Update on PFO closure in patients with Cryptogenic Stroke

Atish Mathur MD MPH
Structural Heart Disease
Interventional Cardiology
The Valley Hospital
Disclosures

- I, Atish Mathur, DO NOT have a financial interest, arrangement or affiliation with any organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Case 1

41 y/o woman with history of DVT (8yrs ago, while on OCP)
- Presenting with acute onset of L hemiparesis & aphasia
- Received IV tPA without significant improvement in neurologic deficits
- Subsequent cerebral angiography demonstrated R MCA M1 occlusion
  - Successful thrombectomy
  - Neurologic improvement
Case 3

- 34 y/o female smoker on estrogen therapy
- Presented with sudden onset of speech difficulty (Brocas Aphemia)
Case 3

- Patient has quit smoking but is unwilling to discontinue feminizing hormone therapy
  - Does this matter?
  - Would you recommend something different if she agreed to stop estrogen therapy?
Case 4: 45 year old male presenting with bilateral occipital infarcts

Past medical hx
- None

Past surgical hx
- None

Medications
- None
Post hospital course

- Started on Aspirin
- Carotid Doppler US – normal
- TTE – bubble study positive for intra-cardiac shunting
- Subsequent TEE c/w patent foramen ovale with R -> L shunting
- Hypercoaguatable work up negative
- Started on Xarelto
- Loop recorder was implanted – followed up 8 months – no occurrence of occult atrial fibrillation
- Now referred for PFO closure
GORE Cardioform device
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)

**References**

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.**

### Rate of Recurrent Ischemic Stroke According to Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PFO 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>Shunt size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None, trace or moderate</td>
<td>13/247 (5.3)</td>
<td>12/244 (4.9)</td>
<td>0.96 (0.44–2.11)</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Substantial</td>
<td>5/247 (2.0)</td>
<td>16/231 (6.9)</td>
<td>0.26 (0.10–0.71)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>3/179 (1.7)</td>
<td>13/170 (7.6)</td>
<td>0.20 (0.06–0.70)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>15/320 (4.7)</td>
<td>15/311 (4.8)</td>
<td>0.86 (0.47–1.76)</td>
<td>0.68</td>
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</tr>
</tbody>
</table>

PFO Closure vs Medical Therapy
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.

Amplatzer 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.
Indications for Use: Amplatzer PFO Occluder

“The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (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.”
GORE® CARDIOFORM Septal Occluder

**Indications:**

- Ostium secundum atrial septal defects (ASDs).
- Patent foramen ovale (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.

**Expansion of Indication FDA Approval:**
March 30, 2018
“…. it seems reasonable that the presence of a PFO and a sizable interatrial shunt should …. no longer result in the categorization of a stroke as cryptogenic.”

Tipping Point for Patent Foramen Ovale Closure

Allan H. Ropper, M.D.

NEJM 377;11:1093-1094.
Classification of Recommendations and Level of Evidence for PFO Closure

2014-2016

CLASS III No Benefit or CLASS III Harm

<table>
<thead>
<tr>
<th>Procedure/Test</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>COR III:</td>
<td></td>
</tr>
<tr>
<td>No benefit</td>
<td>Not Helpful</td>
</tr>
<tr>
<td>Excess Cost o/w Benefit or Harmful</td>
<td>Harmful to Patients</td>
</tr>
</tbody>
</table>

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Sufficient evidence from multiple randomized trials or meta-analyses

2019?

CLASS I

Benefit >>> Risk

Procedure/Treatment SHOULD be performed/administered

- Recommendation that procedure or treatment is useful/effective
- Sufficient evidence from multiple randomized trials or meta-analyses

Prediction

Class 1a recommendation that defines age group and includes PFO characteristics. Class 2a-b for others.
FDA Indications

✓ Indication for secondary prevention of stroke – not primary
  ✓ Patients who have had a stroke – TIA not included

✓ No indication for hypoxemia from right to left shunting

✓ No indication for migraine
Updates on Patient Evaluation – Selection

✓ The need to exclude PAF with longer-term monitoring
  ✓ Individualized approach recommended

✓ When to perform hypercoagulability testing
  ✓ Individualized approach recommended
  ✓ Exclude arterial thrombophilia’s, i.e. APL?

✓ RoPE score useful for general “gestalt” of likelihood
PFO is pathogenic versus incidental but has not been validated.
Uncertainties in Patient Selection: Three Common Scenarios Encountered in Practice

1. **Age > 60:** Consider PFO closure when patient has a paucity of vascular risk factors, strong evidence/hints of a paradoxical embolic mechanism, extensive monitoring to exclude PAF. *Shared-decision making.*

2. **Presence of overt VTE:** May build stronger case for paradoxical embolism. Is need for anticoagulation short-term or longer term? PFO closure prevents stroke not VTE. *Shared-decision-making.*

3. **Presence of traditional vascular risk factors:** Is case for paradoxical embolism strong, is PFO incidental, comprehensive approach to secondary prevention. *Shared-decision making.*
PFO Clinic: A Multispecialty Approach

- Decision-making in the individual patient is often highly nuanced and requires a multidisciplinary evaluation, thoughtful reasoning that includes understanding to what degree do the results of research studies apply to the patient in from of you, and facilitating the patient making an informed decision incorporating her/his preferences.
## Ten Key Questions for PFO Clinic

| #1 | Was the index event an ischemic stroke based on history, physical exam, and brain imaging?  
|    | • Is there evidence of prior strokes? | Neurologist |
| #2 | Did the stroke not have a clear cause, i.e. was it cryptogenic?  
|    | • Was the evaluation comprehensive and complete? | Neurologist and Cardiologist |
| #3 | Does the stroke have features consistent with an embolic mechanism?  
|    | • Were other causes of embolic strokes excluded including occult paroxysmal atrial fibrillation? | Neurologist and Cardiologist |
| #4 | Is there a PFO and what are its characteristics and related structures? | Cardiologist |
| #5 | Is there current evidence of VTE, a past history of VTE, or risk factors for VTE?  
|    | • What degree of screening for VTE is needed for this patient? | Cardiologist |

# Ten Key Questions

| #6 | Does the totality of data build a reasonable case for the PFO being pathogenic rather than incidental?  
   |   | - What is the RoPE score?  
   |   | - Other clinical clues? | Neurologist and Cardiologist |
| #7 | Does the patient-specific assessment of risk/benefit of PFO closure warrant considering PFO closure? | Neurologist, Cardiologist, and Patient |
| #8 | Does the patient prefer PFO closure?  
   |   | - How knowledgeable is she/he about key issues? | Patient, Cardiologist, and Neurologist |
| #9 | Are there any special considerations in planning and performing PFO closure? | Patient, Cardiologist, and Neurologist |
| #10 | What post-PFO closure issues needed to be addressed including other stroke secondary prevention recommendations that should also be instituted?  
    |   | - Medications, lifestyle, habits, etc. | Patient, Cardiologist, and Neurologist |
All treatment decisions are sensitive to preference to some degree, and patient engagement should be encouraged as part of good practice.

What additional steps physicians must take beyond high-quality preprocedure informed consent to satisfy the shared decision-making requirement?

At its core, shared decision making involves a discussion between the patient and the physician that presents risks and benefits of alternative treatments in a balanced manner, elucidates each patient’s preferences and goals, and engages patients in decision making.

Merchant S and Dickert F. Mandatory Shared Decision Making by the Centers for Medicare & Medicaid Services for Cardiovascular Procedures and Other Tests. JAMA August 21, 2018 Volume 320, Number 7: 641
Summary

- The indications for PFO closure are clearly presented in the FDA approval process and are now being further elucidated in professional society guidelines. Secondary stroke indication.

- Patient Selection:
  - Straightforward when patient is similar to those in trials
  - Always ask: What are the chances the PFO is incidental?
  - Challenging when patient characteristics differ from those in RCTs
  - Two key aspects to optimizing the process of patient selection
    - Multidisciplinary approach
    - Shared-decision making
Time to Update the Guidelines

• 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.

• This information should be incorporated in the guidelines.

• The guidelines, however, should be written in such a way that can easily be applied to the individual patient.
HEART BRAIN TEAM: Where to Start and How to Break the ICE

- Learn about the people on the other side (positions, credentials, interests, etc.)
- Understand reasons for negative view of PFO closure and other interventions (lack of data, insufficient information, prior experiences, etc.)
- Outline a collaboration strategy
  - Knowledge sharing (joint conferences, JC, tumor-board like discussions, etc.)
  - Define mutual areas of interest and collaboration both in patient care and research
  1. PFO and embolic stroke
  2. Post-procedural stroke (TAVR, PCI, etc.)
  3. Stroke prevention in AF
  4. Post-ischemic stroke MI
Joint Heart Brain Team Evaluation

PFO + Cryptogenic Stroke
Ascertainment of Pathological Association

- Absence of other potential stroke etiologies
  - ROPE Score
  - AF and Carotid Disease
  - Hypercoagulopathy
- High-risk PFO Characteristics
  - Large R-L Shunt
  - Septal Aneurysm
- Clinical Clues to Paradoxical Embolism
  - Concomitant VTE
  - Prolonged Travel
  - Migraine
- Neuro imaging suggestive of cardioembolic stroke
  - Cortical versus. Lacunar Infarct

Shared Decision Making

Heart Brain Team Evaluation

Aggressive Risk Factor Modification +

Determine Post Closure Medical Therapy

Device Closure

Medical Therapy

Antiplatlets Anticoagulants
The Heart Brain Team; Collaboration Beyond PFO Closure

Cardiologists
- Primary and secondary
- CVD prevention
- Anticoagulation handling in AF
- Percutaneous closure of PFO and LAA
- Prevention of procedural strokes
- Poststroke myocardial infarction
- Stress-induced cardiomyopathies
- Muscular dystrophies
- Syncope

Neurologists
- Primary and secondary
- CVD prevention
- Management of hemorrhagic stroke
- Risk stratification of cryptogenic stroke
- Management of procedural strokes
- Poststroke myocardial infarction
- Stress-induced cardiomyopathies
- Muscular dystrophies
- Syncope

Heart-Brain Team
- CVD prevention
- Cardioembolic stroke
- Procedure-related stroke
- Poststroke myocardial infarction
- Stress-induced cardiomyopathies
- Muscular dystrophies
- Syncope
- Heart-brain connection

The Heart-Brain Team—Towards an Optimal Team-Based Coordinated Care

Alkhouli M, Holmes DR. JAMA Cardiology 2018
The Heart Brain Team; Ready for Prime Time
Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy alone for management of cryptogenic stroke? A clinical practice guideline
**Comparison 1**

- **PFO closure**
  - Percutaneous closure of PFO followed by antiplatelet therapy
  - Strong

- **Antiplatelets**
  - Antiplatelet therapy alone
  - Weak

We recommend PFO closure followed by antiplatelet therapy over antiplatelet therapy alone.

**Key practical issues**

**PFO closure**
- Procedure takes under 2 hours
- In-hospital stay is usually one day
- Most activities can be resumed within a few days
- Full recovery within a few weeks

**Antiplatelets**
- No key practical issues
Comparison 2

**PFO closure**
Percutaneous closure of PFO followed by antiplatelet therapy

**Anticoagulants**
Anticoagulation therapy

We suggest PFO closure followed by antiplatelet therapy over anticoagulation therapy. Discuss both options with each patient.

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**Key practical issues**

**PFO closure**
- Procedure takes under 2 hours
- In-hospital stay is usually one day
- Most activities can be resumed within a few days
- Full recovery within a few weeks

**Anticoagulants**
- Initial frequent testing required to achieve appropriate dose
- Periodic testing required while taking medication
Comparison 3

Anticoagulants
Anticoagulation therapy

OR

Antiplatelets
Antiplatelet therapy

Anticoagulants
Strong
Weak

Antiplatelets
Weak
Strong

We suggest anticoagulation over antiplatelet therapy.
Discuss both options with each patient.

Key practical issues

Anticoagulants
Initial frequent testing required to achieve appropriate dose
Periodic testing required while taking medication

Antiplatelets
No key practical issues
Thank You!

970 Linwood Avenue Suite 102
Ridgewood, NJ 07450

Office: 201 251 3243
Cell: 248 252 2495
Email: mathat@valleyhealth.com