Update on Clinical Trials PFO and Stroke

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Disclosure

• Research Grants: NMT Medical, Atritech, St Jude’s Medical,

• Speakers Bureau: Boston Scientific, Siemens

• Consultant: NMT Medical, Acunav, Gore Medical
Patent Foramen Ovale and Stroke

- In a general population the presence of PFO is not an independent risk factor for stroke
- Pts with a history of stroke and large PFO and ASA are at sig risk for recurrent events if just on aspirin
- Atrial septal aneurysm without a PFO is not a risk factor for recurrent stroke
Optimal Treatment to Prevent strokes in patients with a PFO

• Currently there are no established treatment options

• Options available:
  – Antiplatelet therapy
  – Anticoagulant treatment
  – Surgical Closure
  – Percutaneous Closure
The great Irony

- Physicians & regulatory bodies, lawyers not patients need prospective double blind randomized trials to believe that something works, yet
  - Most physicians will NEVER refer their patients to randomized studies
  - Physician, lawyer patients are never involved in randomized studies
The Challenges

- Physician’s Bias
- Patient Bias
- Availability of off label devices
- Reimbursement/Insurance
Transcatheter Closure vs Medical Therapy
PFO and Presumed Paradoxical Thromboemboli

10 Transcatheter Closures Studies
1355 Patients

6 Medical Management Studies
895 Patients

Recurrent neuro event @ 1 Yr

0 - 4.9%

3.8% - 12%

Khairy, et al. Annals of Internal Medicine, 4 Nov. 2003
Techniques of Closure
PFO Occluder in Clinical Trial

STARFlex (NMT Med)  
PFO occluder (AGA Med)

Helex Septal Occluder (Gore)
### 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>
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<tr>
<td>Inclusion</td>
<td>Stroke</td>
<td>Stroke or TIA</td>
<td>Stroke or MRI TIA</td>
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<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>
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- **Completed enrollment**
- **Different Populations, Devices, Endpoints Essential to Building a Body of Evidence**
CLOSURE I: Study Flow (Superiority Study)

- Age 18-60yrs
- Documented Cryptogenic Stroke Or TIA
- PFO

910 patients Enrolled between June 2003 and October 2008

1 month visit
6 month visit
1 year visit
2 year visit

Control Group: Aspirin and/or Coumadin 2 years

Device Group: Starflex Septal Occuder and Aspirin

Aspirin 2 years
Clopidogrel 6 mths

Primary End points
- All case death at 30 days
- 2 year Stroke or TIA
- Neurological death >30 days
CLOSURE I: Preliminary Results

- Did not achieve its primary endpoint defined as treatment by device closure is superior to the current best medical therapy.
- However, STARFlex® did provide a small, but not statistically significant, benefit over current best medical therapy.
- Safety profile of the STARFlex® device showed a low rate of complications, similar to that of current best medical therapy.
  - Very low rate of thrombus formation.
- Closure rates in the trial were 86.5%.
- Full dataset to be presented at AHA in November 2010.
RESPECT Trial

- >600 pts enrolled
- Design is event driven not patient driven
- Medical arm
  - Aspirin or coumadin, or Clopidogrel, Aggrenox
- Device Arm:
  - Aspirin for 6 months, Clopidogrel for 1 mth
REDUCE Trial

- 40 sites enrolling (Europe and US)
- Approximately 15% enrolled
- Unique Features of the Trial
  - 2:1 randomization
  - 5 year follow up required
  - MRI for all patients at 2 years
  - Medical arm: Antiplatelet therapy (Aspirin preferable)
Conclusions

• The exact role of PFO closure for patients with Cryptogenic stroke and PFO is not well defined

• Randomized trials have been very challenging to enroll
  – Patient and physician bias
  – Availability of off label device

• CLOSURE I trial is the only trial that has completed enrollment
  – Did not reach is primary endpoint
  – Device seems safe and slightly superior to medical treatment
Do we really need randomized Studies

• What if the trial is negative
  – Cardiologists won’t believe it

• What if it is positive
  – Neurologist won’t believe it

• What if trial is positive and both the cardiologists and neurologist believe it
  – The FDA still won’t approve it

• What if the FDA approves it
  – CMS won’t pay for the procedure

• What if CMS agrees to pay for the procedure/device
  – There will be a new health reform to block it
Large PFO with atrial septal aneurysm (ASA)
Paradoxical Embolism causing a stroke
Heart Disease and Stroke Statistics
2008 Update: Circulation 117; January 29, 2008

- 2.6% of population >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.
Prevalence of PFO in patients with "cryptogenic" stroke

<table>
<thead>
<tr>
<th></th>
<th>Cryptogenic Stroke</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lechat 1988</td>
<td>54%</td>
<td>10%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Webster 1988</td>
<td>50%</td>
<td>15%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>De Belder 1992</td>
<td>13%</td>
<td>3%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Di Tullio 1992</td>
<td>47%</td>
<td>4%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Hausmann 1992</td>
<td>50%</td>
<td>11%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Cabanes 1993</td>
<td>56%</td>
<td>18%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>PICCS Trial 2002</td>
<td>39%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PICCS Trial (known stroke type)</td>
<td>30%</td>
<td></td>
<td>&lt;0.02</td>
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Patent Foramen Ovale: Innocent or Guilty

• Objective:
  – Determine the association of Patent Foramen Ovale (PFO) and ASA (atrial septal aneurysm) and stroke prospectively in an unselected population sample.

• Methods:
  – TEE was to identify PFO (single echocardiographer) in 585 randomly subjects >45 yrs in a single community participating in Stroke Prevention: Assessment of Risk in a Community (SPARC) study

Meissner et al. J Am Coll Cardiol 2006
Patent Foramen Ovale: Innocent or Guilty

- PFO present 140 pts (24%)
- ASA present 11 (1.9%)
- 6 pts (4.3%) of PFO pts had ASA also

**Conclusion:** This prospective population based data suggests after correction of age and co morbidity, PFO is not an independent risk factor for future cerebrovascular events in a general population

*Meissner et al. J Am Coll Cardiol 2006*
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
Patent Foramen Ovale and Older Cryptogenic Stroke Patients

Force M et al., Clin Neurol Neurosurg. 2008 Jun
62 yr old lady with DM, and hemiplegia
Migraine and PFO

- Association of Migraine and PFO
- Association of migraine and stroke
- PFO closure reduced headaches in stroke pts with a history migraine
MIST Trial

- **135 Migraine with Aura pts** with PFO randomized

- **Primary Endpoint**: Cessation of Migraine attack (MHA)
  - 3 pts in device and 3 in control group

- **Secondary Endpoint**: 50% reduction of MHA days
  - Device: 42% of pts  \( p < 0.04 \)
  - Control: 23% of pts

- **PFO closure effectiveness data**: controversial

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*Dowson et al. Circulation 2008*
Indication for closure of PFO

- **Stroke Prevention**
  - Primary prevention: No role
  - Pts with recurrent cryptogenic stroke despite medical treatment
  - Pts with first cryptogenic neurological event with a high risk PFO (large right to left shunt with septal aneurysm)

Pts with first event and a PFO should be encouraged to participate in a clinical trial.
Indication for closure of PFO

• Other Indications
  – Scuba divers with a history of decompression illness and a PFO
  – Orthodoxia Platypnoea
  – Pts with intractable migraines and history of TIAs

Pts with Migraine and a PFO should be encouraged to participate in a clinical Trial
Challenges of randomized trials

- Slow enrollment
- Closure device old generation
- Neurologist and Cardiologist bias
- Patient Bias
- Low risk patients are enrolled
Trial Results

• Most likely will be negative
• However if negative:
  – Cardiologists won't believe it
• If positive
  – Neurologists won't believe it
• Therefore clinical judgement and common sense will dictate treatment
Conclusions

- There is an association of stroke, decompression illness and possibly migraine in patients with PFO.

- Percutaneous closure of PFO is indicated in pts with recurrent strokes, decompression illness.

- Percutaneous closure of PFO possibly reduces the risk of recurrent stroke.

- Pts should be encouraged to participate in clinical trials of PFO and stroke.
The Interventional Cardiologist’s Brain

- Physical Needs & Desires
- Technical Details
- Oculostenotic, right to left shunt Reflex Lobe
- Memory storage for complications
- Motor Control Center