and proximal radiopaque marker bands
- MR conditional
- End screw to facilitate optimal handling

**Current status:**
- CE-Mark in 1998; currently available in > 80 countries worldwide
- FDA approved for PFO closure
# PFO Stroke Trials

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Long term follow up: Mean 5.9 years
Randomized to Amplatzer PFO occlude or
Medical treatment (Antiplatelet or oral anticoagulant)
RESPECT Final Results

Freedom from Recurrent Ischemic Stroke (Intention to Treat)

- **AMPLATZER™ PFO Occluder**
  - # strokes = 18
- **Medical Management**
  - # strokes = 28

Risk Reduction: 45%
HR: 0.55 (95% CI: 0.305, 0.999)
Log-rank 2-sided p-value: 0.046
## Subpopulation Differential Treatment Effect: RESPECT

<table>
<thead>
<tr>
<th>Factor</th>
<th>PFO Closure</th>
<th>Medical Management</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-45</td>
<td>4 (1.7%)</td>
<td>5 (2.4%)</td>
<td>0.53</td>
</tr>
<tr>
<td>46-60</td>
<td>5 (1.9%)</td>
<td>11 (4.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (1.9%)</td>
<td>10 (3.7%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Female</td>
<td>4 (1.7%)</td>
<td>6 (2.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Shunt Size</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None, trace or Moderate</td>
<td>7 (2.8%)</td>
<td>6 (2.5%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Substantial (Grade 3)</td>
<td>2 (0.8%)</td>
<td>10 (4.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Atrial Septal Aneurysm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>2 (1.1%)</td>
<td>9 (5.3%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Absent</td>
<td>7 (2.2%)</td>
<td>7 (2.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Index Infarct Topography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>5 (1.8%)</td>
<td>12 (4.5%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Small Deep</td>
<td>2 (3.5%)</td>
<td>1 (1.4%)</td>
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<tr>
<td>Other</td>
<td>2 (1.3%)</td>
<td>3 (2.2%)</td>
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</tr>
<tr>
<td><strong>Planned Medical Regimen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>4 (3.0%)</td>
<td>3 (2.5%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>5 (1.4%)</td>
<td>13 (3.6%)</td>
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**Primary Assessment**

- **Favors PFO Closure**
- **Favors MM**
# PFO Stroke Trials

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- **PC trial**
  - Close 664
  - 2:1 randomization
- **Control Arm:** Antiplatelet therapy (US and EU guidelines)
- **Any approved PFO device**
- **Amplatzer PFO**
- **Cryptogenic Stroke or retinal ischemia with a large PFO**
- **Composite all cause mortality, stroke, TIA, peripheral embolism**
- **Fatal and non fatal stroke**
- **MRI WMLs**
Co-Primary Endpoints

• Freedom from **recurrent clinical ischemic stroke** through at least 24 months

• Incidence of **new brain infarct** (defined as clinical ischemic stroke or silent brain infarct*) through 24 months

*New T2 hyperintense MRI lesion with diameter ≥3 mm; adjudicated by MRI core lab
Probability of Freedom from Clinical Evidence of Recurrent Ischemic Stroke.

77% reduction of risk of stroke

Hazard ratio for recurrent stroke, 0.23 (95% CI, 0.09–0.62)

P=0.002 by log-rank test

Annualized event rates
Closure: 0.39 per 100 person-years
Medical: 1.70 per 100 person-years

Second co-primary endpoint: new brain infarct, intention-to-treat

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<tr>
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<th>Closure (N=441)</th>
<th>Medical (N=223)</th>
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<tr>
<td>Subjects without Evaluation</td>
<td>58</td>
<td>46</td>
</tr>
<tr>
<td>Brain Infarct Evaluable</td>
<td>383</td>
<td>177</td>
</tr>
<tr>
<td><strong>Brain Infarct Present</strong></td>
<td><strong>22 (5.7%)</strong></td>
<td><strong>20 (11.3%)</strong></td>
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<tr>
<td>Recurrent Stroke Only</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Both</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Silent Brain Infarct Only</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Brain Infarct Absent</td>
<td>361 (94.3%)</td>
<td>157 (88.7%)</td>
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- Difference in incidence of new brain infarct of 5.6%
- Relative risk 0.51; 95% CI: 0.29 to 0.91
- p=0.024 after adjustment for multiple testing
- silent infarcts about twice as common as clinical stroke
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<td>Key Secondary Endpoints</td>
<td>Academic driven multicenter study</td>
<td>Sponsored by French Ministry of health</td>
<td>Mean follow up: 5.3 years</td>
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- **Close**
  - Any approved PFO device
  - Fatal and non fatal stroke

**Notes:**
- Academically driven multicenter study
- Sponsored by French Ministry of health
- Mean follow up: 5.3 years

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**Source:**
- Cedars-Sinai Medical Center
# CLOSE

## Methods

### Key inclusion criteria
- Recent (\(\leq 6\) months) ischemic stroke, confirmed by neuroimaging, mRS \(\leq 3\)
- Strictly defined causes of stroke other than PFO ruled out by appropriate investigations
- PFO with ASA \(> 10\) mm (TTE), PFO with large shunt \(> 30\) microbubbles (TTE,TEE) confirmed by echo core lab before randomization

### Key exclusion criteria
- Contraindication to oral anticoagulants and PFO closure
- Contraindication to antiplatelet therapy
- Increased bleeding risk
- Expected poor compliance or inability to attend follow-up visits
- Anatomical to device placement

## Outcomes
- **Primary**: fatal or nonfatal stroke
- **Secondary**: composite of ischemic stroke, TIA, or systemic embolism, all-cause mortality, vascular death, success of device implantation and success of PFO closure
- **Safety**: major procedural complications and major hemorrhagic complications
PFO closure vs. Antiplatelet therapy

HR = 0.03 (95% CI, 0 to 0.25); P < 0.001

Oral anticoagulants vs. Antiplatelet therapy

HR = 0.43 (95% CI, 0.1 to 1.5); P = 0.17

5-yr absolute risk reduction = 4.9%
1 avoided stroke at 5 years for every 20 (17 to 25) patients treated with closure

Safety issues

- Very low device or procedure related events
- No Device related deaths
- Slight increase in incidence of atrial fibrillation (5%) in the first few months following procedure
Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D.,
Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D.,
David S. Marks, M.D., and David L. Tirschwell, M.D.,
for the RESPECT Investigators®

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D.,
Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc.,
Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D.,
Christina Sjöstrand, M.D., Ph.D., Risto O. Roiné, M.D.,
David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D.,
for the Gore REDUCE Clinical Study Investigators®

Patent Foramen Ovale Closure vs. Antiplatelets after Stroke

J-L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouff, C. Arquizan, Y. Béjot, F. Vuillier,
O. Detante, C. Guidoux, S. Canaple, C. Vaduva, N. Dequatre-Ponchelle, I. Sibon, P. Garnier, A. Ferrier, S. Timsit,
E. Robinet-Borgomano, D. Sablé, J-C. Lacour, M. Zuber, P. Favrole, J-F. Pinel, M. Apoil, P. Reiner, C. Lefebvre,
P. Guérin, C. Piot, R. Rossi, J-L. Dubois-Randé, J-C. Eicher, N. Meneveau, J-R. Lusson, B. Bertrand, J-M. Schleich,
F. Godart, J-B. Thambo, L. Leborgne, P. Michel, L. Pierard, G. Turc, M. Barthelet, A. Charles-Nelson, C. Weimar,
T. Moulin, J-M. Juliard, and G. Chatellier, for the CLOSE Investigators®
October 18, 2016: FDA approves first PFO device

- The AMPLAZTER PFO device is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients,
  - predominantly between the ages of 18 and 60 years,
  - who have had a cryptogenic stroke due to a presumed paradoxical embolism,
  - as determined by a neurologist and cardiologist
  - following an evaluation to exclude known causes of ischemic stroke.
March 2018

• FDA approved the Gore Septal Occluder for PFO closure for secondary prevention of cryptogenic stroke
Summary (All PFO trials)

- In selected patients with cryptogenic stroke, PFO closure is safe and effective in reducing the risk of recurrent stroke compared to antiplatelet therapy/anticoagulant therapy alone.

- PFO with large right to left shunt and/or atrial septal aneurysms benefit the most from closure.

- Oral anticoagulants do not significantly reduce the risk of stroke recurrence in comparison to antiplatelet agents. However, there is a trend in favor of oral anticoagulants.

- These results are likely to change clinical practice and reduce the risk of stroke for this population.
Cardioembolic stroke

- Atrial fibrillation
- Valvular heart disease
- Cardiomyopathy
- Tumors
- Endocarditis
- Paradoxical embolism through a PFO
Left atrial appendage and stroke

• Ischemic stroke is the major complication associated with atrial fibrillation (AF)

• Long term anticoagulant therapy though effective in stroke prevention, have important limitations:
  – Compliance
  – Bleeding risk
  – Drug failure
In non-valvular AF, >90% of stroke-causing clots that come from the left atrium are formed in the LAA.

- In Valvular AF, stasis and clot formation can occur in any part of the left atrium.  

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Left atrial appendage closure (LAAC) strategies

Only FDA approved LAA closure device For stroke prophylaxis

Watchman Device Gen II

Amulet Device Coherex Device (Investigational in US)

Lariat device

Atriclip device
The interatrial septum is crossed using a standard transseptal access system and the procedure is performed with fluoroscopy and transesophageal echocardiography (TEE).
Access sheath is advanced over the guidewire into the left atrium and then navigated into the distal portion of the LAA over a pigtail catheter.
WATCHMAN Implant

Procedure: Navigating to the LAA

WATCHMAN is then deployed and released in the LAA.
Heart tissue grows over the WATCHMAN Implant, and the LAA is permanently sealed after approximately 45 days.
Clinical Evidence

- Randomized studies (Watchman device)
  - Two clinical trials
- Registries
- Post market registries
5-Year Outcomes After Left Atrial Appendage Closure
From the PREVAIL and PROTECT AF Trials

Vivek Y. Reddy, MD, Shephal K. Doshi, MD, Saibal Kar, MD, Douglas N. Gibson, MD, Matthew J. Price, MD, Kenneth Huber, MD, Rodney P. Horton, MD, Maurice Buchbinder, MD, Petr Neuzil, MD, PhD, Nicole T. Gordon, BSEE, David R. Holmes, Jr, MD, on behalf of the PREVAIL and PROTECT AF Investigators
Patient-Level Meta-Analysis
PROTECT AF and PREVAIL 5 years

<table>
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<th>Outcome</th>
<th>HR</th>
<th>p-value</th>
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<td>Efficacy</td>
<td>0.82</td>
<td>0.3</td>
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<td>0.9</td>
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<td>Ischemic stroke or SE</td>
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<td>0.08</td>
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<tr>
<td>Hemorrhagic stroke</td>
<td>0.2</td>
<td>0.0022</td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt;7 days</td>
<td>1.4</td>
<td>0.3</td>
</tr>
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<td>CV/unexplained death</td>
<td>0.59</td>
<td>0.03</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.73</td>
<td>0.04</td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>0.91</td>
<td>0.6</td>
</tr>
<tr>
<td>Major bleeding, non procedure-related</td>
<td>0.48</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Hazard Ratio (95% CI)

Favors WATCHMAN ← 1 → Favors warfarin

Cedars-Sinai Medical Center
### Patient-Level Meta-Analysis

**WATCHMAN Comparable To Warfarin For Ischemic Stroke**

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The diagram illustrates the comparison of WATCHMAN and warfarin for various clinical events, with hazard ratios and p-values provided for each.
Results

WATCHMAN Comparable to Warfarin for Ischemic Stroke

Patient-Level Meta-Analysis
WATCHMAN Superior for Hemorrhagic Stroke, CV Death, All-Cause Death, Post-procedure Bleeding

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<td>All stroke or SE</td>
<td>0.96 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.7 (0.08)</td>
<td></td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td>0.2 (0.0022)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt;7 days</td>
<td>1.4 (0.3)</td>
<td></td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>0.59 (0.03)</td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.73 (0.04)</td>
<td></td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>0.91 (0.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Major bleeding, non procedure-related</strong></td>
<td>0.48 (0.0003)</td>
<td></td>
</tr>
</tbody>
</table>
Patient-Level Meta-Analysis
WATCHMAN Superior Reduction in Disabling Strokes

Disabling Stroke defined as MRS ≥2
Two strokes in PREVAIL are excluded because the baseline MRS score was unavailable
Summary: 5 year follow up

- LAAC with the Watchman device provides stroke prevention in NVAF patients to a similar degree as oral anticoagulation

- By minimizing major bleeding, particularly hemorrhagic stroke, LAAC results in less disability or death than warfarin

Watchman Clinical Experience

- > 45,000 implants worldwide
- > 3500 cases performed in China
- Approved in US since March 2015
- Approved in most countries in Asia
- SALUTE trial completed in Japan
  - (Expected approval in 2019)
- Most well studied device:
  - 2000 patients with 6000 pt-year follow up
Who is the ideal patient with non-valvular AF for LAA closure: be a good clinician

Ideal for patients who are at risk for stroke, but:

- Cannot not
- Should not
- Will not

Take long term anticoagulants
Cardioembolic stroke

- Atrial fibrillation
- **Valvular heart disease**
- Cardiomyopathy

Cerebral Protection during TAVR

- Endocarditis
- Paradoxical embolism through a PFO
US TVT Registry Stroke Rate

% 30 Day Stroke

- 2012: 2.6
- 2013: 2.6
- 2014: 2.6
- 2015: 2.4

Stroke is not disappearing even with new TAVR Valves
Embolic Debris is Derived from a Variety of Sources During TAVR

- Arterial wall and calcific and atherosclerotic material from ascending arch
- Arterial wall and calcific and atherosclerotic material from transverse arch
- Foreign material from TAVR devices
- Myocardium
- Valve leaflet tissue and calcific deposits from stenotic valve

Courtesy: Dr Makkar
Claret Medical® Sentinel®
Cerebral Protection System

- Dual independent filters for embolic debris capture and removal
- Right transradial 6F sheath access
- Deflectable sheath facilitates cannulation of LCC
- Low profile in aortic arch to minimize interaction with TAVR delivery catheter
Claret Medical™ Sentinel™ Cerebral Protection System

Embolic Debris Captured from TAVI Procedures
Average STS score was 6.0% for SENTINEL subjects
Cerebral protection captured debris in 99% of patients and reduced cerebral damage by >42%

- Average STS score 6.0% (SD 3.2%)
- Cerebral embolic debris was captured in 99% of SENTINEL patients treated with Claret (n=103)

SENTINEL study shows neurologist adjudicated stroke rate for the control arm (unprotected TAVR) of 9.1%

<table>
<thead>
<tr>
<th>30-day Clinical Outcomes</th>
<th>Device Arm (n=234)</th>
<th>Control Arm (n=111)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any MACCE†</td>
<td>7.3% (17/234)</td>
<td>9.9% (11/111)</td>
<td>0.40</td>
</tr>
<tr>
<td>Death (all-cause)</td>
<td>1.3% (3/234)</td>
<td>1.8% (2/111)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>5.6% (13/231)</td>
<td>9.1% (10/110)</td>
<td>0.25</td>
</tr>
<tr>
<td>Disabling</td>
<td>0.9% (2/231)</td>
<td>0.9% (1/109)</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-disabling</td>
<td>4.8% (11/231)</td>
<td>8.2% (9/110)</td>
<td>0.22</td>
</tr>
<tr>
<td>AKI (Stage 3)</td>
<td>0.4% (1/231)</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td>TIA</td>
<td>0.4% (1/231)</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Sentinel Access Site Complications</td>
<td>0.4% (1/244)</td>
<td>N/A</td>
<td>0.53</td>
</tr>
</tbody>
</table>

†MACCE defined as All Death, All Stroke, Acute Kidney Injury (Stage 3) as 72 hours or discharge, whichever occurs first.

SENTINEL study shows significant procedural stroke reduction

Results from SENTINEL multi-national randomized trial of n=363 TAVI patients with vs. without protection using Sentinel™ cerebral embolic protection system shows a significant reduction in procedural stroke (63%)

SENTINEL trial. Data presented at Sentinel FDA Advisory Panel, February 23, 2017
Sentinel™ CPS captured debris in 99% of TAVI patients in SENTINEL

Clinical summary

• Transcatheter cerebral embolic protection (TCEP) is safe

• Embolic debris was captured in 99% of patients

• No significant reduction of new lesion volume by MRI

• Jun 5, 2017:
• FDA clears Claret Medical’s Sentinel TAVR stroke protection device for U.S. market
Is Cerebral Protection Necessary?

Would you take a chance and drive without a seatbelt?

You never know when you’ll need protection
Conclusions

• Cardioembolic stroke is a serious medical condition

• Device based therapies are available in prevention of stroke in a vulnerable population.

• Ongoing clinical trials will expand the indication and availability of new devices