Percutaneous Closure of Patent Foramen Ovale in Migraine with Aura

PRIMA


On Behalf of the PRIMA Investigators
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

**Affiliation/Financial Relationship**
- Grant/Research Support
- Consulting Fees/Honoraria

**Company**
- St. Jude Medical
Migraine and PFO - Background

- Migraine is common
  - estimated prevalence of 8% to 13%
  - ~55 million people across USA and Europe

- PFO closure associated with high rate of resolution of incidental migraine

- Hypothesis of right-to-left shunting of chemical or physical triggers for migraine
MIST
(Migraine Intervention with Starflex)
MIST

• Failed to meet primary endpoint
• Secondary endpoints: promising trends
  • Migraine frequency
  • Migraine severity
PRIMA

• Purpose
  • To evaluate whether percutaneous PFO closure is effective in reducing migraine headache in patients who have migraine with aura refractory to medical treatment
PRIMA

• Design
  • Multicenter: 20 sites
    • Canada, Germany, Switzerland, United Kingdom
  • Prospective, Randomized, “Open label”
  • Closure Group
    • Amplatzer PFO Occluder implantation
    • 3 months clopidogrel; 6 months aspirin
  • Medical Group
    • Continuation of current medication
    • 3 months clopidogrel; 6 months aspirin
PRIMA

• Sample Size
  • Reduction in migraine days
    • 50% closure group
    • 25% medical group
  • Planned 144 subjects

• Sponsor
  • St. Jude Medical, St. Paul, MN
  • Study initiated under AGA Medical, Plymouth, MN
Study Governance and Organization

**Steering Committee**
- Werner Becker, MD, University of Calgary-Foothills Hospital
- Stefan Evers, MD, University Hospital, Muenster
- David Hildick-Smith, MD, Brighton and Sussex University Hospitals
- Heinrich Mattle, MD, Bern University Hospital
- Bernhard Meier, MD, Bern University Hospital

**Clinical Endpoint Committee**
- James R. Couch, MD, PhD, University of Oklahoma Health Sciences Center
- Lawrence D. Robbins, MD, Robbinsville Headache Clinic

**Data Safety Monitoring Board**
- Felix Berger, MD, German Heart Center, Berlin
- Marek Jauss, MD, OEHK Hospital, Muehlhausen / Thueringen
- Volker Limmroth, MD, Merheim Hospital, Cologne
- Frederick Taylor, MD, Park Nicollet Headache Clinic and Research Center
- Marc Schwartz, Biostatistician

**Echo Core Lab**
- Victor Davila-Roman, MD, CVR Consulting, PC
Sites involved in PRIMA

St. Mary’s Hospital
London, United Kingdom
J. Chataway, I. Malik

University Hospital of Muenster
Muenster, Germany
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Davisville Medical Center
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D. Hildick-Smith, A Romi Saha

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H. Mattle, B. Meier

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L. Bruch, I. Schmehl

Quebec Heart and Lung Institute/Laval University
Quebec City, Canada
J. Rodés-Cabau, D. Rivest

Martin Luther University Halle-Wittenberg
Halle, Germany
S. Gielan, S. Zierz
Inclusion criteria

- Migraine headache with aura
- Migraine onset before age 50
- > 3 migraine attacks or 5 migraine days per month
- < 14 headache days per month
- Failed >=2 commonly accepted migraine medications
- Preventative migraine medications stable for 4 weeks prior to and during screening
- Right-to-left shunt documented by TTE or TCD
- PFO documented by TEE
Exclusion criteria

- Patient age <18 years or >65 years
- Medication overuse (defined by IHS criteria)
- Contraindication to aspirin and/or clopidogrel
- Clinical indication for aspirin/clopidogrel/warfarin
- Severe nickel allergy
Study endpoints

- Primary Endpoint
  - Reduction in migraine days 1 year after randomization
    - Mean number of migraine days in months 10-12, subtracted from...
    - Mean number of migraine days in months “-3” to 0 (3 months roll-in)
Study endpoints

Secondary Endpoints
- Change in responder rate
  - (≥50% reduction in number of migraine days)
- Change in the number of monthly migraine attacks
- Change in use of acute migraine medications
- Change in MIDAS score
- Quality of life measures
- Beck Depression Inventory Score
- Effects of antiplatelet medication during study
- Completeness of PFO closure at 12 months
Screening Visit 1

Neurologist
- Consent
- Inclusion/exclusion criteria
- Compliance with possible PFO closure
- Compliance with headache diaries
Cardiologist
• TTE or TCD to demonstrate presence/absence of R to L shunt
• TEE to confirm presence/absence of PFO
Screening Visit 2 and 3

Neurologist
- Headache diary review
- Medication review
- MIDAS
- Depression inventory
- QOL
Randomization
Device Arm (Closure)
Both Groups
Patient Flow

Patients Consented (n = 705)

Subjects Enrolled
N = 107

Randomized to Medical Group
N = 54

Subjects Enrolled
N = 107

Randomized to Closure Group
N = 53

45 agreed to have device implantation

Device Implanted
N = 41

Randomized to Medical Group
N = 54

Medical Management
N = 54

Completed 12-Month Follow Up
N = 43

Completed 12-Month Follow Up
N = 40

Not Enrolled
N = 598

Screening Failure
N
Right-to-left shunt not demonstrated
303
PFO not confirmed
73
Subject not willing to consent
37
Responsive to preventative medication
36
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Closure</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=53, n (%)</td>
<td>N=54, n (%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>44 ± 11</td>
<td>43 ± 11</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>45 (85%)</td>
<td>45 (83%)</td>
</tr>
<tr>
<td><strong>Mood disorder</strong></td>
<td>1 (2%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>4 (8%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td><strong>Arrhythmia</strong></td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Transient ischemic attack (TIA)</strong></td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Unresponsive to two medications</strong></td>
<td>52 (98%)</td>
<td>53 (98%)</td>
</tr>
<tr>
<td><strong>IHS classification - migraine with aura</strong></td>
<td>53 (100%)</td>
<td>53 (98%)</td>
</tr>
<tr>
<td><strong>Majority of migraines with aura</strong></td>
<td>28 (55%)</td>
<td>30 (58%)</td>
</tr>
</tbody>
</table>
RESULTS
## Primary Endpoint
### Reduction in Migraine Days

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean Days at Baseline</th>
<th>Mean Days at Months 10-12</th>
<th>Mean Reduction</th>
<th>Std Deviation (Min, Max)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Closure</strong></td>
<td>40</td>
<td>8.0</td>
<td>5.1</td>
<td>-2.9</td>
<td>4.7 (-11.7, 9.0)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td>41</td>
<td>8.3</td>
<td>6.5</td>
<td>-1.7</td>
<td>2.4 (-6.3, 3.5)</td>
<td></td>
</tr>
</tbody>
</table>
Secondary Endpoint
Reduction in Migraine with Aura Days

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean at Baseline</th>
<th>Mean at Months 10-12</th>
<th>Mean Reduction</th>
<th>Std Deviation (Min, Max)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closure</td>
<td>40</td>
<td>4.1</td>
<td>1.7</td>
<td>-2.4</td>
<td>3.6 (-9.7, 7.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Medical</td>
<td>40</td>
<td>4.0</td>
<td>3.4</td>
<td>-0.6</td>
<td>2.7 (-9.1, 5.5)</td>
<td></td>
</tr>
</tbody>
</table>

-6 -5 -4 -3 -2 -1 0

Mean Reduction in Migraine with Aura Days 1 year after randomization
## Secondary Endpoint
Reduction in Migraine with Aura Attacks

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean at Baseline</th>
<th>Mean at Months 10-12</th>
<th>Mean Reduction</th>
<th>Std Deviation (Min, Max)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Closure</strong></td>
<td>40</td>
<td>3.0</td>
<td>1.0</td>
<td><strong>-2.0</strong></td>
<td>2.0 (-7.16, 1.00)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td>40</td>
<td>2.8</td>
<td>2.3</td>
<td><strong>-0.5</strong></td>
<td>1.5 (-3.3, 3.4)</td>
<td></td>
</tr>
</tbody>
</table>
### Secondary Endpoint

**Effect of aspirin and clopidogrel on headache days**

<table>
<thead>
<tr>
<th>Antiplatelet treatment</th>
<th>Mean at Baseline</th>
<th>Mean at Months 1-3</th>
<th>Mean at Months 4-6</th>
<th>Mean at Months 10-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closure</td>
<td>None</td>
<td>Aspirin</td>
<td>Aspirin</td>
<td>None</td>
</tr>
<tr>
<td>Medical</td>
<td>9.2</td>
<td>6.7</td>
<td>5.8</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>9.4</td>
<td>7.7</td>
<td>8.2</td>
<td>7.5</td>
</tr>
</tbody>
</table>
## Secondary Endpoint
### Responder Rate

<table>
<thead>
<tr>
<th></th>
<th>Responder</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Closure</strong></td>
<td>15 (37.5%)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td>6 (14.6%)</td>
<td></td>
</tr>
</tbody>
</table>
## Secondary Endpoint

**Freedom from Migraine**

<table>
<thead>
<tr>
<th></th>
<th>Freedom from Migraine</th>
<th>Freedom from Migraine with Aura</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Closure</strong></td>
<td>4 (10%)</td>
<td>16 (40%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td>0 (0%)</td>
<td>4 (10%)</td>
<td></td>
</tr>
</tbody>
</table>
Adverse Events

• Closure group:
  • Major vascular complication with bleeding (n=1)
  • Atrial fibrillation requiring DC cardioversion (n=1)

• Medical group:
  • none
Limitations

- High screen-to-recruitment ratio
- Long recruitment phase
- Patients not blinded to allocation
- High dropout post-randomization
- Failure to undergo randomized treatment
- Early termination
CONCLUSIONS

• Interventional studies in migraine/aura patients are difficult to do
• 40% of patients in PRIMA had a R to L shunt
• PFO closure is safe in these patients
• PFO closure did not reduce total migraine days significantly compared to medical therapy
CONCLUSIONS

• Migraine with aura days significantly reduced
• 40% of device closure patients had headache burden reduced by ≥50%
• 10% of closure patients became migraine free
• 40% of closure patients became free of migraine with aura
CONCLUSIONS

• There remains an intriguing relationship between PFO, PFO closure, migraine and migraine with aura

• This relationship is unequivocal

• Real and tangible benefit accrues to some migraine patients after PFO closure

• Results of PREMIUM are awaited with interest