PFO and Stroke:
Take an aspirin and call me when we prove closure works

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Director, Vascular Neurology fellowship
Hospital of the University of Pennsylvania
Disclosures

- Consulting:
  - Glaxo Smith Kline, protocol development

- Research:
  - Local Principal Investigator Gore REDUCE PFO Closure Trial
  - National Co-Principal Investigator Glaxo Smith Kline Prophylactic neuroprotectant study in high risk surgical patients
  - NIH:
    - U01-DK060990 (Prospective renal insufficiency cohort, stroke endpoint adjudication committee)
    - UM1 HL088957-06 NIH/NHLBI (CT Surgery Network, sub-investigator)

- I will be talking about off-label PFO closure!
Patent Foramen Ovale (PFO)

- Fibrous adhesions fail to seal the foramen ovale
  - An integral component of the fetal circulation
Patent Foramen Ovale (PFO)

• Common finding:
  - Autopsy studies report prevalence ranging from 17-29%
  - Echo studies range widely depending on methods used

• Few population-based TEE studies
  - Largest had 581 subjects, 25.6% had a PFO

Association of PFO and Stroke

Meta-analysis of case control studies comparing 2014 stroke patients to 2020 non-stroke controls

OR 1.8 (95% CI: 1.3-2.7) overall

OR 3.1 (95% CI: 2.3-4.2) <55 years old

Association Between PFO and Stroke May Be Weaker Than Thought

- Case-control study including 1072 subjects who underwent TEE, including 519 randomly selected controls from population
  - Adjusted for age, sex, and vascular risk factors
  - Blinded echo interpretation
- No association of stroke with PFO
  - Stroke of known cause OR 0.95 (95%CI: 0.6-1.6)
  - Cryptogenic stroke OR 1.3 (95%CI: 0.8-2.1)
- No impact of size or detection of PFO at rest

PFO and Stroke Mechanism

- Paradoxical Embolism is most commonly ascribed:
  - Right-to-left shunting of venous emboli
  - 2-22% of these patients have been shown to have proximal leg or pelvic thrombosis
  - Among 60 Patients with pulmonary embolism, 6 had DWI lesions on MRI
    - 15/60 (25%) had a PFO on TEE
    - DWI lesions were seen in 33% of patients with PFO vs 2.2% of patients without PFO

Alternative Stroke Mechanisms

• *In situ* thrombosis within the PFO or ASA
  - PFO patients are more likely to have reduced LA EF and LA spontaneous echo contrast

• Atrial arrhythmia
  - Higher rate of inducible atrial arrhythmia in patients with PFO undergoing EP studies
  - Atrial arrhythmias also associated with ASA

PFO Closure Debates
Important Questions

• What is the risk of stroke recurrence in patients with stroke or TIA and a PFO?
• What is the optimal approach to secondary stroke prevention in patients with a PFO?
• Does biologic plausibility = clinical efficacy?
PFO and Risk of Stroke Recurrence
Risk of Paradoxical Embolism (RoPE) Study

- Patient level meta-analysis of 12 cryptogenic stroke cohorts
- RoPE score predicts likelihood of identifying a PFO
  - Start with 10 points
  - Subtract 1 point for each of the following:
    - HTN, DM, smoker, history of stroke, subcortical infarct and each decade from 30 up to 70
  - 71 year-old with HTN, DM, smoking, prior stroke, and acute lacune has a RoPE score of 0
  - 29 year-old with an acute cortical infarct and no vascular risk factors has a RoPE score of 10

RoPE Score Predicts Presence of PFO

<table>
<thead>
<tr>
<th>RoPE score</th>
<th>No. of patients</th>
<th>Prevalence of patients with a PFO, % (95% CI)(^a)</th>
<th>PFO-attributable fraction, % (95% CI)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>613</td>
<td>23 (19-26)</td>
<td>0 (0-4)</td>
</tr>
<tr>
<td>4</td>
<td>511</td>
<td>35 (31-39)</td>
<td>38 (25-48)</td>
</tr>
<tr>
<td>5</td>
<td>516</td>
<td>34 (30-38)</td>
<td>34 (21-45)</td>
</tr>
<tr>
<td>6</td>
<td>482</td>
<td>47 (42-51)</td>
<td>62 (54-68)</td>
</tr>
<tr>
<td>7</td>
<td>434</td>
<td>54 (49-59)</td>
<td>72 (66-76)</td>
</tr>
<tr>
<td>8</td>
<td>287</td>
<td>67 (62-73)</td>
<td>84 (79-87)</td>
</tr>
<tr>
<td>9-10</td>
<td>180</td>
<td>73 (66-79)</td>
<td>88 (83-91)</td>
</tr>
</tbody>
</table>

RoPE Score Predicts Freedom From Stroke Recurrence

<table>
<thead>
<tr>
<th>POINT SCORE</th>
<th># CS patients with PFO*</th>
<th>Estimated Two Year Stroke Recurrence Rate (Kaplan-Meier, with 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>108</td>
<td>16% (9% to 24%)</td>
</tr>
<tr>
<td>4</td>
<td>148</td>
<td>9% (4% to 14%)</td>
</tr>
<tr>
<td>5</td>
<td>186</td>
<td>3% (0% to 6%)</td>
</tr>
<tr>
<td>6</td>
<td>236</td>
<td>4% (2% to 7%)</td>
</tr>
<tr>
<td>7</td>
<td>263</td>
<td>2% (0% to 4%)</td>
</tr>
<tr>
<td>8</td>
<td>233</td>
<td>3% (0% to 5%)</td>
</tr>
<tr>
<td>9-10</td>
<td>150</td>
<td>1% (0% to 2%)</td>
</tr>
</tbody>
</table>

PFO is Low Risk for Recurrence

Among 15 studies with medically treated PFO patients, the absolute rate of recurrent ischemic stroke was:

1.6 events per 100 person-years

(95% CI: 1.1 – 2.1)

### RoPE Study

<table>
<thead>
<tr>
<th>TEE Findings</th>
<th>All PFO Patients With At Least Some TEE Data (n=1294)</th>
<th>RoPE Score &gt;6 (n=637)</th>
<th>RoPE Score ≤6 (n=657)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large no. of bubbles vs not large</td>
<td>64.4% (695/1079)</td>
<td>67.4% (347/515)</td>
<td>61.7% (348/564)</td>
<td>0.5286</td>
</tr>
<tr>
<td>Shunt at rest vs no shunt</td>
<td>69.6% (484/695)</td>
<td>67.6% (238/352)</td>
<td>71.7% (246/343)</td>
<td>0.4474</td>
</tr>
<tr>
<td>Hypermobile septum vs not</td>
<td>25.3% (320/1265)</td>
<td>23.0% (144/626)</td>
<td>27.5% (176/639)</td>
<td>0.1063</td>
</tr>
</tbody>
</table>

PFO indicates patent foramen ovale; RoPE, Risk of Paradoxical Embolism; and TEE, transesophageal echocardiography.

*P values from generalized mixed models (TEE variables only) after adjusting for random site effect.
Optimal Treatment of Stroke Patients With PFO
Treatment Options for PFO Patients

- Antiplatelet drugs
- Anticoagulation
- Closure*
  - Surgical
  - Percutaneous

*Closure does not preclude long term medical therapy
Medical Therapy

- There are no class I data
- The existing data have failed to find a statistical difference between warfarin and aspirin
- Warfarin is beneficial in high risk cardioembolic sources, antiplatelet medication is best in other stroke etiologies
Review of PFO Closure Studies

- Closure I (North America)
  - Began enrollment in 2003, published in 2012

- PC Trial (Europe)
  - Began enrollment in 2000, published in 2013

- RESPECT trial (North America)
  - Began enrollment in 2003, published in 2013
Review of PFO Closure Studies

- REDUCE study (Europe and North America)
  - 2008 – ongoing (planned completion in 2015)
  - Enrolled ~500 of planned 660

- CLOSE Study (France)
  - 2007 – ongoing (planned completion 2016)
  - Enrolled ~600 of planned 900

Total: ~2,800 patients randomized since 2000

3 studies completed
Why Have PFO Closure Studies Been So Slow to Enroll?
Possible PFO-related Stroke is Rare?

- Strokes in the US annually: 700,000
- ~1/3 are patients < 65 years: 233,333
- ~1/3 are “cryptogenic”: 77,777
- ~45% will have a PFO: 35,000
So What Is The Issue Here?

MR. LAZY
by Roger Hargreaves

MR. GREEDY
by Roger Hargreaves
Perhaps PFO Closure is Unpopular?

The number of procedures performed has exploded

Increasing by 5800% from 1998 - 2004

PFO Humanitarian Device Exemption

In 2006, the FDA rescinded the Humanitarian Device Exemption (HDE) that applied to PFO occluder devices primarily due to the fact that they were being used > 4,000 times per year.

Since that time, PFO closure devices are only available using an investigational device exemption (IDE).

Off label use of ASD occluder devices to close PFOs has persisted at an uncertain rate.

Percutaneous Closure

- At one academic center that was participating in a PFO closure RCT, off-label closure outnumbered closure in the study 3:1
  - Patients who were closed off-label were older, had a higher prevalence of vascular risk factors, and a larger shunt volume compared to those in the study

CLOSURE-I

A prospective, multicenter, randomized controlled trial to evaluate the safety and efficacy of the STARFlex Septal Closure System vs. best medical therapy in patients with a stroke or TIA due to presumed paradoxical embolism through a patent foramen ovale

**CLOSURE-I Design**

- **Stroke or TIA in prior 6 months**
- **PFO confirmed by TEE**
- **Age ≤ 60**
- **No hypercoagulable disorder, DVT**
- **Randomized 909 subjects 1:1**
  - Medical therapy (n=462)
    - aspirin or warfarin or both
  - PFO closure with STARFlex device (n=447)
    - with aspirin and clopidogrel x 6 months then aspirin alone
- **Primary endpoint: 2-year stroke or TIA, all cause death first 30 days, neurological death after 30 days**
  - Locally not blinded to randomization
  - Centrally adjudicated by blinded events committee
## CLOSURE I—Key Results

<table>
<thead>
<tr>
<th></th>
<th>STARFlex</th>
<th>Medical</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>5.5%</td>
<td>6.8%</td>
<td>0.37</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.9%</td>
<td>3.1%</td>
<td>0.79</td>
</tr>
<tr>
<td>TIA</td>
<td>3.1%</td>
<td>4.1%</td>
<td>0.44</td>
</tr>
</tbody>
</table>
## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>STARFlex</th>
<th>Medical</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major vascular complications</td>
<td>3.2%</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.6%</td>
<td>1.1%</td>
<td>0.11</td>
</tr>
<tr>
<td>AFib</td>
<td>5.7%</td>
<td>0.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombus by TEE (2 of 4 had strokes)</td>
<td>1.0%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Periprocedural stroke</td>
<td>0.8%</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Causes of the Recurrent Strokes

Alternate causes of recurrent TIA or stroke were apparent in 87% of patients in the closure group and 76% of patients in the medical-therapy group

- **STARFlex**
  - 3 periprocedural
  - 3 Afib
  - 1 cardiac cath complication
  - 3 lacunar
  - 3 cryptogenic

- **Medical therapy**
  - 3 lacunar
  - 1 Afib (s/p off label closure)
  - 1 arch atheroma
  - 1 vasculitis
  - 6 multiple (migraine, risk factors, psychogenic)
  - 1 cryptogenic
CLOSURE I Conclusions

- First completed RCT of PFO closure for stroke prevention
- PFO closure with STARFlex not better than medical therapy alone
- Device associated with complications including AFib and stroke
CLOSURE I Pitfalls

- Enrolled TIAs
  - Clinically “definite” definition was laudable
  - MRI negative TIAs face very low risk of stroke

- Alternative causes for recurrent stroke
  - Alternative causes for index stroke!

- Device-specific issues
  - Nearly half of strokes in device arm were related to the device, a quarter in 1st 30 days
  - AFib frequent

- Inadequate power, inadequate follow up
Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

Bernhard Meier, M.D., Bindu Kalesan, Ph.D., Heinrich P. Mattle, M.D., Ahmed A. Khattab, M.D., David Hildick-Smith, M.D., Dariusz Dudek, M.D., Grethe Andersen, M.D., Reda Ibrahim, M.D., Gerhard Schuler, M.D., Antony S. Walton, M.D., Andreas Wahl, M.D., Stephan Windecker, M.D., and Peter Jüni, M.D., for the PC Trial Investigators*

- 414 patients with cryptogenic stroke and PFO
  Randomized to closure with the Amplatzer PFO device vs medication
- At least 2 years of clinical follow-up
- Primary outcome: composite of death, stroke, TIA, or peripheral embolism
- Europe, Canada, Brazil, Australia
PC Trial Results

- The mean duration of follow-up was 4.1 years
- Primary end point occurred in 7/204 closure patients (3.4%) and 11/210 medical patients (5.2%)
  - HR 0.63; 95% CI, 0.24 to 1.62; P = 0.34
- Nonfatal stroke occurred in 1 (0.5%) closure patient and 5 (2.4%) medical patients
  - HR, 0.20; 95% CI, 0.02 to 1.72; P = 0.14
## PC Trial Results

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PFO Closure</th>
<th>Medical Therapy</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>7/204 (3.4)</td>
<td>11/210 (5.2)</td>
<td>0.63 (0.24–1.62)</td>
<td>0.10</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 yr</td>
<td>1/91 (1.1)</td>
<td>6/97 (6.2)</td>
<td>0.16 (0.02–1.31)</td>
<td>0.63</td>
</tr>
<tr>
<td>≥45 yr</td>
<td>6/113 (5.3)</td>
<td>5/113 (4.4)</td>
<td>1.22 (0.37–3.99)</td>
<td>0.99</td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4/47 (8.5)</td>
<td>2/51 (3.9)</td>
<td>2.09 (0.38–11.4)</td>
<td>0.09</td>
</tr>
<tr>
<td>No</td>
<td>3/157 (1.9)</td>
<td>9/159 (5.7)</td>
<td>0.32 (0.09–1.18)</td>
<td>0.78</td>
</tr>
<tr>
<td>Cardiovascular index event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>5/165 (3.0)</td>
<td>8/163 (4.9)</td>
<td>0.58 (0.19–1.76)</td>
<td>0.83</td>
</tr>
<tr>
<td>Transient ischemic attack or pulmonary embolism</td>
<td>2/39 (5.1)</td>
<td>3/47 (6.4)</td>
<td>0.78 (0.13–4.66)</td>
<td>0.22</td>
</tr>
<tr>
<td>&gt;1 Previous cardiovascular event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2/76 (2.6)</td>
<td>6/79 (7.6)</td>
<td>0.28 (0.06–1.41)</td>
<td>0.09</td>
</tr>
<tr>
<td>No</td>
<td>5/128 (3.9)</td>
<td>5/131 (3.8)</td>
<td>0.99 (0.29–3.45)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
• 900 patients with cryptogenic stroke and PFO
• Randomized to closure with the Amplatzer PFO device versus current medical standard of care
• At least 2 years of clinical follow-up
• Primary outcome: stroke
• US and Canada
Primary Endpoint Analysis – ITT Cohort

- 3/9 device group patients did not have a device at time of second stroke
RESPECT – Secondary Analyses

- Per protocol
  - 6 strokes vs 14 strokes, HR 0.37; 95% CI 0.14 – 0.96, p =0.03

- As treated
  - 5 strokes vs 16 strokes, HR 0.27; 95% CI 0.10 – 0.75, p0.007)
### RESPECT Trial Results

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Closure Group</th>
<th>Medical-Therapy Group</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value by Log-Rank Test</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>9/499 (1.8)</td>
<td>16/481 (3.3)</td>
<td>0.49 (0.22–1.11)</td>
<td>0.08</td>
<td>0.52</td>
</tr>
<tr>
<td>Age 18–45 yr</td>
<td>4/230 (1.7)</td>
<td>5/210 (2.4)</td>
<td>0.70 (0.19–2.60)</td>
<td>0.59</td>
<td>0.73</td>
</tr>
<tr>
<td>Age 46–60 yr</td>
<td>5/262 (1.9)</td>
<td>11/266 (4.1)</td>
<td>0.41 (0.14–1.17)</td>
<td>0.08</td>
<td>0.73</td>
</tr>
<tr>
<td>Sex Male</td>
<td>5/268 (1.9)</td>
<td>10/268 (3.7)</td>
<td>0.45 (0.15–1.31)</td>
<td>0.13</td>
<td>0.73</td>
</tr>
<tr>
<td>Sex Female</td>
<td>4/231 (1.7)</td>
<td>6/213 (2.8)</td>
<td>0.57 (0.16–2.02)</td>
<td>0.38</td>
<td>0.73</td>
</tr>
<tr>
<td>Shunt size</td>
<td></td>
<td></td>
<td>0.07</td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>None, trace, or moderate</td>
<td>7/247 (2.8)</td>
<td>6/244 (2.5)</td>
<td>1.03 (0.35–3.08)</td>
<td>0.95</td>
<td>0.73</td>
</tr>
<tr>
<td>Substantial</td>
<td>2/247 (0.8)</td>
<td>10/231 (4.3)</td>
<td>0.18 (0.04–0.81)</td>
<td>0.01</td>
<td>0.73</td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
<td></td>
<td></td>
<td>0.10</td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Present</td>
<td>2/180 (1.1)</td>
<td>9/169 (5.3)</td>
<td>0.19 (0.04–0.87)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>7/319 (2.2)</td>
<td>7/312 (2.2)</td>
<td>0.89 (0.31–2.54)</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Index infarct topography</td>
<td></td>
<td></td>
<td>0.39</td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Superficial</td>
<td>5/280 (1.8)</td>
<td>12/269 (4.5)</td>
<td>0.37 (0.13–1.04)</td>
<td>0.05</td>
<td>0.73</td>
</tr>
<tr>
<td>Small deep</td>
<td>2/57 (3.5)</td>
<td>1/70 (1.4)</td>
<td>1.76 (0.16–19.93)</td>
<td>0.64</td>
<td>0.73</td>
</tr>
<tr>
<td>Other</td>
<td>2/157 (1.3)</td>
<td>3/139 (2.2)</td>
<td>0.56 (0.09–3.34)</td>
<td>0.52</td>
<td>0.73</td>
</tr>
<tr>
<td>Planned medical regimen</td>
<td></td>
<td></td>
<td>0.20</td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>4/132 (3.0)</td>
<td>3/121 (2.5)</td>
<td>1.14 (0.26–5.10)</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>5/367 (1.4)</td>
<td>13/359 (3.6)</td>
<td>0.34 (0.12–0.94)</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>
Meta-analysis (Random Effects) PFO Closure Studies (ITT)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Hazard ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>Lower limit</td>
</tr>
<tr>
<td>Closure I</td>
<td>0.780</td>
<td>0.450</td>
</tr>
<tr>
<td>PC Trial</td>
<td>0.630</td>
<td>0.242</td>
</tr>
<tr>
<td>RESPECT</td>
<td>0.490</td>
<td>0.216</td>
</tr>
<tr>
<td></td>
<td>0.666</td>
<td>0.442</td>
</tr>
</tbody>
</table>

\[ I^2 = 0 \]
### Study name

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<td>PC Trial</td>
<td>0.630</td>
<td>0.242</td>
</tr>
<tr>
<td>RESPECT</td>
<td>0.490</td>
<td>0.216</td>
</tr>
<tr>
<td></td>
<td>0.545</td>
<td>0.293</td>
</tr>
</tbody>
</table>

**Meta-analysis (Random Effects)**

**PFO Closure Studies (ITT)**

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**Favors Closure**

**Favors Control**
Meta-Meta-Analysis

- 12 meta-analyses published since 2013
  - 10 in cardiology journals, 1 gen med, 1 neurology
- 2 concluded no benefit for Stroke/TIA
- 2 concluded benefit for stroke/TIA
- 5 concluded no benefit for stroke
  - 2 reported benefit in Amplatzer studies
- 2 concluded no benefit for stroke/TIA/death
- 1 concluded no benefit in stroke/death

Wolfrum et al. Heart. 2014 Mar;100(5):389-95
Kitsios et al. Stroke. 2013 Sep;44(9):2640-3
Thoughts

• Potential bias in stroke ascertainment in open label study (PC Trial)

• Per protocol and as treated analyses fail to account for bias and confounding
  ➢ Drop out rate and cross over rate are major issues

• Why was the effect of atrial septal aneurysm so different in the two studies?
Thoughts

- Outcome rate was very low (consistent with RoPE study)
  - Unstable results:
    - If there had been just 1 more stroke in closure arm 10/499 and 16/481: RR 0.60 (0.28-1.31) p=0.20
    - And just 1 less stroke in the medical arm 10/499 and 15/481: RR 0.64 (0.29-1.42) p=0.27
  - Small absolute benefit if one exists

- Enrollment extended for a very long period of time likely related to off-label PFO closure
  - Undermines validity and generalizability

- Meaningful adverse events rare but they occur
Potential Risks of Percutaneous PFO Closure
Risk of Atrial Fibrillation

Khan et al. JACC Cardiovasc Interv. 2013 Dec;6(12):1316-23
Risk of Atrial Fibrillation

- 7 day event loop recorder studies in 70 stroke patients with known etiology compared to 40 stroke patients with recent PFO closure found an equal rate of atrial fibrillation (~15%)  
- However, the PFO closure patients had significantly fewer risk factors for atrial fibrillation:
  - 16 years younger on average
  - Less hypertension and diabetes
  - Smaller left atrial dimension, left ventricular mass, and less mitral regurgitation on echocardiogram.

Estimated the rate of device embolization to be 0.3% - 3.5%

Between 2002 – 2011 the FDA received reports of >100 patients who experienced septal erosion

- Leads to tamponade emergent cardiac surgery
- Estimated the rate of septal erosion to be 0.1 – 0.2%
- Appears limited to Amplatzer device
- At least 6 reported cases in off-label use for PFO closure

FDA Safety Warning of ASD/PFO Closure Devices From October, 2012
Cost of Percutaneous PFO Closure

- At our center the total reimbursement from insurance companies is >$25,000
- The billing charges are >$95,000!!!
A Neurologist’s Perspective on PFO and Stroke

- Biologically plausible interventions have failed numerous times in the past when tested rigorously
- The risk of recurrent stroke on aspirin is very low
- Percutaneous PFO closure is expensive, has a small but real risk of complication with unknown long term sequelae, and does not replace medical therapy
- Off-label PFO closure has been, and continues to be, rampant and greatly undermines studies
- Most recent studies suggestive but it is uncertain who, if anyone benefits
  - Meta-analyses make post-hoc decisions and assumptions
AAN Practice Parameter 2004 still holds today:

“Clinicians who encounter patients with cryptogenic stroke and PFO (and/or atrial septal aneurysm) should encourage them to consider participating in research protocols.”
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Can the recurrent stroke be from a defined mechanism or are they once again cryptogenic?

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Increasing Infarct Size →

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Incidence rates of recurrent cerebrovascular events by type of medical treatment (antiplatelet vs anticoagulant) in medical treatment

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<th>Outcome [total n of studies (n of comparative studies)]</th>
<th>Antiplatelets IRs (per 100 person-years) including all studies</th>
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<td>Total events [10(8)]</td>
<td>5.77 (3.49-9.54)</td>
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<td>3.32 (1.91-5.78)</td>
<td>2.53 (1.38-4.67)</td>
<td>0.56 (0.32-1.00)</td>
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IRR of anticoagulants vs antiplatelets (95% CI), including only comparative studies

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CS patients with PFO presented at European Stroke Conference, Lisbon, 2012. Thaler et al
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