Stroke prevention:
Patent foramen ovale closure

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Declaration of Interest

Nothing to disclose
Cryptogenic stroke

- Ca. 25% (10-40%) of patients with ischemic stroke have no probable cause found after standard workup (TTE, 24-hour Holter monitoring, MRI or CT of of the infarct in the brain / neck and brain arteries, blood work).
- Embolic strokes of undetermined source (nonlacunar brain infarcts without substantial proximal arterial stenosis or major cardioembolic sources) represent 80 to 90% of all cryptogenic ischemic strokes.
- Occult, low-burden, paroxysmal atrial fibrillation is increasingly recognized as a source of cryptogenic stroke, especially in older patients (>60 y. of age).
- Low risk of recurrence with aspirine: 1-2% per year.

Cryptogenic stroke (CS) is a diagnosis of exclusion

Conventional classification:

- Atherosclerotic
- Small arterial occlusion
- Cardioembolic
- Other causes
- Cryptogenic

Potential etiologies of CS:

- Paroxysmal atrial fibrillation
- Aortic arch atheromas
- Inherited thrombophilias
- Patent foramen ovale

Patent foramen ovale (PFO)

- Persistent opening between the atrial septum primum and secundum at the level of the fossa ovalis
- Prevalence: 27.3%\(^1\)
- Mean size ca. 5 mm
- Larger shunt size:
  - atrial septal aneurym
  - prominent valvula Eustachii

PFO and stroke

**NEJM 1988**¹

- 60 adults < 55 years with ischemic stroke and normal cardiac exam
- PFO prevalence
  - controls: 10%
  - stroke with identif. cause: 21%
  - stroke with risk factor: 40%
  - stroke without identif. cause: 54%

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PFO closure and stroke: 1992-2016

**Circulation 1992**¹

- Case series of 36 patients with presumed paradoxical embolism (strokes, TIAs, systemic arterial emboli, brain abscesses)
- Transcatheter closure can be accomplished with little morbidity

**Clinical trials**


None of the trials showed superiority of PFO closure vs. medical therapy in the prevention of recurrent vascular events.

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PFO and stroke

RoPE score 2013¹

- Age, cortical infarct, nonsmoker, first event, no diabetes nor hypertension

- Score 10: 29 y. old with cortical infarction and no CV risk factor

- Score 0: 70 y. old smoker with hypertension, diabetes, prior stroke and no cortical infraction

<table>
<thead>
<tr>
<th>ROPE Score</th>
<th>PFO %</th>
<th>Attrib. Risk</th>
<th>Recurr. Rate @2y</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>23</td>
<td>0</td>
<td>20 (12-28)</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>38</td>
<td>12 (6-18)</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>62</td>
<td>8 (4-12)</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>84</td>
<td>6 (2-10)</td>
</tr>
<tr>
<td>9-10</td>
<td>73</td>
<td>88</td>
<td>2 (0-4)</td>
</tr>
</tbody>
</table>

PFO and stroke – what have learned so far

• Paradoxical embolism can lead to stroke but is usually a diagnosis of presumption
• There are „incidental“ PFOs and there are „dangerous“ PFOs

• 2014 AHA stroke prevention guidelines: 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; Level of Evidence A).

• Study design matters: identification of „dangerous“ PFOs, length of f/u, not all devices are performing equally well

PFO closure and stroke – a new era begins (2017)

PFO closure

yes

no
<table>
<thead>
<tr>
<th></th>
<th>RESPECT ext. f/u (n=980; 46 y.)</th>
<th>CLOSE (n=664; 43y.)</th>
<th>REDUCE (n=664; 45 y.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Event driven</td>
<td>900 pts.</td>
<td>N=664</td>
</tr>
<tr>
<td></td>
<td>1:1 rand.</td>
<td>1:1:1</td>
<td>2:1</td>
</tr>
<tr>
<td></td>
<td>Device vs. medical therapy</td>
<td>Antiplatelet vs. OAC vs. device</td>
<td>Device + ASA vs. antiplatelet</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>5.9 y (IQR 4.2-8y)</td>
<td>5 +/- 2 y.</td>
<td>3.2 y (IQR 2.2-4.8)</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Stroke</td>
<td>Stroke</td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
<td></td>
<td>Brain infraction</td>
</tr>
<tr>
<td><strong>Device</strong></td>
<td>Amplatzer</td>
<td>11 diff. devices</td>
<td>HELEX or GSO</td>
</tr>
<tr>
<td></td>
<td>ASA for 6 mo.</td>
<td></td>
<td>Plus antiplat. tx.</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>18-60 y. of age</td>
<td>16-60 y. of age</td>
<td>18-59</td>
</tr>
<tr>
<td></td>
<td>CS* (270 days prior)</td>
<td>CS* (6 months prior)</td>
<td>CS* (180 days prior)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Closure superior</td>
<td>Closure superior to antiplatelet</td>
<td>Closure superior (stroke prevention)</td>
</tr>
<tr>
<td></td>
<td>HR 0.55 (0.31-0.999)</td>
<td>HR 0.04 (0-0.27)</td>
<td>HR 0.23 (0.09-0.62)</td>
</tr>
</tbody>
</table>

**CS*** cryptogenic stroke
PFO and stroke – Assessing the evidence for closure

• „A PFO and a sizable interatrial shunt should no longer result in the categorization of a stroke as cryptogenic.”\(^1\)

• PFO closure patients < 60 y. of age and “cryptogenic stroke“ are 30-50% less likely to have a stroke recurrence than patients with antiplatelet therapies (NNT ca. 20-40 for 1 stroke over 5 years).\(^2\)

• Device-related complications: 2-3%;
  Atrial fibrillation after device implantation: 6%

Cryptogenic stroke
PFO present

- Age < 60 y.
  - Large shunt or with atrial septal aneurysm
    - PFO closure
- Age < 60 y.
  - Small-moderate shunt
    - RoPE Score > 5
    - PFO closure
- Age < 60 y.
  - Small-moderate shunt
    - RoPE Score ≤ 5
    - Consider PFO closure vs. medical therapy
- Age ≥ 60 y.
  - Medical therapy