Long-term Comparison of Patent Foramen Ovale (PFO) Closure versus Medical Therapy after Cryptogenic Stroke: Final Results of the RESPECT Trial

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On Behalf of RESPECT Investigators
# Disclosure Statement of Financial Interest

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

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
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<tbody>
<tr>
<td>• Grant/Research Support</td>
<td>St Jude Medical, Steering Committee, RESPECT Trial</td>
</tr>
<tr>
<td>• Consulting Fees/Honoraria</td>
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<tr>
<td>• Major Stock Shareholder/Equity</td>
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<td>• Royalty Income</td>
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<tr>
<td>• Ownership/Founder</td>
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<tr>
<td>• Intellectual Property Rights</td>
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<tr>
<td>• Other Financial Benefit</td>
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</table>
Background

• ~25% of all ischemic strokes are “cryptogenic”¹
• 34-46% of ischemic strokes occur between 18-60 years²,³
• PFO present in 40-50% of cryptogenic stroke patients⁴,⁵
• Young and middle aged patients have continued exposure to PFO-related recurrence risk
• No RCT has reported long-term outcomes of PFO closure

⁴ Lechat et al. NEJM 1988;318:1148-1152.  
Background

• In the ITT population, early and medium-term results in RESPECT showed point estimates in favor of closure but did not reach statistical significance.

• RESPECT protocol required follow-up until an FDA regulatory decision.

• Food and Drug Administration (FDA) Advisory Panel in May 2016 (data lock, August 2015).

• Following panel meeting, FDA requested a final analysis of long-term outcomes using updated data (data lock, May 2016) – these are presented today.

• Low event rates increase importance of longer follow-up.
Device Description:

- Self-expandable double disc device lined with thin polyester fabric and 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
RESPECT Trial

• Randomized, event-driven, open-label trial with blinded endpoint adjudication

• Patients randomized 1:1 to AMPLATZER PFO Occluder (device) vs. guideline-directed medical management (MM)

• 980 subjects enrolled from 2003 to 2011

• 69 sites in U.S. and Canada
Primary Endpoint

• Composite of:
  • Recurrent nonfatal ischemic stroke
  • Fatal ischemic stroke
  • Early post-randomization death (within 45 days)

• Stroke definition:
  • Acute focal neurological deficit due to cerebral ischemia with:
    • Neuroanatomically relevant infarct on imaging
    or
    • Symptoms >24 hours
Enrollment Criteria

Key Inclusion Criteria
• Cryptogenic stroke within last 9 months
• TEE-confirmed PFO
• 18-60 years
  - Patients > 60 at higher risk of recurrent stroke from non-PFO mechanisms

Key Exclusion Criteria
• Stroke due to identified cause such as:
  - Large vessel atherosclerosis (e.g., carotid stenosis)
  - Atrial fibrillation
  - Intrinsic small vessel disease (lacunar infarcts)
  - 11 other specific etiologies
• Inability to discontinue anticoagulation
Patient Flow

Enrolled

Assigned guideline-recommended medication regimen

Randomized 1:1

Device
- Implant within 21 days
- 1 month of aspirin + clopidogrel, then aspirin until 6 months
- Physician discretion thereafter

Medical Management
- Assigned guideline-recommended medication regimen

Follow-up:
- 1, 6, 12, 18, and 24 months
- Yearly after 24 months

- Warfarin
- Aspirin
- Clopidogrel
- Aspirin + dipyridamole
- Aspirin + clopidogrel (eliminated in 2006)
Objective of This Analysis

• To evaluate long term outcomes in RESPECT comparing the AMPLATZER™ PFO Occluder with guideline directed medical management
Methods

• Data from **August 2003 - May 2016**
• Intention-to-treat population
• Outcomes:
  - Recurrent ischemic strokes
  - Recurrent ischemic strokes of unknown mechanism
• Adjudications
  - **Adverse events** by the independent Data Safety Monitoring Board
  - **Ischemic stroke** by a blinded Clinical Events Committee
  - *Post hoc* adjudication of **cause** of recurrent ischemic stroke by a blinded committee of neurologists and a neuroradiologist (ASCOD phenotyping)
Baseline Characteristics Balanced Between Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AMPLATZER™ PFO Occluder (N=499)</th>
<th>Medical Management (N=481)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean ± SD</td>
<td>48 ± 10</td>
<td>46 ± 10</td>
</tr>
<tr>
<td>Male</td>
<td>54%</td>
<td>56%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>39%</td>
<td>41%</td>
</tr>
<tr>
<td>Family h/o CAD</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>COPD</td>
<td>0.8%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.6%</td>
<td>0%</td>
</tr>
<tr>
<td>History of DVT</td>
<td>4.0%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
<td>36%</td>
<td>35%</td>
</tr>
<tr>
<td>Substantial shunt</td>
<td>50%</td>
<td>48%</td>
</tr>
</tbody>
</table>
Procedural Results and Follow-up

• Technical Success*  99.1%
• Procedural Success**  96.1%
• Mean Follow-up:  5.9 years (0-12 years)
  - **Device**
    • Mean 6.3 years; Total 3141 patient-years
  - **Medical Management**
    • Mean 5.5 years; Total 2669 patient-years

*Delivery and release of the device
**Implantation without in-hospital SAE
Antithrombotic Medication Use During Follow-up

- **Device**: 79% of patients received medical management.
  - 6% received no medication.
  - 12% received other therapy.
  - 11% received dual antiplatelet treatment.
  - 20% received warfarin alone.

- **Medical Management**: 65% of patients received medical management.
  - 20% received warfarin alone.
  - 11% received dual antiplatelet treatment.
  - 6% received other therapy.
  - 64% received no medication.
RESULTS
RESPECT Final Results

Freedom from Recurrent Ischemic Stroke
(Intention to Treat)

Event-free Probability

- 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

# at Risk (KM Estimates)
AMPLATZER
499 (0%) 476 (1.4%) 464 (1.6%) 447 (1.6%) 421 (1.9%) 352 (2.6%) 262 (3.3%) 197 (4.5%) 128 (5.0%) 77 (5.0%) 41 (5.0%)

Medical Management (MM)
481 (0%) 433 (1.8%) 394 (3.2%) 380 (3.7%) 354 (4.7%) 282 (5.0%) 218 (5.0%) 150 (6.6%) 104 (7.3%) 59 (8.5%) 31 (12.5%)
RESPECT Final Results

Freedom from Recurrent Ischemic Stroke of Unknown Mechanism (Intention to Treat)

Event-free Probability

Risk Reduction: 62%
HR: 0.38 (95% CI: 0.18, 0.79)
Log-rank 2-sided p-value=0.007

# at Risk (KM Estimates)
AMPLATZER | 499 (0%) | 476 (1.2%) | 464 (1.2%) | 447 (1.2%) | 421 (1.5%) | 352 (2.0%) | 262 (2.3%) | 197 (2.3%) | 128 (2.3%) | 77 (2.3%) | 41 (2.3%)
MM | 481 (0%) | 433 (1.3%) | 394 (2.7%) | 380 (3.5%) | 354 (4.0%) | 282 (4.0%) | 218 (4.0%) | 150 (5.1%) | 104 (5.8%) | 59 (7.0%) | 31 (11.1%)
RESPECT Final Results

Freedom from Recurrent Ischemic Stroke
(Intention to Treat – Patients censored at age 60 years)

Event-free Probability

- AMPLATZER PFO Occluder (# strokes = 12)
- Medical Management (# strokes = 25)

Risk Reduction: 58%
HR: 0.42 (95% CI: 0.21, 0.83)
Log-rank 2-sided p-value = 0.010

Time from Randomization (Years)

# at Risk (KM Estimates)
- AMPLATZER
  - 475 (0%)
  - 443 (1.3%)
  - 418 (1.8%)
  - 383 (1.8%)
  - 345 (2.0%)
  - 285 (2.6%)
  - 203 (3.0%)
  - 150 (3.0%)
  - 97 (3.0%)
  - 55 (3.0%)
  - 29 (3.0%)
- MM
  - 463 (0%)
  - 402 (1.8%)
  - 353 (3.4%)
  - 321 (3.9%)
  - 289 (4.9%)
  - 220 (5.2%)
  - 159 (5.2%)
  - 109 (6.7%)
  - 76 (7.7%)
  - 44 (7.7%)
  - 22 (13.2%)
Interpretation

• These analyses support the hypothesis that PFO closure is preventing PFO-related recurrent strokes

• PFO-closure cannot prevent strokes from non-PFO related causes

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>Risk Reduction</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>0.55 (0.305-0.999)</td>
<td>45%</td>
<td>0.046</td>
</tr>
<tr>
<td>Stroke without known mechanism</td>
<td>0.38 (0.18-0.79)</td>
<td>62%</td>
<td>0.007</td>
</tr>
<tr>
<td>Age-censored analysis (&lt;60y)</td>
<td>0.42 (0.21-0.83)</td>
<td>58%</td>
<td>0.01</td>
</tr>
</tbody>
</table>
DSMB Adjudicated Procedure or Device Related SAEs

- No intra-procedural strokes
- No device embolization
- No device thrombosis
- No device erosion
- Major vascular complications (0.9%) and device explants (0.4%)
## Adjudicated SAEs of Interest

<table>
<thead>
<tr>
<th>Event Type</th>
<th>AMPLATZER™ PFO Occluder (N=499) [3141 Pt-Yrs]</th>
<th>Medical Management (N=481) [2669 Pt-Yrs]</th>
<th>P-value**</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Rate*</td>
<td>Events</td>
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<tr>
<td>Atrial fibrillation</td>
<td>8</td>
<td>0.25</td>
<td>4</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>18</td>
<td>0.57</td>
<td>15</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>7</td>
<td>0.22</td>
<td>11</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>18</td>
<td>0.57</td>
<td>4</td>
</tr>
</tbody>
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* Rate expressed as number of events per 100 patient-years
**Based on the normal approximation to a difference in Poisson rates
Conclusions

• In the RESPECT trial, PFO closure with the AMPLATZER™ PFO Occluder was more beneficial than medical management alone

• Collaboration between a cardiologist and neurologist is important for proper patient selection

• For patients with cryptogenic stroke and PFO, closure with the AMPLATZER™ PFO Occluder is an appropriate treatment option that reduces the risk of recurrent stroke
Thank You!

• To the incredible patients that volunteered to participate in this trial for their patience and willingness to help us answer this important question

• To the investigators and their tireless research teams for their professionalism and perseverance
The AMPLATZER™ PFO Occluder 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.