The Patent Foramen Ovale
A Preventable Stroke Etiology ? !

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Conflict of Interest Statement

I have a financial interest in Coherex Medical.
2.7% of men and 2.5% of women >18 years of age have a history of stroke.

17.8% of the population over 45 years of age reported at least 1 stroke symptom.

The prevalence of silent cerebral infarction between 55 and 64 years of age is approximately 11% and increases to 43% above 85 years.

PFO Prevalence:
- >20% general population
- >40% cryptogenic stroke population

Common Disorders intersecting create the perfect storm.
All or None Polarization

“... our results offer no justification for the use of potentially dangerous or aggressive treatments. Hence, although this was not one of the objectives of our study, we are led to conclude that invasive treatments such as percutaneous PFO occlusion should be performed only within the framework of a current clinical trial.”

Where are we today?

- Randomized Trials of PFO closure in Stroke and Migraine are ongoing (Closure I completed enrollment last week).
- Many patients referred for PFO consultation do not meet entry criteria for randomized trials.
- Physicians and patients often prefer off-label closure with ASD indicated devices.
- There is little prospective data regarding PFO closure complications and success.
- While PFO closure is technically straightforward, counseling patients regarding PFO closure is challenging.
The PFO Cardiologist?

“We just load the trucks.”

Cardiologists must be prepared to discuss complex decisions with intimate knowledge of the PFO space.

No Truck Leaves Empty
Defer to Neurology
Does PFO Closure Prevent Strokes Beyond All or None

Cryptogenic Stroke
  - < 55 yo
  - > 55 yo
Stroke with suspected alternate etiology
Silent Stroke (MRI)
Transient Ischemic Attack
Systemic Embolism
  - MI
  - Organs (spleen, bowel)
  - Extremities
Venous Thrombus
  - DVT
  - SVT
  - UE thrombus
  - PE

Procoagulant Disorders
  - Central venous foreign body
    - permanent pacemakers
    - chronic indwelling catheters
PFO Characteristics
  - Atrial Septal Aneurysm
  - High Flow/Low Flow TCD
Pre-Operative (Liver Transplant, Complex Orthopedic)
Hypoxia (OSA, platypnea orthodeoxia)
Migraine
  - migrainous infarction
  - non visual aura (TIA-like)
  - WMLs MRI
<table>
<thead>
<tr>
<th>Cheerleader Camp</th>
<th>Cynical Corner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anecdotal Observations</td>
<td>Observations of Cardiologists</td>
</tr>
<tr>
<td>Prevalence Data</td>
<td>Population Observations</td>
</tr>
<tr>
<td>Retrospective Comparisons</td>
<td>Lack of Data</td>
</tr>
<tr>
<td>Device Safety</td>
<td>Device Complications</td>
</tr>
<tr>
<td>Common Sense</td>
<td>Common Sense</td>
</tr>
</tbody>
</table>
Transcatheter Closure vs Medical Therapy
PFO and Presumed Paradoxical Thromboemboli

10 Transcatheter Closures Studies
1355 Patients

6 Medical Management Studies
895 Patients

RNTE @ 1 Year

0 - 4.9%

3.8% - 12%

Khairy, et al. Annals of Internal Medicine, 4 Nov. 2003
Recurrent Cerebrovascular Events Associated with PFO, Atrial Septal Aneurysm, or Both

- 581 patients with cryptogenic CVA
- ASA 300 mg/day
- 4 year F/U

Mas, et al. NEJM Dec 13, 2001
Prevalence of PFO in Patients With "Cryptogenic" Stroke

Lechat 1988
Webster 1988
De Belder 1992
Di Tullio 1992
Hausmann 1992
Cabanes 1993

Cryptogenic Stroke
Control
Patent Foramen Ovale and Older Cryptogenic Stroke Patients

Cum Hoc, Ergo Propter Hoc
Association ≠ Causation

PFO prevalence is associated with:
- cryptogenic stroke
- migraine with aura, chronic migraine
- sleep apnea
- chronic fatigue syndrome

Association intuitively, but not necessarily indicates:
1) contribution to disease process
2) likelihood of impacting treatment with intervention
Although our data suggest that the absolute risk of stroke from a PFO in the general population is low, the search may still be on for individual subjects in whom PFO carries an increased risk. . .

Di Tullio MR, J Am Coll Cardiol. 2007 Feb 20;49(7):797-802.
Patent Foramen Ovale: Innocent or Guilty? Evidence From a Prospective Population-Based Study

Contrast TEE
N= 585
PFO – 140 (24%)    No PFO - 437

Atrial Septal Aneurysm
N = 11

HR 1.4 (0.74 - 2.88, p = 0.28)

HR 3.7 (0.88 – 15.71, p = 0.07)

2,206 Patients

Ischemic CVA

Warfarin
(INR 1.4 – 2.8)

ASA
325 mg/day

Death or Recurrent CVA at 2 Years

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>ASA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (2206)</td>
<td>17.8%</td>
<td>16.0%</td>
<td>0.25</td>
</tr>
<tr>
<td>Cryptogenic CVA (576)</td>
<td>15.0%</td>
<td>16.5%</td>
<td>0.68</td>
</tr>
</tbody>
</table>
Effect of Medical Treatment in Stroke Patients with Patent Foramen Ovale

601 WARSS Patients evaluated by TEE

<table>
<thead>
<tr>
<th></th>
<th>Cryptogenic CVA (250)</th>
<th>CVA etiology suspected (351)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFO</td>
<td>39% (98)</td>
<td>30% (105)</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Warfarin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or Death %</td>
<td>17.9</td>
<td>8.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Circulation 2002 Jun 4;105(22):2625-31
Recurrent Stroke and Massive (TCD 4 or 5) Right-to-Left Shunt. CODICIA Group

<table>
<thead>
<tr>
<th></th>
<th>R-L shunt</th>
<th>TCD 4/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (486)</td>
<td>61.1%</td>
<td>41.2%</td>
</tr>
<tr>
<td>Age &lt;55 (229)</td>
<td>70.7%</td>
<td>51.5%</td>
</tr>
</tbody>
</table>

Cryptogenic CVA
N=486

- Antplatelet 79%
- Warfarin 21%
- F/U 729 +/- 411 Days

Recurrent CVA = 28 (5.8%)

Recurrent Stroke and Massive (TCD 4 or 5) Right-to-Left Shunt.

Recurrent Stroke (%)

<table>
<thead>
<tr>
<th></th>
<th>TCD 4/5</th>
<th>TCD 1/2</th>
<th>TCD 0</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5.0</td>
<td>6.2</td>
<td>4.5</td>
<td>0.58</td>
</tr>
<tr>
<td>Age &lt;55</td>
<td>3.4</td>
<td>2.3</td>
<td>4.5</td>
<td>0.75</td>
</tr>
</tbody>
</table>

“Because the risk of stroke recurrence was low and no significant differences were found between the use of antiplatelet and anticoagulant agents, our results offer no justification for the use of potentially dangerous or aggressive treatments. Hence, although this was not one of the objectives of our study, we are led to conclude that invasive treatments such as percutaneous PFO occlusion should be performed only within the framework of a current clinical trial.”
Half Empty or Half Full?

- PFO → CVA Adjusted HR 1.64, 1.4, 3.7 unselected population is provocative
- PICSS 2 year stroke or death: 18% aspirin, 9% warfarin is unacceptable & demands PFO closure

<table>
<thead>
<tr>
<th>CODICI A</th>
<th>Cryptogenic Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFO Mediated</td>
<td>Atherosclerosis Mediated</td>
</tr>
</tbody>
</table>

Recurrent Stroke = 5.8% in all patients

Treat HTN, DM, AF, Tob ?PFO
• PFO mediated stroke signals are ubiquitous.
• If there were no PFOs, there would be fewer strokes.
• PFO Closure complications are minimal.
• “PFO Vaccination” ready for prime time?
The Interventional Cardiologist’s Brain

- Physical Needs & Desires
- Technical Details
- Oculostenotic, right to left shunt
- Reflex Lobe

Memory storage for complications

Motor Control Center
Stroke Trials

Enrolled population
Operator experience & procedural complications
Device performance

Magnitude Stroke Reduction
Complications: Procedural Device Medications
<table>
<thead>
<tr>
<th>Event</th>
<th>Study Arm</th>
<th>Adjudicated Relationship to Device, Procedure, or Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Fib with aberrant conduction</td>
<td>Implant</td>
<td>Possible Device</td>
</tr>
<tr>
<td>Tamponade</td>
<td>Implant</td>
<td>Procedure</td>
</tr>
<tr>
<td>Pericardial Effusion</td>
<td>Implant</td>
<td>Procedure</td>
</tr>
<tr>
<td>Retroperitoneal Bleed</td>
<td>Implant</td>
<td>Procedure</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>Implant</td>
<td>Possible Device</td>
</tr>
<tr>
<td>A Fib</td>
<td>Implant</td>
<td>Possible Device</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>Implant</td>
<td>Possible Device, Procedure, Meds</td>
</tr>
<tr>
<td>Stroke</td>
<td>Sham</td>
<td>None</td>
</tr>
<tr>
<td>Mennorhagia/Anemia</td>
<td>Sham</td>
<td>Possible Meds</td>
</tr>
<tr>
<td>Groin Ooze</td>
<td>Sham</td>
<td>Procedure/Possible Meds</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Amplatzer (N=220)</th>
<th>Helex (N=220)</th>
<th>CardioSeal/StarFlex (N=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device Embolization</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemopericardium</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamponade &amp; Surgical Explant</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device Thrombus</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>3</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>30 Day Closure</td>
<td>65%</td>
<td>53%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Comparison of Three PFO Closure Devices in a Randomized Trial

Taafe M. Am J Cardiol. 2008 May 1;101(9):1353-8.
Recurrent Focal Neurologic Events after Transcatheter PFO Closure

216 Patients
CardioSeal Closure

Retrospective Review

Focal Neurologic Events – 20/216, 3.4%/year
CVA – 4 (2 likely device related)
TIA – 10 (etiology undetermined)

# Ongoing PFO Stroke Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Respect</th>
<th>Closure I</th>
<th>Reduce</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>500+</td>
<td>900</td>
<td>664</td>
</tr>
<tr>
<td>Device (Company)</td>
<td>Amplatzer (AGA)</td>
<td>StarFlex (NMT)</td>
<td>Helex (Gore)</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Stroke</td>
<td>Stroke or TIA</td>
<td>Stroke or MRI TIA</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Stroke</td>
<td>Stroke or TIA</td>
<td>Stroke or MRI TIA</td>
</tr>
<tr>
<td>Key Secondary Endpoints</td>
<td>? Migraine</td>
<td>? Migraine</td>
<td>MRI WMLs</td>
</tr>
</tbody>
</table>

Different Populations, Devices, Endpoints Essential to Building a Body of Evidence Translated Results Cannot be Assumed.
## Risk of Ischaemic Stroke in People with Migraine: A Meta-Analysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine (any)</td>
<td>2.16</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>2.88</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>1.83</td>
</tr>
<tr>
<td>Migraine among women &lt; 45 yrs</td>
<td>2.76</td>
</tr>
<tr>
<td>Migraine + oral contraceptives</td>
<td>8.72</td>
</tr>
</tbody>
</table>

Burden of Atherosclerosis and Risk of Venous Thromboembolism in Patients with Migraine

Migraine and Subclinical Brain Lesions.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control N=140</th>
<th>Migraine no aura N=134</th>
<th>Migraine with aura N=161</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior Circulation Infarct</td>
<td>1 (0.7%)</td>
<td>3 (2.2%)</td>
<td>13 (8.1%)</td>
</tr>
</tbody>
</table>

Kruit, et al., JAMA 2004 Jan 28

~50% of migraineurs have MRI white matter lesions
Independent of right to left shunt

PFO Prevalence: Compounded with CVA + Migraine

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12%</td>
</tr>
<tr>
<td>Migraine with Aura</td>
<td>38%</td>
</tr>
<tr>
<td>CVA no Migraine</td>
<td>56%</td>
</tr>
<tr>
<td>CVA Migraine no Aura</td>
<td>75%</td>
</tr>
<tr>
<td>CVA Migraine with Aura</td>
<td>84%</td>
</tr>
</tbody>
</table>

Am J Cardiol 2006;98:831-3
1) Migraine and stroke are associated without causation (PFO causes both).
2) PFO closure diminishes migraine induced brain pathology.

Assumes:
- Migraine causes brain pathology
- PFO closure diminishes migraines
Ongoing, Struggling Research Regarding PFO Closure of Migraine Patients will Provide Little Insight Regarding Stroke Prevention

<table>
<thead>
<tr>
<th></th>
<th><strong>Premium</strong></th>
<th><strong>Mist II</strong></th>
<th><strong>Escape</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Device (Company)</strong></td>
<td>Amplatzer (AGA)</td>
<td>Biostar (NMT)</td>
<td>Premere (St. Jude)</td>
</tr>
<tr>
<td><strong>Inclusion</strong></td>
<td>Refractory To Medications</td>
<td>Refractory To Medications</td>
<td>Refractory To Medications</td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
<td>Stroke TIA</td>
<td>Stroke TIA</td>
<td>Stroke TIA</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>50% reduction Headache Days</td>
<td>50% reduction Headache Days</td>
<td>50% reduction Headache Days</td>
</tr>
</tbody>
</table>

• High risk patients are excluded.
Will closing PFOs in OSA patients prevent strokes?

- Sleep apnea is associated with an increased risk of stroke.

- PFO closure may be associated with diminished sleep hypoxia.

Prevalence of PFOs in OSA

Conclusions I

- Closure I, Respect, and Reduce will be scrutinized regarding:
  - Closure efficacy
  - Device and procedural related complications
  - Characteristics of enrolled population
- Results of ongoing trials (+ or -) cannot be translated to alternate devices given device specific efficacy and safety profiles.
Conclusions II

• Physicians must respect patients’ rights to direct their care.
• PFO consultation should include discussion regarding:
  – Observational population data
  – Ongoing randomized trials
  – Lack of FDA indication for PFO closure
  – Lack of prospective complication and closure data
  – MIST complications
• Randomization should be encouraged when inclusion criteria are met.
Conclusions III

Additional research is indicated beyond ongoing randomized trials.
  – Appropriately powered high risk population studies
    • Atrial septal aneurysm
    • Thrombotic risk (PE, DVT, SVT, procoagulant disorders, chronic indwelling catheter, pacemaker)
  – PFO closure in high risk migraine population (nonvisual aura, WMLs, thrombotic risk)
  – PFO closure in sleep hypoxia
Conclusions IV

Cardiologists participating in PFO closure require a fund of neurology knowledge.
- industry support
- cardiology meetings