Heinrich Mattle

Disclosures
Speaker’s and consulting honoraria in the past 3 years

Bayer, Biogen-Idec, BMS, Boehringer-Ingelheim, Boston Scientific, Covidien, Daiichi-Sankyo, Merck-Serono, Neuravi, Novartis, Pfizer, Research Council of Norway, Sanofi-Genzyme, Swissmedic, Teva
Paradoxical Embolism
„Caught in the act“: thrombus riding through PFO

First description of paradoxical embolism

Cohnheim 1877:
Necropsy study of a young woman with stroke and PFO
Lechat P et al, NEJM 1988; 318: 1148-52

PFO in cryptogenic stroke is more frequent than in stroke of known cause or in non-stroke controls

Potential stroke mechanisms in patients with PFO

- Paradoxical embolism of thrombus from the venous system
- Thromboembolism from the endocardial surface of the interatrial septum
- Paroxysmal atrial fibrillation
- Other than PFO-related

Courtesy of Dr. Cichon
PFO as incidental finding

Patent Foramen Ovale and Atrial Septum Aneurysm in TEE Studies

- Prevalence of PFO: 26%
- Prevalence of ASA: 4.6%

Homma S, Sacco RL, Circulation 2005; 112, 1063ff
Mas JL et al, NEJM 2001; 345, 1740 ff
Septal Abnormalities and Cerebrovascular Events
Prospective Population-based Study

- Stroke Prevention: Assessment in a Community (SPARC)
- 585 subjects, age > 45 years, follow-up 5.1 years
- PFO 140 (24%), ASA 11 (1.9%), ASA in PFO 6 (4.3%)
- death, stroke, TIA): 41

Hazard ratio (95% CI)

PFO (HR 1.46; CI 0.74-2.88)
ASA (HR 3.72; CI 0.88-15.71)

Meissner I et al., JACC 2006; 47: 440-5

PFO and the risk of stroke in a multiethnic population (NOMAS)

Di Tullio MR et al, JACC 2007; 49: 797-802

HR 1.64 (CI: 0.87 - 3.09)
PFO as incidental finding

No action required

PFO after TIA and stroke
Prevalence of PFO in cryptogenic stroke vs known cause of stroke

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Odds Ratio (OR)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 55 y</td>
<td>2.69</td>
<td>2.0-3.62</td>
</tr>
<tr>
<td>Age &lt; 55 y</td>
<td>5.77</td>
<td>3.65-9.13</td>
</tr>
</tbody>
</table>

Mattle H et al., Int J Stroke 2010; 5: 92-102

Evidence of Association of Septal Abnormalities and Stroke

is proved by
- case reports
- case control studies

but not (yet?) by
- population based studies
Risk of recurrent events in patients with cryptogenic stroke and PFO

Recurrent Strokes and Deaths
The French PFO-ASA-Study
Mas JL et al. NEJM 2001; 345: 1740-6

Free from Stroke or TIA (%)

ASA alone
No PFO or ASA
PFO alone
PFO and ASA

Hazard Ratio 4.17 (1.47-11.84)
Can PFO closure reduce the risk of recurrent events in patients with cryptogenic stroke and PFO?

1992

Introduction of catheter based PFO closure

Amplatzer PFO Occluder

- two flat, self-expandable retention discs interconnected by a short flexible waist
- PFO closure by passive counter-tension

10-Year Follow-up After PFO Closure

Propensity-Matched Cohorts

Stroke, TIA, or Peripheral Embolism

HR 0.43; 95% CI 0.20–0.94; P = 0.033

<table>
<thead>
<tr>
<th></th>
<th>Conservative</th>
<th>Device Closure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Years 0</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Years 5</td>
<td>78</td>
<td>94</td>
</tr>
<tr>
<td>Years 10</td>
<td>20</td>
<td>26</td>
</tr>
</tbody>
</table>

Wahl et al. Circulation 2012; 125: 803-12
Randomized Trials

- Closure
- Respect
- PC Trial
- Close (ongoing)
- Gore Reduce (ongoing)

Closure

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

HR, 0.78; 95% CI, 0.45-1.35; P = 0.37

No. at Risk
Closure 447 411 406 399 392 389 384 380 254
Medical therapy 462 421 405 388 378 365 359 356 242
Star Flex Septal Closure System

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Closure ns of patients/total no. (%)</th>
<th>Medical Therapy ns of patients/total no. (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall modified intention-to-treat population</td>
<td>22/400 (5.6)</td>
<td>29/453 (6.9)</td>
<td></td>
<td>0.78 (0.44-1.35)</td>
<td>0.37</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7/208 (3.4)</td>
<td>15/232 (6.9)</td>
<td></td>
<td>0.50 (0.20-1.22)</td>
<td>0.13</td>
</tr>
<tr>
<td>Female</td>
<td>15/192 (7.9)</td>
<td>14/219 (6.4)</td>
<td></td>
<td>1.13 (0.55-2.34)</td>
<td>0.74</td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15/249 (6.2)</td>
<td>20/293 (7.4)</td>
<td></td>
<td>0.81 (0.42-1.99)</td>
<td>0.55</td>
</tr>
<tr>
<td>Yes</td>
<td>7/151 (4.6)</td>
<td>9/160 (5.6)</td>
<td></td>
<td>0.78 (0.30-2.13)</td>
<td>0.64</td>
</tr>
<tr>
<td>Shunt size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or trace</td>
<td>8/118 (6.9)</td>
<td>10/155 (6.4)</td>
<td></td>
<td>0.99 (0.59-1.66)</td>
<td>0.99</td>
</tr>
<tr>
<td>Moderate</td>
<td>7/144 (5.0)</td>
<td>12/163 (7.4)</td>
<td></td>
<td>0.81 (0.34-1.55)</td>
<td>0.30</td>
</tr>
<tr>
<td>Substantial</td>
<td>3/87 (3.5)</td>
<td>3/85 (4.9)</td>
<td></td>
<td>0.72 (0.15-3.57)</td>
<td>0.69</td>
</tr>
<tr>
<td>Entry event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>15/300 (5.1)</td>
<td>15/324 (5.1)</td>
<td></td>
<td>1.01 (0.49-2.07)</td>
<td>0.98</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>7/200 (3.5)</td>
<td>14/128 (11.4)</td>
<td></td>
<td>0.60 (0.24-1.49)</td>
<td>0.27</td>
</tr>
<tr>
<td>Baseline medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0/13 (0)</td>
<td>2/38 (5.9)</td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>Aspirin alone</td>
<td>15/286 (5.3)</td>
<td>16/252 (6.7)</td>
<td></td>
<td>0.79 (0.39-1.60)</td>
<td>0.50</td>
</tr>
<tr>
<td>Warfarin alone</td>
<td>1/25 (4.2)</td>
<td>8/113 (7.1)</td>
<td></td>
<td>0.52 (0.06-4.12)</td>
<td>0.33</td>
</tr>
<tr>
<td>Aspirin plus warfarin</td>
<td>6/72 (8.3)</td>
<td>2/40 (5.4)</td>
<td></td>
<td>1.59 (0.32-7.89)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Closure Better Medical Therapy Better
Respect
Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

A Intention-to-Treat Cohort

Event-free Probability

Years to Event

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

Respect
Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

B As-Treated Cohort

Event-free Probability

Years to Event

Closure group (N=5)
Medical-therapy group (N=16)

Hazard ratio, 0.27 (95% CI, 0.10–0.75)
P=0.007 by log-rank test
Respect
Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

PC Trial
Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism
PC Trial
Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PFO Closure</th>
<th>Medical Therapy</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>7/204 (3.4)</td>
<td>11/210 (5.3)</td>
<td></td>
<td>0.63 (0.44–1.12)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>1/93 (1.1)</td>
<td>6/97 (6.2)</td>
<td></td>
<td>0.16 (0.02–1.34)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>6/111 (5.4)</td>
<td>5/113 (4.4)</td>
<td></td>
<td>1.22 (0.37–3.99)</td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
<td></td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Yes</td>
<td>4/47 (8.5)</td>
<td>2/51 (3.9)</td>
<td></td>
<td>2.09 (0.38–11.4)</td>
</tr>
<tr>
<td>No</td>
<td>3/107 (2.8)</td>
<td>3/118 (2.6)</td>
<td></td>
<td>0.12 (0.09–1.38)</td>
</tr>
<tr>
<td>Cardiovascular index event</td>
<td></td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>Stroke</td>
<td>5/165 (3.0)</td>
<td>8/163 (4.9)</td>
<td></td>
<td>0.58 (0.10–1.96)</td>
</tr>
<tr>
<td>Transient ischemic attack or pulmonary embolism</td>
<td>2/39 (5.1)</td>
<td>3/47 (6.4)</td>
<td></td>
<td>0.78 (0.13–4.66)</td>
</tr>
<tr>
<td>≥1 Previous cardiovascular event</td>
<td></td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Yes</td>
<td>2/78 (2.6)</td>
<td>6/79 (7.6)</td>
<td></td>
<td>0.28 (0.06–1.41)</td>
</tr>
<tr>
<td>No</td>
<td>5/128 (3.9)</td>
<td>5/131 (3.8)</td>
<td></td>
<td>0.99 (0.20–3.45)</td>
</tr>
</tbody>
</table>

Not all PFO occluding devices are equal
PFO – Closure vs. Medical Therapy
PC Trial and Respect (ITT Results)

<table>
<thead>
<tr>
<th>Trials</th>
<th>Closure</th>
<th>Medical</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPECT</td>
<td>9/499</td>
<td>16/481</td>
<td>0.49 (0.22, 1.11)</td>
</tr>
<tr>
<td>PC-Trial</td>
<td>1/204</td>
<td>5/210</td>
<td>0.20 (0.02, 1.72)</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.446)</td>
<td></td>
<td></td>
<td>0.44 (0.20, 0.94)</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Carroll JD et al, RESPECT, NEJM 2013; 368: 1092-100.
Meier B et al, PC-Trial, NEJM 2013; 368: 1083-91

Percutaneous Closure of PFO in Patients with Cryptogenic Embolism: A Network Meta-Analysis
Stortecky S et al, Eur Heart J 2015; 36: 120-8
**Percutaneous Closure of PFO in Patients with Cryptogenic Embolism: A Network Meta–Analysis**

Stortecky S et al, Eur Heart J 2015; 36: 120-8

- **Stroke**
  - AMP: 0.39 (0.17, 0.84)
  - GTT: 1.61 (0.44, 2.41)
  - HLX: 0.71 (0.17, 2.78)

- **Transient ischaemic attack**
  - AMP: 0.65 (0.31, 1.39)
  - STF: 1.15 (0.49, 2.87)
  - HLX: 1.22 (0.24, 6.55)

- **All-cause mortality**
  - AMP: 0.76 (0.25, 2.45)
  - STF: 0.67 (0.17, 2.55)
  - HLX: 0.90 (0.17, 4.53)

- **Atrial fibrillation**
  - AMP: 2.14 (1.00, 4.62)
  - STF: 7.87 (3.25, 19.83)
  - HLX: 1.33 (0.33, 4.50)

---

**Device Closure of PFO after Stroke: Meta-analysis of Individual Participant Data**


2303 cryptogenic stroke patients aged 18-60 years from Closure, Respect and PC Trial
- Primary composite outcome: stroke, TIA, death
- Recurrent ischemic stroke
- Secondary composite outcome: stroke, TIA, early death
Device Closure of PFO after Stroke: Meta-analysis of Individual Participant Data

ALL TRIALS

A. Composite Outcome (Ischemic Stroke/TIA/Death)  B. Recurrent Ischemic Stroke Outcome

Log Rank p = 0.0517

Log Rank p = 0.0407

DATA FROM TRIALS OF THE DISC OCCLUDER

C. Primary Composite Outcome (Ischemic Stroke/TIA/Death)  D. Recurrent Ischemic Stroke Outcome

Log Rank p = 0.0885

Log Rank p = 0.0103
Device Closure of PFO after Stroke:  
Meta-analysis of Individual Participant Data  

**Intention to treat analysis**

2303 cryptogenic stroke patients aged 18-60 years from Closure, Respect and PC Trial
- Primary composite outcome: stroke, TIA, death  
  - HR 0.69 (0.47–1.01), p = 0.0517
- Recurrent ischemic stroke  
  - HR: 0.58 (0.34–0.98), p = 0.0407
- Secondary composite outcome: stroke, TIA, early death  
  - HR 0.68 (0.46–1.00), p = 0.0488

Device Closure of PFO after Stroke:  
Meta-analysis of Individual Participant Data  

**As treated analysis**

2303 cryptogenic stroke patients aged 18-60 years from Closure, Respect and PC Trial
- Primary composite outcome: stroke, TIA, death  
  - HR 0.64 (0.43–0.95), p = 0.025
- Recurrent ischemic stroke  
  - HR: 0.53 (0.30–0.92), p = 0.023
- Secondary composite outcome: stroke, TIA, early death  
  - HR 0.63 (0.42–0.94), p = 0.022
Device Closure of PFO after Stroke:  
Meta-analysis of Individual Participant Data  

### Table 3: Composite Outcomes and Recurrent Ischemic Stroke (Intention-to-Treat Analyses)

<table>
<thead>
<tr>
<th>Outcome Rate</th>
<th>Log-Rank p Value</th>
<th>Cox PH Model</th>
<th>Covariate-Adjusted Cox PH Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device Closure</td>
<td>Medical Therapy</td>
<td>HR (95% CI), p Value</td>
</tr>
<tr>
<td>Primary composite outcome</td>
<td>1.5 (45/3,057)</td>
<td>2.3 (63/2,792)</td>
<td>0.0517</td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>0.7 (22/2,099)</td>
<td>1.3 (36/2,899)</td>
<td>0.0407</td>
</tr>
<tr>
<td>Secondary composite outcome (ischemic stroke, TIA, early death)</td>
<td>1.4 (43/3,057)</td>
<td>2.2 (65/2,792)</td>
<td>0.0488</td>
</tr>
</tbody>
</table>

**Analyses Limited to Disc Occluder Device Trials (i.e., RESPECT and PC Trial) (n = 1,394)**

<table>
<thead>
<tr>
<th>Outcome Rate</th>
<th>Log-Rank p Value</th>
<th>Cox PH Model</th>
<th>Covariate-Adjusted Cox PH Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device Closure</td>
<td>Medical Therapy</td>
<td>HR (95% CI), p Value</td>
</tr>
<tr>
<td>Primary composite outcome</td>
<td>1.0 (22/2,274)</td>
<td>1.6 (32/2,031)</td>
<td>0.0885</td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>0.4 (10/2,301)</td>
<td>1.1 (23/2,044)</td>
<td>0.0103</td>
</tr>
<tr>
<td>Secondary composite outcome (ischemic stroke, TIA, early death)</td>
<td>0.9 (20/2,274)</td>
<td>1.6 (32/2,031)</td>
<td>0.0451</td>
</tr>
</tbody>
</table>

Values are % per person-year (events/person-year) unless otherwise indicated.  *Adjusted for age, sex, race, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke, smoking status, index event (stroke versus TIA), hypermobile septum, and PFO short axis (large versus small). Adjusted HRs were estimated using Cox PH models combined from 10 multiply imputed datasets. In meta-analyses, source study was included in the model as a stratification term.

**CI = confidence interval; HR = hazard ratio. PH = proportional hazards; other abbreviations as in Table 1.**

---

Device Closure of PFO after Stroke:  
Meta-analysis of Individual Participant Data  

### Table 4: Composite Outcomes and Recurrent Stroke (As-Treated Analyses)

<table>
<thead>
<tr>
<th>Outcome Rate</th>
<th>Log-Rank p Value</th>
<th>Cox PH Model</th>
<th>Covariate-Adjusted Cox PH Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device Closure</td>
<td>Medical Therapy</td>
<td>HR (95% CI), p Value</td>
</tr>
<tr>
<td>Primary composite outcome</td>
<td>1.4 (40/2,948)</td>
<td>2.3 (66/2,877)</td>
<td>0.025</td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>0.6 (19/2,985)</td>
<td>1.3 (37/2,929)</td>
<td>0.023</td>
</tr>
<tr>
<td>Secondary composite outcome (ischemic stroke, TIA, early death)</td>
<td>1.3 (38/2,948)</td>
<td>2.2 (64/2,887)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

**Analyses Limited to Disc Occluder Device Trials (i.e., RESPECT and PC Trial) (n = 1,394)**

<table>
<thead>
<tr>
<th>Outcome Rate</th>
<th>Log-Rank p Value</th>
<th>Cox PH Model</th>
<th>Covariate-Adjusted Cox PH Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device Closure</td>
<td>Medical Therapy</td>
<td>HR (95% CI), p Value</td>
</tr>
<tr>
<td>Primary composite outcome</td>
<td>0.8 (18/2,207)</td>
<td>1.7 (34/2,063)</td>
<td>0.018</td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>0.3 (7/2,303)</td>
<td>1.2 (24/2,091)</td>
<td>0.001</td>
</tr>
<tr>
<td>Secondary composite outcome (ischemic stroke, TIA, early death)</td>
<td>0.7 (16/2,207)</td>
<td>1.7 (34/2,063)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Values are % per person-year (events/person-year) unless otherwise indicated.  *Adjusted for age, sex, race, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke, smoking status, index event (stroke versus TIA), hypermobile septum, and PFO short axis (large versus small). Adjusted hazard ratios estimated using Cox PH models combined from 10 multiply imputed datasets. In meta-analyses, source study was included in the model as a stratification term.

**Abbreviations as in Tables 1 and 3.**
Device Closure of PFO after Stroke: Meta-analysis of Individual Participant Data

Conclusion from randomized trials

Current data indicate that PFO closure after stroke with the Amplatzer device is effective and safe to protect from recurrent stroke

<table>
<thead>
<tr>
<th>TABLE 5 Safety Outcomes (As-Treated Analyses)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Analyses using data from all 3 trials (n = 2,281)</td>
</tr>
<tr>
<td>Device Closure</td>
</tr>
<tr>
<td>1,067</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Analyses limited to disc occluder device trials (n = 1,372)</td>
</tr>
<tr>
<td>Device Closure</td>
</tr>
<tr>
<td>663</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
</tbody>
</table>

Values are n or % per person-year (events/total person-years) unless otherwise indicated. *Unadjusted HRs and p values from Cox PH model; source study was included in the model as a stratification term. †See Table 3 for the
Practical questions

Are all PFOs in stroke patients pathogenic?
Is this PFO in this patient pathogenic or incidental?
What medical treatment is best?

More risk factors mean lesser probability that PFO is causal and important

PFO
Risk factors
- Age
- Hypertension
- Dyslipidemia
- Smoking
- Diabetes
- etc
The Risk of Paradoxical Embolism (RoPE) Study

David M Kent and David E Thaler

NINDS R01 NS062153-01

Tufts Medical Center

Goal of RoPE

- To build the largest data base of patients with cryptogenic stroke
- To answer clinical questions with adequate statistical power
**Component databases of RoPE**

<table>
<thead>
<tr>
<th>Database</th>
<th>Collaborator(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CODICIA</td>
<td>Joaquin Serena</td>
</tr>
<tr>
<td>French PFO/ASA</td>
<td>Jean-Louis Mas</td>
</tr>
<tr>
<td>APRIS</td>
<td>Marco DiTullio</td>
</tr>
<tr>
<td>Bern (published)</td>
<td>Krassen Nedeltchev, Marie-Luise Mono</td>
</tr>
<tr>
<td>Bern (unpublished)</td>
<td>Heinrich Mattle</td>
</tr>
<tr>
<td>PICSS</td>
<td>Shunichi Homma</td>
</tr>
<tr>
<td>Lausanne</td>
<td>Patrik Michel</td>
</tr>
<tr>
<td>Toronto</td>
<td>Cheryl Jaigobin</td>
</tr>
<tr>
<td>Sapienza</td>
<td>Emanuele Di Angelantonio, Federica Papetti</td>
</tr>
<tr>
<td>Tufts</td>
<td>David Thaler</td>
</tr>
<tr>
<td>German</td>
<td>Christian Weimar</td>
</tr>
<tr>
<td>NOMASS</td>
<td>Mitchell Elkind</td>
</tr>
</tbody>
</table>

**Pathogenic vs incidental PFOs**

- **Cryptogenic stroke**: PFO
- **No PFO**: PFO

**RoPE**
Pathogenic vs incidental PFOs

Neuroimaging Findings in Cryptogenic Stroke Patients With and Without Patent Foramen Ovale

David E. Thaler, MD, PhD; Robin Ruthazer, MPH; Emanuele Di Angelantonio, MD, MSc; Marco R. Di Tullio, MD; Jennifer S. Donovan, MS; Mitchell S.V. Elkind, MD, MS; John Griffith, PhD; Shumichi Homma, MD, FACC; Cheryl Jaquish, MD, FRCP, MSc; Jean-Louis Mas, MD; Heinrich P. Mattle, MD; Patrik Michel, MD; Marie-Luise Mono, MD; Krassen Nedeltchev, MD, FESC; Federica Papetti, MD; Joaquín Serena, MD, PhD; Christian Weimar, MD; David M. Kent, MD, CM, MSc

Background and Purpose—Patent foramen ovale (PFO) and cryptogenic stroke are commonly associated but some PFOs are incidental. Specific radiological findings associated with PFO may be more likely to indicate a PFO-related cause. We examined whether specific radiological findings are associated with PFO among subjects with cryptogenic stroke and known PFO status.

Methods—We analyzed the Risk of Paradoxical Embolism (RoPE) Study database of subjects with cryptogenic stroke and known PFO status, for associations between PFO and: (1) index stroke seen on imaging, (2) index stroke size, (3) index stroke location, (4) multiple index strokes, and (5) prior stroke on baseline imaging. We also compared imaging with purported high-risk echocardiographic features.

Results—Subjects (N=2680) were significantly more likely to have a PFO if their index stroke was large (odds ratio [OR], 1.36; P=0.0025), seen on index imaging (OR, 1.53; P=0.003), and superficially located (OR, 1.54; P<0.0001). A prior stroke on baseline imaging was associated with not having a PFO (OR, 0.66; P=0.0001). Finding multiple index strokes was unrelated to PFO status (OR, 1.21; P=0.161). No echocardiographic variables were related to PFO status.

Conclusions—This is the largest study to report the radiological characteristics of patients with cryptogenic stroke and known PFO status. Strokes that were large, radiologically apparent, superficially located, or unassociated with prior radiological infarcts were more likely to be PFO-associated than were unapparent, smaller, or deep strokes, and those accompanied by chronic infarcts. There was no association between PFO and multiple acute strokes nor between specific echocardiographic PFO features with neuroimaging findings. (Stroke. 2013;44:675-680.)
Neuroimaging Findings in Cryptogenic Stroke Patients With and Without Patent Foramen Ovale

Subjects (N=2680) were more likely to have a PFO if their index stroke was
• large (OR 1.36; P =0.0025) and
• superficially located (OR, 1.54; P <0.0001)

The ROPE Score

An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke.

Derived from the RoPE data base by statistical modelling
ROPE Score: An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke.


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
<th>RoPE Score</th>
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<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 previous 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>
<tr>
<td>Age (in years): 18-29</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Total score (sum of individual points, max. 10, min 0)

Increasing RoPE score
→ Increasing PFO prevalence, and
→ Increasing PFO attributable fraction

RoPE Study group, Kent D et al. Neurology 2013; 81: 619-25; graph provided by P Michel
Transesophageal Echocardiography in Cryptogenic Stroke and Patent Foramen Ovale
Analysis of Putative High-Risk Features From the Risk of Paradoxical Embolism Database

Benjamin S. Wesslen, MD; David E. Thaler, MD, PhD; Robin Ruthazer, MPH; Christian Weimar, MD; Marco R. Di Tullio, MD; Mitchell S.V. Elkind, MD, MS; Shunichi Homma, MD; Jennifer S. Lutz, MS; Jean-Louis Mas, MD; Heinrich P. Mattle, MD; Bernhard Meier, MD; Krassen Nedeltchev, MD; Federica Papetti, MD; Emanuele Di Angelantonio, MD, MSc, PhD; Mark Reisman, MD; Joaquin Serena, MD, PhD; David M. Kent, MD, CM, MSc

Background—Patent foramen ovale (PFO) is associated with cryptogenic stroke (CS), although the pathogenicity of a discovered PFO in the setting of CS is typically unclear. Transesophageal echocardiography features such as PFO size, associated hypermobile septum, and presence of a right-to-left shunt at rest have all been proposed as markers of risk. The association of these transesophageal echocardiography features with other markers of pathogenicity has not been examined.

Methods and Results—We used a recently derived score based on clinical and neuroimaging to stratify patients with PFO and CS by the probability that their stroke is PFO-attributable. We examined whether high-risk transesophageal echocardiography features are seen more frequently in patients more likely to have had a PFO-attributable stroke (n=637) compared with those less likely to have a PFO-attributable stroke (n=657). Large physiologic shunt size was not more frequently seen among those with probable PFO-attributable strokes (odds ratio [OR], 0.92; P=0.53). The presence of neither a hypermobile septum nor a right-to-left shunt at rest was detected more often in those with a probable PFO-attributable stroke (OR, 0.80; P=0.45; OR, 1.15; P=0.11, respectively).

Conclusions—We found no evidence that the proposed transesophageal echocardiography risk markers of large PFO size, hypermobile septum, and presence of right-to-left shunt at rest are associated with clinical features suggesting that a CS is PFO-attributable. Additional tools to describe PFOs may be useful in helping to determine whether an observed PFO is incidental or pathogenically related to CS. (Circ Cardiovasc Imaging, 2014;7;125-131.)
Transesophageal Echocardiography in Cryptogenic Stroke and PFO. Analysis of Putative High-Risk Features From the RoPE Database

TEE markers such as
- large PFO size,
- hypermobile septum,
- right-to-left shunt at rest
are not associated with clinical features (ROPE score) suggesting that a cryptogenic stroke is attributable to PFO

Probability that a „cryptogenic“ stroke is not related to a detected PFO

= 1 : Odds Ratio

Age < 55 y (OR 5.77; CI 3.65-9.13)  1 : 5.77 = 17%
Age > 55 y (OR 2.69; CI 2.0-3.62)  1 : 2.69 = 37%

Mattle, Meier, Nedeltchev, Int J Stroke 2010; 5: 92-102
Recurrent stroke after „cryptogenic“ stroke may be unrelated to PFO

- 159 patients with „cryptogenic“ TIA or stroke and PFO
- Mean follow-up 8.1 years
- 1.3% annual recurrence for stroke
- 3.5% for stroke and TIA
- For 12 recurrent events (39%) concurrent etiologies found
- 19 recurrent events (61%) cryptogenic

Mono ML et al, Stroke 2011; 42: 2891-5

Conclusion

Medical treatment should not be stopped after device closure
Anticoagulation vs Antiplatelet Therapy in Patients with Cryptogenic Stroke and PFO: An Adjusted Individual Patient Data and RoPE Score Stratified Meta-Analysis.

**TAcTiCS-PFO**

Adj. Hazard Ratio  
95% CI

- Stroke (HR 0.75; CI 0.44-1.27)
- Stroke, TIA, death (HR 0.76; CI 0.52-1.12)


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Ongoing PFO research
Ongoing RCT on PFO closure vs medical therapy

- RESPECT 5 year FU
  - Increasing benefit of closure with longer FU reported, to be published
- CLOSE
  - 664 pts randomized,
  - Results expected in early 2017
- GORE REDUCE
  - 664 pts randomized
  - Results expected in early 2017
Summary

- PFO is associated with stroke
- Stroke recurrence because of PFO is low
- The RoPE Score helps to identify pathogenic PFOs
- PFO closure with the Amplatzer device is effective to prevent recurrent stroke
- Medical treatment should not be stopped after PFO closure
- Antiplatelet agents and anticoagulants equally effective for secondary prevention in PFO

Conclusions on PFO-Closure

<table>
<thead>
<tr>
<th>PFO as / in</th>
<th>Medical treatment</th>
<th>Device closure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidental finding</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cryptogenic stroke</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Stroke with concurrent etiology</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Stroke and many risk factors / PFO ± ASA</td>
<td>Yes</td>
<td>Use RoPE Score for decision</td>
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</table>