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Percutaneous Closure of Patent Foramen Ovale in Patients With Migraine

The PREMIUM Trial

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ABSTRACT

BACKGROUND Migraine is a prevalent and disabling disorder. Patent foramen ovale (PFO) has been associated with migraine, but its role in the disorder remains poorly understood.

OBJECTIVES This study examined the efficacy of percutaneous PFO closure as a therapy for migraine with or without aura.

METHODS 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) was a double-blind study investigating migraine characteristics over 1 year in subjects randomized to medical therapy with a sham procedure (right heart catheterization) versus medical therapy and PFO closure with the Amplatzer PFO Occluder device (St. Jude Medical, St. Paul, Minnesota). Subjects had 6 to 14 days of migraine per month, had failed at least 3 migraine preventive medications, and had significant right-to-left shunt defined by transcranial Doppler. Primary endpoints were responder rate defined as 50% reduction in migraine attacks and adverse events. Secondary endpoints included reduction in migraine days and efficacy in patients with versus without aura.

RESULTS Of 1,653 subjects consented, 230 were enrolled. There was no difference in responder rate in the PFO closure (45 of 117) versus control (33 of 103) groups. One serious adverse event (transient atrial fibrillation) occurred in 205 subjects who underwent PFO closure. Subjects in the PFO closure group had a significantly greater reduction in headache days (-3.4 vs. -2.0 days/month, $p = 0.025$). Complete migraine remission for 1 year occurred in 10 patients (8.5%) in the treatment group versus 1 (1%) in the control group ($p = 0.01$).

CONCLUSIONS PFO closure did not meet the primary endpoint of reduction in responder rate in patients with frequent migraine. (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management [PREMIUM]; NCT00355056)
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Migraine is one of the most commonly disabling disorders worldwide (1). There have been significant advances in the understanding of migraine, but many questions remain about its fundamental pathophysiology (2). Current therapies for migraine are effective for some, but for many migraine sufferers, these therapies are either poorly tolerated or ineffective (3,4). Because migraine is a heterogeneous and variable disorder (5), individual therapies may not be effective for all patients, and there is also a need for better strategies to predict which patients will respond to which therapies.

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Multiple studies have reported a significant association between migraine, particularly migraine with aura, and the presence of a patent foramen ovale (PFO) (6,7). The foramen ovale remains patent after birth in approximately 20% of the population (8). Investigations using transcranial Doppler (TCD) measurements following agitated saline intravenous injections have demonstrated right-to-left shunt (RLS) in 41% to 48% of patients with migraine with aura (9,10). Causes of RLS other than PFO have also been associated with migraine; adults with congenital RLS (11) and people with hereditary hemorrhagic telangiectasia, who may have RLS due to pulmonary arteriovenous malformations, have an increased prevalence of migraine (12). Observational studies have indicated that closure of RLS due to PFO, atrial septal defects, or pulmonary arteriovenous malformations reduces the frequency and severity of migraine, particularly in patients with migraine with aura (13–15).

The hypothesis of 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 was that percutaneous closure of a PFO with large RLS would provide a significant reduction in the frequency of migraine attacks with or without aura in patients who had headache on 6 to 14 days per month that was not effectively prevented by current medical therapies. To test this hypothesis, a prospective, randomized, double-blinded, sham-controlled study was performed in 230 subjects at 29 institutions in the United States.

METHODS

Subjects were screened by a neurologist and study inclusion required an historical migraine frequency of 6 to 14 headache days per month and failure (due to lack of efficacy or tolerability) of at least 3 different migraine preventive medications. A TCD study was performed to determine the presence and severity of an RLS (16). Inclusion in the study required a high degree of RLS, manifested as a grade 4 or 5 shunt (>100 bubbles/min, up to too numerous to count) either at rest or following a Valsalva maneuver with 40 mm Hg pressure exerted against a manometer. Subjects underwent skin patch testing to determine nickel allergy, which was an exclusion criterion. Subjects who met initial inclusion criteria completed a diary over 60 days. Those with 6 to 14 headache days per month confirmed prospectively underwent cardiac catheterization, at which time they were randomized to PFO closure or a sham procedure. A complete list of inclusion and exclusion criteria is provided in the Online Appendix. Migraine-preventive medications and their dosage were not changed until after the 12-month follow-up visit.

ABBREVIATIONS AND ACRONYMS

PFO = patent foramen ovale

RLS = right-to-left shunt

TCD = transcranial Doppler

TTE = transthoracic echocardiogram

RANDOMIZATION AND INTERVENTIONAL PROCEDURE. Subjects were pre-treated with aspirin 325 mg and clopidogrel 600 mg orally before cardiac catheterization. To help safeguard the blind, subjects were maintained with a deep level of conscious sedation by intravenous midazolam (1- to 2-mg boluses) and fentanyl (25- to 50-μg boluses) during the procedure. The femoral vein was accessed with an 8-F sheath and a second 6-F sheath. Anticoagulation was obtained with heparin 5,000 units intravenously. An intracardiac ultrasound probe (Acuson, Siemens AG, Malvern, Pennsylvania) was used to assess anatomy of the interatrial septum. A 6-F multipurpose diagnostic catheter was then advanced and a J-tipped guidewire was used to probe the atrial septum. If the guidewire successfully entered the left atrium, this defined the presence of a PFO. This procedure ensured that only subjects with a PFO were included in the randomization assignment. After intracardiac ultrasound and confirmation of PFO, patients were randomized by blocks according to the institution and whether the subject had migraine with or without aura. Randomization with envelopes was performed by the sponsor, not the individual implanting sites. Once the physician had crossed the PFO, the research coordinator called the randomization phone number, which connected them to a live person with the sponsor. The sponsor's clinical representative verified the randomization stratification questions, pulled the next sequential envelope, and relayed the randomization assignment to the unblinded coordinator. If the subject was assigned to the control arm, the catheters were removed and hemostasis was obtained. If the subject was assigned to the device arm, an appropriately sized Amplatzer PFO Occluder

(St. Jude Medical, St. Paul, Minnesota) was placed through an 8-F or 9-F catheter across the atrial septum. Subjects were usually discharged home the same day.

The subject and the treating neurologist were blinded to treatment assignment. Subjects filled out a daily diary questionnaire that included questions regarding the quality and duration of headache and associated symptoms, as well as medications taken. Subjects returned at 1, 3, 6, and 12 months to review their headache diary with the neurologist. The neurologist assessed whether attacks met criteria for migraine with or without aura based on International Classification of Headache Disorders 2. Attacks were diagnosed as migraine with aura if subjects reported visual, sensory, or language symptoms before or during headache. All subjects were on stable preventative medications prior to enrollment and preventive therapy was not altered for the 1-year duration of the trial. The blind was broken at the end of 12 months. Subjects in the control arm had the option to undergo PFO closure electively at no cost. These unblinded implant procedures were used for safety analysis but not efficacy analysis.

ENDPOINTS. The primary efficacy endpoint was the 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 months 10 through 12 in the treatment phase (device group vs. control group). The primary safety endpoint was the proportion of subjects (including both blinded treatment and unblinded crossover) who experienced a device-related major adverse event through 12 months of follow-up.

The pre-specified secondary endpoints included:

1. Change in the mean number of migraine days from baseline to treatment phase.
2. Subjects experiencing 75%, 95%, or greater reduction in migraine headache attacks during treatment phase as compared to baseline phase analyzed at 12 months.
3. Successful closure of the defect, defined as TCD grade 2 or less residual shunt at the 12-month follow-up.

An independent data safety monitoring board adjudicated adverse events, oversaw the study, and safeguarded the interests of study subjects. Independent core labs assessed transthoracic echocardiograms and reviewed the TCD studies. A steering committee, comprising 2 headache neurologists and 2 interventional cardiologists, proposed the trial and wrote the protocol in conjunction with the sponsor (with guidance from the U.S. Food and Drug Administration). The study was sponsored by AGA Medical, which was acquired by St. Jude Medical in 2010 during the course of the trial.

STATISTICAL METHODS. Continuous variables were summarized using mean ± SD. Categorical variables are summarized using frequencies and percentages. For comparison between device group and control group, the 2-sample Student's *t*-test for normally distributed continuous data or Wilcoxon rank-sum test for non-normally distributed continuous data were performed. Chi-square test or Fisher exact test were performed for categorical variables. Statistical significance was achieved if a 2-sided test obtained a p value of <0.05. Version 9.0 or higher of the SAS statistical software package (SAS Institute, Cary, North Carolina) was used for all statistical analyses.

The sample size of the PREMIUM trial was 230 subjects and was determined using the coprimary efficacy and safety endpoints. Briefly, both endpoints assumed a type I error of 5% and an overall power of 80%. The remaining sample size assumptions can be found in the Online Appendix.

RESULTS

The PREMIUM trial began in 2006 and required 7 years to complete enrollment of 230 subjects (Figure 1). Of the 1,653 subjects who consented, 1,423 did not meet the entry criteria, predominantly (69%) due to failure to have a large enough shunt on TCD. Due to the assignment by block, of the 230 participants, there were 123 subjects randomized to the device group and 107 to the control group. The groups were adequately randomized for age, sex, body mass index, Migraine Disability Assessment Survey and depression scores, as well as the distribution of subjects who had migraine with or without aura (Table 1). There was no difference in the average number of migraine days in the device group and the control group at baseline or in migraine attacks per month. Of the 123 subjects who were randomized to PFO closure, 119 received a PFO occluder implantation. The 4 subjects who did not have a PFO occluder implanted had anatomy not amenable to closure per the operator's judgment or device-sizing guidelines. Ten subjects dropped out of the study prior to the 12-month follow-up; 6 in the device group and 4 in the control group. Catheterization procedural characteristics are presented in Table 2.

EFFICACY ENDPOINTS. The primary efficacy endpoint, the responder rate for a 50% reduction in

migraine attacks (with or without aura) was not met; 38.5% in the device arm and 32% of the control subjects had a 50% reduction in migraine attacks, p = 0.32 (Table 3). The rate difference for the primary efficacy endpoint was 6.4% (95% confidence interval: −6.2 to 19.0).

For the secondary endpoints, there was a significant decrease in the mean number of migraine days per month in the device versus control groups: -3.4 ± 4.4 days versus -2.0 ± 5.0 days (p = 0.025) (Table 4). There was no difference in the percentage of subjects who had 75% or greater reduction in migraine attacks, 20.5% (24 of 117) versus 16.5% (17 of 103), p = 0.45, but there was a significant difference in subjects who had complete cessation of migraine attacks: 8.5% (10 of 117) in the device arm versus 1.0% (1 of 103) in the control arm (p = 0.01). Of these, there were 6 subjects with frequent aura who had complete remission, whereas 4 subjects with infrequent or no aura also responded with complete remission of migraine after PFO closure.

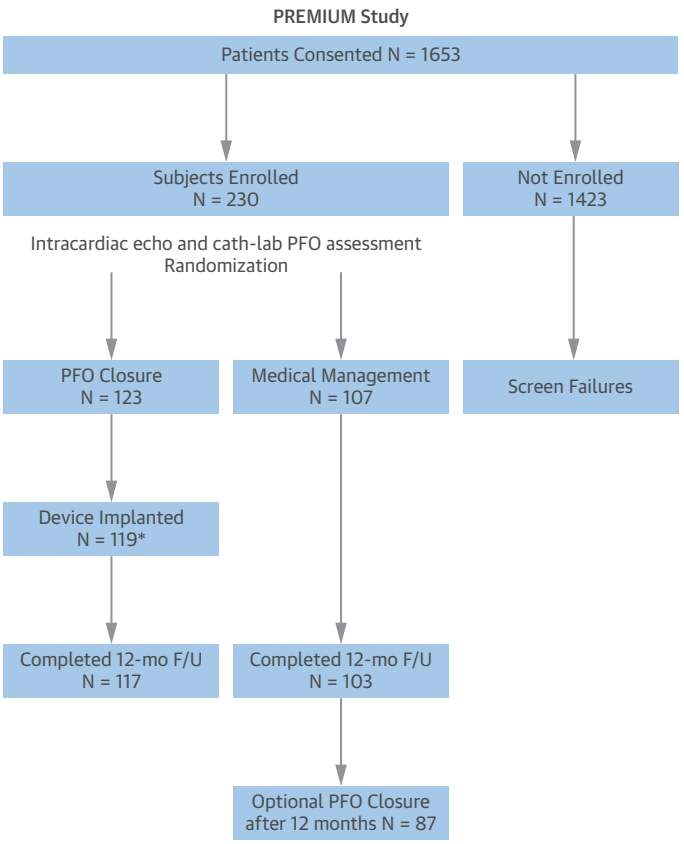
The change in Migraine Disability Assessment Survey score from baseline to 12 months was not different in the entire cohort between the groups nor was the change in quality of life questionnaire, the mental component score, or the improvement in the Beck Depression Inventory.

SAFETY DATA. There were 6 major procedure-related adverse events in 205 (2.9%) implantations with adequate follow-up data. Procedure-related complications were self-limited and most represented common adverse events associated with any right heart catheterization, including arm phlebitis from an intravenous line, groin hematoma and pain, transient hypotension, tachycardia, and a vasovagal episode. There was 1 (0.5%) device-related adverse event of nonsustained atrial fibrillation, which occurred during the deployment of the device.

To protect the blind, the rate of successful closure was assessed only at 12 months post-procedure. Adequate closure was defined as a residual TCD grades 0 to 2 (<30 bubbles in 1 min) with straining and was obtained in 83% of the 104 subjects in the device arm with available data. At 12 months, a TCD grade 3 was present in 11% of subjects, grade 4 in 2%, and grade 5 in 5%. The blind was broken prior to 12 months in 4 of 230 subjects (2%). The reasons for breaking the blind early included clinical symptoms that the treating cardiologist or an outside physician suspected could be related to the device. The symptoms were adjudicated as not related to the device in all 4 cases.

The sensitivity of TCD was greater than that of transthoracic echocardiogram (TTE) for identifying patients with a large RLS. TTE was unable to obtain a satisfactory study in 10 of 230 cases (4%). Of the remaining 220 subjects, there was agreement in 211 (96%) and disagreement in 9 (4%). All 9 discordant results involved a negative TTE finding and a positive TCD finding. All of these patients had a PFO with RLS documented during heart catheterization.

FIGURE 1 Flow Chart of the PREMIUM Protocol



*Pooled safety data includes all subjects with 6 months of post-implant follow-up (118 in randomization group and 87 in optional closure group). F/U = follow-up; PFO = patent foramen ovale; PREMIUM = Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management.

DISCUSSION

The PREMIUM trial of PFO closure to prevent migraine did not meet the primary endpoint of a superior 50% or greater reduction in migraine attacks compared with sham control. The trial did meet the secondary endpoint of significant reduction in headache days after PFO closure for subjects with or without aura (Central Illustration). The classification

TABLE 1 Baseline Clinical Characteristics

	PFO Closure (n = 123)	Control (n = 107)
Age, yrs	42.8 ± 10.3	43.7 ± 10.2
Female	110/123 (89.4)	95/107 (88.8)
BMI, kg/m^2	26.7 ± 5.3	25.8 ± 5.3
History of head trauma or serious injury	17/123 (13.8)	16/107 (15.0)
Palpitations	25/123 (20.3)	24/107 (22.4)
Hypercholesterolemia	25/123 (20.3)	24/107 (22.4)
Snoring	40/123 (32.5)	35/107 (32.7)
Mood disorder	35/123 (28.5)	42/107 (39.3)
Birth control/HRT	95/123 (77.2)	81/107 (75.7)
Steroid use	57/123 (46.3)	46/107 (43.0)
Substance abuse in last month	3/123 (2.4)	2/107 (1.9)
Migraine with aura	80/123 (65.0)	71/107 (66.4)
MIDAS score	45.7 ± 27.9	48.8 ± 33.0
BDI score	7.2 ± 7.5 (122)	6.6 ± 7.7 (106)

Values are, n/N (%) or mean ± SD (n).

BDI = Beck Depression Inventory; BMI = body mass index; HRT = hormone replacement therapy; MIDAS = Migraine Disability Assessment Survey; PFO = patent foramen ovale.

subcommittee of the International Headache Society recommends 1 of 2 primary endpoints in migraine preventive trials: the number of migraine attacks per evaluation interval or the number of migraine days per evaluation interval. Because of the difficulty in defining migraine attacks, many trialists prefer migraine days as the endpoint (17). In addition, 8.5% of subjects who had migraine with or without aura had complete resolution of migraine, which persisted to the last diary follow-up at 1 year. The PFO closure procedure was generally safe in the 205 patients who received it. Except for a single subject who developed nonsustained intraprocedural atrial fibrillation, the adverse events were self-limited mild events that

TABLE 2 Procedure Characteristics

	PFO Closure (n = 123)	Control (n = 107)	p Value
Atrial septal aneurysm by ICE imaging	28 (23)	19 (18)	0.35
Total procedure time, min	59.5 ± 57.4	43.1 ± 42.2	<0.001
Fluoroscopy time, min	7.7 ± 5.5	4.7 ± 4.0	<0.001
Device size implanted			
18 mm	20/119 (16.8)	–	
25 mm	94/119 (79.0)	–	
35 mm	5/119 (4.2)	–	

Values are n (%), mean ± SD, or n/N (%). Categorical p values are based on Fisher exact test. Continuous p values are based on Student's *t*-tests.

ICE = intracardiac echo; PFO = patent foramen ovale.

TABLE 3 Average Number of Migraine Attacks at Baseline and at Months 10 to 12

	Device (n = 117)	Control (n = 103)	p Value
Responder rate	45/117 (38.5)	33/103 (32.0)	0.32
Baseline phase	4.8 ± 1.3 (117)	4.6 ± 1.4 (103)	0.14
Months 10–12	2.9 ± 1.8 (116)	3.2 ± 1.7 (103)	0.67

Values are n/N (%) or mean ± SD. Categorical p values are based on Fisher exact test. Continuous p values are based on Student's *t*-tests.

may occur with any right heart catheterization procedure.

Although the study was designed to investigate both migraine with aura and migraine without aura, twice as many of those enrolled had a diagnosis of migraine with aura (66%) than without aura (34%). In the general population, the prevalence of migraine with aura is roughly one-half that of migraine without aura (18,19). The over-representation of patients with migraine with aura in this study is likely due to the screening requirement for a significant RLS, which selects for patients with aura (9,10,20).

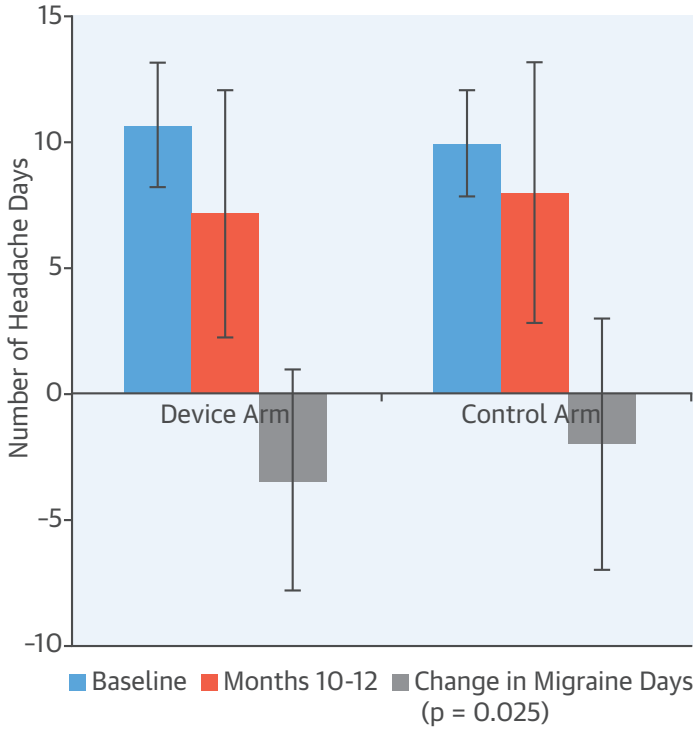
The fact that PFO may represent a source of paradoxical embolism through an RLS has led to the hypothesis that the increased risk of stroke in migraine could be related to the increased prevalence of PFO in migraine (9,20). There have been 11 observational studies encompassing 1,632 patients who have had their PFO closed predominantly to prevent cryptogenic stroke. Migraine with or without aura was present in 34% (547) of these patients (21). In the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial, a randomized controlled study of PFO closure to prevent recurrent cryptogenic stroke, the frequency of migraine was 39%, which is 3× the expected frequency in the general population (12%) (22).

TABLE 4 Mean Number of Migraine Days and Change From Baseline

	Average Migraine Days		
	Device (n = 116)	Control (n = 103)	p Value
Baseline phase	10.7 ± 2.5	10.0 ± 2.1	0.03
Months 10–12	7.2 ± 4.9	8.0 ± 5.2	0.28
Change in migraine days	−3.4 ± 4.4	−2.0 ± 5.0	0.025

Values are mean ± SD. p values are based on Student's *t*-tests.

CENTRAL ILLUSTRATION **Percutaneous Closure With a PFO Occluder for Migraine Prevention**



Tobis, J.M. et al. J Am Coll Cardiol. 2017;70(22):2766–74.

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 was a double-blind study investigating migraine characteristics over 1 year in subjects randomized to medical therapy with a sham procedure (right heart catheterization) versus medical therapy and patent foramen ovale (PFO) closure with the Amplatzer PFO Occluder device (St. Jude Medical, St. Paul, Minnesota). Subjects had 6 to 14 days of migraine per month, had failed at least 3 migraine preventive medications, and had significant right-to-left shunt defined by transcranial Doppler. The trial did not meet the primary endpoint of responder rate, defined as 50% reduction in migraine attacks.

PRIOR RANDOMIZED CLINICAL TRIALS FOR MIGRAINE. The MIST (Migraine Intervention with STARFlex Technology) trial was the first randomized, double-blinded, sham-controlled trial to evaluate the effect of PFO closure on migraine with aura (23). Based on prior observational studies, the primary endpoint of the study was chosen as complete cessation of migraine. Secondary endpoints included a change in the incidence, severity, frequency, or character of migraine or an overall change in the quality of life. The MIST trial showed no significant effect for either primary or secondary endpoints. Of the 74 patients in the treatment arm, only 3 reported migraine cessation, which was no different than 3 of the 73 patients in the sham group who also reported complete cessation of headaches at 6 months. Concerns about the MIST trial included the effectiveness of this early generation PFO closure device and the complication rate of the procedure (14%).

The PRIMA (Percutaneous Closure of Patent Foramen Ovale in Migraine With Aura) trial studied 107 patients with migraine with aura at 20 sites in Europe and Canada randomized without blinding to the Amplatzer PFO Occluder plus preventive medical therapy versus medical therapy alone. PFO closure did not meet the primary endpoint of significantly greater reduction in migraine days per month as compared with medical therapy, but device implantation did significantly reduce the number of migraine with aura days ($p = 0.01$) and attacks ($p < 0.01$) (24). PFO closure was associated with a greater responder rate (≥50% reduction in number of migraine days) compared with medical therapy (38% vs. 15%; $p = 0.02$). More closure patients reported freedom from migraine (10% vs. 0%, $p = 0.055$) and

TABLE 5 Subjects Whose Majority of Migraines Are With Aura

	Device (n = 39)	Control (n = 40)	p Value
Migraine attack responder rate	19/39 (49)	9/40 (23)	0.015*
Baseline phase: migraine attacks	4.8 ± 1.2	4.9 ± 1.1	0.70
Months 10–12: migraine attacks	2.3 ± 1.7†	3.4 ± 1.6	0.004
Baseline phase: migraine days per month	11.2 ± 3.0	10.0 ± 2.3	0.06
Months 10–12: migraine days per month	6.8 ± 6.1	9.0 ± 5.8	0.11

Values are n/N (%) or mean ± SD. *Based on chi-square analysis, Student's *t*-tests for others. †n = 38.

freedom from migraine with aura (40% vs. 10%, p = 0.004) than those treated with medical therapy. Although limited by the lack of blinding and a sham procedure control (25), the PRIMA trial results have some similarities with those of the PREMIUM trial; both found that PFO closure resulted in a significant reduction of migraine with aura days, and in both studies, a small but significant percentage had complete resolution of migraine.

There has been interest in the use of botulinum toxin injection for the treatment of migraine. The PREEMPT (Phase 3 Research Evaluating Migraine Prophylaxis Therapy) trial showed a benefit of botulinum toxin injections for patients with chronic migraine, defined as >15 headache days per month (26). The patient population for the PREMIUM trial had episodic migraine, defined as 6 to 14 headache days per month. The botulinum toxin studies for people with episodic migraine did not show a difference in migraine frequency compared with people on placebo (27,28).

The placebo response in the PREMIUM study was 32%. Although this placebo response is high, it is within the range of control arm responses observed in other studies of migraine-preventive therapy (17,29). This observation underscores the importance of having an adequate sham control and double-blinding in clinical trials of device interventions for migraine (25).

POTENTIAL MECHANISMS FOR INVOLVEMENT OF PFO IN MIGRAINE. A transient increase in right atrial pressure during straining or exercise opens the flap of the septum primum of a PFO and permits bursts of venous blood to enter the arterial circulation. One hypothesis for the connection between migraine and PFO is that substances or microemboli that reach the brain through an RLS, bypassing metabolism or filtration by the lungs, could trigger a migraine attack. In a rat model, carotid injection of microemboli evokes cortical spreading depression, the slowly propagated wave of brain activity believed to be the physiological mechanism underlying the migraine aura (30). An alternative hypothesis is that transient changes in oxygen content of blood delivered to the brain could play a role in induction of migraine. Normobaric hypoxia or high altitude has been reported to be a migraine trigger (31,32) and treatment with nasal oxygen has been reported to avert or diminish migraine attacks (33,34). Other unidentified venous substances normally metabolized by the lung could also act as migraine triggers.

PFO is associated to a greater degree with migraine with aura as compared to migraine without aura (6,7). The reasons for the particular relationship between PFO and migraine with aura are not clear. The diagnosis of migraine with aura is associated with different genetics and comorbidities, and migraine attacks with aura may have different clinical features and responses to therapies (35). On the other hand, a majority of patients who have migraine with aura also have migraine without aura. Whereas data from animal models indicate that cortical spreading depression may cause pain, in humans, aura is neither necessary nor sufficient for causing migraine headache (36). Further investigation of the specific relationship between PFO and the migraine aura may provide important new insight into how aura occurs and what role it plays in migraine.

STUDY LIMITATIONS. The sample size assumptions included a responder rate that was twice the response rate for the control group, which is a large treatment effect. This may have led to the study being underpowered.

CONCLUSIONS

SUBGROUP ANALYSIS FOR NONSPECIFIED ENDPOINTS. Although the PREMIUM trial did not demonstrate efficacy for PFO closure using the primary endpoint of responder rate, an additional subgroup analysis was performed that evaluated subjects who had aura as a consistent component of their migraine attacks (>50% of episodes). For this subgroup, there was a significant difference in the responder rate: 49% (19 of 39) versus 23% (9 of 40) for device versus control group, p = 0.015. For subjects with frequent aura, 15.4% (6 of 39) had complete cessation of their migraine attacks versus 2.5% (1 of 40) in the control group, p = 0.04 (**Table 5**). Because this subgroup was not pre-specified, these observations can only be used to generate the hypothesis that a future clinical trial of PFO closure might be beneficial in subjects where aura is a frequent component (>50%) of the migraine episodes.

PFO CLOSURE AS A MIGRAINE THERAPY? Not the PREMIUM trial nor the MIST or PRIMA trials provide evidence to support the use of PFO closure as a preventive therapy for migraine. The 8.5% of patients in the PREMIUM trial who experienced a complete remission of migraine over a 1-year time period raises the hypothesis that an atrial shunt may play a causative role for a subset of patients with migraine.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a randomized trial, percutaneous closure failed to ameliorate migraine headache in patients with PFO.

TRANSLATIONAL OUTLOOK: Further studies are needed to confirm whether patients in whom migraine is associated with frequent aura respond more favorably to percutaneous PFO closure, as suggested in a subset analysis of this trial.

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KEY WORDS Amplatzer PFO Occluder device, aura, double-blind randomized clinical trial, migraine, patent foramen ovale

APPENDIX For supplemental material, please see the online version of this paper.