PFO

Hong Kong Core Cardiology Certificate Course
8/12/2019 12:05pm to 12:35pm

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PFO

• Incomplete postnatal fusion of septum primum and secundum

• Communication particularly
  • during actions causing sudden rise and fall in intrathoracic pressure, eg.
    • Coughing
    • Sneezing
    • Straining
    • Valsalva Manoeuvre
The foramen ovale is necessary for blood flow across the fetal atrial septum beginning at 4 weeks of pregnancy.

Closure of foramen ovale soon after birth

First Breath → Negative Intrathoracic Pressure → foramen ovale Closed

In PFO overlapping anatomy of primum/secundum forms a flap valve

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**Figure 2. Development of the Atrial Septum**

The primitive atrium is a single cavity. A solid crest of tissue grows down from the roof of the atrium, the primary septum (gray) (A), toward the developing inferior and superior endocardial cushions (pink). The primary foramen, the area between the leading edge of the developing primary septum and endocardial cushions, becomes smaller in size as the septum grows closer toward the endocardial cushions. They eventually fuse so that the foramen disappears. Multiple small perforations begin to develop at the superior aspect of the primary septum to form the secondary communication between the developing atria known as the secondary foramen (ostium secundum) (B). The atrial roof begins to fold inward (C) and grows down along the right side of the primary septum and is known as the secondary septum or “septum secundum” (yellow). It comes to lie over the secondary foramen, except for an area inferiorly (D). This region where the primary atrial septum is exposed on the right atrial side is the fossa ovalis. Hence a flaplike valve (patent foramen ovale [PFO]) is formed between the 2 atria.
Incidence of PFO

- Overall incidence 27.3%
- Incidence decreases with age

3rd decades – 34.3%
4th to 8th decades – 25.4%
9th to 10th decades – 20.2%
### Patent Foramen Ovale (PFO)

<table>
<thead>
<tr>
<th><strong>Anatomy</strong></th>
<th>Failure of fusion of primum and secundum atrial septa leading to flap valve opening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shunt</strong></td>
<td>Right-to-left shunt when right atrial pressure exceeds left atrial pressure (usually transient)</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>20–34% of adult population¹</td>
</tr>
<tr>
<td><strong>Consequences</strong></td>
<td>Harmless in most people but may permit paradoxical embolus</td>
</tr>
</tbody>
</table>

### Atrial Septal Defect (ASD)

<table>
<thead>
<tr>
<th><strong>Anatomy</strong></th>
<th>Deficiency in atrial septum resulting in failure of overlap (hole in atrial septum)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shunt</strong></td>
<td>Continuous left-to-right shunting</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>1.6 per 1,000 live births⁸</td>
</tr>
<tr>
<td><strong>Consequences</strong></td>
<td>Continuous left-to-right shunt may cause volume loading of right heart, which may reduce long-term survival if not corrected. May increase pulmonary artery pressure, reduce exercise tolerance and promote arrhythmia. Can also permit paradoxical embolus, and this is an indication for closure</td>
</tr>
</tbody>
</table>
Morphology of PFO
Echocardiographic appearance - PFO
PFO and Stroke
PFO and Stroke

• Association first described in 1877
• Julius Friedrich Cohnheim, German pathologist
• Necropsy on a 35 year-old woman
  • Fatal stroke
  • Long thrombus in lower extremity
  • Very large PFO

Cryptogenic Stroke

• Stroke which, despite extensive investigations, a clear cause cannot be found

• Exclusion of
  • AF
  • Atherosclerotic disease
  • Carotid dissection
  • Intracerebral pathology (eg. Haemorrhage/SOLs)

• Cause of stroke remains unknown in 40%
Evidence supporting paradoxical embolic stroke

- Cortical location of infarcts
- Strokes in multiple vascular distributions
- Infarcts of different ages in the same vascular territory

Other indirect evidences

- Absence of conventional stroke risk factors
- History of DVT
- Recent events predisposed to venous stasis
- Valsalva manoeuvre preceding stroke event

RoPE
(Risk of Paradoxical Embolism) Score

- High score = Increased likelihood PFO being culprit
- PFO attributable fraction of stroke
  - 7 (72%)
  - 8 (84%)
  - 9 (88%)

Workup for Cryptogenic Stroke

- Occult AF up to 16% has been identified within 90 days of randomization
- 30-days > 24 hr ECG
- TTE - TEE

PFO Evaluation
Evaluation of PFO - TTE

• Doppler if large shunts
• Strain manoeuvre
Evaluation of PFO - TTE

- Bubble Study
- Standard apical 4-chamber view
- Administration of agitated saline
- Timing – within 3 cardiac cycles

To differentiate intracardiac vs transpulmonary shunts
(*need detailed imaging for particular large pulmonary shunts*)

**Shunt grading**
- Grade 1: 5 bubbles
- Grade 2: 5 to 25 bubbles
- Grade 3: 25 bubbles
- Grade 4: opacification of chamber

with manoeuvres to increase right atrial pressure

Evaluation of PFO - TEE

• Indications for TEE
  • 1/ Contrast study negative but the index of suspicion for possible cardiac embolism is high
    • To rule out left atrial appendage thrombus, spontaneous echo contrast, aortic atheroma, cardiac masses, vegetations
    • Detailed assessment of the atrial septum anatomy
  • 2/ Suboptimal or equivocal TTE bubble study

• 3/ Contrast study positive for RLS
  • Detailed assessment of the atrial septum anatomy/other atrial septal defect/abnormalities
  • Rule out other pulmonary shunts
  • Intervention planning
• **Atrial Septal Aneurysm**
  • redundant or excessive tissue of the atrial septum
    • sway into either atrium of 10 mm (from an imaginary midline), or
    • a total excursion of 15 mm
• PFO Tunnel
  • Overlap between the flap and septum secundum is variable, PFO anatomy is also variable
  • Resulting in a tunnel of different width and length, ranging from 5-13 mm and 1-6 mm, respectively
Evaluation of PFO - TCD

• **TransCranial Doppler**
  • Agitate saline through peripheral vein
  • TCD Recording of microbubbles in MCA as microembolic signals
    • Sensitivity 95%
    • Specificity 75%
  • Appearance of at least 1 bubble on TCD trace within 40 s of injection

• **Shunt grading**
  • Negative: no microbubbles
  • Low-grade shunt: 1 to 10 microbubbles
  • Medium-grade shunt: >10 microbubbles
  • High-grade shunt: “curtain effect”/ numerous microbubbles
Thrombus-in-transit
PFO Thrombus-in-transit

- Thrombus straddling the patent foramen ovale
- Rare
- Classical thrombus taken shape of veins
- Severe PE
  - increased pulmonary and right ventricle pressures
  - could support clot migration across the PFO
  - interatrial pressure gradient reversal
Clinical Trials for Closure
# PFO Closure Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Device</th>
<th>n</th>
<th>Endpoints</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOSURE I&lt;sup&gt;a&lt;/sup&gt;</td>
<td>STARFlex Septal Closure System</td>
<td>909</td>
<td>Composite of death (0-30 days), neurological death (≥31 days), stroke or TIA at 2-year follow-up</td>
<td>Non-significant reduction in primary endpoint (HR 0.78; 95% CI [0.45–1.35]; p=0.37)</td>
<td>Poor effective closure at 2 years, with evidence of left atrial thrombus formation in closure group</td>
</tr>
<tr>
<td>PC-Trial&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AMPLATZER PFO Occluder</td>
<td>414</td>
<td>Composite of death, stroke, TIA or peripheral embolism at mean 4.5 years</td>
<td>Non-significant reduction in primary endpoint (HR 0.63; 95% CI [0.24–1.62]; p=0.34)</td>
<td>Underpowered trial with substantial cross-over during follow-up</td>
</tr>
<tr>
<td>RESPECT&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>AMPLATZER PFO Occluder</td>
<td>980</td>
<td>Composite of early death, stroke or TIA</td>
<td>Non-significant reduction in primary endpoint at median follow-up of 2.1 years (HR 0.49; 95% CI [0.22–1.11]; p=0.08)</td>
<td>Benefit for closure in early as-treated analysis</td>
</tr>
<tr>
<td>GORE REDUCE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Helex Septal Occluder or Cardioform Septal Occluder</td>
<td>664</td>
<td>Co-primary endpoints of clinical stroke and incidence of new brain infarction</td>
<td>Significant reduction in clinical stroke at median follow-up of 3.2 years (HR 0.23; 95% CI [0.09–0.62]; p=0.002). Significant reduction in new brain infarction (relative risk 0.51; 95% CI [0.29–0.91]; p=0.04)</td>
<td>2:1 randomisation to PFO closure</td>
</tr>
<tr>
<td>CLOSE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Multiple devices</td>
<td>663</td>
<td>Stroke</td>
<td>Significant reduction in stroke with occlusion compared to antiplatelet therapy only (HR 0.03; 95% CI [0.00–0.26]; p&lt;0.001)</td>
<td>1:1:1 randomisation PFO closure versus antiplatelets versus anticoagulation</td>
</tr>
<tr>
<td>DEFENSE PFO&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AMPLATZER PFO Occluder</td>
<td>120</td>
<td>Stroke, vascular death or Thrombolysis in Myocardial Infarction-defined major bleeding at 2-year follow-up</td>
<td>Significant reduction in primary endpoint with PFO closure. No events in PFO closure arm versus a 12.9% 2-year event rate in medication-only arm (p=0.013)</td>
<td>+ ve</td>
</tr>
</tbody>
</table>

<sup>a</sup> PFO = patent foramen ovale; TIA = transient ischaemic attack.
## Previously published PFO Closure Data

<table>
<thead>
<tr>
<th>Trial Name (Year of Publication)</th>
<th>No. of Patients</th>
<th>Mean or Median No. of Years of Follow-up</th>
<th>Comparator</th>
<th>Primary Outcome</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLOSURE I</strong> (2012)$^1$</td>
<td>909</td>
<td>2</td>
<td>Antiplatelet therapy, warfarin, or both</td>
<td>Composite of stroke or transient ischemic attack at 2 years, death from any cause during first 30 days, or death from neurologic causes between 31 days and 2 years after randomization</td>
<td>0.78</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>PC</strong> (2013)$^2$</td>
<td>414</td>
<td>4.1 PFO closure group, 4.0 (medical therapy group)</td>
<td>Antiplatelet therapy or anticoagulation</td>
<td>Composite of death, stroke, transient ischemic attack or thromboembolism</td>
<td>0.63</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>RESPECT</strong> (2013)$^3$</td>
<td>980</td>
<td>2.1</td>
<td>Antiplatelet therapy or warfarin</td>
<td>Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization</td>
<td>0.49</td>
<td>0.08</td>
</tr>
</tbody>
</table>


TCT: Two PFO Closure Trials Miss Primary Endpoints

Two trials presented today at the TCT meeting in Miami testing the benefits of PFO closure in patients with cryptogenic stroke have failed to convincingly demonstrate any significant benefit for the controversial procedure.

The RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial randomized 980 patients to PFO closure with the Amplatzer PFO Occluder device or medical therapy. According to the lead investigator John Carroll, the rate of recurrent stroke was low in both arms of the trial: 1.6% in the closure group and 3% in the medical group.

This difference between the groups did not achieve significance in the intention-to-treat (ITT) analyses:
St. Jude Medical RESPECT Trial for PFO Closure Provides Clinical Evidence of Risk Reduction in Prevention of Recurrent Cryptogenic Stroke

By Business Wire | More Articles
October 25, 2012 | Comments (0)

St. Jude Medical RESPECT Trial for PFO Closure Provides Clinical Evidence of Risk Reduction in Prevention of Recurrent Cryptogenic Stroke

Results offer compelling evidence for closure with the AMPLATZER PFO Occluder over conventional medical management alone

ST. PAUL, Minn.--(BUSINESS WIRE)-- St. Jude Medical, Inc. (NYSE: STJ), a medical device company, today announced results from its RESPECT trial, which studied the AMPLATZER™ PFO Occluder in the prevention of recurrent cryptogenic stroke. Evidence presented at a late breaking trial session during the 24th Annual Transcatheter Cardiovascular Therapeutics (TCT) scientific symposium, sponsored by the Cardiovascular Research Foundation, shows that the primary analysis was not statistically significant but trended
PFO Closure May Be Superior to Medical Therapy in Preventing Stroke

ScienceDaily (Oct. 25, 2012) — Results of a large-scale, randomized clinical trial called RESPECT revealed that patent foramen ovale (PFO) closure may be superior to medical therapy in preventing recurrent stroke, according to a presentation of findings today at the Transcatheter Cardiovascular Therapeutics (TCT) conference in Miami.

"In contrast to a previously reported randomized trial for the treatment of cryptogenic stroke, the RESPECT trial enrolled only patients with documented cryptogenic embolic strokes and excluded patients with other potential causes of stroke and/or TIA. The period of follow-up approached nine years and was not restricted to only events within the initial two years of follow-up," said Richard Smalling, M.D., Ph.D., James D. Wood Distinguished Chair in Cardiovascular Medicine at the University of Texas Health Science Center at Houston (UTHealth), who

Related Stories

Study Suggests a Relationship Between Migraine Headaches in Children and a Common Heart Murmure
St. Jude Device to Close Heart Holes Fails to Stop Stroke

By Michelle Fay Cortez - Oct 26, 2012 4:13 AM GMT+0800

St. Jude Medical Inc. (STJ)’s device to plug openings in the heart after a stroke failed to definitively prevent repeat incidents in patients under age 60 compared with non-surgical drug treatment, two studies found.

The data calls into question broader use of the procedure and the product, used for nearly two decades at a cost of about $20,000 for each of about 9,000 surgeries done yearly.

Neither study determined that St. Jude’s Amplatzer PFO Occluder significantly reduced risk of a second stroke. One, funded by the St. Paul Minnesota-based company, found the device was beneficial once researchers adjusted the data to consider different dropout rates and types of treatment. The twin reports suggest the surgery isn’t a panacea for those who inexplicably suffer a stroke, and the twice when.
Highlights from the Landmark RESPECT Trial

- Randomized, event-driven, open label trial with blinded endpoint adjudication
- Patients randomized 1:1 to AMPLATZER PFO Occluder or medical management (aspirin, warfarin, clopidogrel, or aspirin with dipyridamole)
- 980 Subjects enrolled from 2003 to 2011, followed through 2016
- 69 sites in US and Canada
- Primary Endpoint:
  - Composite of:
    - Recurrent nonfatal ischemic stroke
    - Fatal ischemic stroke
    - Early post-randomization death (within 45 days)

RESPECT 2013\textsuperscript{1}

*Initial Analysis Period*

- Mean follow-up 2.6 years
- ITT analysis shows 51\% *relative reduction* in favor of PFO closure for primary endpoint, reducing recurrent ischemic stroke or early death ($p = 0.08$)
- Per protocol analysis shows significant 63\% *relative risk reduction* in favor of PFO closure for reducing recurrent ischemic stroke or early death ($p = 0.03$)
- ITT analysis shows 83\% *relative risk reduction* in favor of PFO closure for reducing recurrent cryptogenic ischemic stroke ($p = 0.07$)

RESPECT 2017\textsuperscript{2}

*Extended Follow-Up Period*

- Mean follow-up 5.9 years
- ITT analysis shows 45\% *relative risk reduction* in favor of PFO closure for reducing any recurrent ischemic stroke ($p = 0.046$)
- ITT analysis shows significant 62\% *relative risk reduction* in favor of PFO closure for reducing recurrent cryptogenic ischemic stroke ($p = 0.007$)

RESPECT - Efficacy Endpoints

All recurrent ischemic stroke and early death

Risk Reduction: 45%
HR: 0.55 (95% CI: 0.305, 0.999)
Log-rank 2-sided p-value = 0.046

Recurrent ischemic stroke of undetermined cause

Risk Reduction: 62%
HR: 0.38 (95% CI: 0.18, 0.79)
Log-rank 2-sided p-value = 0.007

45% relative risk reduction for any recurrent ischemic stroke or early death over 5.9 years of follow-up

62% relative risk reduction for recurrent ischemic stroke of undetermined cause

[NNT]=45

# Adjudicated SAE of Interest

<table>
<thead>
<tr>
<th>Event Type</th>
<th>PFO Closure Group (N=499; 3141 pt-yrs)</th>
<th>Medical Management Group (N=481; 2669 pt-yrs)</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Rate*</td>
<td>Events</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>9</td>
<td>0.29</td>
<td>4</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>18</td>
<td>0.57</td>
<td>15</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>7</td>
<td>0.22</td>
<td>11</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>18</td>
<td>0.57</td>
<td>4</td>
</tr>
</tbody>
</table>

- Rate of serious atrial fibrillation events was comparable between the two groups.
- Higher rate of DVT/PE events in device group likely due to lower anticoagulant use in device group, which is known to be protective from DVT/PE.

*Rate expressed as a number of events per 100 patient-years

**Based on the normal approximation to a difference in Poisson rates
GORE REDUCE Trial

- Randomized, open-label
- **664 subjects** randomized 2:1 to:
  - PFO closure with HELEX device (N=158; used until 2012, no longer available) or CARDIOFORM (N=250) plus antiplatelet therapy
  - Medical management: antiplatelet therapy alone
- **63 sites**, 7 countries
- PI’s: Scott Kasner, MD (U of Penn), John Rhodes, MD (Duke Univ), Lars Søndergaard MD (Righospitalet, Denmark), Lars Thomassen, MD (Haukeland Univ Hospital, Norway)

**REDUCE Primary Efficacy (ITT)**

**Co-primary endpoint 1:**
77% relative risk reduction in favor of PFO closure in reducing risk of recurrent stroke

**Co-primary endpoint 2:**
Incidence of new brain infarctions significantly lower in PFO group, but incidence of silent brain infarction did not differ significantly between groups

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**Table 2. Coprimary End Points of Freedom from Clinical Ischemic Stroke and Incidence of New Brain Infarction.**

<table>
<thead>
<tr>
<th>End Point</th>
<th>PFO Closure Group</th>
<th>Antiplatelet-Only Group</th>
<th>Effect Size</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical ischemic stroke</strong> †</td>
<td>6/441 (1.4)</td>
<td>12/223 (5.4)</td>
<td>0.23 (0.09-0.62) ‡</td>
<td>0.002 ‡</td>
</tr>
<tr>
<td><strong>New brain infarction</strong> †</td>
<td>22/333 (6.7)</td>
<td>20/177 (11.3)</td>
<td>0.51 (0.29-0.91)</td>
<td>0.04**</td>
</tr>
<tr>
<td>Recurrent clinical ischemic stroke</td>
<td>5/333 (1.5)</td>
<td>12/177 (6.8)</td>
<td>0.19 (0.07-0.54)</td>
<td>0.005**</td>
</tr>
<tr>
<td>Silent brain infarction</td>
<td>17/333 (5.1)</td>
<td>8/177 (4.6)</td>
<td>0.98 (0.43-2.3)</td>
<td>0.97**</td>
</tr>
</tbody>
</table>

*Freedom from clinical ischemic stroke is reported here as the number of recurrent strokes through at least 24 months. New brain infarction was a composite of clinical ischemic stroke or silent brain infarction detected on imaging at 24 months.*

† *Clinical evidence of ischemic stroke is reported through the time of available follow-up, with a minimum of 2 years, maximum of 5 years, and median of 3.2 years.*

‡ *Data are presented as a hazard ratio with a 95% confidence interval in the PFO closure group as compared with the antiplatelet-alone group.*

§ *The P value was calculated with the use of a log-rank test.*

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>PFO closure group</th>
<th>Antiplatelet-only group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFO closure group</strong></td>
<td>441</td>
<td>233</td>
</tr>
<tr>
<td>422</td>
<td>202</td>
<td>194</td>
</tr>
<tr>
<td>417</td>
<td>173</td>
<td>163</td>
</tr>
<tr>
<td>398</td>
<td>116</td>
<td>102</td>
</tr>
<tr>
<td>278</td>
<td>78</td>
<td>30</td>
</tr>
</tbody>
</table>

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\[\text{NNT} = 25\]
CLOSE Study

CLOSE: Closure of Patent Foramen Ovale, Oral Anticoagulants or Antiplatelet Therapy to Prevent Stroke Recurrence

- Randomized, open label multi-center study, France (32 sites) & Germany (2 sites)
- Study funded by French Ministry of Health
- 663 patients included from 2008 to 2014; follow-up until December 2016
- Patients 16 to 60 years of age who had had a recent stroke attributed to PFO, with an associated atrial septal aneurysm or large interatrial shunt
- Patients enrolled regardless of contraindication to anticoagulant therapy or PFO closure
- Investigator could choose any PFO device; 11 devices used in study – most commonly AMPLATZER PFO Occluder (51%)

Randomization:
- Group 1: Randomized 1:1:1 to PFO closure + Antiplatelet therapy vs Antiplatelet therapy alone vs Anticoagulant Therapy alone
- Group 2 (contraindication to anticoagulation): Randomized 1:1 to PFO closure + Antiplatelet therapy vs Antiplatelet therapy
- Group 3 (contraindication to PFO closure): Randomized 1:1 to Anticoagulation therapy alone vs. Antiplatelet therapy alone

CLOSE Efficacy Outcomes

ITT results showed highly significant benefit of PFO closure vs antiplatelet therapy for preventing stroke recurrence
- Hazard Ratio 0.03, P=<0.001)
- One stroke avoided at 5 years for every 20 treated patients

- Anticoagulant vs antiplatelet: Stroke occurred in 3 patients in anticoagulation group and 7 patients in antiplatelet-only group. Hypothesis test was not carried out because the study was not adequately powered to compare outcomes in these groups
- Device implantation success 99.6%; PFO closure rate 88.6%
  - Multiple device types used; all patients in study had atrial septal aneurysm or large intra-atrial shunt
Key Points to Remember: CLOSE Trial

- Results showed highly significant, **97% relative risk reduction in risk of recurrent ischemic stroke with PFO closure vs antiplatelet therapy**

- Difference in results from the other trials may be explained by:
  - Restricted patient characteristics in trial
    - Atrial septal aneurysm or large atrial shunt in all patients
    - Reduced HTN, DM, other risk factors
  - Reference treatment group: antiplatelet therapy alone (no use of anticoagulation)

- Rate of AF significantly higher in PFO closure group vs antiplatelet-only group
  - Most cases detected within 1 month after procedure
  - Only one occurrence of AF after 1 month post-procedure, compared with 2 in the antiplatelet-only group

*Study was not adequately powered to compare differences between anticoagulation and antiplatelet therapy or anticoagulation only and device.*

\[\text{[NNT]}=17\]
# 3 positive trials for PFO closure published simultaneously in the NEJM

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>No. of Patients</th>
<th>Mean or Median No. of Years of Follow-up</th>
<th>Comparator</th>
<th>Primary Outcome</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPECT¹</td>
<td>980</td>
<td>5.9</td>
<td>Antiplatelet therapy or warfarin</td>
<td>Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization</td>
<td>0.55</td>
<td>0.046</td>
</tr>
<tr>
<td>REDUCE²</td>
<td>664</td>
<td>3.2</td>
<td>Antiplatelet therapy</td>
<td>Ischemic stroke and new brain infarction on imaging</td>
<td>0.23</td>
<td>0.002</td>
</tr>
<tr>
<td>CLOSE³</td>
<td>663</td>
<td>5.3</td>
<td>Antiplatelet therapy or anticoagulation‡</td>
<td>Stroke</td>
<td>0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DEFENSE PFO</td>
<td>120</td>
<td></td>
<td>AMPLATZER PFO Occluder</td>
<td>Stroke, vascular death or Thrombolysis In Myocardial Infarction-defined major bleeding at 2-year follow-up</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


[NNT]= 8
Combined Kaplan-Meier curves with individualised patient data based on the type of intervention for ischaemic stroke

Appendix 4: PFO closure vs antiplatelet therapy forest plots (Direct evidence only)

| Study or Subgroup | PFO Closure | | | Antiplatelet | | | | | | | | | | Odds Ratio | | | | | | | | | | M-H, Fixed, 95% CI | | | | | | | | | | Odds Ratio | | | | | | | | | | M-H, Fixed, 95% CI | | | | | | | | | | Total (95% CI) | | | | | | | | | | Total events | | | | | | | | | | Heterogeneity: Chi² = 2.49, df = 2 (P = 0.29), I² = 20% | | | | | | | | | | Test for overall effect: Z = 4.58 (P < 0.00001)

eFigure 1: Ischaemic stroke

| Study or Subgroup | PFO Closure | | | Antiplatelet | | | | | | | | | | Odds Ratio | | | | | | | | | | M-H, Fixed, 95% CI | | | | | | | | | | Odds Ratio | | | | | | | | | | Total (95% CI) | | | | | | | | | | Total events | | | | | | | | | | Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74), I² = 0% | | | | | | | | | | Test for overall effect: Z = 1.44 (P = 0.15)

eFigure 5: Major bleeding
Appendix 5: PFO closure vs Anticoagulation forest plots (Direct evidence only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PFO Closure+Antiplatelet Events</th>
<th>Total</th>
<th>Anticoagulation Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Difference MH, Random, 65% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mas 2017</td>
<td>0</td>
<td>173</td>
<td>3</td>
<td>180</td>
<td>100.0%</td>
<td>0.02 [0.94, 0.00]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>173</td>
<td>3</td>
<td>180</td>
<td>100.0%</td>
<td>-0.02 [-0.04, 0.00]</td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>100.0%</td>
<td>-0.02 [-0.04, 0.00]</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect Z = 2.09 (P = 0.04)

eFigure 5: Major bleeding
Guidelines on PFO Closure
European Position Paper – Executive summary

- PFO closure reduces stroke recurrence in comparison with medical therapy
- Careful assessment of the role of a PFO in a thrombo-embolic event is required
- An interdisciplinary collaboration, shared decision making is key
- What needs to be considered in for the decision making is the young age of the patient
- Recommendation:
  - “Position of our societies to perform percutaneous closure of PFO in carefully selected patients from 18 to 65 years with confirmed cryptogenic stroke, TIA or systemic embolism and estimated high probability of causal role of PFO as assessed by clinical, anatomic and imaging features.”

Authors: Christian Pristipino, M.D.; Horst Sieske, M.D.; Fabrizio Ioffreda, M.D.; Jean Louis Mac, M.D.; Bernhard Meier, M.D.; Paolo Sacco, M.D.; David Wijck-Smith, M.D.; Francesco Guala, M.D.; Danilo Toni, M.D.; Paul Kyrle, M.D.; John Thorne, M.D.; Geneviève Bermeu, M.D.; PhD; Enzo Spadola, M.D.; Dirk Silbering, M.D.; Peter Gerbespyr, M.D.; Sergio Bert, M.D.; Maximo Cerina, M.D.; Francesco Solopini, M.D.; Durranta Ruble, M.D.; Muriel Hennem, M.D.; Jose Zernam, M.D. (joint task force of European Association of Percutaneous Cardiovascular Interventions (EAPCI); European Stroke Organization (ESO); European Heart Rhythm Association (EHRA); European Association for Cardiovascular Imaging (EACVI); European Pediatric and Congenital Cardiology (EAPC); ESC Working group on GICH; ESC Working group on Thrombus; European Hemostasis Society (EHS); European Underwater and Baromedical Society (EUBS)).

Pristipino, C. et al; European Position paper on the management of patients with patent foramen ovale; EuroIntervention/ 2018
Current AHA/ASA Guidelines for PFO Closure are Out of Date Given Current Evidence

• **THE 2014 AHA/ASA GUIDELINES for Prevention of Stroke in Patients with Ischemic Stroke or Transient Ischemic Attack** recommend the following:
  • There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO. Class IIb, LOE B.
  • For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended. Class I, LOE B.
  • For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics. When anticoagulation is contraindicated, an inferior vena cava filter is reasonable. Class IIa, LOE C.
  • For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure. Class III, LOE A.
  • In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT. Class IIb, LOE C.
There is now sufficient evidence to recommend PFO Closure for very carefully selected patients aged 60 years and younger with an unexplained embolic event who are found to have a PFO and who do not require chronic anticoagulation therapy for another reason.
In patients between 16 and 60 years with a (after neurological and cardiological clarification) cryptogenic ischemic stroke and open foramen ovale with moderate or pronounced right-left shunt an interventional PFO closure should be performed. 
PFO Clinical Scenarios

1. Decompression Sickness
2. Migraine with Aura
3. Platypnoea-orthodeoxia Syndrome
4. Liver Transplantation
Decompression Sickness

• Rapid ascent – dissolved nitrogen oversaturation – formation of vascular and extravascular bubbles

• Pulmonary DCS [nitrogen bubbles accumulation in pulmonary capillaries]
  • Pain
  • Cough
  • Dyspnea

• PFO
  • Paradoxical embolization of bubbles

• Neurological and Cutaneous DCS
  [muscle pain/joint pain//headache/dizziness/fatigue/rash/paraesthesia/breathing difficulties/confusion/motor incoordination/paralysis]
• First described in 1989 – echo and doppler in divers
  • 5 X risk of DCS
  • Proportional to PFO size


• Case-control study
  • 47 divers with unprovoked DCS + documented PFO
  • 1:1 PFO closure vs med Rx
  • TTE for venous bubbles and TCD for arterial bubbles after test dive
  • No significant difference in appearance of venous bubbles in both group
  • Complete elimination of arterial bubbles in PFO closure group
  • No DCS events

• **Longitudinal, non-randomized follow-up study**
  - Reduction in both symptomatic neurological events and total brain lesions
  - Recreational divers with DCS with PFO
  - PFO closure vs no closure


• **Recommendations**
  - Divers with History of DCS and PFO – Cessation of Diving/Conservative Approach to Diving/Consideration of PFO Closure
  - Professional/Recreational Divers
Migraine with Aura

• Theories
  • Persistent right-to-left PFO mediated shunt
  • Passage of vasoactive amines and humoral substances
    • Prostaglandin E1, E2, serotonin, bradykinin, angiotensin I
    • +/- Microthrombi/emboli from PFO entering posterior circulation

• MIST [Migraine Intervention with STARFlex Technology] Trial
  • Prospective, multicenter, double-blind, sham controlled in UK
  • No significant difference

• MIST II
  • US, terminated due to slow recruitment

• PRIMA [Percutaneous Closure of PFO in Migraine and Aura]
  • Migraine with aura, 53 PFO vs 54 med Rx
  • No significant difference

• PREMIUM [Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using Amplatzer PFO Occluder to Medical Management]
  • No meeting primary endpoint
Platypnea-Orthodeoxia Syndrome

• Increased right-to-left shunting of blood on assuming an upright position
• Shunting usually at PFO / ASD, but can be extracardiac
  (1) right atrial pressure > left atrial pressure, or
  (2) mechanical distortion of fossa ovalis

• e.g. aortic aneurysm, obstructive and restrictive pulmonary diseases, kyphoscoliosis
Platypnea-Orthodeoxia Syndrome

Enlarged aortic root -> compresses on right atrium -> increases R-to-L shunt
Platypnea-Orthodeoxia Syndrome

Table 1: Conditions associated with cardiac POS

<table>
<thead>
<tr>
<th>Group A: Anatomic preferential blood flow across the inter-atrial communication</th>
<th>Group B: Transient reversal of left-to-right pressure gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital abnormality</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Absent superior vena cava</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Ascending aortic aneurysm</td>
<td>Pneumonectomy</td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Ebstein’s anomaly</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Partial anomalous venous return</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Persistent left superior vena cava</td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>Prominent Eustachian valve</td>
<td>Pericardial adipose deposition</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>Pneumonectomy</td>
</tr>
<tr>
<td>Unroofed coronary sinus</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Post-surgical repair</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Ascending aorta repair</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Atrial switch procedure</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Fontan procedure</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Tumours</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Cardiac cyst/mass</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Lipomatous hypertrophy of the inter-atrial septum</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Other</td>
<td>Pneumonectomy</td>
</tr>
<tr>
<td>Eosinophilic endomyocardial disease</td>
<td>Pneumonectomy</td>
</tr>
<tr>
<td>Hepatic cyst</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Tricuspid regurgitation or stenosis</td>
<td>Pulmonary embolism</td>
</tr>
</tbody>
</table>

Table 2: Non-cardiac conditions associated with platypnea-orthodeoxia syndrome

<table>
<thead>
<tr>
<th>Pulmonary</th>
<th>Abdominal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>Paralytic ileus</td>
<td>Chest wall trauma</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>Hepatopulmonary syndrome</td>
<td>Diabetic autonomic neuropathy</td>
</tr>
<tr>
<td>Cryogenic fibrosing alveolitis</td>
<td>Alcoholic liver cirrhosis</td>
<td>Organophosphate poisoning</td>
</tr>
<tr>
<td>Fat embolism</td>
<td>Autoimmune hepatitis</td>
<td>Paraesophageal hernia repair</td>
</tr>
<tr>
<td>Hemidihaphragmatic dysfunction</td>
<td>Hepatitis A</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Noncompensatory portal hypertension</td>
<td>Vertebral fractures</td>
</tr>
<tr>
<td>Pneumocystis and CMV pneumonia</td>
<td>Pneumonectomy</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>Pulmonary arteriovenous malformations</td>
<td>Kyphoscoliosis</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Radiation-induced bronchial stenosis</td>
<td></td>
</tr>
<tr>
<td>Radiation-induced bronchial stenosis</td>
<td>Traumatic bronchial rupture</td>
<td></td>
</tr>
</tbody>
</table>

- Case series
  - 54 patients – feasibility study, safe and effective

Liver Transplantation and PFO

• Air embolism/thromboembolism during or immediately following surgery

• PFO as conduit for air embolism
  • Placement of central lines
  • Veno-venous bypass
  • Caval clamping
  • Inadequate flushing of harvested transplant

• Retrospective studies
  • Transplant patients with PFO – no improvement in LOS in ICU, postop O2 requirements, 30-days mortality, stroke


Case illustrations - PFO
Case 1/CLN

- F/83
- HT, DM, OSA, renal impairment
- Noted desaturation when sitting up
- TEE found PFO
- Plan for percutaneous closure
Case 2/LMW

• F/90
• DM, HT, Old CVA at age of 70
• Admission for # hip and deconditioning
• Transferred to convalescence hospital
• Noted genuine desaturation
• Desaturation despite 100% O2 mask while in upright position and corrected quickly when lying supine
• Transfer back to acute hospital
• CT thorax to rule out pulmonary embolism
Case 3/CY

- M/58
- Crytogenic stroke
Best Practice Consideration for PFO Clinics

• Collaboration Between Cardiology and Neurology Is Important for Patient Selection

NEUROLOGY-CARDIOLOGY TEAMWORK
Prior to Seeing Patient: Review brain imaging and TTE/TEE to share key findings with each other
Discussion with Patient and Family: Provide a joint consultation as a multidisciplinary team with both clinicians providing their assessment, recommendations, and answering questions and concerns

ENGAGE AND EDUCATE THE PATIENT
• Will they be seeing both the cardiologist and neurologist?
• Recommendations on lifestyle, meds, and diet. Scuba diving?
• What is a PFO closure procedure consist of and what is recovery?

SUPPORT FROM STAFFING
• Assess patient’s understanding of issues and goals of care
• NP: complete H & P
• ROPE Score calculation
• Distribute and use resources to educate: Patient guide, demo of AMPLATZER™ PFO occluder, and procedure animation video

RULE OUT KNOWN CAUSES OF STROKE
• Is evaluation complete?
• Are the imaging data consistent with an embolic mechanism?
• Does the RoPE score suggest a pathogenic PFO?
• Any hx of VTE, BCP, hypercoag states?

CARDIAC EVALUATION AND PROCEDURE PLANNING
• Any other cardiac issues present?
• Has PAF been excluded?
• What are the characteristics of the PFO?
• Presence of other PFO related syndromes: hypoxemia and migraines?
• Discussion of PFO closure

*Compliments of Dr John Carroll, University of Colorado Hospital
New Technique – HeartStitch

NobleStitch™ EL, used in combination with the KwitKnot™, provides the simplest, most intuitive, least invasive solution to cardiovascular sutures and PFO closure. Click on the animation below to watch the fluoroscopically guided procedure in action.
The Carag Bioresorbable Septal Occluder: A Concept Device
Conclusion

• Unique anatomy of PFO and Imaging evaluation
• Long Journey on topic of transcatheter PFO closure vs best medical therapy
• Careful evaluation and labelling of cryptogenic stroke
• PFO-mediated stroke
• Heart-brain Team
• Extended FU for exiting trial patients
Potential unresolved issues

- Cryptogenic stroke + PFO + age > 60
- Role of Neuroimaging for Silent Infarct
- PFO Closure in non-stroke correlations
- Optimal long-term antithrombotic treatment
- Venous thrombosis screening and management
- Optimal patient selection/Universal screening
- Pure NOAC vs Closure comparison
- Optimal device design and selection
Thank you!

See you in 2020!