ASD/PFO and paradox embolism: an update in indications for intervention

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Disclosures: Consultant & Proctor – Abbott
Blood Clot or Thrombus?

• Blood clot formation is the cornerstone of hemostasis and can be **lifesaving**

• Embolization of thrombus in vital organs causes ischemia, disability and may be **lethal**

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Blood Clot vs Thrombus
Balance

Stroke reduction vs Bleeding
Balance

Elderly patients with AF
Stroke prevention

Cardiology vs Neurology?

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Stroke prevention

PFO occlusion

LAA occlusion

The Neuro-Heart Team!
ASD and paradoxical embolism

• Ostium secundum ASDs >5 mm should be closed in the following scenarios:

1. Presence of symptoms such as exercise intolerance, shortness of breath, heart failure or atrial arrhythmias

2. Evidence of RV or RA dilatation on echocardiogram or cardiac CT/MRI with or without symptoms

3. Presence of paradoxical embolism regardless of the size of the defect

4. Documentation of orthodeoxia-platypnea

ACC/AHA Guidelines
PFO

- Remnant of the fetal circulation
- Valve-like opening
- Most frequent inter-atrial communication
  - 15-25% in autopsy studies
  - 10-15% in TEE
- Allows right-to-left shunt by-passing the lungs (filter)
- Arterial de-saturation
- Paradoxal embolization

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PFO – device closure

• Many devices have been introduced to clinical practice
• The most widely used and studied: Amplatzer PFO Occluder
PFO – device closure

Procedure step-by-step

1. Obtain femoral vein access
2. Advance a regular J-wire in the IVC, through the PFO towards the LUPV
3. Advance delivery sheath, remove the J-wire
4. Advance PFO occluder to form the LA disk
5. Pull back and un-sheath to form the RA disk
6. Check stability and release
7. Remove sheath and compress access site for 5-10’
PFO closure case example

- 36 yo male
- Recent cryptogenic stroke (MRI +)
- No other relevant condition
- PFO with IAS aneurysm and significant shunt
PFO closure case example
PFO closure case example

Without Valsalva
PFO closure case example
PFO closure case example
PFO closure case example
PFO – device closure

PFO – Stroke History
Heated Debate for > 20 Years

Stroke Neurologists
Interventional Cardiologists

Does PFO Closure Work Better than Blood Thinning Medication?
PFO device closure Data – the past

• Despite the association between PFO and cryptogenic stroke, three early randomized clinical trials (CLOSURE I, PC trial, and RESPECT short-term) did not show a clear benefit of PFO closure for secondary stroke prevention.

• These results led to a generally decreased interest in PFO closure for stroke prevention.
In March 2016 a meta-analysis of patient-level data from CLOSURE I, PC, and RESPECT was published.

PFO closure was superior to medical therapy for the prevention of recurrent ischemic stroke.

When the analysis was restricted to the trials in which only the Amplatzer PFO occluder device was used (PC and RESPECT) the benefit appeared even greater.

In October 2016, the US FDA approved the Amplatzer PFO occluder device for patients 18-60 years old with PFO and cryptogenic stroke.
PFO – device closure – Data

• In 2017, 2 new RCTs of PFO closure vs medical therapy were published: CLOSE and REDUCE

• They used stricter enrollment criteria than the three previous trials

• In CLOSE, eligible patients were 16-60 years old, had had a cryptogenic stroke with corroborating imaging findings within the prior 6 months, had a PFO, and had a large interatrial shunt or atrial septal aneurysm

• After a mean follow-up of 5.3 years, subjects who underwent PFO closure had a lower risk of recurrent stroke than those maintained on antiplatelet therapy (0% vs. 6%; HR, 0.03; 95% CI, 0-0.26).
In REDUCE, eligible patients were 18-59 years, had had a recent cryptogenic stroke within the prior 6 months, had symptoms lasting ≥24 hours or positive imaging, and had a PFO.

After a median follow-up of 3.2 years, subjects who underwent PFO closure had a lower risk of recurrent stroke than those maintained on antiplatelet therapy (1.4% vs. 5.4%; HR, 0.23; 95% CI, 0.09-0.62).

In both REDUCE and CLOSE, PFO closure was associated with a higher risk of atrial fibrillation, which was believed to be primarily due to the closure procedure itself (i.e., self-limited).
PFO – device closure – Data

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

Saver JL et al. NEJM 2017
PFO – device closure – Data

Freedom from Recurrent Ischemic Stroke
(Intention to Treat)

Event-free Probability

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

# at Risk (KM Estimates)
AMPLATZER
499 (0%)  476 (1.4%)  464 (1.6%)  447 (1.6%)  421 (1.9%)  352 (2.6%)  262 (3.3%)  197 (4.5%)  128 (5.0%)  77 (5.0%)  41 (5.0%)

MM
481 (0%)  433 (1.5%)  394 (3.2%)  380 (3.7%)  354 (4.7%)  282 (5.0%)  218 (5.0%)  150 (6.6%)  104 (7.3%)  59 (8.5%)  31 (12.5%)

Saver JL et al. NEJM 2017
PFO – device closure – Data

Freedom from Recurrent Ischemic Stroke of Unknown Mechanism (Intention to Treat)

Event-free Probability

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

Saver JL et al. NEJM 2017
PFO – device closure – Data

Cryptogenic Stroke = PFO-related Stroke?
European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism

Christian Pristipino¹ *, MD; Horst Sievert²,³, MD; Fabrizio D’Ascenzo⁴, MD; Jean Louis Mas⁵, MD; Bernhard Meier⁶, MD; Paolo Scacciatella⁷, MD; David Hildick-Smith⁸, MD; Fiorenzo Gaita⁹, MD; Danilo Toni¹⁰, MD; Paul Kyrle¹¹, MD; John Thomson¹², MD; Genevieve Derumeaux¹³, MD, PhD; Eustaquio Onorato¹⁴, MD; Dirk Sibbing¹⁵, MD; Peter Germonpré¹⁶, MD; Sergio Berti¹⁷, MD; Massimo Chessa¹⁸, MD; Francesco Bedogni¹⁸, MD; Dariusz Dudek¹⁹, MD; Marius Hornung¹⁰, MD; Jose Zamorano¹⁰, MD;

joint task force of European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Stroke Organisation (ESO), European Heart Rhythm Association (EHRA), European Association for Cardiovascular Imaging (EACVI), Association for European Paediatric and Congenital Cardiology (AEPC), ESC Working group on GUCH, ESC Working group on Thrombosis, European Haematological Society (EHA), European Underwater and Baromedical Society (EUUSB).

EuroIntervention 2018;14-online publish-ahead-of-print August 2018
# European position paper – PFO diagnosis

<table>
<thead>
<tr>
<th>PFO diagnosis</th>
<th>Strong</th>
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<tr>
<td>To achieve the maximal accuracy in PFO diagnosis, the combined use of different techniques is warranted</td>
<td></td>
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<td>The technique achieving the highest sensitivity should be used as a first-line investigation in PFO diagnosis</td>
<td>Strong</td>
<td>C</td>
</tr>
<tr>
<td>c-TCD has a higher sensitivity than c-TTE as a first-line investigation to detect a R-T-L shunt</td>
<td>Conditional</td>
<td>A</td>
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<tr>
<td>c-TTE has a lower sensitivity for small shunts than other techniques</td>
<td>Conditional</td>
<td>A</td>
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<td>c-TOE should be performed by experienced operators in PFO assessment</td>
<td>Strong</td>
<td>C</td>
</tr>
<tr>
<td>A strict methodology should be used performing c-TOE</td>
<td>Strong</td>
<td>C</td>
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<tr>
<td>c-TOE should be performed to stratify the risk</td>
<td>Strong</td>
<td>C</td>
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</table>
European position paper – PFO diagnosis
Table 2. PFO variables to be assessed for decision making and interventional treatment.

- PFO morphology: size, location, length of the tunnel
- Spatial relationship and distances between the PFO and the aortic root, vena cava, valves and the free walls of the atrium
- Comprehensive evaluation of the atrial septum, including inspection for atrial septal aneurysms, movement, and other atrial septal defects
- Presence/absence of a Eustachian valve and/or Chiari network
- Thickness of the septum primum and secundum
- Colour Doppler evaluation of the shunt at rest and after a Valsalva manoeuvre
<table>
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<th>Recommendation</th>
<th>Strength</th>
<th>Grade</th>
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<tr>
<td>The evaluation of the role of the PFO in left circulation thromboembolism should be individualised with critical clinical judgement in an interdisciplinary collaboration between physicians, weighting clinical, anatomical and imaging characteristics</td>
<td>Strong</td>
<td>C</td>
</tr>
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<td>When a PFO is considered to play a pathogenic role in an embolism, the episode should not be classified as cryptogenic anymore</td>
<td>Strong</td>
<td>A</td>
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<td>The presence of other risk factors does not exclude a causative role of PFO; however, it is more likely when patients are young and lack other risk factors</td>
<td>Strong</td>
<td>B</td>
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</table>
PFO-associated embolism – exclude AF work-up

Clinical event or incidental finding of embolism at imaging → First-line diagnostic workup for embolism → Plausible causes → STOP

First-line diagnostic workup for arrhythmias
- 12-lead ECG
- In-hospital telemetry
- 24-hour Holter ECG monitoring

PFO diagnostic workup
PFO YES → PFO-associated embolism

Interdisciplinary evaluation of the role of the PFO → Likelihood of causative role

Evaluate major AF risk factors

Age <55 years old → Yes → ICM
Age 55-64 years old → Yes → AF risk factor(s)
Age ≥65 years old

Evident PFO causative role → Yes
AF Detected → STOP

Recurrence risk

AF RISK FACTORS

HIGH-RISK
- Uncontrolled hypertension
- Structural heart alterations (LVH, LAE)
- Uncontrolled diabetes
- Congestive heart failure

- Obesity
- Atrial runs
- Pulmonary disease
- Thyroid disease

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Coming soon...

Recommendations for the management of patients with cryptogenic stroke and patent foramen ovale: a clinical guide by the Hellenic Stroke Organization and the Hellenic Society of Cardiology

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Conclusions

- PFO closure is indicated in patients with cryptogenic stroke
- PFO closure is a safe, relatively easy procedure with recent strong evidence in large RCTs
- Diagnosis, risk stratification, and decision for PFO closure should follow a strict, pre-specified plan
- Collaboration between stroke specialists and interventional cardiologists is one of the keys for success and best clinical practice in stroke prevention!
Thank you!