PFO Update 2017: Objectives

- Review recently released late outcomes of RESPECT trial and subsequent FDA approval of PFO closure with Amplatzer PFO occluder
- Discuss potential methods to assess CVA patients with PFO and determine if closure would be beneficial
- Discuss Cardiology-Neurology collaboration in the evaluation and management of PFO patients presenting with CVA
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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Chairman of Neurology, Tufts University School of Medicine

On Behalf of RESPECT Investigators
Background

• ~25% of all ischemic strokes are “cryptogenic”\(^1\)
• 34-46% of ischemic strokes occur between 18-60 years\(^2,3\)
• PFO present in 40-50% of cryptogenic stroke patients\(^4,5\)
• Young and middle aged patients have continued exposure to PFO-related recurrence risk
• No RCT has reported long-term outcomes of PFO closure

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 an analysis of long-term outcomes using updated data – these final analyses (data lock, May 2016) of RESPECT are presented today
• Low event rates increase importance of longer follow-up
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
    - 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
# 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
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)

<table>
<thead>
<tr>
<th></th>
<th>AMPLATZER</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>499 (0%)</td>
<td>481 (0%)</td>
</tr>
<tr>
<td>1</td>
<td>476 (1.4%)</td>
<td>433 (1.8%)</td>
</tr>
<tr>
<td>2</td>
<td>464 (1.6%)</td>
<td>384 (3.2%)</td>
</tr>
<tr>
<td>3</td>
<td>447 (1.6%)</td>
<td>380 (3.7%)</td>
</tr>
<tr>
<td>4</td>
<td>421 (1.9%)</td>
<td>364 (4.7%)</td>
</tr>
<tr>
<td>5</td>
<td>402 (2.6%)</td>
<td>262 (5.0%)</td>
</tr>
<tr>
<td>6</td>
<td>202 (5.3%)</td>
<td>218 (5.0%)</td>
</tr>
<tr>
<td>7</td>
<td>197 (4.5%)</td>
<td>150 (6.6%)</td>
</tr>
<tr>
<td>8</td>
<td>128 (5.0%)</td>
<td>104 (7.3%)</td>
</tr>
<tr>
<td>9</td>
<td>77 (5.0%)</td>
<td>60 (8.5%)</td>
</tr>
<tr>
<td>10</td>
<td>41 (5.0%)</td>
<td>31 (12.5%)</td>
</tr>
</tbody>
</table>
RESPECT Final Results

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

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

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

Risk Reduction: 58%

HR: 0.42 (95% CI: 0.21, 0.83)

Log-rank 2-sided p-value=0.010

# at Risk (Kaplan-Meier Estimation)

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLATZER</td>
<td>475(3%)</td>
<td>443(1.3%)</td>
<td>443(1.3%)</td>
<td>391(1.8%)</td>
<td>346(2.0%)</td>
<td>298(2.8%)</td>
<td>202(3.0%)</td>
<td>150(3.0%)</td>
<td>97 (3.0%)</td>
<td>55(3.0%)</td>
<td>20 (3.0%)</td>
</tr>
<tr>
<td>MM</td>
<td>463(3%)</td>
<td>402(1.6%)</td>
<td>353(3.4%)</td>
<td>321(3.5%)</td>
<td>299(4.5%)</td>
<td>220(5.2%)</td>
<td>159(5.2%)</td>
<td>108 (6.7%)</td>
<td>76 (7.7%)</td>
<td>44 (7.7%)</td>
<td>22 (13.2%)</td>
</tr>
</tbody>
</table>
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>Relative 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>
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
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.
Clinical Considerations in CVA Patients

- Assessment for occult atrial fibrillation
- Assessment for significant contributing vascular disease: extracranial carotid, intracranial and small vessel
- Assessment for the presence of a hypercoaguable state
- In the case of PFO Defects
  - Assessment of atrial septal aneurysm
  - Assessment of extent of right-left shunting at rest and during strain maneuver
- Assessment for co-morbidities contributing to stroke etiology:
  - HTN
  - Diabetes Mellitus
  - Hyperlipidemia
  - Vascular Disease
RoPE Score (Risk of Paradoxical Embolization)

- Developed by David Thaler, MD Neurologist Tufts and PI of the RESPECT Trial
- 6 Characteristics evaluated
  - HTN
  - DM
  - Prior CVA/TIA history
  - Cigarette Smoking
  - Cortical Infarct on Brain Imaging
  - Age
- Score generated indicating likelihood that the CVA was due to PFO and prediction of risk of recurrent CVA
- While the RoPE score is not advocated as a decision tool for PFO management, it provides significant information about the likelihood that a PFO defect was causative in the CVA event
Case Study #1

- Case Study
- 27 year old female
- Acute CVA with “locked in” syndrome May 2015
- Basilar artery occlusion: successful tPA treatment with complete resolution of symptoms
- TTE and TEE with prominent PFO, atrial septal aneurysm and high level shunt flow
- No atrial fibrillation, normal carotid duplex scan, normal blood pressure, normal blood sugar

- Risk of Paradoxical Embolism (RoPE) Score from MDcalc.com on 2/6/2017
- RESULT SUMMARY:
  - 10 points
  - 88% chance that stroke is due to PFO.
  - 2% risk of 2 year recurrence of stroke/TIA.
- INPUTS:
  - History of hypertension —> No
  - History of diabetes —> No
  - History of stroke or TIA —> No
  - Smoker —> No
  - Cortical infarct on imaging —> Yes
  - Age —> 27 years
Case Study #2

Clinical History and Findings

- 59 y.o. female sudden onset diplopia, nausea, vertigo, impaired gait and balance
- Local ED evaluation with tPA given
- Resolution of symptoms by time of presentation to SMC
- Brain MRI – normal
- TTE and TEE with large PFO vs small secundum ASD with prominent shunting at rest and with contrast injection and Valsalva strain
- Normal Carotid duplex scan

RoPE Score

- Risk of Paradoxical Embolism (RoPE) Score from MDCalc.com on 2/6/2017
- RESULT SUMMARY:
  - 5 points
  - 34% chance that stroke is due to PFO.
  - 7% risk of 2 year recurrence of stroke/TIA.
- INPUTS:
  - History of hypertension –> No
  - History of diabetes –> No
  - History of stroke or TIA –> Yes
  - Smoker –> No
  - Cortical infarct on imaging –> No
  - Age –> 59 years
Case Study # 3

Case History

- 62 year old woman presents with lacunar CVA
- Medical history of DM, HTN, prior TIA, palpitations and intermittent tachycardia
- Echo: normal LV function, moderate Left atrial enlargement, MAC with mild MR, PFO defect of atrial septum noted by color flow and bubble contrast injection
- Cardiac event monitor shows brief episodes of transient atrial fibrillation lasting 2-10 minutes with total Afib burden of 5% over 2 weeks

RoPE Score

- Risk of Paradoxical Embolism (RoPE) Score from MDCalc.com
- RESULT SUMMARY:
  - 2 points
  - 0% chance that stroke is due to PFO.
  - 20% risk of 2 year recurrence of stroke/TIA.
- INPUTS:
  - History of hypertension —> 0 = Yes
  - History of diabetes —> 0 = Yes
  - History of stroke or TIA —> 0 = Yes
  - Smoker —> 1 = No
  - Cortical infarct on imaging —> 0 = No
  - Age —> 62 years
Case Study #4

Case History

- 45 y.o. man presented with acute RLE DVT and left MCA embolic CVA 6/16
- TCD 2/5 rest, 4/5 Valsalva
- TEE: aneurysmal septum with PFO
- Warfarin started, Coag workup shows (+) antiphospholipid Ab
- Rectal bright red blood develops on warfarin 12/16
- GI evaluation: sigmoid colon adenoma, resection and ileostomy, 2/17, ileostomy revision
- Management options
  - Closure yes or no?
  - Long term anticoagulation yes or no?
  - Relationship of hypercoaguable state to the DVT event?

RoPE Score

- Risk of Paradoxical Embolism (RoPE) Score from MDCalc.com
- RESULT SUMMARY:
  - 7 points
  - 72% chance that stroke is due to PFO.
  - 6% risk of 2 year recurrence of stroke/TIA.
- INPUTS:
  - History of hypertension ——> 0 = Yes
  - History of diabetes ——> 1 = No
  - History of stroke or TIA ——> 1 = No
  - Smoker ——> 1 = No
  - Cortical infarct on imaging ——> 1 = Yes
  - Age ——> 45 years
Neuro-Heart Team Model Recommendation

• CVA patients with PFO defects should be evaluated by a dedicated multi-disciplinary team of Neurology and Cardiology specialists dedicated to collaboratively evaluate these patients and make treatment recommendations based upon a mutually agreed upon evaluation protocol.

• A complete evaluation includes, imaging studies (Brain, Vascular, Echo), assessment for possible atrial fibrillation and complete neurologic and cardiac clinical evaluations

• Patients should be presented with treatment options based upon evidence based review of potential therapies and given choices when appropriate for how to proceed with their treatment

• Efforts should be made when possible to achieve a team consensus and recommendation to patients about the most appropriate therapy for their specific clinical scenario
Thank You!

QUESTIONS?