The Clinical Problem

- Stroke is a leading cause of death and long term disability worldwide
- 85% of strokes are ischemic and most ischemic strokes occur in persons older than 65 years of age
- 40% of all ischemic strokes are considered cryptogenic
- Patent foramen ovale (PFO) has been associated with cryptogenic stroke

Circulation. 2002;105:2625-2631
PFO Anatomy

- PFO, which is present in 15% to 35% of unselected adults, is a vestige of fetal circulation
- Results from failure of the primum and secundum septa to fuse postnatally
- Persistence of the one-way valve allows right to left blood flow when the right atrial pressure exceeds left atrial pressure

Circulation 2005;112:1063-72

PFO Anatomy


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PFO and the Risk of Stroke

- A case controlled study first suggested that there was a markedly higher frequency of PFO in patients with cryptogenic stroke who were younger than 55 years of age
- 54% vs 10%


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PFO and the Risk of Stroke

Cryptogenic stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Cryptogenic stroke (%)</th>
<th>Atrial septal anomaly (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>study1</td>
<td>30.1</td>
<td>1.2</td>
<td>2.5 (1.2-5.5)</td>
<td>20.3</td>
</tr>
<tr>
<td>study2</td>
<td>25.0</td>
<td>1.1</td>
<td>3.0 (1.5-6.3)</td>
<td>15.7</td>
</tr>
</tbody>
</table>

- Gateway to the arterial circulation for venous thromboemboli
- In situ thrombosis
- Atrial tachyarrhythmia (although patients with interatrial septal abnormalities and stroke have a lower thresholds for induction of atrial fibrillation, this arrhythmia is almost never documented in patients with cryptogenic stroke and PFO)

Cryptogenic Stroke

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Evaluation

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Treatment

- Treatment options include pharmacologic approach with antiplatelet or anticoagulant agents and mechanical approaches surgical or percutaneous.

Percutaneous Closure

- Following a Decision to treat
  - Standard Rt. Heart cath procedure
  - TEE or ICE recommended
  - Average time < 1 hour
  - Typically home within 1 day
  - Standard follow-up
  - Minimum 325mg ASA daily (some also prescribe Plavix for 1-6 mos post-implant)
HELEX OCCLUDER

Percutaneous Closure

Balloon sizing of the PFO further delineates size and anatomical considerations
(i.e. compliance of overlapped septum primum.)
Percutaneous Closure

CardioSEAL is placed in the PFO with Left, Right atrial arms appropriately deployed.

PFO is occluded as a pathway for embolic event.
Acute Complications

- Malposition / device embolization
- Device fracture
- Cardiac perforation
- Air embolism or thrombus on wire or sizing balloon
- Arrhythmia usually atrial reported about 2 - 3% usually self-terminating weeks to months
- Vascular complications
- Death
- Fatal Pulmonary Emboli
- Major Hemorrhage

Late Complications

- Residual shunt that can occur in up to 20% of patients
- Thrombus on device 1.2 - 2.5%
- TIA or Stroke 0.2 - 4.9%
- Device erosion 0.1%
- Late device embolization
- Infection
- Atrial arrhythmia

CardioSEAL in a sheep heart explanted at 90 days.

Note excellent endothelial response.
CLOSURE I is the first randomized controlled trial to be completed that compares the safety and efficacy of percutaneous PFO closure to medical therapy alone for secondary transient ischemic attack (TIA) and stroke prevention. Investigators led by Anthony J. Furlan, MD, of Case Western Reserve University School of Medicine (Cleveland, OH), randomized 910 patients age 60 or younger with both PFO and either cryptogenic stroke or TIA to 1 of 2 strategies: Medical therapy (aspirin 325 mg daily, warfarin target INR 2.0-3.0, or a combination of the two) Percutaneous PFO closure with the StarFlex closure device (NMT Medical, Boston, MA) plus anticoagulation (diploged 75 mg for 6 months and aspirin 325 mg for 2 years), the primary composite endpoint (stroke or TIA at 2 years, 30-day mortality, or neurologic mortality from 31 days to 2 years) was nonsignificantly improved in the device closure group, driven by a slight improvement in TIA. Stroke rates, meanwhile, were almost identical (table 1).

**Table 1. CLOSURE I: Two-Year Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>StarFlex</th>
<th>Medical Therapy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>5.9%</td>
<td>7.7%</td>
<td>0.30</td>
</tr>
<tr>
<td>TIA</td>
<td>3.3%</td>
<td>4.6%</td>
<td>0.39</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>3.1%</td>
<td>3.4%</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Baseline shunt size and presence of atrial septal aneurysm made no difference in the ability of PFO closure to prevent the primary endpoint, and alternative explanations that had nothing to do with paradoxical embolism could be found for roughly 80% of the recurrent strokes and TIA.

RESPECT TRIAL

- We enrolled 980 patients (mean age, 45.9 years) at 69 sites. The medical-therapy group received one or more antiplatelet medications (74.8%) or warfarin (25.2%). Treatment exposure between the two groups was unequal (1,184 patient-years in the medical-therapy group, P = 0.009) owing to a higher dropout rate in the medical-therapy group. In the intention-to-treat cohort, 8 patients in the closure group and 16 in the medical-therapy group had a recurrence of stroke (hazard ratio with closure, 0.49; 95% confidence interval [CI], 0.22 to 1.11; P = 0.08). The between-group difference in the rate of recurrent stroke was significant in the prespecified per-protocol cohort (6 events in the closure group vs. 14 events in the medical-therapy group; hazard ratio, 0.37; 95% CI, 0.14 to 0.96; P = 0.03) and in the as-treated cohort (5 events vs. 16 events; hazard ratio, 0.27; 95% CI, 0.10 to 0.75; P = 0.07). Serious adverse events occurred in 23.9% of the patients in the closure group and in 21.6% in the medical-therapy group (P = 0.63). Procedure-related or device-related serious adverse events occurred in 23.9% of the patients in the medical-therapy group, but the rate of atrial fibrillation or device thrombus was not increased.
**RESPECT TRIAL**

- **CONCLUSIONS** In the primary intention-to-treat analysis, there was no significant benefit associated with closure of a patent foramen ovale in adults who had had a cryptogenic ischemic stroke. However, closure was superior to medical therapy alone in the prespecified per-protocol and as-treated analyses, with a low rate of associated risks. (Funded by St. Jude Medical; RESPECT ClinicalTrials.gov number, NCT00465270.)

**PC TRIAL**

- **PC Trial: Closure Not Effective** The PC Trial, led by Bernhard Meier, MD, of Bern University Hospital (Bern, Switzerland), enrolled 414 patients with PFO and prior ischemic stroke, transient ischemic attack (TIA), or peripheral thrombotic event at 29 centers worldwide. Patients were randomized to receive medical therapy (n = 210) or PFO closure (n = 214) with the Amplatzer device. Over a mean follow-up duration of approximately 4 years, results for the primary endpoint (composite of death, nonfatal stroke, TIA, or peripheral embolism) as well as the individual component endpoints of nonfatal stroke and TIA all favored closure but did not reach statistical significance (Table 2). Table 2. PC Trial: Intention-to-Treat Analysis (n = 214).

<table>
<thead>
<tr>
<th></th>
<th>Closure (n = 214)</th>
<th>Medical Therapy (n = 210)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Composite</strong></td>
<td>3.4%</td>
<td>5.2%</td>
<td>0.63 (0.24-1.62)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Nonfatal Stroke</strong></td>
<td>0.5%</td>
<td>2.4%</td>
<td>0.20 (0.02-1.72)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>TIA</strong></td>
<td>2.5%</td>
<td>3.3%</td>
<td>0.71 (0.23-2.24)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

However, with lower than expected event rates, the trial is underpowered, the researchers caution. “Thus, there is a risk of a type II error in our trial,” they write, “that is, a clinically relevant benefit of the closure of patent foramen ovale might exist but we were unable to detect it.”

**CONCLUSIONS**

- Next steps will likely include pooling the CLOSURE I, PC Trial, and RESPECT studies to understand what high-risk patients might benefit from PFO closure.
- **REDUCE study, sponsored by Gore Medical, is currently ongoing.** As an aside, many doctors point out that it is quite likely future trials—**WILL HAVE A HARD TIME enrolling patients because many physicians were already convinced that PFO closure was effective for reducing the risk of stroke.**

"HELLO HERE IS YOUR COUMADIN FOR LIFE OR WOULD YOU PREFER CLOSURE AND PLAVIX FOR 6 MONTHS?"
ASD – SEPTUM SECUNDUM

• 1) the presence of an ostium secundum ASD, 2) left to right shunting across the ASD, 3) maximal ASD diameter of <20 mm, 4) a distance of >5 mm from the margins of the defect to the mitral and tricuspid valves, superior vena cava, right upper pulmonary vein and coronary sinus, and 5) dilation of the right ventricle with evidence of right ventricular volume overload. 6) QP/QS now controversial (historically >1.5:1). 7) Atrial fibrillation.

THANK YOU

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