PFO Closure for Stroke Prevention: Meta-Analysis Evidence from Non-Randomized Trials

David Thaler, MD, PhD, FAHA
Director, The Comprehensive Stroke Center at Tufts Medical Center
## Conflicts

<table>
<thead>
<tr>
<th>RESPECT Trial</th>
<th>Steering Committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA Medical Corporation</td>
<td>Consultant (modest)</td>
</tr>
<tr>
<td>WL Gore Associates</td>
<td>Consultant (modest)</td>
</tr>
<tr>
<td>RoPE Study, NINDS</td>
<td>Co-PI</td>
</tr>
</tbody>
</table>
Points of agreement

- PFO is common in the general population
- PFO is causally related to stroke – probably via paradoxical embolism
- Not all discovered PFOs in stroke patients are pathogenic
- Not all discovered PFOs in cryptogenic stroke patients are pathogenic
- Closing incidental PFOs is not likely to offer benefit
- For any treatment the benefit (reduced stroke) must outweigh the risks (hemorrhage, procedural complications, late device complications) in a medically meaningful way
Current literature RE: PFO Closure

- Mostly case series
- Poor, non-standard case selection
- Small numbers
- Unblinded outcomes adjudication by non-neurologists
- Clinical (not scheduled) f/u
Figure 2. Cumulative number of patients recruited in studies of different designs over a period of 16 years.
## Meta-Analysis of Observational Studies

(Kitsios et al, in press)

<table>
<thead>
<tr>
<th></th>
<th>Medical treatment studies</th>
<th>Percutaneous closure studies</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of studies</td>
<td>19</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Total N of included patients</td>
<td>2020</td>
<td>7104</td>
<td></td>
</tr>
<tr>
<td>Prospective design</td>
<td>68%</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>Mean age of patients (median, (25th - 75th percentile), n)</td>
<td>47 (43-53), n=19</td>
<td>46.8 (43-50.5), n=48</td>
<td>0.711</td>
</tr>
<tr>
<td>% Males (median, (25th - 75th percentile), n)</td>
<td>56.7 (51-60), n=18</td>
<td>53 (48-56), n=45</td>
<td>0.052</td>
</tr>
<tr>
<td>% Atrial septal aneurysm (median, (25th - 75th percentile), n)</td>
<td>20.9 (15.9-33.6), n=12</td>
<td>31.2 (22.7-36.2), n=44</td>
<td>0.069</td>
</tr>
<tr>
<td>% Hypertension (median, (25th - 75th percentile), n)</td>
<td>23.9 (16.5-31.3), n=16</td>
<td>22.5 (17-33), n=33</td>
<td>0.945</td>
</tr>
<tr>
<td>% Diabetics (median, (25th - 75th percentile), n)</td>
<td>5 (3-9), n=15</td>
<td>5.5 (3.5-7.5), n=28</td>
<td>0.895</td>
</tr>
<tr>
<td>% Hyperlipidemia (median, (25th - 75th percentile), n)</td>
<td>16.1 (13.1-28.9), n=12</td>
<td>24 (15-32), n=25</td>
<td>0.496</td>
</tr>
<tr>
<td>% Smoking (median, (25th - 75th percentile), n)</td>
<td>32.5 (24.5-41.9), n=15</td>
<td>22.7 (16.4-33), n=29</td>
<td>0.024</td>
</tr>
<tr>
<td>% with stroke as the index event (median, (25th - 75th percentile), n)</td>
<td>75.8 (67.7-100), n=18</td>
<td>65 (47.3-72), n=40</td>
<td>0.009</td>
</tr>
<tr>
<td>Use of structured screening instrument for recurrent stroke detection</td>
<td>79%</td>
<td>46%</td>
<td>0.014</td>
</tr>
<tr>
<td>Recurrent events ascertained by Neurologist</td>
<td>79%</td>
<td>54%</td>
<td>0.058</td>
</tr>
<tr>
<td>Recurrent events documented by neuroimaging</td>
<td>53%</td>
<td>44%</td>
<td>0.521</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of cohort studies investigating incidence rates of recurrent cerebrovascular events in patients with PFO and under medical treatment or PFO closure.

* Mann-Whitney test or Chi-square test, as appropriate.

IQR: interquartile range
Infection 8y after CardioSEAL implantation by Dr. X complicated by stroke

“Dr. X told me that he’s never had a long term complication of a PFO closure.” – My patient enrolled in RESPECT
Meta-Analysis of Observational Studies

(Kitsios et al, in press)
Meta-Analysis of Observational Studies

(Kitsios et al, in press)

Incidence Rates of Recurrent Strokes (per 100 person-years)

- Medical arm, RCT: 1.4 (0.7-2.4)
- Medical arms, Observational studies: 2.7 (1.8-3.9)
- Closure arm, RCT: 1.3 (0.7-2.3)
- Closure arms, Observational studies: 0.4 (0.2-0.6)
The results of CLOSURE I challenge the credibility of a substantial body of observational evidence strongly favoring mechanical closure over medical therapy.

Further randomized trial data are needed to determine precisely the effects of closure on stroke recurrence.
The endpoint of interest is recurrent paradoxical embolism *not* recurrent stroke.

PFO May Be Causal For The First Stroke But Unrelated To Subsequent Ischemic Events

*Mono et al and CLOSURE I*
What happens when you have multiple causes of recurrent events?

_The PICSS conundrum_
PICSS: Results

2-year rates of recurrent stroke or death in patients with different PFO size and shunt

<table>
<thead>
<tr>
<th></th>
<th>No PFO (n=398)</th>
<th>Small PFO (n=119)</th>
<th>Large PFO (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event rate</td>
<td>15.4</td>
<td>18.5</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Combination of PFO and atrial septal aneurysm (n=44) no riskier than PFO alone (n=159)

Mohr et al NEJM 345: 1444, 2001
Proportion of patients with CS and PFO with incidental PFO

Case A
Proportion of CS patients with PFO: 40%
Proportion of controls with PFO: 25%

Patients with CS & PFO
(50% of PFOs are incidental)

Patients with CS unrelated to PFO
(PFO rate=25%, identical to controls)

Probability PFO is incidental in CS cases =

\[
\text{Prevalence of PFO in controls} \times (1 - \text{Prevalence of PFO in CS cases}) \\
\text{Prevalence of PFO in CS cases} \times (1 - \text{Prevalence of PFO in controls})
\]

Risk of recurrent paradoxical embolism

= “PFO propensity” x Probability of stroke recurrence
Risk of Paradoxical Embolism (RoPE) Study
NINDS R01 NS062153-01
Risk of Paradoxical Embolism (RoPE) Study

1. To build the largest database of CS using existing cohort studies of patients with CS studied with TEE, both with and without PFO.
2. Model 1: Characteristics that predict PFO
3. Model 2: Characteristics that predict recurrent CS
4. Combine Models 1 & 2: Characteristics that predict PFO-related recurrence
5. Validation of the combined model on clinical trial populations (RESPECT, PC-Trial, CLOSURE I, REDUCE)
## Results: Component databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Collaborator(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CODICIA</td>
<td>Joaquin Serena</td>
</tr>
<tr>
<td>French PFO/ASA</td>
<td>Jean-Louis Mas</td>
</tr>
<tr>
<td>APRIS</td>
<td>Marco DiTullio</td>
</tr>
<tr>
<td>Bern (published)</td>
<td>Krassen Nedeltchev, Marie-Luise Mono</td>
</tr>
<tr>
<td>Bern (unpublished)</td>
<td>Heinrich Mattle</td>
</tr>
<tr>
<td>PICSS</td>
<td>Shunichi Homma</td>
</tr>
<tr>
<td>Lausanne</td>
<td>Patrik Michel</td>
</tr>
<tr>
<td>Toronto</td>
<td>Cheryl Jaigobin</td>
</tr>
<tr>
<td>Sapienza</td>
<td>Emanuele Di Angelantonio, Federica Papetti</td>
</tr>
<tr>
<td>Tufts</td>
<td>David Thaler</td>
</tr>
<tr>
<td>German</td>
<td>Christian Weimar</td>
</tr>
<tr>
<td>NOMASS</td>
<td>Mitchell Elkind</td>
</tr>
</tbody>
</table>
Results: Clinical Variables

- Age (at time of stroke)
- Gender
- Sex
- Race
- Coronary artery disease
- Diabetes
- Hypertension
- Hyperlipidemia
- Prior spells: number, date(s), event(s)
- Smoking status: current
- Medication at time of spell:
  - Statin
  - Antiplatelet
  - Anticoagulant
  - OCP/HRT
- Index event: date
Results: Neuroradiological variables

1. Index stroke seen: yes, no
2. Location: superficial, deep
3. Size: large, small
4. Multiple: yes, no
5. Prior stroke: yes, no
Results: Echocardiographic variables

1. Mobility of septum
   - hypermobile (ASA), normal
2. PFO size
   - large, small
3. Shunt at rest
   - yes, no
Results: PFO prevalence by site according to RoPE

PFO Prevalence by Study

- Bern (n=159)
- Bern (Unpub) (n=249)
- Toronto (n=121)
- Tufts (n=113)
- Lausanne (n=92)
- CODICIA (n=485)
- French PFO/ASA (n=581)
- PICSS (n=250)
- Sapienza (n=343)
- NOMASS (n=60)
- German (n=1122)
- APRIS (n=90)

Percent with PFO
### Results: Prevalence of clinical variables

<table>
<thead>
<tr>
<th>Incident event type, % stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Status</strong></td>
</tr>
<tr>
<td>n=</td>
</tr>
<tr>
<td>Age in years, mean</td>
</tr>
<tr>
<td>Gender, % male</td>
</tr>
<tr>
<td>Race, % white</td>
</tr>
<tr>
<td>CAD, % yes</td>
</tr>
<tr>
<td>DM, % yes</td>
</tr>
<tr>
<td>HTN, % yes</td>
</tr>
<tr>
<td>Cholesterolemia, % yes</td>
</tr>
<tr>
<td>Current Smoker, % yes</td>
</tr>
<tr>
<td>History of Stroke, % yes</td>
</tr>
<tr>
<td>History of Tia, % yes</td>
</tr>
<tr>
<td>Hx Stroke or Tia, % yes</td>
</tr>
<tr>
<td>Statins, % yes</td>
</tr>
<tr>
<td>Antiplatelets, %yes</td>
</tr>
<tr>
<td>Anticoagulants, %yes</td>
</tr>
<tr>
<td>Incident event type, % stroke</td>
</tr>
<tr>
<td>HRT/OCP, % yes (females only)</td>
</tr>
</tbody>
</table>
### Results: Outcomes

<table>
<thead>
<tr>
<th>Location</th>
<th>Total</th>
<th>Stroke</th>
<th>TIA</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRIS</td>
<td>21</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Bern (pub)</td>
<td>25</td>
<td>7</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>CODICIA</td>
<td>40</td>
<td>10</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>French PFO/ASA</td>
<td>42</td>
<td>23</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Lausanne</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PICSS</td>
<td>47</td>
<td>24</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Tufts</td>
<td>9</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>German</td>
<td>133</td>
<td>61</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>322</strong></td>
<td><strong>143</strong></td>
<td><strong>105</strong></td>
<td><strong>74</strong></td>
</tr>
</tbody>
</table>
Model 1: “PFO propensity”

Clinical variables
Consistency Across Sites of Relationship of *Gender* (Male v. Female) and Odds of having a PFO

* adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers

In Males, PFO is less likely (OR<1)  
In Males, PFO is more likely (OR>1)
In older cases, PFO is more likely (OR>1)

In older cases, PFO is less likely (OR<1)

* adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers.
In cases with DM, PFO is more likely (OR>1)

In cases with DM, PFO is less likely (OR<1)
In cases with HTN, PFO is more likely (OR>1)

In cases with HTN, PFO is less likely (OR<1)

Consistency Across Sites of Relationship of *Hypertension* and Odds of having a PFO

* adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers

Odds Ratio (OR) for HTN (vs. no HTN)
Consistency Across Sites of Relationship of Smoking and Odds of having a PFO

In cases with Smoking, PFO is more likely (OR>1)

In cases with Smoking, PFO is less likely (OR<1)

* adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers

Odds Ratio (OR) for Current Smoking (vs. not)
Consistency Across Sites of Relationship of *History of Stroke or TIA* and Odds of having a PFO*

<table>
<thead>
<tr>
<th>Site</th>
<th>Odds Ratio (OR) for History of Stroke or TIA (vs. not)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CODICIA</td>
<td></td>
</tr>
<tr>
<td>FRENCH PFO/ASA</td>
<td></td>
</tr>
<tr>
<td>PICSS</td>
<td></td>
</tr>
<tr>
<td>LAUSANNE</td>
<td></td>
</tr>
<tr>
<td>SAPIENZA</td>
<td></td>
</tr>
<tr>
<td>GERMAN</td>
<td></td>
</tr>
<tr>
<td>APRIS &amp; NOMASS</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td></td>
</tr>
</tbody>
</table>

* adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers.

In cases with Hx Stroke/TIA, PFO is less likely (OR<1)

In cases with Hx Stroke/TIA, PFO is more likely (OR>1)
Subjects were significantly more likely to have a PFO if they had:
- Younger age
- No DM
- No HTN
- No smoking
- No prior h/o stroke/TIA

A trend to more likely to have a PFO if they had:
- No hyperlipidemia
- No CAD
- No statin use at time of index event
- No antiplatelet use at time of index event

There was no effect of:
- Gender
- Race
Model 1: “PFO propensity”
Neuroradiological variables
If seen, PFO is more likely (OR>1)

If seen, PFO is less likely (OR<1)

*Age adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers
If Superficial, PFO is more likely (OR>1)

If Superficial, PFO is less likely (OR<1)

*Age adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers.*
Consistency Across Sites of Relationship of *Large Infarct vs. Small/not seen* and Odds of having a PFO*

*Age adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers.*

If Large, PFO is less likely (OR<1)

If Large, PFO is more likely (OR>1)
Consistency Across Sites of Relationship of *Infarcts are Multiple vs. Single/Not Seen* and Odds of having a PFO*

*Age adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers.

- If Multiple, PFO is less likely (OR<1)
- If Multiple, PFO is more likely (OR>1)
With a prior stroke, PFO is more likely (OR>1)

With a prior stroke, PFO is less likely (OR<1)
Neuroradiological variables: Findings & Results

- Subjects were significantly *more likely to have a PFO* if they had:
  - An index stroke seen on neuroimaging
  - A large stroke
  - A superficial stroke

- A *trend to more likely to have a PFO* if they had:
  - No prior (*i.e.* chronic) infarct seen

- There was *no effect* of:
  - Multiple v single infarcts
## Estimated Probability of Pathogenic PFO by Propensity Quartile

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Sample Size</th>
<th>q1:less pfo</th>
<th>q2</th>
<th>q3</th>
<th>q4:more pfo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3022</td>
<td>755</td>
<td>756</td>
<td>756</td>
<td>755</td>
</tr>
<tr>
<td>pred</td>
<td>42%</td>
<td>22%</td>
<td>35%</td>
<td>47%</td>
<td>66%</td>
</tr>
<tr>
<td>pfo_03</td>
<td>42%</td>
<td>25%</td>
<td>30%</td>
<td>48%</td>
<td>66%</td>
</tr>
<tr>
<td>CR=15%</td>
<td>76%</td>
<td>46%</td>
<td>59%</td>
<td>81%</td>
<td>91%</td>
</tr>
<tr>
<td>CR=20%</td>
<td>66%</td>
<td>24%</td>
<td>42%</td>
<td>73%</td>
<td>87%</td>
</tr>
<tr>
<td>CR=25%</td>
<td>54%</td>
<td>0%</td>
<td>23%</td>
<td>64%</td>
<td>83%</td>
</tr>
</tbody>
</table>

CR = control rate (i.e. prevalence in the general population)
Conclusion

- The RoPE Study has successfully merged several databases of existing cohort studies.
- This is the largest database in existence of patients with CS and PFO that includes detailed clinical, neuroradiological, and echocardiographic data.
- Further analysis to model PFO propensity and the risk of recurrent CS are ongoing.
- These data will inform decisions regarding CS diagnosis and (hopefully) treatment decisions.
Acknowledgments

**Boston RoPE Team**
Jennifer Donovan
Marcia Landa
Robin Ruthazer
John Griffith
Morgan Clark-Coller

**Cardiology**
Jeffrey Kuvin
Jon Finley
Jessica Haffajee
Erica Brooks

**Neuroradiology**
Josh Kornbluth
Ed Feldmann

**RoPE Study Group**
Emanuele Di Angelantonio
Marco DiTullio
Mitchell Elkind
Shunichi Homma
Cheryl Jaigobin
David Kent (Principle Investigator)
Jean-Louis Mas
Heinrich Mattle
Patrik Michel
Marie-Luise Mono
Krassen Nedeltchev
Celine Odier
Federica Papetti
Joaquin Serena
David Thaler
Christian Weimar
What is certain?

- Predictors of recurrence are *not* firmly established
- Devices close holes
- Some FOs remain P after “closure”
- Devices seem to be LOW risk (but *not* NO risk)
- Even a low rate of procedure or device-related adverse events could nullify most or all of the potential benefit
- Case series are completely inadequate (and possibly misleading) for determining the risk:benefit of closure
- We must be honest with patients about what is known
- *More data are needed!***
Ongoing trials

• RESPECT: www.respectstudy.com

• REDUCE: www.clinical.goremedical.com/REDUCE
What’s the difference between a chicken and a pig’s approach to ham & eggs for breakfast?
The chicken has an interest but the pig is truly committed!
Thank you!