Interventional Closure of Patent Foramen Ovale 2019
Where We Are and Where we are Going
POMA 2019

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Allentown, PA

Disclosures

- I have no disclosures related to this topic

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HIGH VASCULAR RESISTANCE

Lungs Expand
Reduced Resistance

Cryptogenic Stroke- PFO

- Foramen Ovale Closes Shortly after Birth in the Majority
- Up to 25% The foramen remains open but is functionally closed as LA Pressure >> RAP
Transmitral or Sustained Reversal of the Left Atrial to Right Atrial Pressure Gradient

- Early Systole
- Valsalva/Mueller
- Coughing
- Pulmonary Hypertension
- COPD
- Pregnancy
- Asthmatics
- Wind Instruments
- Decompression Sickness (Diving)
- High Altitude Flying
- Obstructive Sleep Apnea

PFO Has Been Linked to Increased Risk of:

- Stroke
- Migraine Headaches
- Decompression Illness in Scuba Divers
- Platypnea-Orthodeoxia
- Economy Class Stroke Syndrome
- Multi-Infarct Dementia
- Cerebral microemboli following TKR

First LVHN PFO Closure Patient: 1/12/2001

- 50 YO RHWM Brief episode of visual change; later that morning R leg weak, R arm numb; MRI L parietal stroke
- Workup negative except PFO
- Treated w Coumadin and then closed with 28 mm Cardioseal — complicated due to long tunnel and incomplete R sided expansion — no residual flow by TTE
- 6/08/2007 — L Arm ataxia, dysarthria, R cerebellar infarction: tPA
- Repeat Closure 35 mm Amplatzer PFO device
First LVHN PFO Closure patient

PFO Story Began with Observation of DVT’s passing through PFO, causing Stroke

Circumstantial Evidence: Prevalence of PFO in Patients With “Cryptogenic” Stroke
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### Patent Foramen Ovale

**Evidence From a Prospective Population-Based Study**

![Graph showing cerebrovascular event rate over time](image)

- **Contrast TEE**
  - N = 585
  - PFO – 140 (24%) vs. No PFO – 437

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### PFO and Cryptogenic Stroke

- The contribution of a patent foramen ovale (PFO) to cerebral ischemia-suspected but unproven
  - PFO - twice as prevalent in patients who have experienced a cryptogenic stroke compared to the general population
  - Observational data suggest a reduction of recurrent stroke with PFO closure, but...

- Three randomized trials of PFO closure did not show significant reduction in stroke risk in their primary intention-to-treat analysis

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### CLOSURE-1

- N = 909 patients with stroke or TIA (not imaging verified) within 6 months
- RCT, 1:1 PFO closure with STARFlex + 6 months DAPT followed by aspirin for life or anti-thrombotic therapy with VKA, aspirin or both
- Primary end-point: Stroke/TIA during 2 years, death within 30 days, or death from neurologic cause between day 31 to 2 years

![Graph showing probability of primary end point](image)

- **HR 0.78 (95% CI: 0.45 – 1.35)**
- **P = 0.37**
PC Trial

- N=414 patients with stroke, TIA or extra-cranial thrombo-embolic event
- RCT, 1:1 PFO closure with Amplatzer PFO occluder + APT for at least 1-6 months or anti-thrombotic therapy with OAC, ASA or both
- Primary end-point: Death, non-fatal stroke, TIA, or peripheral embolism

RESPECT

- N=980 patients with stroke or TIA within 9 months
- RCT, 1:1 PFO closure with Amplatzer PFO occluder + 1 month DAPT followed by aspirin for at least 6 months or anti-thrombotic therapy with VKA (25%) or APT (75%)
- Primary end-point: Fatal ischemic stroke, non-fatal ischemic stroke, or early death (45 days after randomization/30 days after closure) – event driven trial (N=25)

RESPECT PFO-Primary Endpoint Analysis – Per Protocol Cohort

63.4% risk reduction of stroke in favor of device
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American Academy of Neurology
(Not Yet Updated)

ACC/AHA guidelines 2011-update 2014
(Not Yet Updated To Include 2017 Data)

Patent Foramen Ovale Recommendations

- For patients with an ischemic stroke or TIA and a PFO who are not on anticoagulation therapy, aspirin therapy is recommended. (Class I, LOE B) Rationale: Class changed from IIa to I.
- For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolization, anticoagulation is indicated, based on the ACC/AHA guidelines. New Recommendations
- For patients with atrial fibrillation and PFO and venous source of embolization, an inferior vena cava filter is recommended. (Class IIa, LOE C) Revised Recommendation
- In the setting of PFO and DVT, PFO closure by transcatheter device might be considered, depending on the risk of recurrent DVT. (Class IIb, LOE C)

ACC/AHA guidelines 2011-update 2014
(Not Yet Updated To Include 2017 data)
Amplatzer PFO and Cribriform ASD devices

PFO Device

Cribriform ASD Device

The positive trials - September 14th, 2017

RESPECT extended f/u  REDUCE  CLOSE

1.) Longer Follow up
2.) Cortical Strokes only-
3.) No TIA
4.) New Brain Infarct- No Lacunes
5.) Restricted Age 18-60

P=0.002
p=0.046
P=0.002
P<0.001

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**RESPECT extended f/u (mean 2.6 -> 5.9 years)**
- N=980 patients with stroke or TIA within 9 months
- RCT, 1:1 PFO closure with Amplatzer PFO occluder + 1 month DAPT and aspirin for at least 6 months or anti-thrombotic therapy with VKA (25%) or APT (75%)
- Treatment exposure: 3,141 patient-years in the PFO closure group vs. 2,669 patient-years in the medical therapy group

![Graph showing event-free probability over time](image)

**CLOSE**

**CLOSURE versus ANTIPLATELET THERAPY**
Mean follow-up (years) = 5.4 ± 1.9 (CLOSURE) vs. 5.2 ± 2.1 (APT)

![Graph showing absolute risk reduction and incidence of events](image)

Intention-to-Treat

HR = 0.03 (95% CI: 0 to 0.25), P < 0.001

5-yr absolute risk reduction = 4.9%
1 avoided stroke at 5 years for every 20 (17 to 25) patients treated with closure

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**CLOSE**

5-year cumulative estimate of the probability of stroke was:

*1.5% in the OAC group and 3.8% in the SAPT group*

The study was not adequately powered to compare outcomes in these groups!

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**REDUCE Study**

- **Aim to establish superiority of PFO closure (WL Gore Septal Occluder) in conjunction with APT over APT alone in reducing the risk of recurrent clinical ischemic stroke or new brain infarct**
- **Randomized, controlled, open-label trial**
  - 664 subjects randomized in a 2:1 ratio to:
    - **Closure**: PFO closure plus antiplatelet therapy
    - **Medical therapy**: antiplatelet therapy alone
- **63 sites in 7 countries**
  - Canada, Denmark, Finland, Norway, Sweden, UK, US

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**Inclusion and Exclusion Criteria**

- **Age 18-59 years**
- **Cryptogenic ischemic stroke within 180 days**
  - Clinical symptoms ≥24 hours or MRI evidence of infarction
  - **Cryptogenic**
    - No stenosis >50% or ulcerated plaque in relevant vessels
    - No atrial fibrillation or high risk source of cardioembolism
    - Non-lacunar (based on syndrome and/or size)
    - No evidence of hyper-coagulable disorder
- **Patent foramen ovale (PFO)**
  - Confirmed by TEE with bubble study (right-to-left shunt)
  - No indication for anticoagulation
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REDUCE Study Design

Medical Therapy
- Antiplatelet standardized options:
  - Aspirin alone (75-325 mg once daily)
  - Combination aspirin (90-100 mg) and dipyridamole (225-400 mg)
  - Clopidogrel (75 mg once daily)
  - Other combinations or the use of anticoagulants was not permitted
- Prescribed for all subjects for the duration of the study
- Each site was expected to treat all subjects with the same antiplatelet therapy
- Follow-up
- MRI imaging at baseline and 24 months if not already performed for an endpoint event

Sondergaard et al. NEJM 2017; 377:1033-42

Co-Primary Endpoints

- Freedom from recurrent clinical ischemic stroke through at least 24 months
- Incidence of new brain infarct (defined as clinical ischemic stroke or silent brain infarct*) through 24 months

*Sondegaard et al. NEJM 2017; 377:1033-42

Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographic / Characteristic</th>
<th>Closure (N=441)</th>
<th>Medical (N=223)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>45.4 ± 9.3</td>
<td>44.8 ± 9.6</td>
<td>0.41</td>
</tr>
<tr>
<td>Days from qualifying event to randomization</td>
<td>100 ± 52</td>
<td>101 ± 53</td>
<td>0.90</td>
</tr>
<tr>
<td>Sex, male</td>
<td>59.2%</td>
<td>61.9%</td>
<td>0.56</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>14.3%</td>
<td>11.2%</td>
<td>0.30</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4.1%</td>
<td>4.5%</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25.4%</td>
<td>26.0%</td>
<td>0.94</td>
</tr>
<tr>
<td>Previous Cerebrovascular Event</td>
<td>14.1%</td>
<td>10.3%</td>
<td>0.22</td>
</tr>
<tr>
<td>Maximal baseline shunt grade (# bubbles)</td>
<td>N=425</td>
<td>N=216</td>
<td>0.32</td>
</tr>
<tr>
<td>Grade 0 Occluded (0)</td>
<td>0.0%</td>
<td>0.0%</td>
<td>-</td>
</tr>
<tr>
<td>Grade I Trivial/Small (1-5)</td>
<td>18.1%</td>
<td>19.9%</td>
<td>-</td>
</tr>
<tr>
<td>Grade II Moderate (6-25)</td>
<td>39.1%</td>
<td>43.5%</td>
<td>-</td>
</tr>
<tr>
<td>Grade III Large (≥26)</td>
<td>42.8%</td>
<td>(did not collect)</td>
<td>-</td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
<td>20.4%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Sondergaard et al. NEJM 2017; 377:1033-42
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Clinical stroke (ITT)

Probability of freedom from recurrent stroke

Hazard ratio for recurrent stroke, 0.23 (95% CI, 0.09–0.62)

Follow-up (months)

PFO closure group
Anti-platelet-only group

New brain infarct (ITT)

Subjects without Evaluation
Brain Infarct Evaluable
Brain Infarct Present
Recurrent Stroke Only
Both
Silent Brain Infarct Only
Brain Infarct Absent

Difference in incidence of new brain infarct of 5.6%
Relative risk 0.51 (95% CI: 0.29 to 0.91)
p=0.024 after adjustment for multiple testing
silent infarcts about twice as common as clinical stroke

Safety

All Enrolled Subjects (N=664)
Closure (N=441)
Medical (N=223)
p-value
Serious bleeding adverse events
Procedure-related
Other
Any Af/Flutter adverse events
Serious Af/Flutter
Serious device adverse events
Device dislocation
Device thrombosis
Aortic dissection
Any DVT or PE

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**Safety**

- Atrial fibrillation/flutter rate higher in the closure group
  - onset in 1st month (79%)
  - resolved within 2 weeks (59%)
  - 1/29 patients with AF after PFO closure had a stroke

- **REDUCE** 6.6% vs. 0.4%
- **CLOSURE** 5.7% vs. 0.7%
- **PC Trial** 2.9% vs. 1.0%
- **RESPECT** 3.0% vs. 1.5%
- **CLOSE** 4.6% vs. 0.9%

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**DEFENCE-PFO**

- N=210 -> 120 patients with ischemic stroke within 6 months and high-risk PFO:
  - Atrial septal aneurysm
  - Hypermobility (excursion ≥10 mm)
  - PFO size ≥2 mm (maximum separation of septum primum from septum secundum)

- RCT, 1:1 PFO closure with Amplatzer PFO occluder + DAPT for at least 6 months or anti-thrombotic therapy with OAC or APT

- Aim: To evaluate whether the benefits of PFO closure can be determined based on morphological characteristics of the PFO

- Primary end-point: Stroke, vascular death, or major bleeding during 2 years f/u

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**DEFENCE-PFO**

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DEFENCE-PFO

Lee et al. (ACC 2018; 71:2335-42)

“... it seems reasonable that the presence of a PFO and a sizable interatrial shunt should ... no longer result in the categorization of a stroke as cryptogenic.”

EDITORIAL

Tipping Point for Patent Foramen Ovale Closure

Allan H. Ropper, M.D.

Devices

“As determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.”
FDA Indications

- Indication for secondary prevention of stroke – not primary
  - Patients who have had a stroke – TIA not included
- No indication for hypoxemia from right to left shunting
- No indication for migraine

Screening/Imaging PFO

1.) Transcranial Doppler (TCD-Bubble)
   a.) Highest Sensitivity
   b.) Low specificity
   c.) No PFO Features (PFO, L Atrium, Appendage)
   d.) Allows for Valsalva/Mueller

2. Transthoracic Echo (TTE) Specific
   Both are initial Screen recommendations in new (and only current) European Guidelines

TCD

- Four level visual categorization:
  (i) Grade 0: no occurrence of micro-embolic signals
  (ii) grade 1, 1-10 signals:
  (iii) grade II, >10 signals but no curtain pattern
  (iv) grade III, Copious bubbles, not curtain
  (v) Grade IV. Curtain effect

- Test negative: no microbubble
- Low grade shunt: 1-10 microbubbles
- Medium grade shunt: >10 microbubbles but without “curtain effect”
- High grade shunt: curtain effect, seen when the microbubbles are so numerous as to be no longer distinguishable separately
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TCD method of grading R to L shunts

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TCD Grades of shunt

Grade 0

Grade 1

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Grade 2

Grade 3

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46

47

48
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Grade 4  Grade 4

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TEE

- Specific, But Sensitivity quite varied, False - as high as 15-30% with large R-L shunts missed often
  a.) number of attempts, inj. agitated saline
  b.) bulge R to L at time of Recording
  c.) Arm vs. Leg vein injection

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Additional features: ASA, Septal Anatomy, Tunnel length, LAA Thrombus

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Hybrid Defects

Intracardiac Echo (ICE)

- Only Real Role is For Intraprocedural Imaging- no Role in Diagnostic Evaluation
- Comparable Imaging to TEE; Single Operator
- Avoids General Anesthesia
- Costly
- Second Vascular Access

Intracardiac Echo (ICE)

- ACUSON AcuNav V™ Ultrasound Catheter
- 19F, 30 cm, 22° x 80° volume, real-time 3D imaging - Image of left and right atria
- Powered by ACUSON T2000 system - TEE speed of 50 frames per second
- Replaces B and 2D with 3D with color
- Potentially in use for procedural guidance and structural heart disease classification

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Intracardiac Echo (ICE)

Patient with initial negative bubble study

Snoring patient with initial negative ICE bubble study
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Inter-atrial septum

Bubble study

Tunnel length
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30mm Gore Cardioform Septal Occluder

RA disc deployed

Confirmation of device position
Is There a Pathogenic PFO?

US PFO Incidence

<table>
<thead>
<tr>
<th>U.S. Stroke, any age</th>
<th>795,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic - 87%</td>
<td>694,000</td>
</tr>
<tr>
<td>Hemorrhagic - 13%</td>
<td>101,000</td>
</tr>
<tr>
<td>Patent Foramen Ovale</td>
<td>155,000</td>
</tr>
<tr>
<td>No PFO, normal heart</td>
<td>515,000</td>
</tr>
</tbody>
</table>

Is There a Pathogenic PFO?
Risk of Paradoxical Embolism (RoPE Score)

<table>
<thead>
<tr>
<th>Age at time of stroke</th>
<th>Traditional Vascular Risk Factors</th>
<th>Neuroimaging Findings at Index Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 points for 18-29</td>
<td>Absence of these factors (1 point for each)</td>
<td>Presence of cortical (superficial) stroke on neuro-imaging (1 point)</td>
</tr>
<tr>
<td>4 for 30-39</td>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>3 for 40-49</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>2 for 50-59</td>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>1 for 60-69</td>
<td>Prior stroke or TIA</td>
<td></td>
</tr>
<tr>
<td>0 for ≥70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total Score Range 0-10

Is There a Pathogenic PFO?
Risk of Paradoxical Embolism (RoPE Score)

<table>
<thead>
<tr>
<th>Total RoPE Score</th>
<th>Prevalence of PFO (%)</th>
<th>PFO-attributable fraction (%)</th>
<th>Estimated 2-year stroke/TIA recurrence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>23</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>62</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>72</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>84</td>
<td>6</td>
</tr>
<tr>
<td>9-10</td>
<td>73</td>
<td>89</td>
<td>2</td>
</tr>
</tbody>
</table>

65 year old man has a lacunar stroke. He is a smoker, diabetic and hypertensive with history TIA. RoPE= 1

36 year old woman has a cortical stroke. She has no vascular stroke risk factors. RoPE= 9
Is There a Pathogenic PFO?
Additional Clues

- Shunting At Rest
- Large Volume of Shunting
- Atrial Septal Aneurism plus PFO
- Anatomically opens > 10 mm
- Prominent Eustacian Valve on Echo

LVHN Neurocardiology Clinic

Best Practice: a PFO Clinic

Pharmacology and Follow-up

Drug therapy and follow up after percutaneous closure

<table>
<thead>
<tr>
<th>Position statement</th>
<th>Strength of statement</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is reasonable to propose dual antiplatelet therapy for 1 to 6 months after PFO closure</td>
<td>Conditional</td>
<td>A</td>
</tr>
<tr>
<td>We suggest a single antiplatelet therapy be continued for at least 2 years</td>
<td>Conditional</td>
<td>C</td>
</tr>
<tr>
<td>The extension of the therapy with single antiplatelet beyond 2 years should be based on the balance between patient’s overall risk of stroke for other causes and hemorrhagic risk</td>
<td>Strong</td>
<td>C</td>
</tr>
<tr>
<td>The choice of the type of antiplatelet drug in the follow-up is currently empirical</td>
<td>Strong</td>
<td>A</td>
</tr>
<tr>
<td>The value of residual shunt after percutaneous closure should be defined from available studies</td>
<td>Strong</td>
<td>C</td>
</tr>
<tr>
<td>Symptomatic, high-quality data on follow-up are needed</td>
<td>Strong</td>
<td>C</td>
</tr>
</tbody>
</table>
**Pharmacology and Follow-up**

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<td>Conditional</td>
<td>A</td>
</tr>
<tr>
<td>We suggest a single antiplatelet therapy be continued for at least 5 years.</td>
<td>Conditional</td>
<td>C</td>
</tr>
<tr>
<td>The continuation of the therapy with single antiplatelet beyond 5 years should be based on the balance between patient's overall risk of stroke for other causes and hemorrhagic risk.</td>
<td>Strong</td>
<td>C</td>
</tr>
<tr>
<td>The choice of the type of antiplatelet drug in the follow-up is currently empirical.</td>
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<td>A</td>
</tr>
<tr>
<td>The value of residual shunt after percutaneous closure cannot be deduced from available studies.</td>
<td>Strong</td>
<td>C</td>
</tr>
<tr>
<td>Systematic, high-quality data on follow-up are needed.</td>
<td>Strong</td>
<td>C</td>
</tr>
</tbody>
</table>

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**Follow up**

- To obtain compatible data we propose to perform:
  - a) TSU prior to hospital discharge
  - b) TCD at least once beyond six months to assess effective PFO closure and thereby, if residual shunt persists, usually anti closure
  - c) TCD or a TCU is case of severe residual shunt at TCD or recent events, or syndrome during follow up

- Patterns should undergo magnetic resonance for any invasive procedure performed in the first six months from PFO closure.

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**Atrial fibrillation Management**

- **First, make sure no AF before the procedure**
  - 30 day monitor
  - ILR in older patients
  - Prefer Amplatzer in older patients (? Stitch devices)
- **If develops after procedure (due to irritation and inflammation)**
  - Rate control
  - Anticoagulation (drop one or both antplatelets)
  - Cardioversion if doesn't resolve during 24 hours
  - Rarely need to use anti-arrhythmics
  - All have resolved on own – discontinued anticoagulation

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Complications of PFO Closure

Intra-procedural Complications
- Air embolism (coronary, brain, systemic)
- Cardiac or vessel damage
- Device embolization
- Bleeding or access site injury
- Thrombus
- Migraine/headache

Post-procedure Complications
- Chest pain
  - Nickel allergy (steroids, prefer Gore)
  - Cardiac or vascular damage (effusions)
  - Erosion
- Device embolization
  - Imaging next day
- Pulmonary embolism/DVT
  - Avoid excessive compression
  - Rule out pre-procedure DVT, especially on inpatients
- Atrial fibrillation
  - Device choice
  - Monitoring
Post-procedure Complications: Long Term

- **Endocarditis**
  - Antibiotic prophylaxis X 1 year

- **Residual shunt**
  - Imaging with bubble study at regular intervals
  - May close over time
  - Associated with recurrent stroke – need further closure

- **Thrombus formation**
  - Seen more with earlier devices

- **Device erosion**
  - Most dreaded complication, extremely rare with PFO devices

**Post-procedure Complications: Long Term**

**Endocarditis**

- Antibiotic prophylaxis X 1 year

**Residual shunt**

- Imaging with bubble study at regular intervals
- May close over time
- Associated with recurrent stroke – need further closure

**Thrombus formation**

- Seen more with earlier devices

**Device erosion**

- Most dreaded complication, extremely rare with PFO devices

---

**Table 3. Serious Adverse Events Related to the Procedure or Device among the 498 Patients in the PFO Closure Group.**

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>Patients with Event</th>
<th>Total No. of Events</th>
<th>Procedure-Related Events</th>
<th>Device-Related Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic drug reaction</td>
<td>1 (0.2)</td>
<td>1</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (0.4)</td>
<td>2</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>1 (0.2)</td>
<td>1</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Cardiac perforation</td>
<td>1 (0.2)</td>
<td>1</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac thrombus</td>
<td>2 (0.4)</td>
<td>2</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Chest tightness</td>
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<td>1</td>
<td>0</td>
<td>1 (0.2)</td>
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<td>Deep-vein thrombosis</td>
<td>1 (0.2)</td>
<td>1</td>
<td>1 (0.2)</td>
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<tr>
<td>Infective endocarditis</td>
<td>1 (0.2)</td>
<td>1</td>
<td>0</td>
<td>1 (0.2)</td>
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<tr>
<td>Ischemic stroke</td>
<td>2 (0.4)</td>
<td>2</td>
<td>0</td>
<td>2 (0.4)</td>
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<tr>
<td>Pericardial effusion</td>
<td>1 (0.2)</td>
<td>1</td>
<td>1 (0.2)</td>
<td>0</td>
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<tr>
<td>Pericardial tamponade</td>
<td>2 (0.4)</td>
<td>2</td>
<td>2 (0.4)</td>
<td>0</td>
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<tr>
<td>Pulmonary embolism</td>
<td>2 (0.4)</td>
<td>2</td>
<td>0</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Residual shunt requiring closure</td>
<td>2 (0.4)</td>
<td>2</td>
<td>2 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (0.2)</td>
<td>1</td>
<td>0</td>
<td>1 (0.2)</td>
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<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>1 (0.2)</td>
<td>1</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Major vascular complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>2 (0.4)</td>
<td>2</td>
<td>2 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Hematomas</td>
<td>1 (0.2)</td>
<td>1</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Vasovagal reaction</td>
<td>1 (0.2)</td>
<td>1</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>21 (4.2)</td>
<td>25</td>
<td>12 (2.4)</td>
<td>13 (2.6)</td>
</tr>
</tbody>
</table>

---

**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. Smallding, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Trischwell, M.D., for the RESPECT Investigators

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#POMA19

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The NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

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Tables, figures, and other content related to the above-mentioned topics.
Safety Outcomes After Percutaneous Transcatheter Closure of Patent Foramen Ovale

- 2005 – 2013
- Closure within 1 year of TIA/stroke
- New York, California and Florida
- Total adverse events 7%
  - Atrial fibrillation / flutter 3.7%
  - Vascular complication 3.0%
  - Hematoma/hemorrhage only 2.7%
  - Cardiac tamponade/perforation 0.5%
  - Death 0.3%
  - Pneumothorax/hemothorax 0.1%

#POMA19

In general, PFO closure is one of our safest procedures
- Benefits from almost 20 years of experience
- New operators should be heavily vetted and only launched once current operators are “maxed out”
  - Reference SCAI/AAN Credentialing Document
- >90% of complications can be avoided or classified as “never events” in experienced hands
- Patients at risk for DVT/PE pre-procedure should remain on warfarin post-procedure
- Erosion exceedingly rare – avoid oversizing
- Atrial fibrillation is best avoided by pre-procedure monitoring, sometimes extensive
  - PAF post-procedure is almost always self-limited

#POMA19

Remaining or Re-Emerging Questions

- 1.) PFO mediated stroke beyond 60
- 2.) PFO in Migraine
- 3.) Primary Prevention

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“Interventional Closure of Patent Foramen Ovale”
Bryan W. Kluck, DO

MIGRAINE

MIST Trial: Study Design

- 232 patients screened age 14-65
- One year medical history of migraines with aura
- Episodes with aura at least 3 times per month
- Headache lasting at least 7 days
- Failed treatments
- Included: FDA approved migraine medication
- Excluded: Pregnancy

Complete Cessation of Migraines (%)

There was no difference between groups in the primary endpoint of complete cessation of migraines with 3 patients in each group.

Unrealistic endpoint, Poor device, Poorly run trial
Interventional Closure of Patent Foramen Ovale

Bryan W. Kluck, DO

POMA 111th Annual Clinical Assembly & Scientific Seminar
May 1-4, 2019

- treated 136 severe MHA patients with PFO and with no stroke, with clopidogrel (open-label)
  - 86% Female
  - 61% Migraine with aura
  - Mean Age = 37.9 +/- 14.7 years (Range 14 – 71)
  - Average headache burden: 14.7 +/- 8.3 days/month

60 (94%)
3 (5%) On-going MHA Relief
1 MHA returned post-P2Y12
1 lost to follow-up

18 (100%)
4 MHA returned post-P2Y12
4 On-going MHA Relief
3 Return of MHA

Interventional Closure of Patent Foramen Ovale

Bryan W. Kluck, DO

PFA – Migraine

MHA Effect of P2Y12 Inhibition

- Suggests that PFO MHAs are “platelet-mediated” and specific to the P2Y12 receptor
- Suggests that the trigger substance crossing PFO is likely a platelet aggregation or platelet activation byproduct
- Suggests that we may be able to predict closure benefit from a beneficial MHA response to P2Y12 inhibition


PFO – Migraine

What’s Really New

- Thienopyridine responsiveness will be used to enrich the study population
- Responding subjects will be randomized/blinded to PFO closure or sham, subsequent P2Y12 withdrawal
- Protocol is being submitted to the FDA for IDE
- Site recruitment Q4 2018, enrollment anticipated to begin Q1–Q2 2019

That’s All Folks!!!
Decompression

19th Century “Caisson Disease”

Pressurized air prevents water from entering workspace.

Decompression

Brooklyn Bridge

- ~20% of caisson workers developed permanent neurologic deficits.
- 1872: Washington Roebling, chief engineer on the Brooklyn Bridge is paralyzed.
- Construction halted on Manhattan tower 30 feet short of bedrock.
Decompression

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Affected Organ</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Pecipitate</td>
<td>Large Joints &amp; Skin (REMS)</td>
<td>Localized, deep, red pain, swelling, joint effusion, paresthesia</td>
</tr>
<tr>
<td>Venous Pecipitate</td>
<td>Lungs</td>
<td>Pulmonary Embolism – CF, SOB, hypoxia</td>
</tr>
<tr>
<td>Paradoxa Embolion</td>
<td>Brain</td>
<td>Headache, nausea, vomiting, visual symptoms, loss of consciousness</td>
</tr>
</tbody>
</table>

Decompression Illness

- Increased incidence of PFO/ASD among divers with decompression illness (56%) Koopsen et al. Neth Heart J 2018
- Divers with PFOs are 2.5 to 4.5 times as likely to develop decompression illness as divers without PFOs. Bove 1998, Schwetzmann. Ann Int Med. 2001; 134(1)24-1.

Position Statement

South Pacific Underwater Medicine Society (SPUMS)
United Kingdom Sports Diving Medical Committee (UKSDMC)

- Routine screening for PFO is not currently justifiable.
- Divers with a history of decompression illness or congenital heart disease are considered to be at higher risk and may consider screening.
- If a shunt is present, advice should be provided by an experienced diving physician taking into account the clinical context and the size of shunt. Reduction in gas load by limiting depth, repetitive dives may be appropriate.
- Divers with decompression illness may consider PFO closure in order to return to diving.
47 Year Old RH Male

- Admitted to hospital with acute R MCA Stroke
- Returned from the Outer Banks by car within the last 2 weeks
- Straining at stool when he noted weakness of L hand
- Tried to stand and his family found him down
- Hospital stroke alert: NIHSS 9, CT R MCA sign 2h; tPA given at 2h15m

24 h: Improved - mild L hemi neglect, mild L Sensory loss, no ataxia; NIHSS=3

48 h: Improved - NIHSS=0
Interventional Closure of Patent Foramen Ovale

Bryan W. Kluck, DO

**TEE**

**TCD Bubbles**

**30 d Cardiac Event Monitor**
- Time: 27d 23h 12m
- AF-Sx: None Indicated
- AF-ASx: None Found
- SVT-Sx: None Indicated
- SVT-ASx: None Found
- Pause/Heart Block: none
RoPE Score:

- 7 – suggests a 72% chance stroke due to PFO
- 6% risk at 2 years
- Works in Maintenance Department - heavy lifting
- Combined Cardio/Neuro conference decision: Close PFO

PFO Closure

- ACCESS: RRA/RCFV/LCFV
- ACCUNAV ICE
- Gore 30mm ASD Occluder
- Uncomplicated
- Discharged following day DAPT

ICE

Baseline

Device across
Deployment

Gore Device

Deployed, Attached

#POMA19
ICE: Pre-release evaluation

Color

Bubbles

#POMA19

ICE: Post Release

Released

Bubble

#POMA19