Patent Foramen Ovale (PFO) Closure For Stroke and Migraine
How Strong is the Evidence?

TCT
September 24, 2009

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Disclosures

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A Principal Investigator for PREMIUM Trial using the Amplatzer PFO Occluder (AGA Medical) in patients with severe migraines.

MAB for ACCESS LAA Occlusion Trial

Consultant for the RESPECT stroke trial.

Consultant to: Boston Scientific Coherex WL Gore Angel Medical
How Strong is the Evidence?

Is it like this guy?  

or like this wanna be?
Controversies in PFO Closure

1. There is no FDA approval for any PFO device.
2. Everything we discuss is off-label.
3. The observational data is impressive but only scientifically useful for generating hypotheses, not for proving cause and effect.
4. But, the RCTs are difficult to perform due to availability of using devices off-label.
## Association of PFO and cryptogenic stroke in young adults (< 55 y/o)

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts</th>
<th>PFO (crypto)</th>
<th>PFO (control)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lechat (1988)</td>
<td>26</td>
<td>54%</td>
<td>10%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Webster (1988)</td>
<td>40</td>
<td>50%</td>
<td>15%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>De Belder (1992)</td>
<td>39</td>
<td>13%</td>
<td>3%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>De Tullio (1992)</td>
<td>21</td>
<td>47%</td>
<td>4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hausmann (1992)</td>
<td>18</td>
<td>50%</td>
<td>11%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Cabanes (1993)</td>
<td>64</td>
<td>56%</td>
<td>18%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>202</td>
<td><strong>46%</strong> (93/202)</td>
<td><strong>11%</strong> (29/271)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
Determinants of High Risk for Stroke in Patient with PFO

1. ASA (atrial septal aneurysm)\(^1\):
   Risk for stroke: PFO alone = OR 3.9
   ASA alone = OR 4.3 (rare)
   PFO + ASA = OR 33.3

2. Size of PFO: conflicting data, depends how you measure
3. Degree of Shunt: probably
4. Past “silent” strokes on MRI. \(^2\)
5. Hypercoaguable State (incl Estrogen Rx) 20% of our pts
6. Prolonged immobility = 10%
7. Valsalva (straining) = 5%
8. Size of Stroke is not related to size of PFO.\(^3\)

3. Tobis and Akhondi SCAI 2009
Medical Therapy vs. PFO Closure: A Review of Observational Studies

<table>
<thead>
<tr>
<th>Medical Therapy</th>
<th>4.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>(9 studies)</td>
<td></td>
</tr>
<tr>
<td>N = 943</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percutaneous PFO Closure</th>
<th>3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>(12 studies)</td>
<td></td>
</tr>
<tr>
<td>N = 1430</td>
<td></td>
</tr>
</tbody>
</table>

This should be $\approx 0\%$

Khairy et. al. Ann Intern Med 2003: 139; 753-60
Windecker et. al. JACC 2004: 44; 750-758
What is the problem with these studies?
Meta-analysis
Medical Rx vs. PFO Closure

What is the problem with these studies?

1. Observational studies, not RCT.
2. They include TIA which is indistinguishable from a TND (transient neurologic deficit) seen with migraine: motor, sensory, cognitive.
3. They underestimate incidence of PFO by using echo instead of TCD. “Recurrent stroke w/o PFO”
Current Randomized Clinical Trials

RESPECT Trial (Amplatzer)
CLOSURE Trial (StarFlex)
REDUCE TRIAL (Gore Helex)

Cryptogenic Stroke within 6 months
18-60 yrs old
PFO present
abnl MRI or CT

Medical Rx
antiplatelet or coumadin

PFO Closure

Endpoints: recurrent stroke, death, +/- TIAs
Safety: adverse events
In all stroke pts (young or >55 yo), PFO is 3x more common with cryptogenic stroke than stroke of known cause.
70 y.o. woman with Wegener’s Granulomatosis PFO and recurrent strokes

No significant atherosclerosis.

PFO closed. In the next year, she had recurrent strokes and died.

20 mm Helex ASD device Left Atrium

Friable ulcerated plaque in ascending aorta
Migraine Observations

1. Migraine headache affects 12% of population (18%F - 6%M) or 27 million people in USA

2. Incidence of PFO in pts with migraine:
   - 48% if migraine with aura
   - 23% if migraine w/o aura
   - 20% in controls

3. Incidence of Migraine in pts with Cryptogenic Stroke and PFO:
   - 52% had migraine with aura
   - 10 of 14 (71%) had suppression post closure

4. Migraine pts have 13x incidence of MRI lesions

References:
1. Anzola, Neurology 52(8):1622-5, 1999
2. Sztajzel, CV Diseases 13(2):102-6, 2002
Observational Studies
Effect of PFO closure on migraine

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence # migraine / # closed (%)</th>
<th>% migraine improved or cured</th>
<th>Length of follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilmshurst 2000</td>
<td>21/37 (57%)</td>
<td>86%</td>
<td>up to 30</td>
</tr>
<tr>
<td>Morandi 2003</td>
<td>17/62 (27%)</td>
<td>88%</td>
<td>all 6</td>
</tr>
<tr>
<td>Schwerzmann 2004</td>
<td>48/215 (22%)</td>
<td>81%</td>
<td>all 12</td>
</tr>
<tr>
<td>Post 2004</td>
<td>26/66 (39%)</td>
<td>65% cured</td>
<td>all 6</td>
</tr>
<tr>
<td>Reisman 2005</td>
<td>57/162 (35%)</td>
<td>70%</td>
<td>all 12</td>
</tr>
<tr>
<td>Azarbal, Tobis 2005</td>
<td>37/89 (42%)</td>
<td>76%</td>
<td>mean 18</td>
</tr>
</tbody>
</table>

**Total:** 206/631 (33%) 78%
Prevalence of Migraine Headaches

- Control: 4 MHA-, 7 MHA+, 11 MH
- All CHD: 9 MHA-, 36 MHA+, 45 MH
- No shunt: 6 MHA-, 32 MHA+, 38 MH
- Left-to-Right: 10 MHA-, 33 MHA+, 44 MH
- Right-to-Left: 10 MHA-, 42 MHA+, 52 MH

395 ACHD pts and 252 sex-matched controls

Tobis AJC Feb 2008
### MIST: Prospective findings in Migraine Patients

<table>
<thead>
<tr>
<th>Result</th>
<th>Total #</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total studied</td>
<td>370</td>
<td>100.0%</td>
</tr>
<tr>
<td>Small shunts (atrial and pulmonary)</td>
<td>61</td>
<td>16.5%</td>
</tr>
<tr>
<td>Large pulmonary shunt</td>
<td>18</td>
<td>4.9%</td>
</tr>
<tr>
<td>ASD</td>
<td>2</td>
<td>0.5%</td>
</tr>
<tr>
<td>Large PFO</td>
<td>139</td>
<td>37.6%</td>
</tr>
<tr>
<td><strong>Large shunts (all types)</strong></td>
<td>159</td>
<td>43.0%</td>
</tr>
<tr>
<td><strong>Total Shunts</strong></td>
<td>220</td>
<td>59.5%</td>
</tr>
</tbody>
</table>

Jan to May 2005

The MIST Trial is sponsored by a research grant from NMT Medical Inc., and is supported by the Migraine Action Association and Migraine in Primary Care Advisors (MIPCA).
MIST Results (Circ. March 2008)

MIST was a negative study....
and we don’t really know why.

Is this due to the specific device with residual shunts?
Or a more general problem of patient selection?
Are some migraine sub-populations more responsive to PFO closure?
The PREMIUM Trial
A Randomized Double Blind Trial of PFO Closure for Severe Migraine Headaches

220 patients with migraine ± aura
assess for PFO with TCD, if +4 or 5, ICE

randomize

Usual HA Rx + ASA & Plavix + Sham Procedure

Usual HA Rx + ASA & Plavix + PFO Closure

Recent approval by FDA of less restrictive entry criteria

Also: Coherex is expecting to begin a migraine trial
MRI changes in migraine headache
WML = white matter lesion

38yo woman migraine + aura since 12yo
“Few small foci of inc. signal in cerebral white matter. Ddx: vasculitis, demyelinating disease (MS), chronic ischemia, or complicated migraine.”

WML = inc. water due to replacement of myelin
Improvement of Migraine After Patent Foramen Ovale Percutaneous Closure in Patients With Subclinical Brain Lesions: A Case-Control Study
Carlo Vigna, et.al. J. Am. Coll. Cardiol. Intv. 2009;2;107-113

82 pts with migraine, PFO, WMLs

<table>
<thead>
<tr>
<th></th>
<th>53 closed</th>
<th>29 not closed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>32 ± 9</td>
<td>36 ± 13</td>
</tr>
<tr>
<td>6 Month Total # Migraines</td>
<td>7 ± 7*</td>
<td>30 ± 21**</td>
</tr>
</tbody>
</table>

*p < 0.001

**p = ns
Headaches and Heart Attacks (AHA Nov 2006)

Men and Women with migraines have a greater risk of ischemic stroke and heart attack

Physicians’ Health Study: 20,084 men
7.2% men with migraine, 56yo, 15.7yrs f/u
Men with Migraine: 24% inc risk for CVD event:
42% inc MI
12% inc ischemic stroke
7% inc CV death
5% inc revasc.

Is this due to a shared metabolic disorder? ....or by paradoxical embolism thru PFO? Perhaps this explains why the incidence of PFO is less in older age groups.
How Strong is the Data?

As Abraham Lincoln noted about economic distribution:

“You can’t make a weak man strong by making a strong man weak, and you can’t make a poor man rich by making a rich man poor.”

Translated with respect to PFO closure:

“You can’t prove a causal relationship, with observational data alone.”

We need to enroll patients into the RCTs.

Thank you.