Patent Foramen Ovale (PFO) Closure in Cryptogenic Stroke

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Patent Foramen Ovale (PFO)  
Background

- The foramen ovale is necessary for blood flow across the fetal atrial septum.

- In utero, oxygenated blood flows from the inferior vena cava into the right atrium and then crosses the PFO to the systemic circulation.

- Typically within 2 years of life (~ 75% of the population), the septum primum and the septum secundum fuse resulting in closure of the foramen ovale.

- A PFO is present in ~ 25% of the general adult population.

Patent Foramen Ovale

Considerations for Patent Foramen Ovale Closure

- Cryptogenic stroke
- Paradoxical embolization
- Decompression syndrome
- Orthodeoxia-platypnoea syndrome
Cryptogenic Stroke

- ~40% of ischemic strokes have no definable etiology, thus are termed cryptogenic.
- In cryptogenic stroke, ~45-55% of patients have a PFO; patients with a PFO tend to be younger and less likely to have traditional risk factors (i.e., hypertension, hypercholesterolemia, or current smoking) for stroke.
- Cryptogenic stroke is believed to be at least partially due to a venous source thrombus with paradoxical embolization to the brain via a PFO.
- Thus, PFO closure may decrease the recurrence of a cryptogenic stroke.


Patent Foramen Ovale (PFO) Closure for Cryptogenic Stroke
Randomized Clinical Trials

- RESPECT Trial (Amplatzer PFO Occluder)
- PC Trial (Amplatzer PFO Occluder)
- CLOSURE I Trial (STARFlex Septal Closure System)
- REDUCE Trial (GORE HELEX Septal Occluder)
- CLOSE Trial

REDUCE Clinical Study. NCT00738894.
Patent Foramen Ovale (PFO) Closure for Cryptogenic Stroke
Randomized Clinical Trials

- **RESPECT Trial** (Amplatzer PFO Occluder)
  - Significant decrease in recurrent stroke with device compared to medical therapy alone

- **PC Trial** (Amplatzer PFO Occluder)
  - No significant difference recurrent stroke/TIA between device and medical therapy alone

- **CLOSURE I Trial** (STARFlex Septal Closure System)
  - No significant difference in recurrent stroke/TIA between device and medical therapy alone


Patent Foramen Ovale (PFO) Closure for Cryptogenic Stroke
Randomized Clinical Trials

- **REDUCE Trial** (GORE Septal Occluder)
  - Significant decrease in recurrent stroke with device compared to anti-platelet therapy alone
  - 77% relative reduction in recurrent strokes with PFO closure at 2 years (number need to treat to prevent 1 new stroke is 28 at 2 years)

- **CLOSE Trial**
  - Significant decrease in recurrent stroke with device compared to medical therapy alone
  - 4.9% absolute risk reduction for recurrent strokes with PFO closure at 5 years (number need to treat to prevent 1 stroke is 20 at 5 years)
  - No significant difference in recurrent stroke between anti-platelet vs anti-platelet therapy

REDUCE Trial. NCT00738896.
CLOSE Trial. NCT00562289.
Primary end-point in PC Trial was a composite of death, nonfatal stroke, TIA, or peripheral embolism.

Primary end-point in RESPECT Trial was a composite of recurrent nonfatal/fatal ischemic stroke or early death after randomization.

Patients with only a TIA did not meet enrollment criteria for RESPECT Trial.

TIA also included as a primary end-point in CLOSURE Trial.

Patients with a lacunar stroke (likely due to intrinsic cerebral small-vessel disease) were excluded in RESPECT Trial.

Higher effective PFO closure (Amplatzer) rates in RESPECT Trial.

Greater procedural/device (STARFlex) related atrial fibrillation in CLOSURE I Trial.
Patent Foramen Ovale (PFO) Closure for Cryptogenic Stroke
Meta-Analysis of Randomized Trials


Amplatzer PFO Occluder
Patent Foramen Ovale (PFO) Closure Compared to Medical Therapy for Recurrent Stroke

RESPECT Trial

- Randomized to Amplatzer PFO occluder (device) vs. medical management (anti-platelet or anti-coagulation).
- 980 subjects (18-60 years old) enrolled from 2003 to 2011 at 69 sites in U.S. and Canada
  - patients > 60 years at higher risk of recurrent stroke from non-PFO mechanisms, thus excluded
- Also excluded from trial if stroke etiology could be identified such as large-vessel disease, lacunar infarct (likely due to intrinsic small-vessel disease), cardioembolic source or arterial hypercoagulable state.

RESPECT. N Engl J Med 2013;368:1092-100

RESPECT Trial: Non-Fatal Ischemic Strokes

Intention-to-Treat Cohort

Hazard ratio, 0.49 (95% CI, 0.22–1.11)
P=0.08 by log-rank test
Respect Trial: Non-Fatal Ischemic Strokes

As-Treated Cohort


Shunt Size and Atrial Septal Aneurysm

RESPECT Trial

Primary End-Point: Stroke or Early Death After Randomization (Intention-to-Treat Cohort):

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Closure Group</th>
<th>Medical-Therapy Group</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Log-Rank Test Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</table>
RESPECT Trial – Freedom from Recurrent Ischemic Stroke
Intention-to-Treat Cohort

Long-Term Follow-up (10 Years)

Defining Etiology of Recurrent Strokes in RESPECT Trial
ASCOD Phenotyping of Ischemic Stroke

- ASCOD:
  - A (atherosclerosis)
  - S (small vessel disease)
  - C (cardiac pathology)
  - O (other cause)
    - e.g., ruptured intracranial aneurysm, DIC, SLE, inflammatory, infectious, others
  - D (dissection)

- If a recurrent stroke could not be attributed to 1 of the 5 phenotypes above, then it was considered a stroke of undetermined mechanism (i.e., cryptogenic stroke).
Cryptogenic Stroke
Atrial Fibrillation

- Screening for atrial fibrillation in patients with a cryptogenic stroke/TIA by outpatient telemetry (up to 30 days) resulted in an atrial fibrillation detection rate of 12-23%.


RESPECT Trial – Freedom from Recurrent Ischemic Stroke of Undetermined Mechanism
Intention-to-Treat Cohort

Long-Term Follow-up (10 Years)

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

Thaler D, on Behalf of RESPECT Investigators. TCT 2016
Risk of Paradoxical Embolism (RoPE) Score

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
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<tbody>
<tr>
<td>No history of hypertension</td>
<td>+1</td>
</tr>
<tr>
<td>No history of diabetes</td>
<td>+1</td>
</tr>
<tr>
<td>No history of stroke or TIA</td>
<td>+1</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>+1</td>
</tr>
<tr>
<td>Cortical infarct on imaging</td>
<td>+1</td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>+5</td>
</tr>
<tr>
<td>30-39</td>
<td>+4</td>
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<tr>
<td>40-49</td>
<td>+3</td>
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<tr>
<td>50-59</td>
<td>+2</td>
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<tr>
<td>60-69</td>
<td>+1</td>
</tr>
<tr>
<td>≥70</td>
<td>0</td>
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</table>

<table>
<thead>
<tr>
<th>RoPE score</th>
<th>PFO-attributable fraction (95% CI)</th>
<th>Estimated stroke/TIA recurrence at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>0% (0-4)</td>
<td>20% (12-28)</td>
</tr>
<tr>
<td>4</td>
<td>28% (25-40)</td>
<td>12% (6-18)</td>
</tr>
<tr>
<td>5</td>
<td>34% (23-55)</td>
<td>7% (3-11)</td>
</tr>
<tr>
<td>6</td>
<td>62% (54-69)</td>
<td>5% (4-12)</td>
</tr>
<tr>
<td>7</td>
<td>72% (66-76)</td>
<td>6% (2-10)</td>
</tr>
<tr>
<td>8</td>
<td>84% (79-87)</td>
<td>6% (2-10)</td>
</tr>
<tr>
<td>9-10</td>
<td>88% (83-91)</td>
<td>2% (0-4)</td>
</tr>
</tbody>
</table>


Amplatzer PFO Occluder
FDA Approved: October 28, 2016

- “This 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.”
Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE)
RESPECT Trial

- An increase in DVT/PE events were seen on follow-up.
- PFO closure group on follow-up had significantly greater DVT/PE events compared to medical therapy group (p=0.006)
  - PFO closure group: 0.57 events per 100 patient years
  - Medical therapy group: 0.15 events per 100 patient years

Thaler D, on Behalf of RESPECT Investigators. TCT 2016
Patent Foramen Ovale (PFO) Closure in Cryptogenic Stroke

Summary

- A PFO is present in ~25% of the general adult population and is due to failure of the septum primum and secundum to fuse.
- There are several causes of ischemic stroke in which ~40% have no definable etiology, termed cryptogenic.
- In cryptogenic stroke, ~45-55% of patients have a PFO.
- Several randomized trials have now shown that PFO closure after a cryptogenic stroke significantly decreases recurrence compared to medical therapy alone, thus should be considered as a therapy.
- Collaboration between a cardiologist and neurologist is essential for proper patient selection.

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