PFO Closure for Cryptogenic Stroke

AJ Conrad Smith, MD FACC
University of Pittsburgh Medical Center
The Tale of PFO and Cryptogenic Stroke (CS)

Game Plan of this Talk:

• Very Brief Epidemiology of Ischemic Stroke
• Prevalence of Cryptogenic Stroke
• PFO and CS association
• Registry evaluations of PFO closure
• Randomized Controlled trials of PFO closure
  • Early
  • Late
• What should we do?
• Where should we go from here?
Annual Incidence of Cryptogenic Strokes

**United States**

- **600,000** Annual Ischemic Strokes in US
  - **480,000 (80%)** Ischemic Strokes > 60 yo
  - **120,000 (20%)** Ischemic Strokes 18-60 yo
    - **84,000 (70%)** Known Cause
    - **36,000 (30%)** Cryptogenic
      - **18,000 (50%)** Without PFO
      - **18,000 (50%)** With PFO

**World**

- **11,500,000** Annual Ischemic Strokes Globally
  - **9,200,000 (80%)** Ischemic Strokes > 60 yo
  - **2,300,000 (20%)** Ischemic Strokes 18-60 yo
    - **1,610,000 (70%)** Known Cause
    - **690,000 (30%)** Cryptogenic
      - **345,000 (50%)** Without PFO
      - **345,000 (50%)** With PFO

How do you prevent a recurrent a stroke of unknown etiology?!
PFO and Cryptogenic Stroke

The Rationale:

• Q: How do you prevent a stroke of unknown etiology?!
• A: First identify an etiology!

• Association of PFO with Cryptogenic stroke
  • PFO 100% in newborns
  • 25% of the general population
  • 40-50% of patients with cryptogenic stroke

• More than an association?
  • CS in patients with concomitant DVT and PE
  • Thrombus in transit

Lechat et al. NEJM 1988;318:1148

Abdelsalam et al. Heart 2012;:-:1. doi:10.1136/heartjnl-2012-301659
Catheter based Closure of PFO

- Femoral venous procedure
- TEE or ICE guidance
- Intracardiac bubble study can be performed
- Discharge same day or next day

Farb et al NEJM 2017;377:1006-1009
## Incidence of Recurrent Stroke

### PFO closure vs Med therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Medical Therapy</th>
<th>PFO Closure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khairy et al Meta analysis</td>
<td>3.8-12/year</td>
<td>0-4.9/year</td>
</tr>
<tr>
<td>Windecker et al Retrospective</td>
<td>24.3/4year</td>
<td>8.5/4 year</td>
</tr>
<tr>
<td>Schuchlenz et al Retrospective</td>
<td>13/year ASA</td>
<td>0.6/year</td>
</tr>
<tr>
<td></td>
<td>5.6/year Warf</td>
<td></td>
</tr>
</tbody>
</table>

*Ann Intern Med 2003;139:753*
*JACC 2004;44L750*
*Schuchlenz Int J Cardio 2005;101:77*
Finally the RCTs
CLOSURE

- 909 pts 18-60 yo with CS and PFO
- Closure with StarFLEX
- Primary endpoint Stroke, TIA, 2yr F/U. Death < 30d, neuro death>30d-2yr
- F/U 2 years
- Closure 5.5% Med 6.8%
  - HR .70(0.45-1.35)p 0.37
- Device thrombogenic
- Increase incidence of Afib Close 5.7 v Med 0.7 p <0.001
- Lower 6 month closure rate 86%

Furlan et al. NEJM 2012;366:991-999
RESPECT

- 980 pts with aged 18-60 with CS
  - Treated with meds and closure with Amplatzer PFO device vs. Meds alone
- Antiplt 74.8% AC 25.2%
- 1375 pt-yrs closure 1184 pt-yrs medical
  - Median F/U 2.1 yrs
- HR 0.49 (0.22-1.11) p=0.08

Carroll et al NEJM 2013;368:1092
PC Trial

• 414 pts age <60 with CS
• Closure with Amplatzer PFO vs medical therapy
• Primary endpoint all cause death, stroke, TIA, periph emboli
  • Closure 3.4% Med 5.2% 0.63(0.24-1.62) p =0.34
• Median 4 year follow up but low number of events gave power of 40%

![Graph showing comparison between PFO closure and medical therapy]
Three Negative Trials:

• No indication to close PFO in CS
• CLOSURE only 10% RRR for stroke, but device was problematic with thrombus formation on device. Previously seen Taaffe AJC 2008;101;1358
• But some positive signals
  • RESPECT as treated analysis
  • PC underpowered but showed an 86% relative risk reduction in ischemic stroke.
Randomized Controlled Trials

• All trials challenged with slow enrollment – significant closures outside of studies
• Lower rate of events than expected – higher risk patients unwilling to enroll?
• All with trends in right directions
• All negative for statistically significant secondary prevention
• Still 2 large trials with continuing enrollment and additional analysis promised for RESPECT
Christmas in September 2017:
For Cryptogenic Stroke patients

Mas et al NEJM 2017;377:1011
Sondergaard et al NEJM 2017:1033
Saver et al NEJM 2017;377:1022
RESPECT Longterm Outcomes

• Additional follow up median 5.9 yrs
• 0.58 strokes/100pt years closure vs 1.07/100 pt years medical
  • P – 0.046
• Recurrent ischemic CVA of undetermined origin 10 vs. 23 HR 0.38 (0.18 -0.79)
• Prevention of PFO related strokes
REDUCE

• 664 pts 2:1 randomization Closure and AP vs AP alone (no AC)
• Median FU 3.2 years
• CoPrimary EP
  • Clinical isch CVA 1.4% close vs. 5.4% Med. HR 0.23 (0.09-0.62) p=0.002
  • New brain infarct – clinical and silent on MRI 5.7 v 11.3% HR 0.51 (0.29-0.91) p=0.04
CLOSE

- 663 patients 16-60 with cryptogenic stroke PFO
- 1:1:1 randomization closure vs AP/OC, closure v AP, AP vs. OC
- Large PFO shunt>30 bubbles
- ASA
- Primary EP Fatal or nonfatal stroke
- 11 different devices
- Analysis Closure vs AP
  - No strokes closure v 14/235 AP
  - 0% vs. 6%
  - HR 0.03 (0-0.26) p=<0.001

Mas et al. NEJM 2017;377:1011
CLOSE

- Slow enrollment – did not reach 900 pts from power calculation
  - Unwillingness to randomize the highest risk patients
- Effective closure 93% at 10.8 months <10 microbubbles
- No cerebral hemorrhage, no systemic emboli, no death in either group
- No explanation for recurrent stroke other than PFO
- Procedural complications Atrial fibrillation 4.6% v 0.9% p=0.02
  - No recurrence up to 4.4 years f/u
  - 10 OAC 7 DC at 6 months
- OAC group 20% d/c’d OAC
  - 74.3% with INR 2-3
DEFENSE PFO

• 120 patients with CS and high risk anatomy, large PFO 2mm excursion, and ASA >10mm
• 1:1 randomization to closure
• Primary endpoint – stroke, vascular death, major bleed
• No events in closure arm but 12.9% in Med arm 5 isch strokes, 1 hem stroke, 2 bleeds, 1TIA
  • P=0.013
• Coumadin used in med arm 25%

Lee et al. J Am Coll Card 2018;71:2335-2342
### All Published RCTs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year of Publication</th>
<th>Enrollment/Follow-Up</th>
<th>Geography</th>
<th>Inclusion Criteria</th>
<th>Event Type</th>
<th>Timing</th>
<th>Age (min-max)</th>
<th>Patient Number</th>
<th>Follow-Up Years (mean)/Patient-Years</th>
<th>Ratio of Follow-Up Dev/Med*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOSURE</td>
<td>2012</td>
<td>E: 2009–2008</td>
<td>United States, Canada</td>
<td>Cryptogenic IS or TIA</td>
<td>≤ 6 mo</td>
<td>18–60</td>
<td>909</td>
<td>1.7/1555</td>
<td>1.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>F: 2003–2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC</td>
<td>2013</td>
<td>E: 2000–2009</td>
<td>Europe, Canada, Brazil, Australia</td>
<td>Cryptogenic IS or periph embolism</td>
<td>No restriction</td>
<td>&lt;60</td>
<td>414</td>
<td>4.1/1681</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>F: 2000–2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RESPECT</td>
<td>2013/2017</td>
<td>E: 2003–2011</td>
<td>United States, Canada</td>
<td>Cryptogenic IS (Tissue-Def)</td>
<td>≤ 9 mo</td>
<td>18–60</td>
<td>980</td>
<td>5.8/5688</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td>CLOSE</td>
<td>2017</td>
<td>E: 2007–2014</td>
<td>France, Germany</td>
<td>Cryptogenic IS (Tissue-Def)</td>
<td>≤ 6 mo</td>
<td>16–60</td>
<td>473 (653)†</td>
<td>5.3/2507</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td>REDUCE</td>
<td>2017</td>
<td>E: 2008–2015</td>
<td>Europe, Canada, United States</td>
<td>Cryptogenic IS (Tissue-Def)</td>
<td>≤ 6 mo</td>
<td>18–59</td>
<td>664</td>
<td>3.4/2232</td>
<td>1.10</td>
<td></td>
</tr>
<tr>
<td>DEFENSE- PFO</td>
<td>2018</td>
<td>E: 2011–2017</td>
<td>South Korea</td>
<td>Cryptogenic IS (Tissue-Def)</td>
<td>≤ 6 mo</td>
<td>18–80</td>
<td>120</td>
<td>1.6+/ =187</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>F: 2011–2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Saver et al. Stroke 2018;49:1541
### All Published RCTs

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Device + MT</th>
<th>Medical Therapy</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>log(HR) SE</td>
<td>Events Pt-Yrs (Pts)</td>
<td>Events Pt-Yrs (Pts)</td>
</tr>
<tr>
<td><strong>Umbrella-clamshell devices</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLOSURE</td>
<td>-0.11 0.40</td>
<td>12 789 (447) 13 766 (462)</td>
<td>24.6%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>12 789 (447)</td>
<td>13 766 (462)</td>
<td>24.6%</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.27 (P = 0.79)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Double disk devices (all or predominantly)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC</td>
<td>-1.97 1.09</td>
<td>1 845 (204) 7 836 (210)</td>
<td>10.1%</td>
</tr>
<tr>
<td>RESPECT-Extended</td>
<td>-0.60 0.30</td>
<td>13 3080 (499) 28 2608 (481)</td>
<td>27.5%</td>
</tr>
<tr>
<td>CLOSE</td>
<td>-3.51 1.11</td>
<td>0 1231 (238) 14 1222 (235)</td>
<td>9.7%</td>
</tr>
<tr>
<td>REDUCE</td>
<td>-1.47 0.50</td>
<td>6 1529 (441) 12 703 (223)</td>
<td>21.7%</td>
</tr>
<tr>
<td>DEFENSE-PFO</td>
<td>-2.40 1.47</td>
<td>0 95 (50) 5 92 (60)</td>
<td>6.4%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>25 6780 (1442)</td>
<td>66 5461 (1209)</td>
<td>75.4%</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.61; Chi^2 = 9.46, df = 4 (P = 0.05); I^2 = 53%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.20 (P = 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>37 7579 (1889)</td>
<td>79 6227 (1671)</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.54; Chi^2 = 13.52, df = 5 (P = 0.02); I^2 = 63%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.89 (P = 0.004)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi^2 = 5.38, df = 1 (P = 0.02), I^2 = 81.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Saver et al. Stroke 2018;49:1541
## Ischemic Stroke rate per year

<table>
<thead>
<tr>
<th>Trial</th>
<th>IS rate/yr Device Group</th>
<th>IS rate/yr Medical Group</th>
<th>Relative reduction</th>
<th>Absolute reduction/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOSURE</td>
<td>1.52%</td>
<td>1.79%</td>
<td>15%</td>
<td>0.27%</td>
</tr>
<tr>
<td>PC</td>
<td>0.12%</td>
<td>0.84%</td>
<td>86%</td>
<td>0.72%</td>
</tr>
<tr>
<td>RESPECT</td>
<td>0.58%</td>
<td>1.07%</td>
<td>46%</td>
<td>0.49%</td>
</tr>
<tr>
<td>REDUCE</td>
<td>0.39%</td>
<td>1.71%</td>
<td>77%</td>
<td>1.32%</td>
</tr>
<tr>
<td>CLOSE*</td>
<td>0%</td>
<td>1.15%</td>
<td>100%</td>
<td>1.15%</td>
</tr>
<tr>
<td>DEFENSE-PFO</td>
<td>0%</td>
<td>5.25%</td>
<td>100%</td>
<td>5.25%</td>
</tr>
</tbody>
</table>

* Data shown for CLOSE device and antiplatelet groups, not CLOSE anticoagulant group

Saver et al. Stroke 2018;49:1541
Antiplatelet vs Anticoagulant

Small numbers of Anticoagulant pts

![Graph and Table]

Saver et al. Stroke 2018;49:1541
Extending the Therapy

• Patients Over 60
  • Would need even more scrutiny
  • Prolonged monitoring for Afib
  • RoPE score may be beneficial
  • Minimal risks and large shunt of ASD

• Hypercoagulable patients
  • Excluded from studies but venous, and maybe mixed should be considered

• Closure vs Anticoagulation
  • PICCS suggests antiplt as good, but meta analyses suggest otherwise
  • Issues with compliance, bleeding and need to stop for procedures
RoPE – Risk of Paradoxical Embolism Score

• Determine the likelihood that an identified PFO is implicated in the development of a cryptogenic stroke
  • 10 point scale
  • PFO more likely – younger age, cortical stroke on imaging
    • Absence of DM, HTN, Smoking, and prior stroke or TIA.
  • PFO prevalence increased from 232% when score 0-3 to 73% in those with score of 9-10
# Stroke location

## Supplementary Figure VI. PFO Closure with Predominantly Double Disk Devices and Recurrent Ischemic Stroke, in Index Ischemic Stroke Topography Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>log[HR]</th>
<th>SE</th>
<th>Events</th>
<th>Pt-Yrs (Pts)</th>
<th>Medical Therapy</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Superficial or Deep+Large</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RESPECT-Extended</td>
<td>-0.81</td>
<td>0.33</td>
<td>14</td>
<td>2697 (436)</td>
<td>26</td>
<td>41.3%</td>
<td>0.44 [0.23, 0.85]</td>
<td></td>
</tr>
<tr>
<td>REDUCE</td>
<td>-1.47</td>
<td>0.50</td>
<td>6</td>
<td>1529 (441)</td>
<td>12</td>
<td>32.2%</td>
<td>0.23 [0.09, 0.62]</td>
<td></td>
</tr>
<tr>
<td>DEFENSE-PFO</td>
<td>-2.40</td>
<td>1.47</td>
<td>0</td>
<td>95 (90)</td>
<td>5</td>
<td>0.3%</td>
<td>0.09 [0.01, 1.62]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>20</td>
<td>4321 (937)</td>
<td>43</td>
<td>3011 (692)</td>
<td>91.1%</td>
<td>0.34</td>
<td>0.20 [0.09, 0.59]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.01; Chi² = 2.04, df = 2 (P = 0.36); I² = 2%
Test for effect: Z = 3.83 (P = 0.0001)

| **Single Penetrator (Deep+Small)** |         |      |        |             |                |        |                               |                               |
| RESPECT-Extended              | 0.81    | 0.87 | 4      | 352 (57)    | 2              | 18.3%  | 2.25 [0.41, 12.33]            |                               |
| Test for effect: Z = 0.93 (P = 0.35) |       |      |        |             |                |        |                               |                               |

| **Total (95% CI)**            | 24      | 4665 (994) | 45    | 3391 (762)  | 100.0%        | 0.42   | 0.17 [1.04]                   |                               |

Heterogeneity: Tau² = 0.40; Chi² = 6.27, df = 3 (P = 0.10); I² = 52%
Test for overall effect: Z = 1.87 (P = 0.06)
Test for subgroup differences: Chi² = 4.24, df = 1 (P = 0.04); I² = 76%
CRYSTAL AF

• PAF undetected on short term monitoring
• Has implications in medical management and decision to close
• Higher incidence in elderly
  • Mean age 65.
Atrial Fibrillation:
Most important Cause of Stroke age >60

• ASSERT trial
  • 2580 pts with PPM or ICD
  • All patients >/= 65 yo
  • 51 pts had stroke or periph emboli
    • 26 had subclinical AF
    • 18 AF before stroke or emboli
    • Only 4/18 within 30 d of event and only 1 had AF at time of event
    • 14/18 had AF >30 before event and median time 339 days before
    • 8 had AF only after event

Brambatti et al. Circulation 2014;129:2094-9

Go et al. JAMA 2001; 285:2370
FDA Approval of Amplatzer PFO Occluder

- Randomized trials were limited by slow enrollment
  - Physicians and patients unwilling to be randomized to med therapy
  - Closure with off label use of other devices
- Later randomized studies had significant attrition in medical therapy arms
- RESPECT at 2.7 and 3.0 years follow up showed HR with 50% relative risk reduction but insignificant p value 0.089.
- Low rate of recurrent stroke 0.6/100 pt-years vs. 1.25/100pt-years
- NNT 27 to prevent one stroke at 5 years
- Late analysis showed significant reduction and safety of the device and procedure
  - “the Amplatzer PFO Occluder met the FDA’s threshold for approval (a reasonable assurance of safety and effectiveness).”
  - Physicians should engage in shared decision making with patients to elicit and consider their values and set reasonable expectations regarding treatment plans
- A deliberate systematic assessment of the patient’s underlying condition and risks is necessary before recommendation for closure of PFO

Farb et al NEJM 2017;377:1006-1009
9.1 Patent Foramen Ovale (PFO) (Revised 2017)

i. Patients with a recent ischemic stroke or TIA attributed to a PFO should have an evaluation by clinicians with stroke and cardiovascular expertise [Evidence Level C].

ii. For carefully-selected patients with a recent ischemic stroke or TIA attributed to a PFO, PFO device closure plus long-term antiplatelet therapy is recommended over long-term antithrombotic therapy alone provided all the following criteria are met [Evidence Level A]:
   a. Age 18–60 years;
   b. The diagnosis of the index stroke event is confirmed by imaging as a nonlacunar embolic ischemic stroke or a TIA with positive neuroimaging or cortical symptoms;
   c. The patient has been evaluated by a neurologist or clinician with stroke expertise, and the PFO is felt to be the most likely cause for the index stroke event following a thorough etiological evaluation to exclude alternate etiologies.

iii. For patients requiring long-term anticoagulation, the decision regarding PFO closure remains unclear, and decisions should be based on individual patient characteristics and risk versus benefit profile [Evidence C].

iv. For patients with a recent ischemic stroke or TIA attributed to a PFO who do not undergo PFO closure and are aged 60 years or younger, either antiplatelet or anticoagulant therapy is recommended for secondary stroke prevention, unless there is a separate evidence-based indication for chronic anticoagulant therapy [Evidence Level B].

v. There is insufficient evidence to make a recommendation regarding the comparative effectiveness of PFO closure vs. anticoagulant therapy.
This expert panel make a

- Strong recommendation in favour of PFO closure plus antiplatelet therapy compared with antiplatelet therapy alone
- Weak recommendation in favour of PFO closure plus antiplatelet therapy compared with anticoagulants
- Weak recommendation in favour of anticoagulants compared with antiplatelet therapy.
Conclusions

• Cryptogenic stroke comprises 40% of ischemic strokes and there is a strong association with PFO

• Closure of PFO leads to a significant reduction in recurrent ischemic strokes
  • Some subgroups realize greater benefit – large shunts, ASA
  • Particularly notable for recurrent cryptogenic strokes

• PFO closure is safe and effective with double disk devices
  • Atrial fibrillation rate was not associated with increased stroke or morbidity and was short term

• Selected patients outside of the demographic of RCTs may also benefit from closure

• A multidisciplinary team should be involved in all recommendations, and shared decision-making with the patient

• “When PFO is considered to play a pathogenic role in an embolism, the episode should not be classified as cryptogenic anymore” European position paper Eurointervention 2018;14 August 2018
My biggest referral source for PFO Closure

Thank you