PFO to close or Not to close?

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Patent Foramen Ovale [PFO]

Image from MayoClinic.com
Prevalence

- Approximately 25% of the population has a PFO
  - this increases to about 40 to 50 percent in patients who have stroke of unknown cause, referred to as cryptogenic stroke. This is especially true in patients who have had a stroke before age 55

- Usually asymptomatic
  - Typically found incidentally or on evaluation for cryptogenic stroke
FIGURE 1. Transesophageal echocardiography demonstrates a 4-cm long thrombus in transit straddling a moderate, 4 mm diameter sized patent fossa ovale (PFO).
PFO and stroke

Background:

• The contribution of a patent foramen ovale (PFO) to cerebral ischemia has been uncertain
  • PFO is twice as prevalent in patients who have experienced a cryptogenic stroke compared to the general population
  • Observational data suggest a reduction of recurrent stroke with PFO closure, but...

• Three randomized trials of PFO closure did not show significant reduction in stroke risk in their primary intention-to-treat analysis
The Randomised trials

• CLOSURE 1  negative
• PC  negative
• RESPECT  negative
PFO Transcatheter Closure for Cryptogenic Ischemic Stroke
Randomized Clinical Trials

- CLOSURE I (2012)
- PC (2013)
- RESPECT (2013 and 2017)
- REDUCE (2017)
- CLOSE (2017)
- DEFENSE-PFO (2018)
RESPECT
Randomized Clinical Trial (2013 & 2017)

- **Amplatzer PFO Occluder vs.** medical therapy (aspirin, clopidogrel, aspirin plus dipyridamole, or warfarin).

- 980 subject (largest) followed for a mean of 5.9 years (longest follow-up).

- Included patients with cryptogenic ischemic stroke symptoms > 24 hours or if < 24 hours confirmation by imaging.

- Significant decrease in recurrent stroke with PFO closure (3.6%) vs. medical therapy alone (5.8%; p=0.046).

- Number needed to treat to prevent 1 stroke in 5 years was 42 patients.

Shunt Size and Atrial Septal Aneurysm

RESPECT Trial

Rate of Recurrent Ischemic Stroke According to Subgroup

**REDUCE**

**Randomized Clinical Trial (2017)**

- *Gore Helex or Cardioform Septal Occluder* vs. medical therapy (aspirin, aspirin plus dipyridamole, or clopidogrel).

- 664 subjects followed for a median of 3.2 years.

- Included patients with cryptogenic ischemic stroke symptoms > 24 hours or if < 24 hours confirmation by imaging.

- Significant decrease in recurrent clinical ischemic stroke in PFO closure (1.4%) vs. medical therapy (5.4%; p=0.002).

- Significant decrease in new brain infarct (clinical ischemic stroke or silent brain infarct by MRI) in PFO closure (5.7%) vs. medical therapy (11.3%; p=0.04).

- Number needed to treat to prevent 1 stroke in 2 years was ~ 28 patients.

CLOSE
Randomized Clinical Trial (2017)

- *Any CE Marked PFO Device* vs. medical therapy (aspirin, aspirin plus dipyridamole, clopidogrel, vitamin K antagonists or DOAC).

- 663 subjects followed for a mean of 5.3 years.

- Included patients with cryptogenic ischemic stroke seen on imaging *plus high-risk PFO features* (atrial septal aneurysm or large interatrial shunt).

- Significant decrease in recurrent nonfatal/fatal ischemic stroke in PFO closure (0%) *vs.* anti-platelet therapy alone (5.9%; p<0.001).

- Number needed to treat to prevent 1 stroke in 5 years was 20 patients.

- In the medically treated group, no significant difference in recurrent stroke between anti-platelet *vs.* anti-coagulation therapy.

DEFENSE-PFO
Randomized Clinical Trial (2018)

- **Amplatz PFO Occluder** vs. medical therapy (aspirin, aspirin plus clopidogrel, aspirin plus cilostazol, or warfarin).

- 120 subjects followed for a median of 2.8 years.

- Included patients with cryptogenic ischemic stroke plus high-risk PFO features (atrial septal aneurysm, hypermobile septum, or increase PFO size).

- Significant decrease in recurrent ischemic stroke in PFO closure (0%) vs. medical therapy (10.5%; p=0.023).

- Number needed to treat to prevent 1 stroke in 2 years was 10 patients.

PFO Closure vs. Medical Therapy Alone in the Incidence of Recurrent Stroke

Meta-Analysis of Cryptogenic Ischemic Stroke Randomized Trials

Favors PFO closure (2.0%) over medical therapy alone (4.2%) in decreasing recurrent stroke (p=0.03).
No significant difference in adverse events between PFO closure and medical therapy alone groups.
PFO Closure and Incidence of Atrial Fibrillation Across Randomized Trials for Cryptogenic Ischemic Stroke

- Meta-analysis showing incidence of atrial fibrillation greater in PFO closure (4.0%) compared to medical therapy alone (0.6%; p=0.0002).

- Risk of atrial fibrillation device/trial dependent:
  - non-significant in PC, RESPECT and DEFENSE-PFO (Amplatzer)
  - significant in CLOSURE I (STARFlex), REDUCE (Gore) and CLOSE (any CE Marked PFO Device)

- ~ 80-90% of atrial fibrillation occurred ≤ 45 days after PFO closure and at least partially related to time of procedure; low or no recurrence of atrial fibrillation on long-term follow-up, however, limited data.
Anticoagulant vs. Antiplatelet Therapy for Stroke Prevention after Cryptogenic Ischemic Stroke with PFO

Meta-Analysis

As of now….

• ....instead of arguing endlessly about WHETHER we should close PFO

• ....we can move on to arguing about WHO should get PFO closure
In selected patients with a PFO and cryptogenic stroke, transcatheter PFO closure is the most effective treatment to reduce the risk of recurrent stroke in accordance with evidence based randomized data.

Large sized-PFO associated with a significant shunt and/or an atrial septal aneurysm may increase likelihood that an ischemic stroke was PFO-related.

FDA recently has approved 2 PFO occluder devices.

No significant difference in overall adverse events between PFO closure and medical therapy alone; however, atrial fibrillation was seen more with PFO closure (majority likely transient peri-procedure).

In those with a PFO and cryptogenic stroke who decline closure or closure is contraindicated, anticoagulants may be slightly superior to antiplatelet therapy.
Pathway to Closure

Biological age ≤ 60 years
Ischemic stroke, and PFO

- Large artery atherosclerosis
- Cardioembolic source
- Small vessel disease
- Arterial dissection
- Hypercoagulable disorder

MEDICAL THERAPY

PERCUTANEOUS PFO CLOSURE
Enhanced reasons for PFO Closure
- Prior venous thromboembolism
- Multifocal cerebral defects
- Large PFO
- Atrial septal aneurysm
- Eustachian valve or Chiari network

- Uncontrolled hypertension
- Uncontrolled diabetes
- Autoimmune disease
- Drug or alcohol abuse

- Atrial fibrillation or flutter (ideally ≥ 30-day cardiac monitoring)

- < 1 year of life expectancy
- End-stage heart, liver, lung or kidney disease
- Cardiac tumor
- Endocarditis or sepsis
- Severe valvular pathology
PFO Occluder Devices
United States FDA Approval

- **Amplatzer PFO Occluder** (October 28, 2016).

- **Gore Cardioform Septal Occluder** (March 30, 2018).

Device indicated for percutaneous transcatheter closure of a 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.
Procedure technique
PFO relationship to surrounding structures
Baseline Assessment

• Interatrial septum anatomy by ICE
  • PFO size
  • Tunnel anatomy
  • ASA
  • Secundum thickness
• Shunt characterization*
  • Saline contrast via femoral vein injection
• Thorough eval for other defects (small ASD/septal fenestrations)
Baseline Assessment
Baseline Assessment
Baseline Assessment
Defect Crossing

- Fluoroscopy based with ICE verification
  - MP catheter + J-tipped 0.035” wire most cases
- Ensure J-tipped wire in pulmonary vein by fluoro
Device Sizing

• ICE-based

• Factors
  • Defect size
  • Tunnel length
  • Tunnel compliance
    • Stiff wire test vs balloon sizing
  • Secundum thickness
  • Other defects
Device Sizing
Defect Closure
Defect Closure
Device Assessment

• Pre and post release

• Device stability
  • ”Push-pull” test
    • Careful observation of both fluoro and ICE
      • Verify tissue insertion between discs
      • Does the device prolapse through the defect?

• Adequacy of closure
  • Color Doppler
  • +/- Saline contrast
Device Assessment
Device Assessment
Device Assessment
### Drug therapy and follow-up after percutaneous closure

<table>
<thead>
<tr>
<th>Position statements</th>
<th>Strength of the statement</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is reasonable to propose dual antiplatelet therapy for 1 to 6 months after PFO closure</td>
<td>Conditional</td>
<td>A</td>
</tr>
<tr>
<td>We suggest a single antiplatelet therapy be continued for at least 5 years</td>
<td>Conditional</td>
<td>C</td>
</tr>
<tr>
<td>The extension of the therapy with single antiplatelet beyond 5 years should be based on the balance between patient’s overall risk of stroke for other causes and haemorrhagic risk</td>
<td>Strong</td>
<td>C</td>
</tr>
<tr>
<td>The choice of the type of antiplatelet drug in the follow-up is currently empiric</td>
<td>Strong</td>
<td>A</td>
</tr>
<tr>
<td>The value of residual shunt after percutaneous closure cannot be deduced from available studies</td>
<td>Strong</td>
<td>C</td>
</tr>
<tr>
<td>Systematic, high-quality data on follow-up are needed</td>
<td>Strong</td>
<td>C</td>
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Follow up

<table>
<thead>
<tr>
<th>To obtain comparable data we propose to perform:</th>
<th>Conditional</th>
<th>C</th>
<th>124,141-147, 55 + Original meta-analyses and Supplementary Appendix</th>
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<tr>
<td>a) a TTE prior to hospital discharge</td>
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<td>b) c-TCD at least once beyond six months to assess effective PFO closure and thereafter, if residual shunt persists, annually until closure</td>
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<tr>
<td>c) c-TOE or c-TTE in case of severe residual shunt at c-TCD, or recurrent events, or symptoms during follow-up</td>
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<tr>
<td>Patients should undergo antibiotic prophylaxis for any invasive procedure performed in the first six months from PFO closure</td>
<td>Conditional</td>
<td>C</td>
<td>-</td>
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PFO Closure in PFO-Mediated (Cryptogenic) Ischemic Stroke

- PFO closure in selected patients appears to be effective in preventing stroke, which should be reflected in the guidelines.
- Close collaboration between a cardiologist and a neurologist is required to define those patients.
- PFO closure is an effective therapy compared to alternative options (i.e., life-long anticoagulation therapy).
- Further research is needed to define the long-term incidence of atrial fibrillation and possible superiority of anticoagulants compared to antiplatelets in those who decline PFO closure or when PFO closure is contraindicated.
- National and international registries will assist in advancing our knowledge in the field and help to better manage this group of patients.