PFO and Stroke: Current Guidelines

Medical Director PIH Health-Whittier Comprehensive Stroke Center
Medical Director PIH Health-Whittier Non-Invasive Vascular Laboratory
I have no actual or potential conflict of interest in relation to this presentation.
Case Scenario

CASE SCENARIO

- 75 year old female with DM, HTN had a fall and broke her right ankle s/p ORIF 2 days later in OSH.
- **Day 4**: Acute SOB on the floor with some chest pain and hypoxemia. Found to have saddle PE and was started on IV Heparin. She had an ECHO which showed Right heart strain + PFO + Atrial septal aneurysm. No intracardiac thrombus.
Day 5: left sided hemiparesis and profound sensory loss, NIH 7. CT head is normal, CTA of the Head and Neck showed acute right carotid artery occlusion with saddle embolus at the bifurcation extending into the ECA. Transferred to CCF main campus.

Her platelets were low at presentation and **HIT** was suspected by vascular medicine.

Hyperacute MRI showed posterior division diffusion restriction with large penumbra and she was taken for thrombectomy.

Post procedure TICI 3. Procedure was done under Bivalirudin due to suspicion of HIT.
CTA Neck
Stroke Mechanism: paradoxical embolism secondary to pulmonary hypertension with right to left shunt via PFO + Atrial septal aneurysm and/or hypercoagulable state from HIT. Later her PF-4 antibodies came back positive.

Day 7: She underwent pulmonary embolectomy a day later with placement of IVC filter as she couldn’t be anticoagulated due to recent stroke. Still recovering.
First Description of a Septal Abnormality

Leonardo da Vinci 1513:

“I have found from a, left auricle, to b, right auricle, the perforating channel from a to b.”
Dr. Leonardo Botallo
Italian surgeon working in France
Described the foramen ovale
“Botallo's Foramen” (PFO)
1877

Julius Friedrich Cohnheim
♥ German Pathologist
♥ Protégé of Virchow
♥ Patent Foramen Ovale

“...a potential conduit for paradoxical embolization leading to cerebral ischemia”

Atrial Septum and ASDs
Mechanism - Paradoxical embolism
2D TEE with Bubble Contrast
TCD

Mild

Moderate (shower effect)

Severe (curtain effect)
TOAST Classifications

<table>
<thead>
<tr>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-artery atherosclerosis</td>
</tr>
<tr>
<td>Cardioembolism</td>
</tr>
<tr>
<td>Small-vessel occlusion</td>
</tr>
<tr>
<td>Stroke of other determined etiology</td>
</tr>
<tr>
<td>Stroke of undetermined etiology</td>
</tr>
<tr>
<td>Two or more causes identified</td>
</tr>
<tr>
<td>Negative evaluation</td>
</tr>
<tr>
<td>Incomplete evaluation</td>
</tr>
</tbody>
</table>

TOAST, Trial of Org 10172 in Acute Stroke Treatment.
Comparison of the CHADS$_2$ and CHA$_2$DS$_2$-VASc risk stratification scores for subjects with nonvalvular AF

<table>
<thead>
<tr>
<th>Definition and scores for CHADS$_2$ and CHA$_2$DS$_2$-VASc</th>
<th>Stroke risk stratification with the CHADS$_2$ and CHA$_2$DS$_2$-VASc scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHADS$_2$ acronym</strong></td>
<td><strong>Score</strong></td>
</tr>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Maximum score</td>
<td>6</td>
</tr>
<tr>
<td><strong>CHA$_2$DS$_2$-VASc acronym</strong></td>
<td><strong>Score</strong></td>
</tr>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
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</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65 to 74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (ie, female sex)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; CHADS$_2$: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism (doubled); CHA$_2$DS$_2$-VASc: Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65-74 years, Sex category; HF: heart failure; LV: left ventricular; MI: myocardial infarction; PAD: peripheral artery disease; TE: thromboembolic; TIA: transient ischemic attack.

* These unadjusted (not adjusted for possible use of aspirin) stroke rates were published in 2012[1]. Actual rates of stroke in contemporary cohorts might vary from these estimates.

Reference:

# Cardioaortic Sources of Cerebral Embolism

## Cardioaortic Sources of Cerebral Embolism

<table>
<thead>
<tr>
<th>Sources with high primary risk for ischemic stroke</th>
<th>Sources with low or uncertain primary risk for ischemic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Cardiac sources of embolism</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>Mitral annular calcification</td>
</tr>
<tr>
<td>Left atrial thrombus</td>
<td>Patent foramen ovale</td>
</tr>
<tr>
<td>Left ventricular thrombus</td>
<td>Atrial septal aneurysm</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>Atrial septal aneurysm and patent foramen ovale</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td></td>
</tr>
<tr>
<td>Recent myocardial infarction (within one month prior to stroke)</td>
<td>Left ventricular aneurysm without thrombus</td>
</tr>
<tr>
<td>Mitral stenosis or rheumatic valve disease</td>
<td>Left atrial spontaneous echo contrast (&quot;smoke&quot;)</td>
</tr>
<tr>
<td>Bioprosthesis and mechanical heart valves</td>
<td>Congestive heart failure with ejection fraction &lt;30 percent</td>
</tr>
<tr>
<td>Chronic myocardial infarction together with low ejection fraction (&lt;28 percent)</td>
<td>Apical akinesis</td>
</tr>
<tr>
<td>Dilated cardiomyopathy (prior established diagnosis or left ventricular dilatation with an ejection fraction of &lt;40 percent or fractional shortening of &lt;25 percent)</td>
<td>Wall motion abnormalities (hypokinesia, akinesia, dyskinesia) other than apical akinesia</td>
</tr>
<tr>
<td>Nonbacterial thrombotic endocarditis</td>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td>Papillary fibroelastoma</td>
<td>Left ventricular hypertrophy/none-compaction</td>
</tr>
<tr>
<td>Left atrial myxoma</td>
<td></td>
</tr>
</tbody>
</table>

The high and low risk cardioaortic sources in this table are separated using an arbitrary 2 percent annual or one-time primary stroke risk threshold.

Data from:

Association of PFO and Stroke

Meta-analysis of case control studies comparing cryptogenic stroke patients to non-stroke controls

OR **3.2** (95% CI, 2.30 to 4.35) overall

OR **6.0** (95% CI, 3.72 to 9.68) <55 years old

Patent Foramen Ovale (PFO)

Vestige of fetal circulation

PFO is a common finding:

Autopsy studies report prevalence ranging from 17-29%

Population-based TEE study found ~25% had a PFO

Patent Foramen Ovale (PFO)

Courtesy of Frank Silvestry MD, University of Pennsylvania
Atrial Septal Aneurysm (ASA)

- Excessive septal wall motion during respiration (>10-15 mm)
- Found in combination with a PFO in about 3/4 of cases
- Incidence in general population assessed by TEE is ~2%

Atrial Septal Aneurysm

Courtesy of Frank Silvestry MD, University of Pennsylvania
PFO and Stroke Mechanism

- Paradoxical Embolism is most commonly ascribed
- 2-22% of patients with stroke and PFO have proximal leg or pelvic thrombosis

PFO and Cryptogenic Stroke

20-30% of healthy population has PFO

20-40% of acute ischemic strokes are cryptogenic

Prevalence of PFO in cryptogenic stroke is around 50%
PFO and Risk of Stroke
Risk of Paradoxical Embolism (RoPE) Study

• Patient level meta-analysis of 12 cryptogenic stroke cohorts

<table>
<thead>
<tr>
<th>Term in modela</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10-y increase</td>
<td>0.72 (0.67–0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.65 (0.51–0.83)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.68 (0.57–0.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.60 (0.50–0.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of stroke or TIA</td>
<td>0.78 (0.62–0.99)</td>
<td>0.0375</td>
</tr>
<tr>
<td>Radiology, deep (vs superficial)</td>
<td>0.68 (0.54–0.84)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

## RoPE Score Calculator

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No history of hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No history of diabetes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No history of stroke or TIA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cortical infarct on imaging</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

### Age (y)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–29</td>
<td>5</td>
</tr>
<tr>
<td>30–39</td>
<td>4</td>
</tr>
<tr>
<td>40–49</td>
<td>3</td>
</tr>
<tr>
<td>50–59</td>
<td>2</td>
</tr>
<tr>
<td>60–69</td>
<td>1</td>
</tr>
<tr>
<td>≥ 70</td>
<td>0</td>
</tr>
</tbody>
</table>

### Total score (sum of individual points)

- Maximum score (a patient < 30 y without vascular risk factors, no history of stroke or TIA, and cortical infarct) = 10
- Minimum score (a patient ≥ 70 y with vascular risk factors, prior stroke, and no cortical infarct) = 0

**Risk of Paradoxical Embolism score**
**PFO Prevalence < 60 years of age**

Table e-4: PFO prevalence, attributable fraction and estimated two year risk of stroke/TIA by point score strata, using control rate of 25%, in patients younger than 60 years of age

In this cohort younger than age 60, the PFO prevalence and attributable fraction by point score strata is almost identical to the overall cohort. Similarly, when the strata with very low numbers are not considered (i.e. RoPE score <= 4), recurrence rates by strata are almost identical to the overall cohort.

<table>
<thead>
<tr>
<th>POINT SCORE</th>
<th>Cryptogenic Stroke (N=1809)</th>
<th>CS Patients with PFO (N=981)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Patients</td>
<td>Prevalence of Patients with a PFO % (95% CI*)</td>
</tr>
<tr>
<td>0-3</td>
<td>41</td>
<td>24% (11% to 38%)</td>
</tr>
<tr>
<td>4</td>
<td>132</td>
<td>28% (20% to 36%)</td>
</tr>
<tr>
<td>5</td>
<td>301</td>
<td>28% (23% to 33%)</td>
</tr>
<tr>
<td>6</td>
<td>434</td>
<td>46% (42% to 51%)</td>
</tr>
<tr>
<td>7</td>
<td>434</td>
<td>54% (49% to 59%)</td>
</tr>
<tr>
<td>8</td>
<td>287</td>
<td>67% (62% to 73%)</td>
</tr>
<tr>
<td>9-10</td>
<td>180</td>
<td>73% (66% to 79%)</td>
</tr>
</tbody>
</table>

*Note: 95% CI for PFO prevalence based on normal approximation to the binomial distribution. Attributable risk and 95% CI for Attributable risk based on PFO prevalence and 95% CI for that estimate.
### RoPE score calculator

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
<th>RoPE score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No history of hypertension</td>
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<td></td>
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<tr>
<td>No history of diabetes</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cortical infarct on imaging</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to 29</td>
<td>5</td>
<td></td>
</tr>
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<td>50 to 59</td>
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<td></td>
</tr>
<tr>
<td>≥70</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Total score (sum of individual points)**

- Maximum score (a patient <30 years with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct): 10
- Minimum score (a patient ≥70 years with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct): 0

**RoPE:** Risk of Paradoxical Embolism; TIA: transient ischemic attack.

PFO Associated with Lower Risk of Stroke Recurrence


<table>
<thead>
<tr>
<th>Prevalence of patients with a PFO, % (95% CI)*</th>
<th>Estimated Two Year Stroke Recurrence Rate (Kaplan-Meier, with 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 (19–26)</td>
<td>16% (9% to 24%)</td>
</tr>
<tr>
<td>35 (31–39)</td>
<td>9% (4% to 14%)</td>
</tr>
<tr>
<td>34 (30–38)</td>
<td>3% (0% to 6%)</td>
</tr>
<tr>
<td>47 (42–51)</td>
<td>4% (2% to 7%)</td>
</tr>
<tr>
<td>54 (49–59)</td>
<td>2% (0% to 4%)</td>
</tr>
<tr>
<td>67 (62–73)</td>
<td>3% (0% to 5%)</td>
</tr>
<tr>
<td>73 (66–79)</td>
<td>1% (0% to 2%)</td>
</tr>
</tbody>
</table>

*PFO Prevalence
Among 15 studies with medically treated PFO patients recurrent stroke rate was 1.6% per year (95% CI: 1.1 – 2.1)

Treatment Options for PFO Patients

- Antiplatelet drugs
- Anticoagulation
- Closure*
- Surgical
- Percutaneous

*Closure does not preclude long term medical therapy
Battle of Stamford Bridge, Peter Nicolai Arbo
Now what!

Where Did This Leave Us?

“C’mon, c’mon—it’s either one or the other.”
ASD Occluders

Multiple Designs for ASD Occluders

- Amplatzer
- ASDOS
- Sideris Button
- Angel Wing
- Helex
- CardioSeal
- Guardian Angel
- Cardioform
- StarFlex
ASD Occluders (cont.)

US Commercially Available Occluders for ASD

Amplatzer Septal Occluder

Amplatzer Cribiform Device

Cardioform
Complications
Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D.,
Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc.,
Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D.,
Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D.,
David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D.,
for the Gore REDUCE Clinical Study Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

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Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

J.-L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouff, C. Arquizan, Y. Béjot, F. Vuillier,
O. Detante, C. Guidoux, S. Canaple, C. Vaduva, N. Dequatre-Ponchelle, I. Sibon, P. Garnier, A. Ferrier, S. Timsit,
F. Godart, J.-B. Thambo, L. Leborgne, P. Michel, L. Pierard, G. Turc, M. Barthelet, A. Charles-Nelson, C. Weimar,
T. Moulin, J.-M. Juliard, and G. Chatellier, for the CLOSE Investigators*
Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators

Tipping Point for Patent Foramen Ovale Closure

Allan H. Ropper, M.D.
Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

CLOSURE-I

- Stroke or TIA in prior 6 months
- PFO confirmed by TEE
- Age ≤ 60
- No hypercoagulable disorder, DVT
- Randomized 909 subjects 1:1
  - Medical therapy (n=462)
    - aspirin or warfarin or both
  - PFO closure with STARFlex device (n=447)
    - with aspirin and clopidogrel x 6 months then aspirin alone

CLOSURE-I

- No difference in stroke rate, 2.9% vs 3.1%
- Increased risk of AF, 5.7% vs 0.7%, p<0.001

HR = 0.78, 95% CI 0.45 to 1.35, p=0.37
Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

Bernhard Meier, M.D., Bindu Kalesan, Ph.D., Heinrich P. Mattle, M.D., Ahmed A. Khattab, M.D.,
David Hildick-Smith, M.D., Dariusz Dudek, M.D., Grethe Andersen, M.D., Reda Ibrahim, M.D.,
Gerhard Schuler, M.D., Antony S. Walton, M.D., Andreas Wahl, M.D., Stephan Windecker, M.D.,
and Peter Jüni, M.D., for the PC Trial Investigators*

- 414 patients with cryptogenic stroke and PFO Randomized to closure with the Amplatzer PFO device vs. medication
- At least 2 years of clinical follow-up
- Primary outcome: composite of death, stroke, TIA, or peripheral embolism
- Europe, Canada, Brazil, Australia
• Stroke occurred in 1 (0.5%) closure patient vs 5 (2.4%) medical patients HR, 0.20, 95% CI, 0.02 to 1.72, P = 0.14
Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

John D. Carroll, M.D., Jeffrey L. Saver, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Scott Berry, Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

- 900 patients with cryptogenic stroke and PFO
- Randomized to closure with the Amplatzer PFO device versus current medical standard of care
- At least 2 years of clinical follow-up
- Primary outcome: stroke
- US and Canada

Carroll et al. NEJM 2013;368:1092-1100
RESPECT Results

**A Intention-to-Treat Cohort**

- **Closure group** (N=9)
- **Medical-therapy group** (N=16)

Hazard ratio, 0.49 (95% CI, 0.22–1.11)
P=0.08 by log-rank test
• Clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischemic stroke outside of a research setting (Level R).

• In rare circumstances, such as recurrent strokes despite adequate medical therapy with no other mechanism identified, clinicians may offer the AMPLATZER PFO Occluder if it is available (Level C).

AAN Guideline Rationale

- All 3 RCTs negative on primary prespecified outcomes
- Open label endpoint ascertainment
- High numbers of loss to follow up and low event rates
- Upfront cost and small risk of closure
- Prevalence of PFO leads to risk of inappropriate closure
- Extensive off-label PFO closure led to slow enrollment
May 24, 2016 – FDA Advisory Committee assessing the Amplatzer PFO Occluder voted:
• 15-1 for safety of the device
• 9-7 for effectiveness
• 11-5 benefits outweigh the risks.

October 28, 2016 – The FDA approved the Amplatzer PFO Occluder device
Before considering the implantation of the AMPLATZER™ PFO Occluder, patients should undergo an evaluation by a neurologist to confirm the diagnosis of a cryptogenic ischemic stroke.
RESPECT Long Term Outcomes

980 subjects enrolled from 2003 to 2011
 Patients followed for a median 5.9 (IQR 4.2 – 8) years
  Compared to median 2.3 years for primary publication
27% were no longer being followed at final database lock
  33% in medical arm vs 21% in closure arm

RESPECT Long Term Outcomes

- Fewer recurrent strokes in the patients who received closure compared to medical-therapy
  - 18 vs 28, event rate 0.58 vs 1.07 per 100 pt years
  - HR: 0.55, 95% CI: 0.31 to 0.99, log-rank p=0.046

### RESPECT Long Term Outcomes

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PFO Closure Group</th>
<th>Medical-Therapy Group</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value by Log-Rank Test</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>18/499 (3.6)</td>
<td>28/481 (5.8)</td>
<td>0.55 (0.30–1.00)</td>
<td>0.046</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–45 yr</td>
<td>6/230 (2.6)</td>
<td>10/210 (4.8)</td>
<td>0.49 (0.18–1.35)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>46–60 yr</td>
<td>12/262 (4.6)</td>
<td>18/266 (6.8)</td>
<td>0.59 (0.28–1.23)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10/268 (3.7)</td>
<td>16/268 (6.0)</td>
<td>0.56 (0.25–1.23)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8/231 (3.5)</td>
<td>12/213 (5.6)</td>
<td>0.55 (0.22–1.34)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Shunt size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>None, trace or moderate</td>
<td>13/247 (5.3)</td>
<td>12/244 (4.9)</td>
<td>0.96 (0.44–2.11)</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Substantial</td>
<td>5/247 (2.0)</td>
<td>16/231 (6.9)</td>
<td>0.26 (0.10–0.71)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Present</td>
<td>3/179 (1.7)</td>
<td>13/170 (7.6)</td>
<td>0.20 (0.06–0.70)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>15/320 (4.7)</td>
<td>15/311 (4.8)</td>
<td>0.86 (0.42–1.76)</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Index infarct topography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Superficial</td>
<td>9/280 (3.2)</td>
<td>18/269 (6.7)</td>
<td>0.43 (0.19–0.96)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Small deep</td>
<td>4/57 (7.0)</td>
<td>2/70 (2.9)</td>
<td>2.25 (0.41–12.32)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5/157 (3.2)</td>
<td>8/140 (5.7)</td>
<td>0.48 (0.16–1.48)</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Planned medical regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>8/132 (6.1)</td>
<td>5/121 (4.1)</td>
<td>1.32 (0.43–4.03)</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>10/367 (2.7)</td>
<td>23/360 (6.4)</td>
<td>0.38 (0.18–0.79)</td>
<td>0.007</td>
<td></td>
</tr>
</tbody>
</table>

664 patients with EMBOLIC cryptogenic stroke and PFO were randomized in a 2:1 ratio to closure with a Gore Helex septal occluder/Cardioform septal occluder or antiplatelet therapy. Median follow up 3.2 years.
• Atrial fibrillation more common with closure, 4.6% vs 0.9% (p=0.02)

Søndergaard et al. NEJM, 2017; 377: 1033-1042.
663 patients with EMBOLIC stroke and PFO with atrial septal aneurysm or a large shunt randomized 1:1:1 to aspirin, anticoagulation, or PFO closure with any CE-marked device

11 devices were used in total, but the St Jude Amplatzer device was most common (51%)

Median 5.3 years follow up

Mas et al. NEJM, 2017; 377: 1011-1022.
CLOSE Trial

- No strokes with closure vs 14 strokes in antiplatelet arm
- AF more common 6.6% vs 0.4% (p<0.001)
Stroke rate not different between anticoagulation and PFO closure, 0 vs 3, p=NS
DEFENSE-PFO Trial

- 120 patients with EMBOLIC stroke and PFO with large shunt or atrial septal aneurysm randomized to closure with the Amplatzer PFO occluder or medical therapy with antiplatelet or anticoagulation
- Stroke recurred in 6/60 (10%) of medically treated compared to 0/60 in patients who underwent closure, p=0.01

Lee et al.  J Am Coll Cardiol. 2018
Methodological Concerns

- Open label endpoint ascertainment
- High loss to follow up and cross over
- Low event rates
Meta-Analysis of Closure Trials

Absolute risk reduction -0.66% per-year
(95% confidence interval -0.31 to -1.0%)
Meta-Analysis

- Percutaneous PFO closure also associated with:
  - Periprocedural complication rate 3.7% (95% CI 2.3% to 5.1%)
  - New-onset non-periprocedural atrial fibrillation increased 0.36% per year (95% CI 0.07% to 0.66%)
Implications of New Data and FDA Approval of 2 Devices

- Absolute stroke risk difference of ~3% at 5 years
- Despite methodological concerns about these studies, PFO closure likely benefits select patients
- Which patients???
What is Cryptogenic stroke?

- Insufficient evaluation
- Multiple competing causes
- Thorough but negative evaluation
For Patients Considering Closure

- Intracranial and cervical vascular imaging (MRA or CTA)
- Transthoracic followed by transesophageal echo
- Prothrombotic testing
- Prolonged cardiac telemetry monitoring?
Monitoring for Atrial Fibrillation

- Prolonged cardiac rhythm monitoring identifies paroxysmal atrial fibrillation in ~5-25% of cryptogenic strokes.

- AF incidence strongly related to increased age
- Other factors may be suggestive
  - Enlarged left atrium
  - NT-proBNP
  - EKG findings

Conclusions

• PFO closure reduces stroke risk in patients with likely PFO-related stroke
  - Under 60, no other cause
  - Embolic appearing stroke
  - Few vascular risk factors
  - Large shunt
  - Atrial septal aneurysm?

• In other patients with PFO, the benefit of closure is uncertain

• Not clear if closure benefits patients who require anticoagulation
  - Prior unprovoked DVT/PE, or high risk thrombophilia
Management of patent foramen ovale (PFO) in cryptogenic stroke

This algorithm represents our general approach to the management of PFO in patients with embolic-appearing cryptogenic ischemic stroke. As shown here, age ≤60 has been used to identify individuals more likely to benefit from PFO device closure. Refer to UpToDate content on other factors that may aid the selection of candidates for percutaneous PFO closure.

ASA: atrial septal aneurysm; DVT: deep venous thrombosis; ECG: electrocardiogram; PFO: patent foramen ovale; TTE: transthoracic echocardiography; TEE: transesophageal echocardiography; VTE: venous thromboembolism.

* The diagnosis of initial or recurrent cryptogenic stroke should exclude definite evidence of other potential stroke mechanisms. These include atrial fibrillation, other cause of cardioembolism, large artery atherosclerosis, small artery disease, large artery disease, hypercoagulable state or other determined etiology, or hemorrhagic stroke.

† On echocardiography (TTE or TEE) performed with agitated saline contrast, a right-to-left shunt is identified by the presence of one or more microbubbles in the left atrium within three beats of appearance of microbubbles in the right atrium at rest, during Valsalva maneuver release, or cough.

‡ For patients with VTE (eg, provoked DVT) who are treated with finite anticoagulation for 3 to 12 months, PFO device closure, if otherwise indicated, can be postponed until anticoagulation is stopped. For patients who have an indication for chronic anticoagulation (eg, unprovoked or recurrent DVT), PFO device closure is not recommended. Refer to appropriate UpToDate topics regarding the management of DVT and VTE.

§ Patients should be selected carefully for possible PFO device closure. This requires a comprehensive evaluation to ensure that the diagnosis is cryptogenic ischemic stroke and that the most likely mechanism is paradoxical embolism through a PFO. Patients with a PFO and a large associated right-to-left shunt or an ASA may be most likely to benefit from PFO closure.

5 Risk factors for occult atrial fibrillation include higher CHA2DS2-VASc score, the presence of cortical or large subcortical infarcts in multiple vascular territories, and evidence of left atrial cardiopathy (eg, left atrial dilatation, strain, reduced emptying fraction, left atrial appendage size and single lobe morphology, P wave dispersion on ECG, and frequent atrial premature beats).
Conclusions

- PFO is common and is not a high risk stroke mechanism
- Deciding upon closure is generally not a STAT issue
- Thorough work up to determine potential stroke etiologies
  - If alternative etiology identified, that is more likely to be the cause

Close collaboration between Neurology, Cardiology, and the patient!
Shared Decision Making

- A key component of patient-centered health care
- Clinicians and patients work together to make decisions about tests and treatments based on clinical evidence, balancing risks and expected outcomes with patient preferences and values
- PFO decision making is an excellent opportunity to practice!
Thank you!