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# Percutaneous Closure of Patent Foramen Ovale for the Treatment of Refractory Migraine Headaches

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# Percutaneous Closure of Patent Foramen Ovale for the Treatment of Refractory Migraine Headaches

## **Abstract**

**Background:** Migraine headaches both with and without aura vary in frequency, duration and intensity, affecting the quality of life of up to 10% of the total population. Migraines are treated with both prophylactic and acute medications. Patent foramen ovale (PFO) is one likely cause of migraine headaches and this is present in up to 25% of the total population. Percutaneous PFO closure is a likely option for definitive treatment for migraine. Once proven refractory to medical treatment, do patients with PFO and migraine respond to percutaneous PFO closure to reduce the frequency, duration and intensity of migraine headaches?

**Methods:** An exhaustive search of available medical literature was conducted using Medline/Ovid, CINAHL and Evidence-Based Medicine Reviews Multifile using the keywords: patent foramen ovale, migraine disorders, therapeutics and refractory. Inclusion criteria consisted of participants with a known patent foramen ovale and migraine headaches refractory to medical treatment, as well as studies performing percutaneous PFO closure measuring cessation or reduction in frequency, duration and intensity of migraine headaches. All articles were assessed for quality using GRADE.

**Results:** One randomized controlled trial, three prospective observational studies and one retrospective observational study fit the inclusion criteria. All observational studies demonstrated resolution of migraine with aura along with improved migraine symptomology in MIDAS score, frequency, duration and intensity of migraines. However the only randomized controlled trial (RCT) to date demonstrated no resolution of migraine headaches after six months. No other endpoints were measured such as frequency, duration or intensity. Many complications, both minor and serious, resulted in this RCT. After GRADE assessment, the RCT was determined to be high validity and all observational studies very low validity.

**Conclusion:** Four observational studies show some benefit to percutaneous PFO closure as treatment for refractory migraine headaches. However, one randomized controlled trial shows no benefit, unable to meet its endpoints. At this time, a recommendation cannot be made for percutaneous PFO closure in patients with refractory migraine headaches until further RCTs are performed and improvements are made in future studies.

## **Degree Type**

Capstone Project

## **Degree Name**

Master of Science in Physician Assistant Studies

## **Keywords**

patent foramen ovale, migraine disorders, therapeutics, refractory

## **Subject Categories**

Medicine and Health Sciences

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**Percutaneous Closure of Patent Foramen Ovale for the Treatment of  
Refractory Migraine Headaches**

Kristina Anderson



A Clinical Graduate Project Submitted to the Faculty of the  
School of Physician Assistant Studies  
Pacific University  
Hillsboro, OR

For the Masters of Science Degree, August 10, 2012  
Faculty Advisor: James Ferguson

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# Biography

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[Redacted for privacy]

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# Abstract

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**Background:** Migraine headaches both with and without aura vary in frequency, duration and intensity, affecting the quality of life of up to 10% of the total population. Migraines are treated with both prophylactic and acute medications. Patent foramen ovale (PFO) is one likely cause of migraine headaches and this is present in up to 25% of the total population. Percutaneous PFO closure is a likely option for definitive treatment for migraine. Once proven refractory to medical treatment, do patients with PFO and migraine respond to percutaneous PFO closure to reduce the frequency, duration and intensity of migraine headaches?

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**Conclusion:** Four observational studies show some benefit to percutaneous PFO closure as treatment for refractory migraine headaches. However, one randomized controlled trial shows no benefit, unable to meet its endpoints. At this time, a recommendation cannot be made for percutaneous PFO closure in patients with refractory migraine headaches until further RCTs are performed and improvements are made in future studies.

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# Table of Contents

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Biography .....	2
Abstract .....	3
Table of Contents .....	4
List of Tables .....	5
List of Abbreviations .....	5
Background .....	6
Methods .....	7
Results .....	7
Discussion .....	14
Conclusion .....	17
References .....	19
Tables .....	22

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# List of Tables

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Table 1: GRADE Quality of Assessment and Summary of Findings

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# List of Abbreviations

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ASA.....	Acetyl Salicylic Acid/Aspirin
HA.....	Headache
HIT-6.....	Headache Impact Test
IHS.....	International Headache Society
ISA.....	Interarterial Septal Aneurysm
MIDAS.....	Migraine Disability Assessment Score
MSS.....	Migraine Severity Score
NSAIDS.....	Non-Steroidal Anti-Inflammatory Drugs
PFO.....	Patent Foramen Ovale
RLS.....	Right to Left Shunt
SF-36v2.....	Short Form 36 Quality of Life Questionnaire
TC-D.....	Transcranial Doppler
TEE.....	Transesophageal Echocardiogram
TIA.....	Transient Ischemic Attack
TTE.....	Transthoracic Echocardiogram

## **Percutaneous Closure of Patent Foramen Ovale for the Treatment of Refractory Migraine Headaches**

### **BACKGROUND**

Migraine headaches can be debilitating and affect quality of life on a daily basis. It is estimated that migraines affect 13% of the total population,<sup>1</sup> largely affecting more females than males. About 36% of migraines are preceded by aura.<sup>2</sup> There are numerous medical treatments that can combat the effects of migraine headaches. Preventive medications include beta blockers, antidepressants, anticonvulsants and calcium channel blockers. Acute medications include triptans, acetyl salicylic acid (ASA), non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, ergotamines, caffeine, opioids and antiemetics. There are many options to treat a migraine, but some patients can be refractory to medical treatment, having tried at least 2 different medications without success, either because they cannot tolerate or do not respond to them. It is not cost effective or efficient to try every option in every class.

A connection has been proven between migraine headaches and patent foramen ovale (PFO), especially with migraine with aura.<sup>3,4</sup> There is a 25% prevalence of patent foramen ovale in the general population and there are no known causes or risk factors.<sup>5</sup> In a 2000 study, Wilmschurst and Nightingale<sup>6</sup> stated, “that in some migraine patients, venous blood contains agents normally removed by passage through the lungs that can trigger an attack of migraine if they reach the brain in sufficient concentrations; alternatively, long-term shunting [through the PFO] of the agents may reduce the threshold for migraine generation in the brain.”<sup>6</sup> In patients with a PFO and migraine headache (HA) refractory to medical treatment, does percutaneous closure of the PFO

reduce the frequency, duration and intensity of migraine headaches? If proven to do so, percutaneous PFO closure could be a definitive treatment for refractory migraine and substantial improvement in quality of life.

## **METHODS**

An exhaustive search was performed using three different search engines. A search of Medline/Ovid was performed using the search terms: patent foramen ovale, migraine disorders, therapeutics and refractory. A search of CINAHL and Evidence-Based Medicine Reviews Multifile was performed using the search terms: patient foramen ovale, migraine and refractory. Furthermore, a search of references of relevant articles was conducted in order to find additional studies. Critical appraisal of each article included was performed for validity, risk of bias and other criteria using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).<sup>7</sup>

Inclusion criteria consisted of patients with a patent foramen ovale and migraine headaches proven refractory to medications, percutaneous transcatheter PFO closure and outcomes measuring cessation or reduction in frequency, duration and intensity of migraine headache. Exclusion criteria consisted of PFO closure for reasons other than migraine headache (cryptogenic stroke, transient ischemic attack, previous cardiac or cerebral events) or lack of enrolled participants proven refractory to migraine medical treatment.

## **RESULTS**

The extensive search of three different databases yielded a total of fifteen articles. Only five studies met inclusion criteria, one randomized controlled trial (RCT)<sup>8</sup> and four

observational studies, three of which were prospective<sup>9-11</sup> and one of which was retrospective.<sup>12</sup>

Other similar systematic reviews<sup>13,14</sup> have been performed on the connection between PFO and migraine, although inclusion criteria did not specify whether a patient was refractory to medical treatment. The most recent systematic review<sup>13</sup> from 2010 addressed the role of percutaneous PFO closure on migraine occurrence. A total of 11 studies were included with 1,306 participants. Of those receiving PFO closure, only 40% suffered from migraine headaches while the remaining suffered from other events, such as ischemic stroke or transient ischemic attack (TIA). Results indicated complete migraine resolution in 46% with significant migraine improvement in 83%. This systematic review<sup>13</sup> indicates a benefit of migraine symptomatology from PFO closure, although “many questions remain unsolved.”<sup>13</sup>

Many other studies have been conducted on PFO closure and migraine incidence, although many of them assess migraine as secondary prevention for paradoxical embolism and risk of stroke.

### **MIST Trial**

This randomized, double-blind, controlled trial<sup>8</sup> assessed 432 participants. Of these, 163 were found to have a moderate to large right to left shunt (RLS). The remaining participants were excluded based on finding of a small or absent RLS. One hundred and forty-seven participants (124 female, 23 male) were randomized either to implant for PFO closure or to undergo sham procedure approved by a multi-center research ethics committee. Those in the cardiac catheterization laboratory, who were required to perform the procedure, were the only ones who knew the true treatment

allocation. Twenty-four hours prior to the procedure, all participants were given ASA 300 mg plus clopidogrel 300 mg. All participants also received general anesthesia plus transesophageal echocardiogram (TEE). The implant group received the STARFlex septal repair implant and heparin 100 IU/kg.<sup>8</sup>

Inclusion criteria consisted of adults aged 18-60 years old with migraine headaches occurring five or more times per month, having at least 7 headache-free days per month, having failed two or more types of prophylactic medications, having failed on average greater than two acute medications and have a moderate to large RLS consistent with PFO. Exclusion criteria consisted of those with cardiologic, hematologic or neurologic disorders; or those who were pregnant.<sup>8</sup>

From the 147 randomized participants, 136 completed treatment, either PFO closure or the sham procedure. The primary outcome measured migraine headache cessation 91 to 180 days post procedure through a headache diary. Only 6 participants achieved migraine cessation, 3 from each group ( $P = 0.51$ ). Secondary endpoints measured changes in severity, frequency, character and quality of life through the Migraine Disability Assessment Score (MIDAS), Headache Impact Test (HIT-6) and Short Form 36 quality of life questionnaire (SF-36v2) assessments. There was no statistical difference between resulting data of the implant and sham groups. There was no resolution of migraine attacks (CI -6.50-7.42,  $P = 1.0$ ). Frequency of migraine attacks per month did not decrease (CI -0.15-1.08,  $P = 0.13$ ). Total MIDAS score remained virtually the same (CI -10-10,  $P = 0.89$ ). Total HIT-6 score remained virtually the same (CI -5-6,  $P = 0.85$ ). The primary and secondary endpoints were not achieved.<sup>8</sup>

Complications were prevalent in this study with most participants experiencing minor adverse events and 16 participants experiencing serious adverse events, such as pericardial effusion, cardiac tamponade, retroperitoneal bleed, incision site bleed, anemia, nose bleed, stroke and others. Whether or not complications were worse in one group than the other is not stated.<sup>8</sup>

The healing phase ended at day 90 and the analysis phase ended at day 180. Follow up concluded at day 180, or at 6 months. Only one participant was lost to follow up while one participant was missing baseline diary cards and thus not included in the resulting data. A transthoracic echocardiogram (TTE) was performed at the end of the analysis phase where a residual shunt was found in 4 participants. The MIDAS assessment was given at baseline, at the end of the healing phase and at the end of the analysis phase. Each participant was required to attend a headache clinic six times at intervals of 30 days +/- 7 days.<sup>8</sup>

### **Rigatelli et al, 2010**

This prospective short term observational study<sup>9</sup> included a total of 86 participants. Forty participants received percutaneous PFO closure based on a MIDAS class of 3-4 while the remaining 46 received medical treatment based on a MIDAS class of 1-2. Because of division based on MIDAS class, no randomization was involved. Of the 40 receiving PFO closure, 34 were female, 6 were male, 34 of the 40 had accompanying aura and the average age was 35 +/- 6.7 years. The setting was performed in a single center. Closure of the PFO was performed using one of three device implants: Amplatzer Occluder family, Premere Closure System or Biostar. The procedure was guided by echocardiography. The group receiving PFO closure was compared to the

medical treatment group, although it did not serve as a true control group since no direct comparisons or calculations were made. Inclusion criteria consisted of adults with migraine headaches refractory to medical treatment, migraine with or without aura, RLS consistent with PFO, anatomic and functional characteristic predisposing to paradoxical embolism with cerebral ischemia, interarterial septal aneurysm (ISA), Eustachian valve and coagulation abnormalities.<sup>9</sup>

The primary outcome showed 100% of the participants experienced improvement of their symptoms. Secondary outcomes showed improvement in MIDAS score of 8.3 +/- 7.8 and 100% of those with auras no longer experienced them. In the medical treatment class, the MIDAS remained virtually the same, from 22.6 +/- 7.1 at baseline to 19.1 +/- 8.2. There were no major or adverse complications.<sup>9</sup>

Follow up continued for a minimum of 6 months with a mean of 29.2 +/- 14.8 months. At one month, a TEE, a TTE, and a transcranial Doppler (TC-D) were performed along with the use of a holter monitor and subsequent clinic visit. At 6 months, a TTE was performed with an additional TEE if a shunt was detected. A clinic visit and MIDAS assessment were also required for these individuals. This was repeated at 12 months. The MIDAS assessment was continued yearly thereafter. Closure of the PFO was found to be complete in 95% with a persistent small shunt in 2 participants.<sup>9</sup>

### **Rigatelli et al, 2012**

This prospective long term observational study<sup>10</sup> included 80 participants, 58 female, 22 male and 63 of the total with aura. The average age was 38.9 +/- 5.8 years. It was performed in a single center. Closure of the PFO was performed with one of three device implants: Amplatzer Occluder family, Premere Closure System or Biostar. The



procedure was guided by echocardiography. No comparison or sham procedure was performed. Inclusion criteria consisted of adults with migraine headaches refractory to medical treatment, migraine with or without aura, RLS consistent with PFO, anatomic and functional characteristics predisposing to paradoxical embolism, ISA, Eustachian valve and coagulation abnormalities.<sup>10</sup>

The primary outcome showed improvement in migraine symptomatology in 70 participants. Secondary outcomes showed improvement in MIDAS score of 33.4 +/- 6.7 to 10.6 +/- 9.8. There was no improvement in 12.5% of participants while auras were cured in 61 out of the 63 patients. There was no worsening in migraine symptomatology in any participant and no major or adverse complications were observed.<sup>10</sup>

Follow up continued for a minimum of 18 months with a mean of 50.1 +/- 16.8 months. At one month, a TEE, a TTE, and a TC-D were performed. A holter monitor was used with a subsequent clinical visit. At 6 months, a TTE was performed with a clinic visit and a MIDAS assessment and then a TEE was performed if a shunt was detected. At 12 months, a TTE was performed along with a clinical visit and a MIDAS assessment. The MIDAS assessment was continued yearly thereafter. Closure of the PFO was complete in 91.2% with a persistent small shunt in 7 participants. After contacting the authors of this study, it was revealed that almost 2/3 of these participants were from the Rigatelli et al 2010 study<sup>9</sup> and were followed up for a longer period of time.<sup>10</sup>

### **Chessa et al**

This prospective observational study<sup>11</sup> included 42 participants, 33 female, 9 male and 28 of the total with aura. The average age was 39 +/- 11.2 years. The setting was

performed in a single center. Percutaneous PFO closure was performed, but details nor type of device were included in the study. Participants were given clopidogrel 75 mg plus ASA 150 mg for 30 days, then ASA 300 mg alone for five months thereafter. No comparisons or sham procedures were performed. Inclusion criteria consisted of adults with migraine headaches, migraine with or without aura, migraine with TIA, migraine with ischemic brain lesions, a long history of unsuccessful medical treatment with various drugs, RLS consistent with PFO and prior neurologic, hematologic and cardiologic assessments.<sup>11</sup>

The primary outcome resulted in resolution of migraine headaches in 11 participants. Secondary outcomes resulted in decrease in frequency of migraines in 22 participants and decrease in aura from 8.8 to 7.5. The Migraine Severity Score (MSS) assessment was given prior and post procedure, which indicated a global score of 8.3 to 4.3 (P value = 0.00001), intensity 2.6 to 1.2 (P value = 0.00001), duration 2.5 to 1.3 (P value = 0.00001), frequency 2.6 to 1.3 (P value = 0.0001) and aura 8.3 to 4.3 (P value = 0.00001). Overall, 78% of participants were cured or showed significant improvement. No major or adverse complications were noted. Follow up lasted 6 months, at which time a TC-D was performed. Closure of the PFO was complete in 73% with a residual shunt remaining in 10 participants. The MSS assessment was performed prior to the procedure and again at 6 months post procedure.<sup>11</sup>

### **Wahl et al**

This retrospective observational study<sup>12</sup> included 17 participants, 13 female, 4 male and 14 total with aura. The average age of enrolled participants was 44 +/- 12 years. The location and setting was not specified. The intervention consisted of PFO

closure using the Amplatzer PFO Occluder, guided by fluoroscopy. After the procedure, participants were given ASA 100 mg daily for five months and clopidogrel 75 mg daily for one month. No comparison or sham procedure was performed. Inclusion criteria consisted of adults with migraine headaches with or without aura refractory to medical treatment and exhibiting RLS consistent with a diagnosis of PFO.<sup>12</sup>

The primary outcome was migraine headache cessation, which occurred in 4 of the 17 participants. Secondary outcomes included improvement in migraine symptomology, which occurred in 8 participants with a 75% reduction in 3 participants, 50% reduction in 3 participants and 25% reduction in 2 participants. Migraines were unchanged in 5 participants. Migraine with aura improved from 82% to 24% (P = 0.002). No patient had worsening of symptoms. Data was collected through a questionnaire developed with criteria from the International Headache Society (IHS) along with self-rating of improving or worsening symptoms. No major or adverse complications occurred.<sup>12</sup>

No patient was lost to follow up. At 6 months post procedure, contrast TEE after Valsalva maneuver was performed. This indicated complete PFO closure in 16 participants with a minimal residual shunt in one. Follow up continued for up to 6 years, mean 2.7 +/- 1.5 years. The IHS questionnaire was given both before and after the procedure.<sup>12</sup>

## **DISCUSSION**

In patients with a PFO and migraine HA refractory to medical treatment, does percutaneous closure of the PFO reduce the frequency, duration and intensity of migraine headaches? Even though the four observational studies<sup>9-12</sup> proved some benefit to

percutaneous PFO closure in patients refractory to medical treatment, the only RCT<sup>8</sup> performed concluded no substantial benefit. Thus, PFO closure is not recommended for treatment of migraine at this time. There are many limitations to all the studies involved. More RCTs are needed before recommending this procedure to patients fitting the inclusion criteria. Based on the results of the studies,<sup>8-12</sup> there may be a more significant prognosis of migraine headache resolution after PFO closure with the presence of aura.

### **Limitations**

Since four of the five included studies are observational studies,<sup>9-12</sup> they are limited due to the fact that there is no blinding or control groups. There was a high risk of selection bias in the Chessa et al<sup>11</sup> and both Rigatelli et al studies<sup>9,10</sup> due to operations being conducted within a single center. The Wahl et al study<sup>12</sup> was retrospective and thus had potential for bias. All the studies were indirect in that they consisted of relatively small sample sizes, less than 100 participants. The Wahl et al study<sup>12</sup> in particular was conducted with a very small sample with only 17 participants. It is noteworthy that the Rigatelli et al 2010 study<sup>9</sup> was conducted before the Rigatteli et al 2012 study,<sup>10</sup> and many of the participants were common to both trials while concluding with the same results. This in itself may increase the validity of each study. There was inconsistency in the Rigatelli et al 2010 study<sup>9</sup> because of the difference in MIDAS classes of the PFO closure group and medical treatment group, the latter, classes 1-2 and the former, classes 3-4. Thus, only the more severe group received PFO closure and is a serious limitation.

The only randomized controlled trial<sup>8</sup> also had limitations, including limited follow up, failure to include appropriate secondary endpoints and inclusion of only very severe migraine patients. There may have been more conclusive results if the follow up

had been longer than 6 months. The primary endpoint measured cessation of migraine headaches, but other secondary endpoints should have been included as well, such as reduction in frequency, duration and intensity of migraines. The researchers included severe migraine patients only, having headaches five or more times per month, seven headache-free days per month, refractory to medication and a moderate to large RLS. What about those migraine patients with headaches less than 5 times per month or more than seven headache-free days per month or with a mild RLS? The benefit of PFO closure may possibly be noticed if treated earlier, before progression to severe migraine headaches. There also seems to be a serious ethical question presented by the sham procedure, although an ethics committee did approve the trial, since general anesthetic and other invasive procedures were conducted without benefit to the sham group.

Other limitations to the studies addressed in this systematic review are inclusion criteria for reasons other than just migraine and PFO. These include cryptogenic stroke, TIA, paradoxical embolism, ischemic brain lesions, etc.<sup>9-11</sup> Clopidogrel plus ASA given either pre or post procedure may have played a role in improvement of migraine symptomology.<sup>8,11-12</sup>

### **Recommendations and Improvements**

Because future studies will be needed for a more conclusive result as to improvement in migraine symptomology after percutaneous PFO closure, there are certain recommendations that could improve the quality and validity, while reducing the bias of future study results. There is potential for recall bias because of the self-reporting headache diaries by enrolled participants. Randomized controlled trials with sham procedure will be necessary, as well as allocation concealment and blinding. A larger

number of participants will need to be enrolled in these RCTs. In addition to migraine cessation as endpoint measurement,<sup>8</sup> frequency, duration and intensity of migraines should also be measured and compared at pre and post procedure using an effective assessment such as the MIDAS.

It was shown in the MIST trial<sup>8</sup> that 6 months was not long enough for follow up. That was also shown in the second Rigatelli et al trial<sup>10</sup> which used 2/3 of the same participants in order to have a longer follow up. No specific length is recommended, however longer follow up may prove more accurate results. Inclusion criteria must only consist of presence of migraine headaches in conjunction with PFO and must not include other reasons for PFO closure, most especially paradoxical embolism or cryptogenic stroke. Lastly, all enrolled participants in said future studies must be proven to be refractory to most migraine medical treatments including both prophylactic and acute medications. Trials such as these are already underway in the United States, Canada and Europe with results expected in the near future. These trials include, but are not limited to, PRIMA<sup>15</sup> and PREMIUM.<sup>16</sup>

## **CONCLUSION**

Based on the four observational studies<sup>9-12</sup> and one RCT<sup>8</sup> that seek to measure migraine symptomology after percutaneous PFO closure in patients refractory to medical treatment, it can be concluded that there is not yet enough unbiased and valid evidence to recommend percutaneous PFO closure as treatment for severe refractory migraine headaches. The overall quality of evidence of all the studies based on the GRADE table is low, thus a strong or even moderate recommendation for PFO closure cannot be given. Further randomized controlled trials are needed based simply on migraine and PFO to

show that the benefits outweigh the risks for percutaneous patent foramen ovale closure for the treatment of refractory migraine headaches.

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**TABLE 1** GRADE Quality of Assessment and Summary of Findings

Quality Assessment							Summary of Findings				
Downgrade Criteria							Number of Patients			Quality	Importance
No. of Studies	Design	Limitations	Indirectness	Imprecision	Inconsistency	Publication bias likely	Study	PFO closure	Sham or medical tx or no PFO closure		
<b>CESSATION of migraine headache</b>											
3	1 RCT 2 Observational	Very serious limitations <sup>a</sup>	Serious indirectness <sup>b</sup>	No serious imprecision <sup>c</sup>	No serious inconsistencies	No bias likely	MIST	3/74	3/73	Low	Critical
							Chessa et al	11/42	-		
							Wahl et al	4/17	-		
<b>Reduction in FREQUENCY of migraine headache</b>											
4	4 Observational	Very serious limitations <sup>a</sup>	Serious indirectness <sup>b</sup>	No serious imprecision	Serious inconsistencies <sup>d</sup>	No bias likely	Rigatelli et al 2010	40/40 MIDAS	0/46	Very Low	Critical
							Rigatelli et al 2012	70/80 MIDAS	-		
							Chessa et al	22/42	-		
							Wahl et al	8/17	-		
<b>Reduction in DURATION of migraine headache</b>											
2	2 Observational	Very Serious limitations <sup>a</sup>	Serious indirectness <sup>b</sup>	No serious imprecision	No serious inconsistencies	No bias likely	Chessa et al	2.5 to 1.3 MSS	-	Very Low	Important
							Wahl et al	Not significantly altered	-		
<b>Reduction in INTENSITY of migraine headache</b>											
4	4 Observational	Very serious limitations <sup>a</sup>	Serious indirectness <sup>b</sup>	No serious imprecision	Serious inconsistencies <sup>d</sup>	No bias likely	Rigatelli et al 2010	40/40 MIDAS	0/46	Very Low	Important
							Rigatelli et al 2012	70/80 MIDAS	-		
							Chessa et al	2.6 to 1.2 MSS	-		
							Wahl et al	9 +/- 1 to 5 +/- 3	-		

Cessation of migraine with AURA											
4	4 Observational	Very Serious limitations <sup>a</sup>	Serious indirectness <sup>b</sup>	No serious imprecision	Serious inconsistencies <sup>d</sup>	No bias likely	Rigatelli et al 2010	32/32	0/10	Very low	Important
							Rigatelli et al 2012	61/63	-		
							Chessa et al	7/28	-		
							Wahl et al	4/14	-		

GRADE: Grading of Recommendations, Assessments, Development and Evaluation

<sup>a</sup>High risk for selection bias in both Rigatelli et al (2010 and 2012) studies and the Chessa et al study because they were conducted in a single center. No control groups used in the Rigatelli et al 2012, Chessa et al and Wahl et al studies. Only a quasi-control group was used in the Rigatelli et al 2010 study. The Wahl et al study was a retrospective study.

<sup>b</sup>Small sample sizes (less than 100) in the Rigatelli et al 2010, Rigatelli et al 2012, Chessa et al and Wahl et al studies. Indirect comparison between PFO closure and medical treatment groups in the Rigatelli et al 2010 study.

<sup>c</sup>Results of the MIST indicate no appreciable benefit or harm.

<sup>d</sup>PFO closure group (MIDAS classes 3-4) prognostically different from medical treatment group (MIDAS classes 1-2) in the Rigatelli et al 2010 study.