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Chapter 11 Randomized Clinical Trials of PFO Closure for Migraine Headache (MIST, PRIMA, PREMIUM)

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CHAPTER

11

Randomized Clinical Trials of PFO Closure for Migraine Headache (MIST, PRIMA, PREMIUM)

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INTRODUCTION

Migraine is a chronic and debilitating neurologic condition that affects 5.6% of men and 17.1% of women in the United States. Despite the severe personal and societal implications associated with it, migraine headache is frequently underdiagnosed and thus, undertreated; over half of migraineurs in the United States have never received a formal diagnosis [1]. Migraine has 2 major subtypes, migraine without aura and migraine with aura [2]. Typical headache attacks last 4–72 hours and are mostly unilateral, pulsating in quality, moderate or severe in pain intensity, aggravated by exertion, and accompanied by nausea or vomiting, with phonophobia and photophobia. In migraine with aura, transient focal neurologic deficits usually precede or accompany the headache. Focal neurologic symptoms are mostly visual, but can be sensory, aphasic, motor, vestibular, or any kind of focal symptom. A patient may have both migraine with and without aura. If headache attacks occur for 15 or more days per month, the headache is characterized as a chronic migraine, where medication overuse may be causing part of the problem in most patients [2].

Epidemiological studies have demonstrated severe personal and professional consequences for patients suffering from migraine. Migraineurs report missing family activities, hindrance in performing household chores, and avoidance of making plans due to the possibility of a migraine attack. Understandably, this also affects the migraineur's family. Twenty to sixty percent of migraineurs' partners report a negative effect on their relationship as a result of

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their partners' headaches [3]. Professionally, migraine is responsible for increased rates of work absenteeism and diminished productivity [1].

Migraine's prevalence, dramatic effect on quality of life and productivity, undertreatment, and often refractoriness to medications make novel device-based therapy very appealing for this disorder. Patent foramen ovale (PFO), a congenital remnant of the fetal circulation, is present in 20%–25% of the general population, but up to 50% of patients who have migraine with aura are found to have a PFO [4–6].

PFO-mediated right-to-left shunting has also been implicated in various clinical conditions, from paradoxical embolism producing stroke (Chapters 4–7), myocardial infarction (Chapter 8), and peripheral embolism (Chapter 9), to unexplained hypoxemia (Chapter 12), and decompression sickness in divers (Chapter 13). The advent of low-risk, nonsurgical percutaneous PFO closure devices has resulted in increased interest in PFO closure for such conditions. Particularly in divers with decompression illness, the prevalence of migraine with aura after dives and during everyday life is high. In 2000, a small observational study by Wilmshurst et al. suggested that PFO closure for decompression sickness may result in an improvement or even cure of migraine symptoms [7]. At least 12 subsequent observational studies also demonstrated an improvement or resolution of migraine symptoms after PFO closure [8–19]. A meta-analysis of these studies showed that 81% of patients who underwent PFO closure had an improvement or cessation of their migraine symptoms [4]. The observational studies of PFO closure for migraine are discussed in Chapter 10 (See Table 11.1).

There are many pathophysiological mechanisms underlying migraine, some proven, some hypothetical. One of the hypotheses postulates that a chemical agent that would otherwise be cleared by the lungs bypasses metabolism through the right-to-left shunt, entering the arterial circulation to reach the cerebral vasculature and trigger migraine headache; mediators such as nitric oxide, histamine, and serotonin have been suggested as potential culprits. Other potential mechanisms have proposed that more acidotic and less oxygenated venous blood entering the left-sided circulation could trigger migraine attacks [20]. The neurophysiological basis of aura in migraine is cortical spreading depression, described first by Leão [21], a wave of depolarization followed by inhibition of the neurons and glia cells that slowly propagates over the cortex [22]. It can be elicited by any focal noxious stimulus including focal ischemia caused by microemboli [23]. Of note, migraine is not a uniform entity or disease. Migraine is the clinical

TABLE 11.1 Observational Studies of the Prevalence of Migraine in Patients Referred for PFO Closure and the Effect of Closure on Migraine.

Study	# Migraines/Total Screened	% Closed	% Migraine Improved or Cured	Length of Follow-Up (months)
Wilmshurst et al. (2000) [7]	21/37	59	86	30
Morandi et al. (2003) [10]	17/62	27	88	6
Schwerzmann et al. (2004) [11]	48/215	22	81	12
Post et al. (2004) [12]	26/66	39	65 (cured)	6
Reisman et al. (2005) [13]	57/162	35	70	12
Azarbal et al. (2005) [8]	37/89	42	76	18
Donti et al. (2006) [14]	35/131	27	91	20
Anzola et al. (2006) [17]	50/163	100	88	12
Kimmelstiel et al. (2007) [15]	24/41	59	83	3
Papa et al. (2009) [16]	28/76	37	82	12
Vigna et al. (2009) [18]	82/156	65	89	6
Wahl et al. (2010) [19]	150/603	100	82	60
Khessali et al. (2012)[a] [9]	204/590	40	76	12
Meta-analysis	779/2391	50	81	16

[a]*Migraine with aura.*
Adapted with permission from Ref. [4].

phenomenon of a cerebral process with potentially many causes. This is illustrated by the fact that migraine with aura enhances the risk of vascular events and stroke, but migraine can also be the initial clinical presentation of a stroke with a different etiology [24]. On the other hand, migraine without aura does not enhance the risk of stroke (see Chapter 10 for a discussion of migraine and stroke).

Novel and less invasive therapies for PFO closure, along with promising observational studies, led to an interest in PFO device closure for migraine treatment. As a result, recruitment began to enroll patients into randomized controlled trials and to determine the efficacy and safety of PFO closure plus standard of care medical therapy versus controls for the treatment of migraines. This chapter will discuss the clinical trials of PFO closure for migraine headache and elaborate on the lessons learned, limitations, and meta-analyses of these studies.

THE MIST TRIAL

The MIST (Migraine Intervention with STARFlex Technology) trial was the first randomized, multicenter, double-blinded sham-controlled study to investigate the efficacy and safety of PFO closure for the treatment of migraine [25]. Patients in the United Kingdom aged 18−60 years were offered screening for enrollment if they met criteria for frequent migraine with aura (at least 5 headache days per month but a minimum of 7 headache-free days per month) and failure of at least 2 classes of preventative agents. Eligible patients were then screened with transthoracic echocardiography for a PFO using an agitated saline bubble study. Of 432 migraine with aura patients screened, 60% had a right-to-left shunt; the majority of these (63%) were attributed to a PFO. In a 1:1 ratio, migraineurs were randomized to either PFO closure with the STARFlex device (NMT Medical Inc, Boston Massachusetts) or a sham procedure (superficial groin incision). General anesthesia was given to all patients to preserve blinding during randomization. Patients in both groups were given acetylsalicylic acid and clopidogrel (both 75 mg daily) for 90 days after the closure or sham procedure. Follow-up consisted of neurologic evaluation in a headache clinic for 6 months. Patients were instructed to continue the same headache regimen and not to start a new medication. A headache diary was used by patients to record their migraine events. At the 6-month follow-up, patients were evaluated by a cardiologist who informed them of their treatment allocation; a 6-month transthoracic echocardiogram was used to assess for residual interatrial shunting in patients who underwent device closure.

The primary efficacy endpoint of the MIST trial was migraine cessation during the analysis phase of the study (days 91−180 after PFO closure or sham procedure), obtained from patients' diary data. This endpoint was based on prior observational studies that reported 60% of patients with migraine plus aura had complete cessation of migraine episodes after PFO closure. The secondary endpoints were a change in the incidence, severity, frequency, or character of migraine headache or a change in quality of life.

A total of 74 patients were randomized to the PFO closure arm and 73 were assigned to the placebo arm. Although the MIST trial confirmed migraine with aura patients to have a high prevalence of right-to-left shunt, no significant treatment effect was found for the primary or secondary endpoints comparing the 2 groups. The primary endpoint was not met, with 3 patients in each arm reporting complete cessation of migraine headaches following PFO closure or a sham procedure. Secondary endpoints also did not differ significantly in the device versus the sham group ($P = \text{NS}$ for all). One patient in the control group, but none in the device group, suffered a stroke during follow-up. This hints at the possibility of collateral benefits when closing a PFO for migraine.

Although the MIST trial failed to achieve its primary or secondary endpoints, further exploratory analysis of the cohort's migraine headache days per month identified 2 patient outliers. The majority of the patients in the study population had 4 or fewer migraine headache days per month. However, the 2 outliers in the device arm had 28−31 headache days per month. When these patients were excluded from the analysis, there was a statistically significant reduction in migraine headache days in the device group compared to the sham group (reduction of 2.2 headache days/month in the device arm vs. 1.3 headache days/month in the sham arm).

A major concern of the MIST trial was a higher than anticipated complication rate associated with the closure procedure. Serious adverse events in all patients were reviewed by an independent data and safety monitoring board. Seven complications were determined to be either definitely or possibly procedure-related in the device arm; these adverse events included atrial fibrillation, chest pain, pericardial effusion, tamponade, and retroperitoneal bleeding. Three patients underwent device withdrawal due to operator dissatisfaction with the initial implant, with deployment of a second device. In order for percutaneous PFO closure to ever be accepted as an adequate treatment of migraine headache, which often occurs in young and otherwise healthy individuals, the device would have to provide a clinical yield that outweighs the short- and long-term procedural risks. The STARFlex device used was subsequently withdrawn from the market while other devices were developed.

Why did the MIST Trial Differ from Previous Observational Studies?

The results of the MIST trial were disappointing to many clinicians who had observed patients describe dramatic improvements in their migraine symptoms after PFO closure. Two prominent theories have been proposed to explain the discrepancy between the MIST trial's result and prior clearly positive observational studies [4]: First, the population of migraineurs investigated in the observational studies, which included predominantly cryptogenic stroke patients who also had migraines, may have been different than the MIST trial patients, who had recurrent, debilitating, and refractory headaches without another indication for PFO closure. Second, it was thought that MIST's failure may be the result of a high prevalence of residual right-to-left shunting post−PFO closure. Residual shunting was assessed in all patients in the device arm with a 6-month transthoracic echocardiogram. Although the MIST results presented in TCT (Transcatheter Cardiovascular Therapeutics) 2007 reported that 94% of the device arm patients achieved effective closure [26], an initial primary investigator of the MIST trial reported that over a third of patients in the device arm had a large residual shunt on further data review [27]. This is in keeping with other studies demonstrating residual shunting in over 28% of PFO closures when devices of the STARFlex family, such as CardioSEAL and BioStar (NMT Medical, Boston, Massachusetts), were utilized [28]. No independent adjudication committee had been assigned to review the transthoracic echocardiograms. If the reason for MIST's failure was inadequate PFO closure, it was thought that subsequent randomized trials using more effective and safer devices may show a benefit of PFO closure in migraineurs who have severe and refractory symptoms, as long as the shunt is effectively sealed. A chemical trigger for PFO-mediated migraine is likely and it is less dependent on shunt size than particulate matter of a large enough size to cause PFO-mediated systemic embolism. Additionally, it is important to recognize that a transthoracic echocardiogram is less sensitive and specific for the detection of a PFO when compared with a transesophageal echocardiogram (TEE) [29−31]; only a TEE can adequately visualize the atrial septal anatomy and provide enough information to confirm satisfactory device closure [32]. A transcranial Doppler (TCD) bubble study is even more sensitive for detecting and quantitating residual shunts [33] and could have been useful in retrospect. Imaging assessment of a PFO, for diagnostic and interventional purposes, is discussed in Chapters 2 and 3, respectively.

THE PRIMA TRIAL

The PRIMA (Percutaneous Closure of PFO in Migraine with Aura) trial was a multicenter (20 centers in Europe and Canada), open-label, randomized clinical study that investigated the efficacy and safety of percutaneous PFO closure for treating medically refractory migraine with aura [34]. Migraineurs with aura were enrolled who had headaches that started before age 50, had >3 migraine attacks or 5 migraine days per month (but <14 headache days per month), had failed at least 2 preventative medications, and were also found to have a PFO. Unlike the MIST trial, PRIMA did not blind the patients to the treatment assigned, as it did not utilize a sham procedure, while the assessors adjudicating the patients' headache diaries were blinded to their treatment assignment.

Patients were randomized to percutaneous PFO closure with the Amplatzer PFO Occluder (Abbott; Chicago, Illinois) plus 3 months of clopidogrel and 6 months of acetylsalicylic acid (53 patients) or the same antiplatelet medications without device closure (54 patients). Any change in the type, dose, or frequency of the preventive migraine medications was discouraged during the trial's course. Patient follow-up occurred at 3-month intervals until 12 months. Participants in the device arm underwent a TEE at the 6-month follow-up to assess for residual interatrial right-to-left shunting; a repeat TEE at 12 months was also performed for those with a residual shunt. Although the initial PRIMA design required that 72 patients be randomized to each group for a power of 80%, the study's sponsor terminated the trial in January 2012 due to slow recruitment. At that time, 53 patients had been assigned to the device arm and 54 patients to the medical therapy arm.

Similar to the MIST trial, PRIMA demonstrated a high prevalence of right-to-left shunts (40%) among patients who had migraine with aura. The primary endpoint of a significant mean reduction in migraine days at 1-year follow-up was not met when device closure was compared to medical therapy (-2.9 ± 4.7 vs. -1.7 ± 2.4, $P = .17$). Yet, secondary endpoints were all in favor of PFO closure including a decrease in migraine with aura days (-2.4 ± 3.6 vs. -0.6 ± 2.7, $P = .01$), decrease in migraine with aura attacks (-2.0 ± 2.0 vs. -0.5 ± 1.5, $P < .01$), ≥50% reduction in migraine days (37.5% vs. 14.6%, $P = .02$), and freedom from migraine (10% vs. 0%, $P < .05$) and migraine with aura (40% vs. 10%, $P < .05$). Compared with the STARFlex device used in the MIST trial, the Amplatzer PFO Occluder used in PRIMA appeared to be safer. One subject in the device arm had bleeding from a

major vascular complication and another had drug-refractory atrial fibrillation requiring cardioversion; no adverse events occurred in the medical therapy arm.

The PRIMA study had several limitations including lack of patient blinding. A potential placebo effect mistakenly had been considered unlikely with a migraine status assessment after a year from the intervention. In both groups, antiplatelet treatment had been stopped for several months at the final assessment. There was also lack of power due to incomplete enrollment, a high dropout rate post-randomization (1 patient in the device group and 11 in the medical therapy group), and failure of 23% (12/53) of patients in the device arm in actually getting a device (8 withdrew consent and 4 failed device implantation). However, despite these limitations, the PRIMA trial demonstrated that migraine with frequent aura appears to respond favorably to PFO closure. Additionally, the trial demonstrated that the Amplatzer device is both effective in closing the PFO (94.2% of patients had grade 0 or grade 1 residual shunting by TEE) and relatively safe (4.5% of patients had serious adverse events related to either the implantation procedure or device, but with no long-term sequelae at 1-year follow-up). *Post hoc* analyses showing a positive response to PFO closure in migraine with aura patients provided a compelling argument for continued research.

THE PREMIUM TRIAL

The PREMIUM (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management) trial, published in November 2017, was a comprehensive, prospective, randomized, double-blinded, sham-controlled study that enrolled 230 patients at 29 different medical centers in the United States [35]. Included patients had episodic migraines (defined as 6−14 headache days per month) and had failed at least 3 different preventative medications. A 60-day migraine diary was used to screen the patients. Unlike PRIMA, migraineurs with and without aura were enrolled in the study. Right-to-left shunt screening was performed with a TCD bubble study; to qualify for the trial, patients had to demonstrate a high degree of right-to-left shunting (grade 4 or 5 shunting on TCD, defined as >100 bubbles/min of shunting either at rest or with Valsalva). Subjects with a positive TCD subsequently underwent a right heart catheterization during randomization with passage of a guidewire across the septum to confirm the presence of a PFO prior to randomization.

A total of 230 patients were randomized by block to either percutaneous PFO closure using the Amplatzer PFO Occluder plus medical therapy (123 patients) or a sham procedure plus medical therapy (107 patients). Patients monitored their migraine attacks with a headache diary 3 months prior to and every day for 12 months after randomization. A comparison of the headache frequency was made between the baseline and the last 3 months of observation. To encourage continued patient enrollment in the sham arm, the blind was broken after the 12 month follow-up, and controls were offered the option of undergoing PFO closure if they preferred. Crossover patients were used in the device safety analyses but were not included in the efficacy analyses.

The primary efficacy endpoint of the PREMIUM trial was the responder rate, defined as a >50% reduction in the frequency of migraine attacks per month during months 10−12 compared to the baseline frequency of migraine attacks prior to randomization. The trial, however, did not meet its primary efficacy endpoint when the responder rate was compared between PFO closure and the controls (38.5% vs. 32%, $P = .32$). Secondary endpoints of PREMIUM included a reduction in migraine days (the difference in the average number of migraine days during months 10−12 from the baseline period), reduction of 75%, 95%, or greater in migraine attacks compared to the baseline phase, and PFO closure success (residual right-to-left shunt grade ≤ 2 on TCD at 1-year follow-up). The trial showed a significant reduction in the mean number of migraine days per month in the PFO closure group versus the controls (−3.4 days vs. −2.0 days, $P = .025$); this was a significant change compared to the mean baseline headache days (10.7 days in the device arm vs. 10.0 days in the control arm, $P = .03$). Although there was no significant difference in patients who had a 75% reduction in migraine attacks, a dramatic reduction was observed with PFO closure among those who experienced complete cessation of their migraine attacks (8.5% vs. 1%, $P = .01$).

Importantly, the PREMIUM trial further explored a subgroup of patients from the PRIMA study who received the greatest benefit from PFO closure; these included patients who experienced aura as a frequent component of their migraine attacks (>50% of episodes). The PREMIUM investigators confirmed that this subgroup of patients had a significantly higher responder rate to PFO closure compared to the controls (49% vs. 23%, $P = .015$). In patients who experienced frequent aura in relation to their migraine attacks, 15.4% had complete cessation of migraine attacks compared with 2.5% in the control group ($P = .04$). Since these observations were not prespecified, it was hypothesized that a future randomized trial of PFO closure for migraine with frequent aura (>50% of headache episodes) may show a significant clinical benefit.

Although the PREMIUM results could not demonstrate a significant reduction in migraine attack frequency, it did reduce the total number of migraine days and also showed that PFO closure with the Amplatzer device is safe (6 self-limited procedure-related adverse events, 1 periprocedural paroxysmal atrial fibrillation). Additionally, in subjects having migraine predominantly with aura, there was a significant reduction in the total headache days with a subset having complete resolution, a rare clinical yield of any medical therapy. The study population was different from that of the MIST and PRIMA trials as patients with and without aura were enrolled, with no restriction on age of onset; patients with chronic migraine were also excluded ($\geq$15 headache days per month) as in PRIMA. The failure to see a decrease in migraine attack frequency in the PREMIUM study may be related to inclusion of patients who had migraine without aura. Migraine without aura subjects were included in PREMIUM because initial observational studies suggested a benefit of PFO closure in this subset. In addition, it is more difficult to show a statistical difference in the endpoint of migraine attacks due to the small numbers per month, compared with migraine days, which was successful in reaching its endpoint. It is curious to note, as a commentary on how multicenter randomized trials are designed, that the Food and Drug Administration required the PREMIUM trial to use frequency of migraine attacks as the primary endpoint instead of migraine days. Subsequently, the Food and Drug Administration reversed its decision and now accepts the frequency of migraine days as a valid endpoint for migraine medication trials. Had this interpretation been in place at the start of the PREMIUM trial, the study would have been interpreted as a positive trial (Table 11.2).

SHOULD FUTURE PFO CLOSURE FOR MIGRAINE TRIALS HAVE A SHAM CONTROL ARM?

The PREMIUM trial was crucial in highlighting the importance of study design for future PFO closure trials that would evaluate migraine prevention. On a scientific basis, it can be argued that a significant placebo effect was observed in the sham arm of PREMIUM, evident by the 32% improvement in the responder rate. Thus, only a future sham control, blinded randomized trial could unequivocally determine the true efficacy of PFO closure for treating migraine headache. The placebo effect demonstrated in the PREMIUM trial suggests that unblinded studies would likely have unacceptably high rates of this phenomenon. This large placebo effect has been described by Henry Beecher when control subjects are carefully attended to in a methodical manner during a clinical trial [36].

However, as a counter-argument to having a sham control arm, the 32% responder rate cannot fully be explained by a placebo effect; migraineurs often visit their physician when their headache frequency and intensity is at its worst, with many of such headaches spontaneously improving over time. In addition, the PRIMA trial showed that PFO closure resulted in a reduction of migraine attacks with aura and migraine days with aura that was greater than the reduction of all types of migraine attacks and days. The unequal and greater effect on migraine with aura likely reflects a true treatment outcome of PFO closure. Furthermore, in a trial without a sham control arm, patients are aware of their treatment assignment, but the adjudicators of the headache diaries can be blinded to the treatment assignment. All these, the ease and relative safety of PFO closure, along with its lifelong protection against paradoxical embolism (Fig. 11.1), make some PFO closure advocates believe that a sham-controlled migraine study is unethical.

META-ANALYSES OF THE TRIALS OF PFO CLOSURE FOR MIGRAINE HEADACHE

A recent study level meta-analysis by Kheiri et al. was published in 2018 [37]. Kheiri et al. analyzed 448 patients enrolled in the 3 trials (MIST, PRIMA, and PREMIUM) with a mean follow-up of 10 months. The meta-analysis confirmed a significant reduction in the mean number of migraine attacks (mean difference of -0.54, $P < .01$) and monthly migraine days (mean difference -1.33 days, $P < .01$) among patients who underwent PFO closure. However, they found no significant difference in patients who experienced complete cessation of migraine attacks ($P = .14$). The authors confirmed that there was no significant difference in the development of new-onset atrial fibrillation between groups ($P = .18$).

In another study level meta-analysis of the 3 trials [38], Elbadawi et al. also confirmed that compared with controls, PFO closure demonstrated a significant reduction in monthly migraine attacks (standardized mean difference = 0.25, 95% CI: 0.06–0.43, $P = .01$) and monthly migraine days (standardized mean difference = 0.30, 95% CI: 0.08–0.53, $P = .01$). Among patients who had the majority of their migraine attacks associated with aura, their meta-analysis also demonstrated a significant reduction in migraine attacks with PFO closure compared to the controls (standardized mean difference = 0.86, 95% CI: 0.07–1.65, $P = .03$) (Table 11.3).

TABLE 11.2 Trials of PFO Closure for Treating Migraine Headaches.

Trial	Patient Population	Treatment Group	Control Group	Follow-up	Primary Endpoint	Primary Endpoint Results	Additional Findings (Secondary Endpoints, *post hoc* Analysis)
MIST [25]	PFO + frequent migraines with aura	STARFlex device	Sham procedure + medical therapy	6 months	Complete migraine cessation	No significant difference	Significant reduction in headache days in device group when eliminating 2 outliers.
PRIMA [34]	PFO + frequent migraines with aura	Amplatzer PFO Occluder	Medical therapy	12 months	Reduction of migraine days	No significant difference	PFO closure showed improvement in responder rate (≥50% reduction in migraine days), freedom from migraine with aura, reduction in migraine with aura headache days, and total migraine attacks. *PFO closure showed reduction in migraine attacks among migraineurs with frequent aura.*
PREMIUM [35]	PFO + frequent migraines with and without aura	Amplatzer PFO Occluder	Sham procedure + medical therapy	12 months	≥50% reduction in migraines attacks	No significant difference	PFO closure showed significant reduction in migraine with aura attacks and headache days per month, and complete headache cessation. *PFO closure showed reduction in migraine attacks among migraineurs with frequent aura.*

MIST, Migraine Intervention with STARFlex Technology; *PRIMA*, Percutaneous Closure of PFO in Migraine with Aura; *PREMIUM*, Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the Amplatzer PFO Occluder to Medical Management.

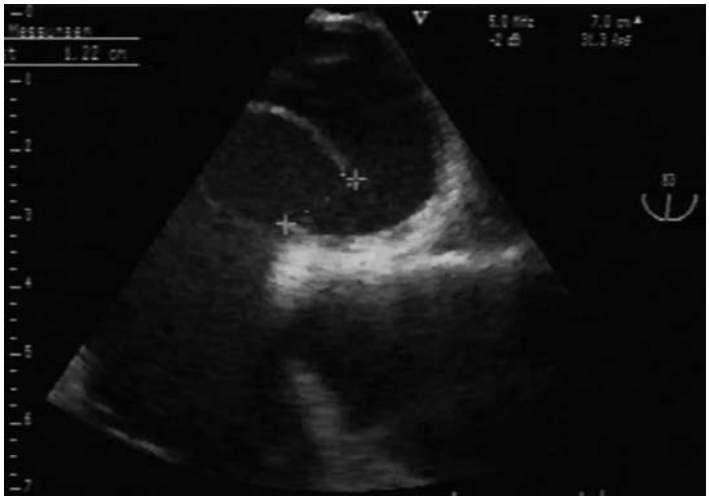

FIGURE 11.1 Large PFO (marks) in the transesophageal echocardiogram of a 39-year-old nurse. The patient had suffered a stroke 2 years ago with permanent aphasia. She had had frequent migraine with aura for over 20 years, and PFO closure cured her migraine. In retrospect, PFO closure should have been performed before the stroke happened.

TABLE 11.3 Summary of the Meta-analyses of PFO Closure for Treating Migraine Headaches.

Meta-analysis	Mean Migraine Attacks/Month	Mean Migraine Days/Month	Complete Cessation of Migraine Attacks	Subgroup Analysis
Kheiri (2018) [37]	PFO closure showed significant reduction (mean difference: −0.54, 95% CI −0.63 to −0.45, $P < .01$)	PFO closure showed significant reduction (mean difference: −1.33, 95% CI −2.32 to −0.33, $P < .01$)	No difference between PFO closure and controls ($P = .14$)	N/A
Elbadawi (2018) [38]	PFO closure showed significant reduction (SMD = 0.25, 95% CI 0.06 to 0.43, $P = .01$)	PFO closure showed significant reduction (SMD = 0.30, 95% CI 0.08 to 0.53, $P = .01$)	No difference between PFO closure and controls ($P = .14$)	PFO closure showed reduction in migraine attacks if majority of migraine attacks occur with aura (SMD = 0.86, 95% CI 0.07 to 1.65, $P = .03$)

SMD, Standardized mean difference.

CONCLUSIONS

Migraine is a prevalent and debilitating neurologic condition. Epidemiologic data suggest that migraine is often underdiagnosed and undertreated [1–3]. At first glance, it may appear that the randomized controlled trials of PFO closure for migraine headache are disappointing, as all 3 trials did not meet their primary endpoints. Given these results, percutaneous PFO closure as a treatment for migraine is not supported in contemporary clinical guidelines, let alone the search for PFO in migraine patients. The trials to date are hypothesis generating and have identified both important areas for future research and insight into the mechanistic role of right-to-left shunting in migraine headache.

Although individual trials did not meet their primary endpoints, there was a trend toward statistical significance, along with multiple secondary endpoints that were met, indicating a potential benefit of PFO closure for a subset of migraineurs. Another interesting observation was that when the PRIMA and PREMIUM trials were compared (the 2 studies using the same Amplatzer device), the primary endpoint of one trial was a secondary endpoint of the other and vice versa. The primary endpoint and a secondary endpoint of the PRIMA trial were a mean reduction of migraine days and the responder rate, respectively, while the primary endpoint and a secondary endpoint of the PREMIUM trial were the responder rate and mean reduction of migraine days, respectively. Had the 2 studies swapped their primary endpoints, both trials would have met their primary endpoints and be considered positive studies [39].

A limitation of all trials was the inclusion criterion requiring failure of 2 or 3 preventive medications before randomization. This led to a highly selective patient group that was included in the studies. Thus, the study populations no longer correspond to an average migraine population, making it difficult to generalize the results.

Specifically, PRIMA and PREMIUM suggested a potential benefit of PFO closure, having a consistent effect on migraine headaches; this was especially observed in the subgroup of migraineurs with frequent aura (>50% of headache episodes). The meta-analysis by Elbadawi et al. also showed that in subjects whose majority of migraine attacks are with aura, there was a reduction in migraine attacks with PFO closure compared to the controls (standardized mean difference = 0.86; 95% CI: 0.07–1.65; $P = .03$) [37].

The finding that a subset of migraineurs may benefit from PFO closure, the relative safety of the procedure, and the high prevalence and significant societal impact of migraine headaches all highlight the importance of continued research to identify the migraineurs who benefit from closure of their right-to-left shunts [40]. Investigating patients who have migraine with frequent aura (>50% of the time in relation to their headaches) would be a good cohort to investigate further. This also suggests that the International Headache Society classification may need revision to include migraine with frequent aura as a separate entity [2]. The International Headache Society classification of "migraine with aura" is defined by any patient who experiences 2 or more aura episodes in their lifetime. Since patients who had "migraine with frequent aura" (>50% of the time in relation to the migraine attacks) responded significantly greater to PFO closure, this phenotype appears to be different than "migraine with rare/occasional aura". Future trials could focus on assessing PFO closure for migraineurs with frequent aura, as these patients appear to benefit more from device closure. Moreover, the inclusion criteria could be liberalized to not require ineffective preventive medications before randomization, since the rare side effects of PFO closure need to be compared also to the quite frequent side effects of long-term preventative migraine medications. The results of these trials and

their meta-analyses suggest that such a study including only migraineurs who have frequent aura, with or preceding their attacks, could yield a positive result.

In a recent retrospective study of 136 migraineurs with a PFO by Sommer et al. [41], patients were treated with thienopyridine therapy (clopidogrel or prasugrel) and those whose headaches responded favorably underwent PFO closure; thienopyridine therapy was discontinued 3 months after device closure. Ninety-four percent of these patients experienced significant relief of their migraines even after medical therapy was discontinued. This study demonstrated that successful P2Y12 platelet inhibition reduces headache symptoms in some migraineurs with PFO, suggesting that the symptoms may have a platelet-based mechanism. It was thought that the near parallel response to PFO closure may mechanistically link venous platelet activation with PFO-mediated right-to-left shunting. Similar results, but less robust were observed with P2Y12 inhibition using ticagrelor [42]. Backed by these data, recruitment is expected to begin for a new clinical trial that will investigate the efficacy and safety of the Gore Cardioform Septal Occluder (W.L. Gore and Associates; Flagstaff, Arizona) to treat migraine headache for 150 thienopyridine responders, who would be randomized to PFO closure or a sham procedure followed by stopping medical therapy [43].

For years, the mainstay of preventative migraine medical therapy has been medications that were originally designed to treat other systemic disorders such as hypertension, seizures, and depression. Recently, calcitonin gene-related peptide (CGRP) blockers (targeting CGRP or its receptor) have emerged as alternative medications for the prevention of migraine attacks [44]. Research suggests that CGRP is released during migraine episodes and this chemical may play a contributory role in migraine induction. Although the studies comparing CGRP blockers to placebo have shown promising efficacious results in preventing migraine attacks, the long-term outcomes of these medications are currently unknown. Additionally, CGRP receptors are also found in the normal vasculature and nervous system. Blocking these receptors may have adverse neurovascular effects, especially in predisposed patients who already have cardiovascular or neurological diseases. Animal studies have shown that CGRP blockers may cause constipation, attenuate wound healing, and affect pituitary hormone homeostasis, albeit there is no clear evidence of these observations in humans [44]. When PFO closure is considered for migraineurs, the risks and benefits of a one-time procedure should be weighed against the risks, benefits and costs of chronic (and possibly lifelong) alternative medical therapies.

Finally, it needs to be kept in mind that the principal risk of a PFO resides in the possibility of paradoxical embolism with stroke, myocardial infarction, or other systemic embolism. Several studies demonstrate an increased risk of migraineurs, particularly those with aura, for such events, and some mention the PFO as a potential common cause [45–51]. Since a right-to-left shunt occurs in 93% of cryptogenic stroke patients who have frequent migraine with aura [52], and considering that migraine has also been linked to altered platelet function and increased venous thromboembolism [49], a PFO may act as a conduit for the passage of blood clots or platelet plugs to cause most of the strokes found in migraineurs with aura. However, this would be difficult to prove in a randomized trial given the low absolute risk of stroke in migraine with aura patients. Thus, closing a PFO for migraine may entail a collateral benefit, even for patients whose migraine does not respond favorably [53–55].

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