PFO Closure is a Therapy for Migraine PRO

Andrew Charles, M.D.
Professor
Director, UCLA Goldberg Migraine Program
Meyer and Renee Luskin Chair in Migraine and Headache Studies
Director, Headache Research and Treatment Program
David Geffen School of Medicine at UCLA
Disclosures

- Amgen – Consultant for educational material
- Eli Lilly – Global scientific advisory board
- eNeura – Medical Advisory Board
- St. Jude Medical – Clinical trial steering committee
- Takeda Pharmaceuticals – Grant support for laboratory research
PFO and Migraine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

### 1.3.1 Unadjusted relative risk of migraine with/without aura

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anoja 1999 [5]</td>
<td>5.2%</td>
<td>2.64</td>
<td>(0.94, 7.18)</td>
</tr>
<tr>
<td>Calviere 2013 [4]</td>
<td>5.7%</td>
<td>2.24</td>
<td>(0.96, 5.29)</td>
</tr>
<tr>
<td>Carlo-Attal 2006 [6]</td>
<td>6.7%</td>
<td>2.08</td>
<td>(1.37, 3.10)</td>
</tr>
<tr>
<td>Dalila Volla 2005 [7]</td>
<td>6.1%</td>
<td>1.80</td>
<td>(0.92, 3.68)</td>
</tr>
<tr>
<td>Domizio 2007 [8]</td>
<td>6.2%</td>
<td>2.01</td>
<td>(1.03, 3.94)</td>
</tr>
<tr>
<td>Domizio 2014 [10]</td>
<td>6.0%</td>
<td>2.04</td>
<td>(0.97, 4.27)</td>
</tr>
<tr>
<td>Garg 2010 [2]</td>
<td>6.5%</td>
<td>1.04</td>
<td>(0.51, 1.76)</td>
</tr>
<tr>
<td>Gu 2014 [12]</td>
<td>6.3%</td>
<td>1.28</td>
<td>(0.65, 2.52)</td>
</tr>
<tr>
<td>Khessabi 2012 [13]</td>
<td>6.3%</td>
<td>43.09</td>
<td>(23.35, 79.55)</td>
</tr>
<tr>
<td>Kinnisde z 2007 [20]</td>
<td>5.7%</td>
<td>3.86</td>
<td>(1.67, 8.95)</td>
</tr>
<tr>
<td>Küper 2013 [14]</td>
<td>6.0%</td>
<td>0.92</td>
<td>(0.43, 1.97)</td>
</tr>
<tr>
<td>Lamy (PFO-ASA) 2002 [21]</td>
<td>6.7%</td>
<td>2.33</td>
<td>(1.52, 3.50)</td>
</tr>
<tr>
<td>Lautz 2013 [15]</td>
<td>4.6%</td>
<td>6.31</td>
<td>(1.76, 22.33)</td>
</tr>
<tr>
<td>Rundek (NOMAS) 2008 [3]</td>
<td>6.8%</td>
<td>0.97</td>
<td>(0.63, 1.53)</td>
</tr>
<tr>
<td>Strakz 2002 [21]</td>
<td>5.5%</td>
<td>1.82</td>
<td>(0.71, 4.65)</td>
</tr>
<tr>
<td>Talinde 2007 [18]</td>
<td>5.2%</td>
<td>3.92</td>
<td>(1.16, 11.26)</td>
</tr>
<tr>
<td>Wiltshire 2006 [19]</td>
<td>4.9%</td>
<td>3.60</td>
<td>(1.12, 11.51)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>100.0%</td>
<td>2.46</td>
<td>(1.55, 3.91)</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.78; Chi² = 125.24, df = 16 (P < 0.0001); I² = 87%
Test for overall effect: Z = 3.83 (P = 0.0001)

### 1.3.2 Adjusted relative risk of migraine with/without aura

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calviere 2013 [4]</td>
<td>14.0%</td>
<td>2.20</td>
<td>(0.96, 5.40)</td>
</tr>
<tr>
<td>Carlo-Attal 2006 [6]</td>
<td>10.6%</td>
<td>3.14</td>
<td>(1.02, 9.69)</td>
</tr>
<tr>
<td>Garg 2010 [2]</td>
<td>14.4%</td>
<td>1.67</td>
<td>(0.70, 4.09)</td>
</tr>
<tr>
<td>Lamy (PFO-ASA) 2002 [21]</td>
<td>23.1%</td>
<td>1.75</td>
<td>(1.08, 2.82)</td>
</tr>
<tr>
<td>Milhous 2003 [16]</td>
<td>14.6%</td>
<td>4.73</td>
<td>(2.00, 11.29)</td>
</tr>
<tr>
<td>Rundek (NOMAS) 2008 [3]</td>
<td>23.3%</td>
<td>1.01</td>
<td>(0.63, 1.63)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>100.0%</td>
<td>1.94</td>
<td>(1.24, 3.05)</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.17; Chi² = 11.69, df = 5 (P = 0.04); I² = 57%
Test for overall effect: Z = 2.88 (P = 0.004)

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**PFO-Migraine Odds Ratios**

- **Migraine with aura**: 3.4 (p < 0.00001)
- **Migraine with or without aura**: 2.5 (p = 0.0001)
- **Migraine without aura**: 1.3 (no statistical significance)

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Original article

A meta-analysis of case-control studies of the association of migraine and patent foramen ovale

Hisato Takagi (MD, PhD), Takuya Umemoto (MD, PhD), for the ALICE (All-Literature Investigation of Cardiovascular Evidence) Group

Department of Cardiovascular Surgery, Shinshu Medical Center, Shinshu, Japan

*Journal of Cardiology* 67 (2016) 493–503
Other Right to Left Shunt and Migraine

Migraine also associated with atrial septal defects (both before and after closure), and pulmonary arteriovenous malformations (e.g. hereditary hemorrhagic telangiectasia)


Possible Mechanisms?

Microemboli evoke cortical spreading depression in rodents – right to left shunt could act as a source of microemboli to brain

Hypoxia evokes migraine in humans – transient bursts of deoxygenated blood reaching brain could act as a migraine trigger


Other Evidence

- Intravenous injection of agitated saline in patients with PFO can evoke a migraine
- Intravenous injection of CT contrast in patients with pulmonary arteriovenous malformations can evoke a migraine


The “MIST” Study

- Failed primary primary endpoint of complete headache remission
- Failed to meet secondary endpoints
The “PREMIUM” study

Trial of the AMPLATZER™ occluder for the preventive treatment of migraine with or without aura

Multi-center – 29 sites in United States

Randomized, sham procedure controlled – all patients received femoral puncture, catheterization to confirm diagnosis of PFO, and intracardiac echo.

Double blind – patient and neurologist blinded
- Blinding steps taken during procedure
- Neurologist unable to access procedure note
- Blinding assessed by survey
Study Design

- Initial screening visit to evaluate historical criteria
- Transcranial doppler with agitated saline to evaluate for right to left shunt (RLS)
- Transthoracic echo with bubble study to verify RLS and no other pathology.
- 60 day baseline diary recording
- Re-screening to evaluate inclusion/exclusion criteria following baseline period
- If criteria met, randomization during catheterization
- Diary recording and neurology visits for subsequent 12 months
- Clopidogrel 75 mg. for 1 month, aspirin 325 for 6 mo.
Inclusion Criteria

- Diagnosis of migraine with and/or without aura, using the ICHD2 Criteria
- Presence of a PFO using Transcranial Doppler with a significant shunt defined as ≥ grade 4 on Valsalva.
- Transthoracic echocardiogram with positive bubble study to confirm shunt
- Subjects refractory to commonly accepted preventive medication trials. Must have failed a trial of at least 3 medications, where 2 must be of different types from a-f below:
  - a. B blockers
  - b. Tricyclic antidepressants
  - c. Verapamil or flunarizine
  - d. Sodium Valproate (or divalproex sodium)
  - e. Topiramate
  - f. Combination Therapy that includes at least one drug of type a-e; the second drug can be from any type (a-e or g-j).
  - g. All other anticonvulsants
  - h. Other treatments with at least one positive randomized controlled trial
  - i. Nonsteroidal anti-inflammatory drugs
  - j. Metabolic enhancers (B2 or CoQ10)
- Subject’s daily preventive headache medications have remained at a stable dose for the 4 weeks preceding the distribution of the 60-day baseline headache diary as documented in the subject’s medical record. Preventive medications and their dosage not changed until after the 12 month follow up visit.
Randomization Criteria

- An average of \( \geq 6 \) migraine headache days and \( \leq 14 \) total headache days for each 30 day period during a 60 day baseline phase.
- Daily preventive headache medications have remained at a stable dose during the 60 day baseline phase.
- Acute medication use has not exceeded an average of 14 days per each 30 day period during the 60-day baseline phase independent of the indication for use except for the use of aspirin, acetaminophen or ibuprofen alone.
- MIDAS score of 11 or greater at the time of final diary review.
- HA diary compliance at 80%.
Primary Efficacy and Safety Endpoints

**Efficacy** - Responder rate, defined as a 50% reduction from the monthly number of migraine attacks during the 60-day baseline phase to the monthly number of migraine attacks during month ten through the twelfth month in the treatment phase (device group versus sham group).

**Safety** - Proportion of subjects who experience a device-related major adverse event (DRMAE) through 12 months of follow-up.
Migraine-Related Secondary Efficacy Endpoints

- Change in the mean number of migraine days across treatment phase as compared to the mean number of migraine days across baseline phase (device group versus sham group) at 12 months.
- Change in MIDAS score from baseline to 12 months (device group versus sham group).
- Subjects experiencing 75%, 95% or greater reduction in migraine headache attacks during treatment phase as compared to baseline phase (device group versus sham group).
- Improvement in quality of life as assessed by the SF-12 V2 Quality of Life Questionnaire.
- Improvement in the depression scale as assessed by BECK Depression Inventory.
PREMIUM Study

Patients Consented N=1653

Subjects Enrolled for Randomization N=230

Not Enrolled N=1423

Intracardiac echo and cath-lab PFO assessment

Randomization

PFO Closure N=123

Medical Management N=107

Device Implanted N=119

Medical Management N=107

Completed 12-mo F/U N=116

Completed 12-mo F/U N=103

Optional PFO Closure after 1 year N=87

69% - Did not meet TCD shunt criteria
5% - Did not meet headache criteria upon baseline diary review
2% - withdrew consent during screening phase
24% - Did not meet other I/E criteria*

Clopidogrel 1 month
ASA 6 months

* - Did not meet other I/E criteria
<table>
<thead>
<tr>
<th>Variable</th>
<th>PFO Closure</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>42.75 ± 10.27 (123) [20.18, 63.61]</td>
<td>43.72 ± 10.16 (107) [22.02, 64.11]</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (10.57%)</td>
<td>12 (11.21%)</td>
</tr>
<tr>
<td>Female</td>
<td>110 (89.43%)</td>
<td>95 (88.79%)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>26.69 ± 5.34 (123) [16.60, 38.70]</td>
<td>25.79 ± 5.33 (107) [16.60, 38.92]</td>
</tr>
<tr>
<td><strong>ICHD Classification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>80 (65.04%)</td>
<td>71 (66.36%)</td>
</tr>
<tr>
<td>Migraine w/o aura</td>
<td>102 (82.93%)</td>
<td>83 (77.57%)</td>
</tr>
<tr>
<td>Migraine both</td>
<td>58 (47.15%)</td>
<td>47 (43.93%)</td>
</tr>
<tr>
<td><strong>MIDAS Score</strong></td>
<td>45.72 ± 27.85 (123) [11, 155]</td>
<td>48.76 ± 33.04 (107) [12, 160]</td>
</tr>
<tr>
<td><strong>BDI Score</strong></td>
<td>7.15 ± 7.51 (122) [0.00, 35.00]</td>
<td>6.64 ± 7.69 (106) [0.00, 38.00]</td>
</tr>
<tr>
<td><strong>Atrial Septal Aneurysm</strong></td>
<td>28 (22.76%)</td>
<td>19 (17.76%)</td>
</tr>
<tr>
<td><strong>Device Size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implanted 18 mm</td>
<td>20 (16.81%)</td>
<td>94 (78.99%)</td>
</tr>
<tr>
<td>25 mm</td>
<td>5 (4.20%)</td>
<td></td>
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</tbody>
</table>
Primary Efficacy Endpoint
50% attack reduction

Did not meet primary efficacy endpoint
Met secondary efficacy endpoint of reduction in mean migraine days per month
## Change in Mean Headache Days/Month

<table>
<thead>
<tr>
<th>Visit Interval</th>
<th>Device</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline - 1st 30 days</td>
<td>10.55 ± 2.85 (123) (5, 24)</td>
<td>10.14 ± 2.6 (107) (5, 16)</td>
</tr>
<tr>
<td>Baseline - 2nd 30 days</td>
<td>10.5 ± 2.85 (103) (4, 18)</td>
<td>9.89 ± 2.38 (90) (5, 15)</td>
</tr>
<tr>
<td>Baseline - 60-day mean</td>
<td>10.61 ± 2.51 (123) (6, 24)</td>
<td>10.09 ± 2.17 (107) (6, 15)</td>
</tr>
<tr>
<td>10 Month</td>
<td>7.47 ± 5.58 (114) (0, 27)</td>
<td>7.9 ± 6 (101) (0, 30)</td>
</tr>
<tr>
<td>11 Month</td>
<td>7.02 ± 5.5 (115) (0, 27)</td>
<td>7.94 ± 5.55 (102) (0, 30)</td>
</tr>
<tr>
<td>12 Month</td>
<td>7.3 ± 5.01 (115) (0, 27)</td>
<td>8.09 ± 5.34 (102) (0, 27)</td>
</tr>
<tr>
<td>Final 90-day mean (months 10-12)</td>
<td>7.24 ± 4.9 (116) (0, 27)</td>
<td>7.99 ± 5.15 (103) (0, 26.67)</td>
</tr>
</tbody>
</table>
Safety Endpoints

- **Primary**: Device related serious adverse events
  - 1/202 (including randomized and optional closure): Transient atrial fibrillation after device placement.

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5% (1/202)</td>
<td>0.01% - 2.73%</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

- **Secondary**: Procedure related SAEs
  - Hypotension
  - Paroxysmal Supraventricular Tachycardia
  - Phlebitis
  - Vascular Hematoma
  - Vascular Pain
  - Vasovagal response
Successful PFO Closure (grade 2 or less residual shunt at 12 months assessed by TCD)

<table>
<thead>
<tr>
<th>Closure definition</th>
<th>Successful Closure</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCD Grade $\leq 2$ at valsalva</td>
<td>86/104 (82.7%)</td>
<td>0.74-.089</td>
</tr>
</tbody>
</table>

Closure adjudicated by independent core lab
Additional Analysis: Responder Rate for Subjects In Whom Majority of Attacks were With Aura

19/39

9/40

P=.015
Additional Analysis: Complete Remission of Migraine

![Graph showing % Complete Headache Remission for Device and Control groups. The Device group shows 10/117 complete remissions, while the Control group shows 1/103. The statistical significance is P=.01.](image)
“PRIMA” STUDY

- Exclusively migraine with aura, smaller study
- Unblinded, no sham control
- Primary endpoint of reduction in migraine days *not met*
- Secondary endpoint of responder rate was met
- Secondary endpoints of reduction in migraine with aura days and attacks were met
- 10% of patients in closure group and none in control group had complete remission
SUMMARY

- There is significant evidence supporting an association between migraine with aura and right to left shunt (either cardiac or pulmonary).
- In animal models, microemboli can evoke spreading depression.
- In humans, IV administration of agitated saline or contrast to patients with right to left shunt can evoke migraine.
- 3 different studies of PFO Closure did not meet primary endpoints.
  HOWEVER, in two randomized controlled studies (PRIMA and PREMIUM) exploratory evaluation of secondary endpoints suggests efficacy for patients in whom aura occurs with the majority of attacks.
- There is a small but significant subset of patients (particularly those with frequent aura) for whom PFO closure may be highly effective.
Conclusions

- PFO closure could possibly be indicated in a subset of migraine patients
  - Patients with aura with the majority of their attacks who fail other migraine preventive therapies
  - Patients with cryptogenic stroke

Even if PFO closure is not indicated for all migraine, the link between right to left shunt and migraine may have something important to tell us about migraine pathophysiology