Patent Foramen Ovale: Diagnosis and Treatment

Anthony DeMaria
Judy and Jack White Chair in Cardiology
University of California, San Diego

At one time or another a Grantee, Sponsored Speaker or Ad-hoc Consultant for nearly all ultrasound contrast agent companies

**Patent Foramen Ovale**

- Congenital lesion resulting in a defect in the fossa ovalis smaller than an atrial septal defect
- Present in about 25% of autopsies and similar prevalence by echo
- Potential source of paradoxical emboli
- Potential role in migraines
- Uncertain role of medical and interventional therapy
Detection of PFO

- Color flow Doppler
- Contrast echo
  - Agitated saline or blood
  - Release of Valsalva
  - Multiple injections (at least two)
  - Higher sensitivity with lower extremity injection
  - Microbubble appearance in 4 cardiac cycles
False Contrast for PFO

• False negatives
  – Incomplete opacification of RA
  – Elevated LA pressure (eg Valsalva)
  – One injection or only brachial artery

• False positives
  – Pulmonary AVM
  – High signal to noise

Table 1  Potential cardioembolic sources

<table>
<thead>
<tr>
<th>Major risk sources</th>
<th>Minor or unclear risk sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>Recent myocardial infarction</td>
<td>Mitral annulus calcification</td>
</tr>
<tr>
<td>Previous myocardial infarction (LV aneurysm)</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathies</td>
<td></td>
</tr>
<tr>
<td>Cardiac masses</td>
<td></td>
</tr>
<tr>
<td>Intracardiac thrombus</td>
<td></td>
</tr>
<tr>
<td>Intracardiac tumours</td>
<td></td>
</tr>
<tr>
<td>Fibroelastoma</td>
<td></td>
</tr>
<tr>
<td>Marantic vegetation</td>
<td></td>
</tr>
<tr>
<td>Rheumatic valve disease (mitral stenosis)</td>
<td>Calcified aortic stenosis</td>
</tr>
<tr>
<td>Aortic arch atheromatous plaques</td>
<td>Atrial septal aneurysm</td>
</tr>
<tr>
<td>Endocarditis</td>
<td></td>
</tr>
<tr>
<td>Mechanical valve prosthesis</td>
<td>Giant Lambi’s excrescences</td>
</tr>
</tbody>
</table>

**Patent foramen ovale**
Role of PFO in Systemic Embolus

- **Con**
  - PFO present in about 25% at autopsy
  - Paradoxical embolism requires transit through a smaller orifice and against a pressure gradient
  - PFO could be a marker recurrence after closure

- **Pro**
  - PFO more prevalent in patients with cryptogenic stroke than the general population
  - Thrombi detected across or straddling PFO
Conclusions: Patent foramen ovale, alone or together with ASA, was not associated with an increased stroke risk in this multi-ethnic cohort.

Methods: . . . 1,100 stroke-free subjects older than 39 years of age (mean age 68.7 ±10 years)

Results: . . . Detected PFO in 164 subjects (14.9%) ; ASA was present in 27 subjects (2.5%) . . . follow-up of 79.7 ±28 months . . . After adjustment for demographics and risk factors, PFO was not found to be significantly associated with stroke (hazard ratio 1.64, 95% confidence interval 0.87 to 3.09). The same was observed in all age, gender, and race-ethnic subgroups.

J Am College of Cardiology Vol 49, No 7, 2007
Transcatheter treatment of ASA + PFO is safe and effective in patients with paradoxical embolism. The procedure effectively abolishes right-to-left shunt and decreases atrial septal mobility. Long-term prevention of recurrent events appears favorable when compared to patients with PFO alone.

Are Closure Devices Safe and Effective in Patients with Cryptogenic Stroke and PFO?
Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel Meeting on Patent Foramen Ovale Closure Devices

While clinical equipoise exists when there is a balance of countervailing forces or evidence, the situation for PFOs can more accurately be described as evidence-lacking. 
– Dr. William Maisel

Early Trials of PFO Closure

<table>
<thead>
<tr>
<th>Trial (year of publication)</th>
<th>N</th>
<th>Comparison</th>
<th>Follow-up (years)</th>
<th>Stroke outcome, N</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOSURE 1 (2012)</td>
<td>909</td>
<td>PFO closure&lt;sup&gt;a&lt;/sup&gt; vs. medical therapy&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
<td>12 vs. 13</td>
<td>0.90 (0.41–1.98) 0.79</td>
</tr>
<tr>
<td>PC trial (2013)</td>
<td>414</td>
<td>PFO closure&lt;sup&gt;a&lt;/sup&gt; vs. medical therapy&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.1</td>
<td>1 vs. 5</td>
<td>0.20 (0.02–1.72) 0.14</td>
</tr>
<tr>
<td>RESPECT (2013)</td>
<td>980</td>
<td>PFO closure&lt;sup&gt;a&lt;/sup&gt; vs. medical therapy&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.1</td>
<td>9 vs. 16</td>
<td>0.49 (0.22–1.11) 0.08</td>
</tr>
</tbody>
</table>

1. Randomized controlled trials of PFO closure to prevent recurrent stroke are required.
2. A “proof of principle” trial with pooled data demonstrating that PFO closure does prevent recurrent stroke could allow this question to be answered in a timely fashion, if sponsors are amenable to cooperating and sharing data. “Proof of device” trials demonstrating that an individual device effectively closes a PFO could be done separately.
3. “Off-label” closure should be discouraged. Enrollment in ongoing trials should be encouraged.
4. Patients and physicians should be educated about the lack of evidence of benefit of closure and the need for completion of trials.
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., Grefte 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 Juni, M.D., for the PC TOAST Investigators *

![Figure 1. Kaplan--Meier Cumulative Estimates of the Rate of the Primary End Point. PFO denotes patent foramen ovale.]

4. For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure (Class III; Level of Evidence A). (Revised recommendation)

5. In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT (Class IIb; Level of Evidence C). (New recommendation)

(Stroke. 2014;45:2160-2236.)
Limitations of Early Trials

- Uncertain diagnosis of stroke
- Short term follow
- Lack of anticoagulants

Subsequently 3 RCTs were published simultaneously in NEJM
Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke


Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Spåstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D., for the CORE REDUCE Clinical Study Investigators

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smallding, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators

Device Closure Versus Medical Therapy Alone for Patent Foramen Ovale in Patients With Cryptogenic Stroke
A Systematic Review and Meta-analysis

Rahman Shah, MD; Mannu Nayyar, MD; Ion S. Jovin, MD, ScD; Abdul Rashid, MD; Beatriz R. Bondy, MD; Tai-Hwang M. Fan, MD, PhD; Michael P. Flaherty, MD, PhD; and Sunil V. Rao, MD

Study Year (Reference) | Events/Patients, n/n | Risk Difference | Risk Difference (95% CI) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device Closure</td>
<td>MTA</td>
<td></td>
</tr>
<tr>
<td>PC, 2013 (7)</td>
<td>1/204</td>
<td>5/210</td>
<td>-0.019</td>
</tr>
<tr>
<td>RESPECT extended, 2017 (12)</td>
<td>18/499</td>
<td>28/481</td>
<td>-0.022</td>
</tr>
<tr>
<td>CLOSE, 2017 (10)</td>
<td>0/238</td>
<td>24/596</td>
<td>-0.040</td>
</tr>
<tr>
<td>REDUCE, 2017 (11)</td>
<td>6/441</td>
<td>12/223</td>
<td>-0.040</td>
</tr>
<tr>
<td>Total</td>
<td>26/1382</td>
<td>69/1510</td>
<td>-0.032</td>
</tr>
</tbody>
</table>

Heterogeneity: Q = 3.11; P = 0.38; I^2 = 3.62%
Atrial Fibrillation

A fib resolves within 30-45 days in 72% of patients
Patent foramen ovale closure versus medical therapy in cases with cryptogenic stroke, meta-analysis of randomized controlled trials

Elsayed Abo-salem ∙ Bernard Chaitman ∙ Tarek Helmy ∙ Eric Adjei Boakye ∙ Hassan Alkhawam ∙ Michael Lim

Journal of Neurology
https://doi.org/10.1007/s00415-018-8750-x

[Graphical representation showing comparisons between patent foramen ovale closure and medical therapy for stroke, transient ischemic attacks, atrial fibrillation, and all-cause death based on age, sex, and shunt size.]
### Why are Recent Trials More Positive?

- **Stricter definition of stroke**
- **More pts with large PFO and/or ASA**
  - 30 microbubbles in LA after 3 cardiac cycles
- **Use of anticoagulants as well as antiplatelets**
- **Longer follow-up**
Evaluation for Cryptogenic Stroke

- CT or MRI
- TEE
- Prolonged ambulatory ECG monitoring
- Intra- and Extracranial imaging
- Assessment for hypercoagulable state
- Cardiology-Neurology collaboration

PFO Closure vs Anticoagulants for A fib

- PFO closure
  - Prevent one stroke in five years in 20 pts

- Anticoagulants for A fib
  - Prevent one stroke in five years for 50 pts
PFO Closure; Unanswered Questions

• What PFO characteristics define risk
  – Size? Septal aneurysm?
• What antithrombotic regimen is optimal?
  – Anticoagulant or antiplatelet, and how long?
• How does age factor into closure benefit?
• Is there a benefit for TIA?
• How treat pts with other stroke risk factors?
• Is there an optimal device?

PFO: When to Close

• Young patients (probably < 55 yrs)
• True cryptogenic stroke
• Large PFO and/or atrial septal aneurysm
• Recurrent neurologic events
• Contraindications or failure of antithrombotics
• High risk for DVT

• Patient discussion (definition of minor procedure)
In patients with paradoxical cerebral embolism, migraine headaches are more frequent than in the general population, and transcatheter closure of the PFO results in complete resolution or marked reduction in frequency of migraine headache.
Closure for PFO

• For cryptogenic stroke – Probably yes
  – Especially with risk profile
  – Stroke is often severe
  – Data are supportive

• For migraines – Probably not
  – Might try for severe disabling refractory symptoms

• *We have been wrong before*
Cardiac perforation is a rare complication

Twenty-nine CEs were identified

Three deaths were reported

Factors Suggesting Need for PFO Closure

- Younger patient (<50 yr)
- No other cause of stroke identified
- Large PFO
- Coexisting atrial septal aneurysm
- Recurrent neurologic events
- Valsalva maneuver with event
- Failure of anticoagulation
- Intolerance of anticoagulation
- High risk for DVT or PE
Patent foramen ovale and migraine: a cross-sectional study from the Northern Manhattan Study (NOMAS)

Circulation. 2008 Sep 30;118(14):1419-24

- In this multiethnic, elderly, population-based cohort, PFO detected with transthoracic echocardiography and agitated saline was not associated with self-reported migraine. The causal relationship between PFO and migraine remains uncertain, and the role of PFO closure among unselected patients with migraine remains questionable.

Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache

- This trial confirmed the high prevalence of right-to-left shunts in patients with migraine with aura. Although no significant effect was found for primary or secondary end points, the exploratory analysis supports further investigation. The robust design of this study has served as the model for larger trials that are currently underway in the United States and Europe.

- Circulation. 2008 Mar 18;117(11):1397-404
Is patent foramen ovale closure indicated for migraine?

PFO Closure Is Not Indicated for Migraine

"Don’t Shoot First, Ask Questions Later"

The Migraine Intervention with STARFlex Technology (MIST) trial published in 2008 was a sham-controlled, blinded trial. The trial was clearly a negative trial in PFO closure for migraine that has dashed hopes for more clarity in the field, let alone a step toward device approval for this indication.

Transcatheter closure of PFO or ASD results in complete resolution of MHA in 60% of patients (75% of patients with migraine and aura) and improvement in symptoms in 40% of the remaining patients.
Transcatheter closure of PFO or ASD results in complete resolution of MHA in 60% of patients (75% of patients with migraine and aura) and improvement in symptoms in 40% of the remaining patients.

Patent foramen ovale and migraine: a quantitative systematic review

- The estimated strength of association between PFO and migraine was 5.13, and between PFO and migraine with aura the OR was 3.21. The grade of evidence was low.
- Six studies of PFO closure suggested improvement in migraine, but had a very low grade of evidence. Although PFO closure seemed to affect migraine patterns favourably, the very low grade of available evidence to support this association precludes definitive conclusions.

- The only prospective sham-controlled study of PFO closure for MA, MIST, was negative for all primary and secondary measures of migraine improvement. MIST did demonstrate an association between MA and severe PFO shunts prospectively. Difficulty with recruitment closed the MIST II and ESCAPE trials; the PREMIUM and PRIMA randomized controlled trials are ongoing at the time of this writing.