Recurrent Events after Patent Foramen Ovale Closure

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## Presenters Disclosures

<table>
<thead>
<tr>
<th>Physician name</th>
<th>Company</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horst Sievert</td>
<td>Abbott, Access Closure, AGA, Angiomed, Ardian, Arstasis, Avinger, Boston, Bridgepoint, CardioKinetix, CardioMEMS, Coherex, Cordis, CSI, Edwards, EndoCross, EndoTex, ev3, FlowCardia, Gore, Guidant, Invatec, Lumen Biomedical, Kensey Nash, Kyoto Medical, Medtronic, NDC, NMT, OAS, Occlutech, Osprey, Ovalis, Pathway, pfm, PendraCare, Percardia, Remon, Rox Medical, Sadra, Sorin, Spectranetics, SquareOne, St. Jude, Terumo, Viacor, Velocimed, Xtent</td>
<td>Consulting fees, Travel expenses, Study honoraria</td>
</tr>
<tr>
<td>Julia Wallenborn</td>
<td>Cardiokinetix, Access Closure, Coherex, Velocimed, CoAptus, Lumen Biomedical</td>
<td>Stock options, Stocks</td>
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<tr>
<td></td>
<td>Nothing to disclose</td>
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Background

• It is well known that cerebral or embolic events may occur after PFO closure.

• This may be due to residual shunts or other causes.

• The purpose of this retrospective analysis was specifically to identify potential causes of recurrent events after PFO closure.
Methods


• 14 different double-disc closure systems and two in-tunnel devices

• Follow up:
  - TEE or TTE after 1, 6 and 12 months
  - ECG after 1, 6 and 12 months
  - Questionnaire every 12 months
Patients

- 46 % female, 54 % male
- Age 15 – 89 years (mean 50 ± 13.3)
- Multiple defects in 49
Indications for PFO Closure

- TIA 51%
- Stroke 54%
- Peripheral embolism 4.5%
- Decompression illness 1.4%
Events prior to PFO Closure

- Total number of cerebrovascular and peripheral embolism: 2720
- History of cerebrovascular and peripheral embolism: 100%
  - Recurrent events: 28%
  - Events per patient: 1.4
- Annual recurrence rate: 22.4%
  - 785 events in 3497 patient years
Implanted Devices

- Amplatzer
- Helex
- Premere
- Starflex/Cardioseal
- Occlutech
- Coherex
- SIDERIS
- Biostar
- SeptRX
- ASDOS
- Angelwings
- Carag
- Solysafe
- Velocimed
- PfoStar
PFO Closure Results

• Device implantation technically successful
  - 1st attempt 98.6 %
  - 2nd attempt 100 %

• 68 patients underwent percutaneous closure of a residual shunt

• 8 patients underwent surgery
  residual shunt (3), thrombus (3), pericardial tamponade (2)
# PFO Closure Rate

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>6 months ( n = 1930 )</th>
<th>12 months ( n = 1930 )</th>
<th>Last FU ( n = 1930 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RS</td>
<td>87.6 %</td>
<td>96 %</td>
<td>92 %</td>
</tr>
<tr>
<td>Minimal RS</td>
<td>7.8 %</td>
<td>2 %</td>
<td>5.5 %</td>
</tr>
<tr>
<td>Moderate – large RS</td>
<td>4.6 %</td>
<td>2 %</td>
<td>2.5 %</td>
</tr>
</tbody>
</table>
What did we do?

- Intensive review of all patient histories
- In case of event extensive chart review
- Interviews with patients and physicians involved
Limitations of the Study

- Retrospective analysis
- Analysis of external medical findings
- Interobserver variability in accessing clinical events
How did we Classify the Recurrent Events?

• Most likely paradoxical embolism:
  - Residual shunt existing, exclusion of all other possible causes

• Questionable paradoxical embolism:
  - Residual shunt existing, other possible causes not excluded or coexisting

• Definitely not paradoxical embolism:
  - Residual shunt excluded
Results

• Follow-up 1 – 167 (mean 39) months

• Recurrent events diagnosed: 63
  - Within 12 months n=21
  - After 12 months n=42

• Annual recurrence rate: 1%
  - 63 events in 6211 patient years

• Death n=36
  - One possibly due to paradoxical embolism (mesenterial infarction)
Kaplan Meier Plot

Freedom from recurrence vs. Follow-up (months):

- n at risk: 1930, 1211, 806, 445, 227, 67, 16, 12, 2
Recurrent Stroke after PFO Closure

Hemorrhagic Stroke
- 8

Ischemic Stroke
- n=25
  - Most likely Paradoxical Embolism
    - 0
  - Questionable Paradoxical Embolism
    - 2
  - Definitely NOT Paradoxical Embolism
    - 23
Recurrent Stroke after PFO Closure

- Hemorrhagic Stroke: 8
- Ischemic Stroke: n=25
  - Most likely Paradoxical Embolism: 0
  - Questionable Paradoxical Embolism: 2
  - Definitely NOT Paradoxical Embolism: 23
Potential Causes of Ischemic Stroke (n=23)

- Arteriosclerosis: 82%
- Cardio-embolism: 17%
- Polycythemia vera: 4%
- Thrombophilia: 4%
- Unknown: 4%
Recurrent TIA after PFO Closure

TIA
n=36

- Most likely Paradoxical Embolism: 0
- Questionable Paradoxical Embolism: 5
- Definitely NOT Paradoxical Embolism: 31
Recurrent TIA after PFO Closure

- TIA
  - n=36
    - Most likely Paradoxical Embolism: 0
    - Questionable Paradoxical Embolism: 5
    - Definitely NOT Paradoxical Embolism: 31
Potential Causes of TIA (n=31)

- Arteriosclerosis: 58%
- Cardio-embolism: 26%
- Unknown: 13%
- Migraine: 10%
- Carotid Stenosis: 6%
- Meningeoma: 6%
- Hypertension: 3%
- Periprocedural ischemia: 3%
Peripheral Embolism after PFO Closure

Peripheral Embolism

n=2

Most likely
Paradoxical Embolism

0

Questionable
Paradoxical Embolism

2

Definitely NOT
Paradoxical Embolism

0
Recurrence Events
n=63

Most likely
Paradoxical Embolism
0

Questionable
Paradoxical Embolism
9

Definitely NOT
Paradoxical Embolism
54

- Overall annual recurrence rate after PFO Closure 1%
- Annual recurrence rate of paradoxical embolism concerning the questionable cases 0.14%
### Prognostic Factors

#### Table 1: Univariate analysis of predictors of recurrent events

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Recurrent Events</th>
<th>Recurrent Event</th>
<th>p-value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>50 ± 13.3; 15-89</td>
<td>56 ± 14.6; 19-84</td>
<td>0.000</td>
<td>1.0</td>
<td>1.02-1.06</td>
</tr>
<tr>
<td>Gender (F)</td>
<td>855 F (46%)</td>
<td>23 F (42%)</td>
<td>0.571</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>26 ± 4.3; 3.6-57.5</td>
<td>26 ± 3.8; 18-35.8</td>
<td>0.618</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Residual shunt</td>
<td>146/1775</td>
<td>9/55</td>
<td>0.011</td>
<td>2.5</td>
<td>1.2-5.0</td>
</tr>
<tr>
<td>AF</td>
<td>74/1875</td>
<td>8/55</td>
<td>0.003</td>
<td>2.9</td>
<td>1.4-6.3</td>
</tr>
<tr>
<td>Thrombus formation</td>
<td>18/1874</td>
<td>4/55</td>
<td>0.000</td>
<td>7.0</td>
<td>2.5-19.5</td>
</tr>
<tr>
<td>No of events</td>
<td>1.4 ± 0.8; 1-11</td>
<td>1.9 ± 1.1; 1-5</td>
<td>0.000</td>
<td>1.5</td>
<td>1.2-1.7</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>591/1872</td>
<td>26/55</td>
<td>0.011</td>
<td>1.9</td>
<td>1.2-3.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>85/1873</td>
<td>8/55</td>
<td>0.000</td>
<td>3.9</td>
<td>1.8-8.4</td>
</tr>
<tr>
<td>Sideris device</td>
<td>9/1875</td>
<td>3/55</td>
<td>0.001</td>
<td>6.2</td>
<td>1.9-20.1</td>
</tr>
<tr>
<td>Multiple defects</td>
<td>46/1875</td>
<td>0/55</td>
<td>0.271</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Strech diameter in mm</td>
<td>9.2 ± 3.6; 1-26.3</td>
<td>8.8 ± 4; 3-17.2</td>
<td>0.273</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*AF* new onset of atrial fibrillation after device implantation, *BMI* body mass index, *No of events* Number of events before PFO closure, *NS* not significant
# Prognostic Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>0.007</td>
<td>1.03</td>
<td>1.01-1.06</td>
</tr>
<tr>
<td>AF</td>
<td>0.036</td>
<td>2.3</td>
<td>1.1-5.0</td>
</tr>
<tr>
<td>Thrombus formation</td>
<td>0.000</td>
<td>6.8</td>
<td>2.4-19.3</td>
</tr>
<tr>
<td>No. of events</td>
<td>0.000</td>
<td>1.4</td>
<td>1.2-1.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.034</td>
<td>2.4</td>
<td>1.1-5.2</td>
</tr>
<tr>
<td>Sideris device</td>
<td>0.007</td>
<td>5.5</td>
<td>1.6-18.6</td>
</tr>
</tbody>
</table>

*AF* new onset of atrial fibrillation after device implantation  
*No. of events* Number of events before PFO closure
Conclusions

- The overall incidence of residual shunts after PFO closure was low.
- The majority of events occurred in patients without a residual shunt.
- Therefore the recurrent events usually have other causes.
- As expected, other risk factors develop during long term follow-up and may cause events.
Thank you!