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ORIGINAL INVESTIGATIONS

Pooled Analysis of PFO Occluder Device Trials in Patients With PFO and Migraine

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ABSTRACT

BACKGROUND Although observational studies have shown percutaneous patent foramen ovale (PFO) closure to be a safe means of reducing the frequency and duration of migraine, randomized clinical trials have not met their primary efficacy endpoints.

OBJECTIVES The authors report the results of a pooled analysis of individual participant data from the 2 randomized trials using the Amplatzer PFO Occluder to assess the efficacy and safety of percutaneous device closure as a therapy for episodic migraine with or without aura.

METHODS The authors analyzed individual patient-level data from 2 randomized migraine trials (the PRIMA [Percutaneous Closure of Patent Foramen Ovale in Migraine With Aura] and PREMIUM [Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the Amplatzer PFO Occluder Compared to Medical Management] studies). Efficacy endpoints were mean reduction in monthly migraine days, responder rate (defined as ≥50% reduction in monthly migraine attacks), mean reduction in monthly migraine attacks, and percentage of patients who experienced complete cessation of migraine. The safety endpoint was major procedure- and device-related adverse events.

RESULTS Among 337 subjects, 176 were randomized by blocks to device closure and 161 to medical treatment only. At 12-month follow-up, the analysis met 3 of the 4 efficacy endpoints: mean reduction of monthly migraine days (−3.1 days vs. −1.9 days; $p = 0.02$), mean reduction of monthly migraine attacks (−2.0 vs. −1.4; $p = 0.01$), and number of subjects who experienced complete cessation of migraine (14 [9%] vs. 1 [0.7%]; $p < 0.001$). For the safety analysis, 9 procedure-related and 4 device-related adverse events occurred in 245 subjects who eventually received devices. All events were transient and resolved.

CONCLUSIONS This pooled analysis of patient-level data demonstrates that PFO closure was safe and significantly reduced the mean number of monthly migraine days and monthly migraine attacks, and resulted in a greater number of subjects who experienced complete migraine cessation. (J Am Coll Cardiol 2021;77:667–76)

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ABBREVIATIONS AND ACRONYMS

MIDAS = Migraine Disability Assessment

PFO = patent foramen ovale

TCD = transcranial Doppler

TEE = transesophageal echocardiography

Migraine is a disabling neurological disorder that affects 12% of the population (1). Current medical therapies are often ineffective or poorly tolerated (2,3). There is also spontaneous fluctuation in migraine frequency, which may help explain the variability in treatment response (4).

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Studies have described a link between the presence of a patent foramen ovale (PFO) and migraine, especially migraine with aura (5–8). PFO is present in 20% to 25% of the adult population (9,10) but in 30% to 50% of those who have migraine with aura (11,12). At least 11 observational studies including 1,632 subjects have described the effect of PFO closure for cryptogenic stroke (13). Migraine (with or without aura) was present in 34% of those subjects, and percutaneous PFO closure was reported to reduce migraine days (>50% reduction in migraine days/month) in 81% of subjects.

Two prospective randomized clinical trials evaluated the efficacy and safety of the Amplatzer PFO Occluder (Abbott Vascular, Santa Clara, California) for reducing the frequency and duration of episodic migraine headaches in subjects who have PFOs (14,15). The 2 trials did not meet their respective primary endpoints, but both showed a significant benefit of PFO closure in most of their secondary endpoints. The aim of this study was to pool the individual participant data from these 2 trials, to increase the power to detect the effect of percutaneous PFO closure for treating patients with migraine compared with medical therapy alone.

METHODS

INCLUDED TRIALS. The PRIMA (Percutaneous Closure of Patent Foramen Ovale in Migraine With Aura) trial randomized, but did not blind, 107 subjects 21 to 61 years of age with PFOs to device closure plus continued medical therapy or medical treatment only. The presence of a PFO was documented with transesophageal echocardiography (TEE) bubble study. Subjects had to be unresponsive to 2 commonly used preventive migraine medications of different classes and were followed for 1 year (14). Acceptable classes of medications were antiepileptic drugs (e.g., topiramate, valproate), antidepressants (e.g., amitriptyline, venlafaxine), beta-blockers (e.g., propranolol, metoprolol), and calcium-channel blockers (e.g., flunarizine) (16). Subjects in both arms received 3 months of clopidogrel 75 mg/day and 6 months of aspirin 75 to 100 mg/day. All patients in the PFO closure arm underwent repeat TEE at 6 months to assess for the presence of significant residual right-to-left shunt, defined as grade 2 or higher, and again at 12 months if 6-month TEE showed incomplete PFO closure.

The PREMIUM (Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the Amplatzer PFO Occluder Compared to Medical Management) trial used a patient- and neurologist-blinded, sham-controlled procedure to randomize 230 subjects with migraine (with or without aura), 18 to 65 years of age, with a 1-year follow-up. Subjects were unblinded after 1 year (15). Study participants were screened for a significant (grade 4 or 5) right-to-left shunt with a transcranial Doppler (TCD) agitated saline bubble study. The diagnosis of PFO was confirmed at the time of the closure procedure randomization by passage of a guidewire across the atrial septum. The inclusion criteria stipulated that all subjects had to be unresponsive to or could not tolerate 3 preventive migraine medications of different classes. Acceptable classes of medications, on the basis of American Headache Society and American Academy of Neurology preventive guidelines and similar to PRIMA, were antiepileptic drugs (e.g., topiramate, valproate), antidepressants (e.g., amitriptyline, venlafaxine), beta-blockers (e.g., propranolol, metoprolol), and calcium-channel blockers (e.g., flunarizine) (16). In both arms of the trial, subjects were treated with 1 month of clopidogrel 75 mg/day and 6 months of aspirin 325 mg/day. Subjects in the medical therapy arm received the same antiplatelet regimen and also underwent a sham right heart catheterization procedure to ensure patient blinding. All patients in the PFO closure arm underwent repeat TCD at 12 months to assess for the presence of significant residual right-to-left shunt, defined as grade 3 or higher. Both PRIMA and PREMIUM required that the preventive migraine

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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medications and their doses remain unchanged during 12-month follow-up.

In both PREMIUM and PRIMA, the criteria of "unresponsiveness" to preventive migraine medications was left to the discretion of the treating headache specialist who performed the intake medication review. However, per local society guidelines, the subject had to experience a ≥50% reduction in headache days per month for the medication to be considered responsive.

The MIST (Migraine Intervention with STARFlex Technology) trial was not included in this analysis, because it used a different PFO-occluding device, the STARFlex septal repair implant (NMT Medical, Boston, Massachusetts). The individual participant data were unavailable (17).

ENDPOINTS. The subjects in both trials filled out a daily questionnaire including questions about the quality and duration of headache and associated symptoms. The headache diaries were blindly adjudicated by headache specialists, on the basis of diagnostic criteria for migraine with and without aura set forth by the International Classification of Headache Disorders Version 2.

The primary endpoint of the PRIMA study was the reduction in monthly migraine days during months 10 to 12 after randomization compared with a 3-month baseline phase before randomization. The primary efficacy endpoint of the PREMIUM trial was the responder rate, defined as a ≥50% reduction from the monthly number of migraine attacks during the first 2-month baseline phase to the monthly number of migraine attacks during the 10- to 12-month follow-up treatment phase (device group vs. control group). As each trial had different primary and secondary efficacy endpoints, all 4 endpoints were chosen for the efficacy endpoints of the pooled analysis and were given equal importance. The 4 endpoints were: 1) mean reduction in monthly migraine days; 2) mean reduction in monthly migraine attacks; 3) responder rate; and 4) complete migraine cessation (defined as a 100% reduction in migraine attacks during the treatment phase compared with the baseline phase analyzed at the last available follow-up point). As both trials showed that subjects who have migraine with aura, particularly frequent aura, may have a better response to device closure, we performed a hypothesis-generating subgroup analysis of all efficacy endpoints for subjects who had migraine with aura and those with frequent aura (defined as aura occurring in 50% or more of the migraine attacks).

The following safety outcomes were evaluated using the definitions from the primary studies: any major procedure-related adverse event, vascular procedural complication, atrial fibrillation, or major bleeding episode.

TABLE 1 Patient Characteristics Across Individual Trials

	PREMIUM (n = 230)	PRIMA (n = 107)	p Value
Age, yrs	43.2 ± 10.2	43.1 ± 10.9	NS
Female	205/230 (89.1)	90/107 (84.1)	NS
History of head trauma or serious injury	33/230 (14.3)	3/106 (2.8)	≤0.0001
Mood disorder	77/230 (33.5)	6/103 (5.8)	≤0.0001
Palpitations	49/230 (21.3)	5/106 (4.7)	≤0.0001
Snoring	75/230 (32.6)	27/103 (26.2)	NS
Steroid use	103/230 (44.8)	2/106 (1.9)	≤0.0001
Migraine with aura	151/230 (65.7)	106/107 (99.1)	≤0.0001
MIDAS score	47.1 ± 30.3 (230)	36.8 ± 27.1 (103)	0.002
BDI score	6.9 ± 7.6 (228)	6.8 ± 6.2 (105)	NS

Values are mean ± SD, n/N (%), or mean ± SD (n). The p values are based on Student's *t*-tests for continuous variables and chi-square tests for categorical variables.

BDI = Beck Depression Inventory; MIDAS = Migraine Disability Assessment; NS = nonsignificant; PREMIUM = Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the Amplatzer PFO Occluder Compared to Medical Management; PRIMA = Percutaneous Closure of Patent Foramen Ovale in Migraine With Aura.

DATA MANAGEMENT. The coordinating investigators of PRIMA and PREMIUM participated in this collaborative analysis. The coded raw data were obtained from Abbott Vascular, the sponsor of the 2 trials. The anonymized individual participant data from both studies were compiled into a single dataset forwarded to the primary investigator for analysis. The sponsor had no role in the statistical analysis of this study. This study was approved by the Institutional Review Board of the University of California, Los Angeles. The ethics board did not require obtaining repeat consent from patients, because this post hoc analysis used deidentified data.

STATISTICAL ANALYSIS. Patient characteristics were compared between the 2 trials, with summary statistics expressed as mean ± SD for continuous values and frequencies for categorical values. For comparison of the variables, we used Student's *t*-test for continuous variables with normal distributions, median tests for continuous variables without normal distributions, and chi-square tests for categorical variables.

An intention-to-treat analysis was adopted primarily for all the efficacy outcomes (i.e., subjects were analyzed in accordance with their assigned treatment arm). To examine the potential benefit of PFO closure in certain subgroups, the following subgroup analyses were performed for the 2 primary efficacy endpoints used in PRIMA and PREMIUM: age (>40 years vs. ≤40 years), sex (male vs. female), history of head trauma, palpitations, snoring, mood

TABLE 2 Patient Characteristics Across Treatment Strategies

	PFO Closure (n = 176)	Control (n = 161)	p Value
Age, yrs	43.1 ± 10.4	43.2 ± 10.4	NS
Female	155/176 (88.1)	140/161 (87.0)	NS
History of head trauma or serious injury	18/176 (10.2)	18/160 (11.3)	NS
Mood disorder	36/174 (20.7)	47/159 (29.6)	NS
Palpitations	26/176 (14.8)	28/160 (17.5)	NS
Snoring	57/174 (32.8)	45/159 (28.3)	NS
Steroid use	59/176 (33.5)	46/160 (28.8)	NS
Migraine with aura	133/176 (75.6)	124/161 (77.0)	NS
MIDAS score	43.4 ± 29.3 (174)	44.6 ± 30.3 (159)	NS
BDI score	6.9 [7.5] (175)	6.9 [8.0] (158)	NS

Values are mean ± SD, n/N (%), mean ± SD (n), or median [interquartile range] (n). The p values are based on Student's *t*-tests for continuous variables and chi-square tests for categorical variables.

PFO = patent foramen ovale; other abbreviations as in Table 1.

disorder, steroid use, Migraine Disability Assessment (MIDAS) score (>20 vs. ≤20), Beck Depression Inventory score (>13 vs. ≤13), and trial group (PRIMA vs. PREMIUM). Safety outcomes were reported for procedural complications for all subjects who received devices, which consisted of randomized subjects as well as subjects in the control arm of the PREMIUM trial who agreed to have their PFOs closed after blinding was removed. Given the nature of safety outcomes, analyses were performed using an "as-treated" protocol. Finally, an analysis for interaction was examined across the subgroups. A 2-sided p value <0.05 and 95% confidence intervals were used for all statistical comparisons. All analyses were performed using SPSS Statistics for Windows version 24.0 (IBM, Armonk, New York).

RESULTS

INCLUDED SUBJECTS. Individual participant data from 337 randomized subjects were pooled in this analysis (176 from the closure arms and 161 from the medical therapy arms) (Table 1). Complete follow-up data were available for 157 of 176 patients (89%) belonging to the PFO closure group and 146 of 161 control subjects (91%). The study populations did not differ in any of the baseline characteristics by treatment strategy (Table 2). At baseline, there was no difference in either group in the average number of migraine days (8.3 ± 3.1 days vs. 8.2 ± 2.8 days; p = 0.80) and migraine attacks (4.9 ± 1.4 vs. 4.8 ± 1.8; p = 0.59). However, there were a number of minor differences between the 2 trials. The PREMIUM trial had higher proportions of subjects with histories of head trauma or serious injury, mood disorders, palpitations, and steroid use, whereas the PRIMA trial had a higher percentage of subjects with migraine with aura and higher MIDAS scores.

EFFECTIVE CLOSURE RATES. In PRIMA, 3% of patients (1 of 38, 2 with missing data) met the threshold for significant residual right-to-left shunt on 12-month follow-up TEE. In PREMIUM, 15% of patients (17 of 112, 5 with missing data) met the TCD threshold for significant right-to-left shunt at 12-month follow-up. Migraine day difference (average number of migraine days 10 to 12 months post-PFO closure minus average number of migraine days 2 months pre-PFO closure) between the "significant residual shunt" and "no significant residual shunt" cohorts did not differ (p = 0.94).

EFFICACY ENDPOINTS. Significant reduction in monthly migraine days at 12 months after randomization, one of the efficacy endpoints in this pooled analysis, was achieved. The mean reduction of monthly migraine days was 1.2 days greater in the PFO closure group compared with the control group (−3.1 ± 4.5 days vs. −1.9 ± 4.2 days; p = 0.02) (Central Illustration). There was no evidence of subgroup interaction when all pre-specified subgroups were examined (i.e., according to trial group, age, sex, history of head trauma, palpitations, snoring, mood disorder, steroid use, MIDAS score, and Beck Depression Inventory score) ($p_{interaction} > 0.05$ for all).

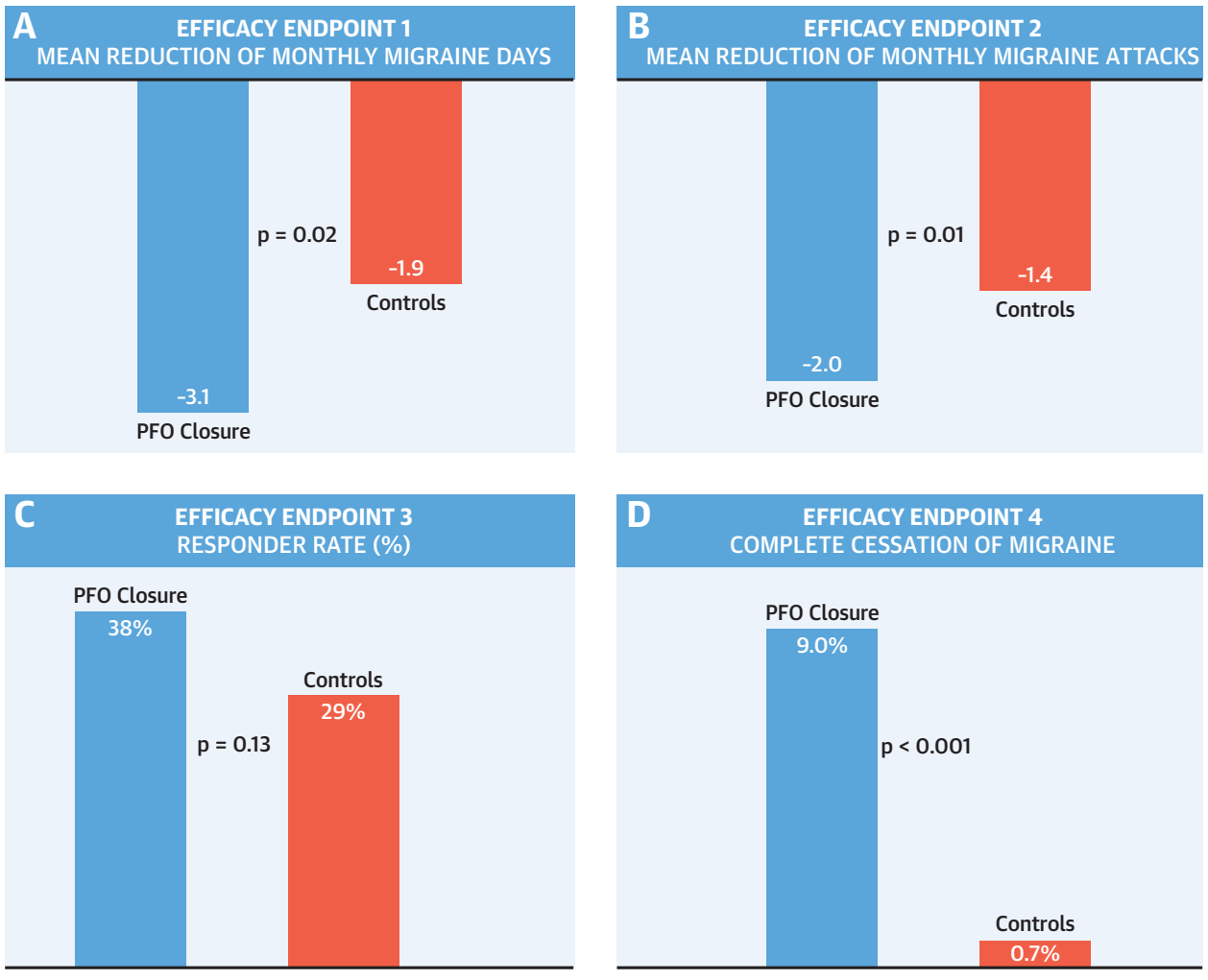
The responder rate, defined as a ≥50% reduction in migraine attacks (with or without aura), did not achieve statistical significance. This endpoint, which was the primary efficacy endpoint in the PREMIUM trial, was met by 38% of subjects (59 of 157) in the device arm and 29% of subjects (43 of 146) in the control arm (p = 0.13) (Central Illustration). There were no differences across the examined subgroups.

Mean reduction in migraine attacks was significantly greater in the PFO closure group compared with the control group (−2.0 ± 2.0 vs. −1.4 ± 1.9; p = 0.01) (Central Illustration).

PFO closure had a higher rate of complete migraine cessation compared with medical therapy (14 of 157 [9%] in the closure arm vs. 1 of 146 [0.7%] in the control arm; p < 0.001) (Central Illustration).

MIGRAINE WITH AURA (AND FREQUENT AURA). Subjects with migraine with aura who underwent PFO closure had a significant reduction in migraine days compared with control subjects (−3.2 ± 4.8 days vs. −1.8 ± 4.4 days; p = 0.03). Subjects with migraine without aura who underwent PFO closure did not have a significant reduction in migraine days compared with control subjects (−2.8 ± 3.4 days vs. −2.2 ± 4.0 days; p = 0.53). The responder rate was not significantly greater for subjects with migraine with aura who underwent PFO closure compared with control subjects (43 of 114 [38%] vs. 32 of 111 [29%];

CENTRAL ILLUSTRATION **Efficacy Endpoints of Patent Foramen Ovale Closure for Treating Migraine Headache Versus Control Subjects at 12-Month Follow-Up Using the Amplatzer PFO Occluder**



Mojadidi, M.K. et al. J Am Coll Cardiol. 2021;77(6):667–76.

Compared with control subjects, patent foramen ovale (PFO) closure yielded a significant mean reduction of monthly migraine days, a mean reduction of monthly migraine attacks, and a greater number of patients with complete migraine cessation ($p \leq 0.05$ for all). There was no significant difference in the responder rate when comparing patients who underwent PFO closure with control subjects.

$p = 0.16$). In addition, the responder rate was not significantly greater for subjects with migraine without aura compared with control subjects (16 of 43 [37%] vs. 11 of 35 [31%]; $p = 0.60$). In subjects with aura, complete headache cessation occurred in 12 of 114 (11%) in the PFO closure group compared with 1 of 111 (0.9%) in the control group ($p = 0.002$). In subjects without aura, complete headache cessation occurred in 2 of 43 (5%) in the PFO closure group compared with 0 of 35 (0%) in the control group ($p = 0.16$).

In subjects with migraine with frequent aura (aura occurring in ≥50% of migraine attacks), PFO closure had a greater reduction in migraine days compared with control subjects (-4.3 ± 5.3 days vs. -1.4 ± 4.8 days; $p = 0.002$). In subjects with infrequent aura (aura occurring during <50% of migraine attacks), PFO closure had no significant reduction in migraine days compared with control subjects (-2.4 ± 3.8 days vs. -2.3 ± 3.7 days; $p = 0.99$). The responder rate was significantly greater in subjects with migraine with frequent aura compared with control subjects (30 of 62 [48%] vs. 16 of 65 [25%]; $p = 0.005$). In contrast, the responder rate was not statistically different for subjects with migraine with infrequent aura

TABLE 3 Analyses of Migraine With Aura and Migraine With Frequent Aura, Comparing Patients Who Underwent Patent Foramen Ovale Closure With Control Subjects

	Migraine With Aura (n = 225)	Migraine Without Aura (n = 78)	Migraine With Frequent Aura (n = 125)	Migraine With Infrequent Aura (n = 100)
Mean reduction in migraine days	−3.2 ± 4.8 vs. −1.8 ± 4.4	−2.8 ± 3.4 vs. −2.2 ± 4.0	−4.3 ± 5.3 vs. −1.4 ± 4.8	−2.4 ± 3.8 vs. −2.3 ± 3.7
p value	0.03	0.53	0.002	0.99
% responder rate	38 vs. 29	37 vs. 31	48 vs. 25	33 vs. 31
p value	0.16	0.60	0.005	0.69
Mean reduction in migraine attacks	−2.0 ± 2.0 vs. −1.4 ± 1.9	−2.0 ± 1.8 vs. −1.0 ± 2.0	−2.7 ± 1.9 vs. −1.5 ± 1.9	−1.5 ± 2.0 vs. −1.4 ± 2.9
p value	0.09	0.03	<0.001	0.52
% complete headache cessation	11 vs. 1	5 vs. 0	13 vs. 1.5	6 vs. 0
p value	0.002	0.16	0.01	0.01

Values are mean ± SD, unless otherwise indicated.

compared with control subjects (27 of 81 [33%] vs. 29 of 95 [31%]; p = 0.69). In subjects with frequent aura, complete headache cessation occurred in 8 of 62 (13%) in the PFO closure group compared with 1 of 65 (1.5%) in the control group (p = 0.01). In subjects with infrequent aura, complete headache cessation occurred in 6 of 95 (6%) in the PFO closure group compared with 0 of 81 (0%) in the control group (p = 0.01) (Table 3).

SAFETY ENDPOINTS. There was a total of 9 procedure-related adverse events and 4 device-related adverse events (Table 4). Procedure-related adverse events were all transient and represented those associated with any right heart catheterization, including access-site hematoma and transient hypotension. The most common device-related adverse event was paroxysmal atrial fibrillation (0.8% [2 of 245]). There were no adverse events with permanent sequelae.

DISCUSSION

This pooled individual participant data analysis of 337 subjects with episodic migraine headaches (between 6 and 15 headache days/month) refractory to medical preventive therapy who had PFOs demonstrated a significant reduction in migraine days after PFO closure compared with control subjects. In addition, there was a significant reduction of migraine attacks and a greater likelihood of complete headache cessation compared with the control population. The responder rate was significantly higher in the closure subgroup of subjects with frequent aura but not in subjects with migraine with infrequent or without aura (14). There were no clinically relevant adverse events.

Subjects with migraine with aura, in particular those with frequent aura, had a significantly greater reduction in migraine days and a higher incidence of complete migraine cessation following PFO closure. In subjects without aura, PFO closure did not significantly reduce migraine days or improve complete headache cessation. However, some patients without aura do respond to PFO closure, which was statistically significant for reduction of migraine attacks (−2.0 vs. −1.0; p = 0.03). The interaction between the brain that is susceptible to migraine and the plethora of potential triggers is complex. A PFO may be the potential pathway for a variety of chemical triggers, such as serotonin from platelets, and although less frequent, some people with migraine without aura may trigger their migraine through this mechanism. This hypothesis will be tested in a future randomized clinical trial called RELIEF (GORE® CARDIOFORM Septal Occluder Migraine Clinical Study; NCT04100135). Currently, migraine is thought to be partially due to activation of the trigeminovascular system, and calcitonin gene-related peptide, a 37 amino acid neuropeptide, has been shown to mediate this system. It is unknown how migraine pathophysiology and the role of this peptide may differ in patients with PFOs who have migraine with frequent versus infrequent or no aura (18). Observational studies have shown that migraineurs with aura are more likely to have PFOs (11–13), indicating that the migraine mechanism involving PFO more often results in aura symptoms. It can be hypothesized that the migraine without aura cohort consists of a higher fraction of incidentally found PFOs, leading to the apparent reduction in observed therapeutic benefit for this group.

Both the PRIMA and PREMIUM trials showed similar results, with PFO closure having a consistent effect on migraine headaches. The different primary endpoints of PRIMA and PREMIUM were secondary endpoints in the respective sister trial. Had the primary endpoints of the studies been selected in reverse manner, both trials would have met their

primary endpoints and be considered positive studies (**Figure 1**) (19). When the sample size was increased by combining the 2 trials in this pooled analysis, the efficacy endpoint of reduction in migraine days was statistically significant. In addition, complete migraine cessation was observed in 9% of subjects in the PFO closure arm, which was significantly greater compared with 1% in medical control subjects.

In a study-level meta-analysis by Elbadawi et al. (20), PFO closure was associated with a significant reduction in monthly migraine attacks and monthly migraine days. In addition, migraine attacks associated with aura responded more favorably to PFO closure. Previous observational studies showed that migraine with aura responds more favorably to PFO closure compared with migraine without aura (5-8,13).

A recent observational study of 474 subjects with migraine who underwent PFO closure predominantly for cryptogenic stroke demonstrated that milder forms of migraine show improvement (21), highlighting a potential benefit of reducing migraines when PFO closure is performed to prevent recurrent stroke. Although speculative, it is reasonable to hypothesize that PFO closure in migraineurs might also have a benefit in reducing the risk for future stroke. Migraine is a known risk factor for stroke, and migraineurs with aura have an even greater risk for both stroke and all-cause mortality than migraineurs with no aura (22). As PFO occurs more frequently in patients who have cryptogenic stroke and migraine with aura, and considering that migraine has been linked to altered platelet function and increased thromboembolism (23-25), a PFO may act as a conduit for the passage of blood clots or platelet plugs to cause stroke or myocardial infarction in patients who have migraine with aura. In the same study (21), the absence of residual right-to-left shunting after device closure was associated with a 4-fold reduction in migraine burden. This suggests that completeness of right-to-left shunt elimination may be an important quality metric for randomized clinical trials of migraine. The different prevalence of residual shunt in the PRIMA and PREMIUM trials was most likely due to the different sensitivities of the methods of assessing shunt (TEE vs. TCD), but other possible reasons include use of different grading scales and use of different interpreters.

Why did the PRIMA and PREMIUM trials not individually meet their respective primary endpoints? One explanation could be a large placebo effect. The Hawthorne placebo effect posits that the behavior of study subjects, and therefore study results, are altered because participants are aware that they are being studied and they receive additional attention. For example, 32% of the control group in PREMIUM and 26% of the control group in PRIMA had ≥50% reductions in migraine attacks. Similarly, 73% (74 of 102) of the control group in PREMIUM and 66% (27 of 41) of the control group in PRIMA experienced some degree of reduction in migraine days at the end of 1 year. An additional explanation is the fluctuation of symptoms in migraine (26). The stronger placebo effect in the PREMIUM control group is possibly a result of patient blinding with a sham procedure, which was not used in PRIMA (27). In addition, PREMIUM included subjects with and without aura, whereas PRIMA included only subjects who had migraine with aura.

TABLE 4 Safety Outcomes

Procedure related	
Access-site bleeding	0.4 (1/275)
Arm phlebitis from intravenous line	0.4 (1/275)
Hematoma	0.7 (2/275)
Hypotension	0.7 (2/275)
Tachycardia	0.4 (2/275)
Vasovagal episode	0.4 (1/275)
Possibly device related	
Fatigue	0.4 (1/245)
Nonsustained atrial fibrillation	0.8 (2/245)
Syncope	0.4 (1/245)

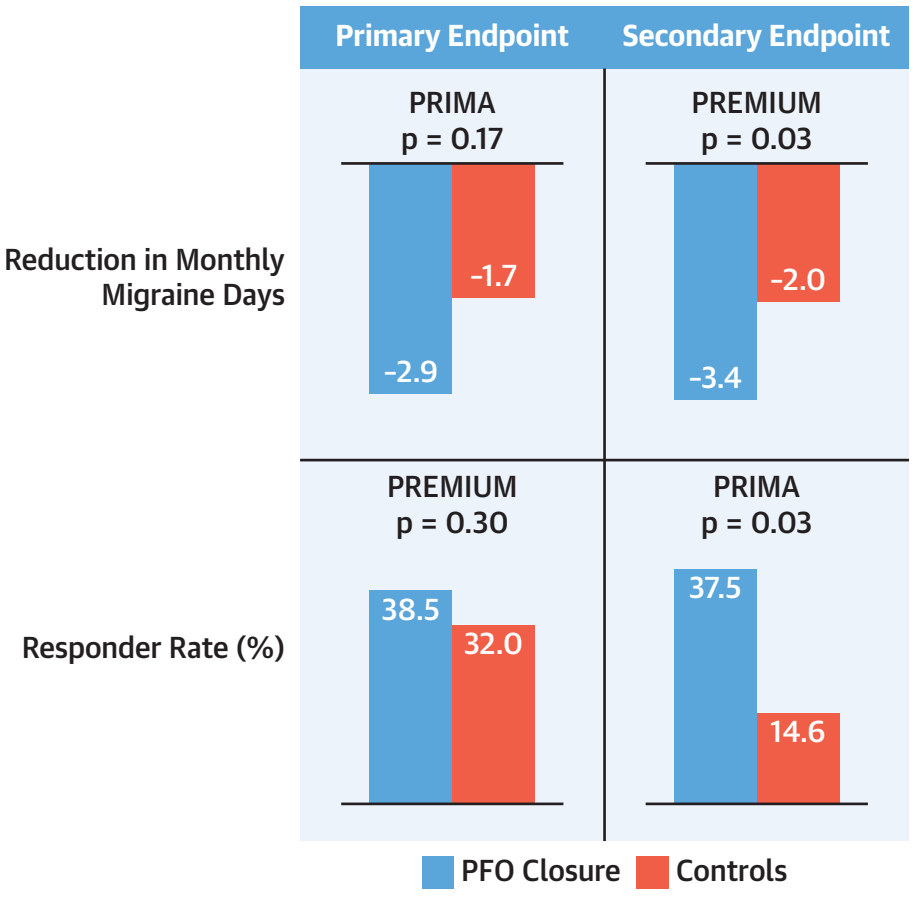
Values are % (n/N).

Although PFO closure appears to be beneficial at 1 year in diminishing migraine burden in select patients with histories of migraine, long-term follow-up data from PREMIUM and PRIMA are lacking. Consequently, it is not known from randomized trials if PFO closure permits a beneficial effect over many years.

Although PFO closure is considered a quick and simple procedure, it is not appropriate for everyone, including patients with contraindications to antiplatelet agents (e.g., aspirin or clopidogrel), complex cardiac anatomy (e.g., presence of a fenestrated septum), and patients with diabetes on insulin, because these groups of patients were excluded from the original trials. Long-term consequences of device implantation also need to be discussed with patients. Although none of the subjects from these randomized controlled trials had to have their PFO closure devices removed, an observational study of 13,736 patients reported a 0.28% frequency of device removal, which requires open heart surgery (28).

STUDY LIMITATIONS. One major limitation of this pooled analysis is the use of efficacy endpoints that were in part primary and in part secondary in PRIMA

FIGURE 1 Effect of PFO Closure on Migraine Headaches in Randomized Controlled Trials Using the Amplatzer PFO Occluder



The different primary endpoints of PRIMA (Percutaneous Closure of Patent Foramen Ovale in Migraine With Aura) and PREMIUM (Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the Amplatzer PFO Occluder Compared to Medical Management) were secondary endpoints in the respective sister trial. Had the primary endpoints of the studies been selected in reverse manner, both trials would have met their primary endpoints and be considered positive studies. PFO = patent foramen ovale.

and PREMIUM. The initial proposal for PREMIUM was to stipulate migraine days as the primary endpoint (the same as PRIMA). At that time, the U.S. Food and Drug Administration required the use of the responder rate of migraine attacks. Later, for medical trials, the Food and Drug Administration changed its position and accepted migraine days as the primary endpoint. This is the current endpoint criterion for episodic migraine trials. Our pooled analysis defined reduction in migraine days as an important efficacy endpoint but included responder rate, mean reduction in migraine attacks, and complete migraine cessation as other efficacy endpoints for thoroughness. As PREMIUM and PRIMA were each powered to assess only 1 of the 4 endpoints defined in this pooled analysis, thereby introducing potential bias, our results should be interpreted with caution. Similarly, as PREMIUM and PRIMA used different sets of inclusion and exclusion criteria, including the number of migraine-preventive medications enrolled subjects needed to be unresponsive to, the 2 study populations are heterogeneous, and combining them could introduce bias. This bias was made evident by comparing baseline patient characteristics across trials (Table 1). However, the randomization process between medical therapy or device closure plus medical therapy showed no difference between the randomized groups (Table 2). In addition, PREMIUM and PRIMA assessed PFO closure effectiveness differently. Whereas PREMIUM used a 12-month follow-up TCD bubble study to determine PFO closure effectiveness, PRIMA used a 6-month follow-

up transesophageal echocardiographic bubble study. Both ultrasound-based bubble studies have their advantages and disadvantages. TEE is semi-invasive and more specific compared with TCD. TCD is noninvasive and more sensitive compared with TEE, but it cannot visualize the atrial septal anatomy and type of right-to-left shunt (29-31).

The addition of clopidogrel to aspirin was found to reduce the incidence of migraine compared with aspirin monotherapy in subjects who underwent transcatheter atrial septal defect closure (32). Although this may be considered a confounder in our study, both the treatment and control arms of the 2 studies were given the same antiplatelet regimen. In months 10 to 12, when the migraine diary was analyzed, the subjects were off all antiplatelet therapy.

Finally, the presence of PFO is common in the general population, and it is possible that clinical trials that assessed the efficacy and safety of device closure for treating migraine or prevention of stroke may have included PFOs that were "innocent bystanders" rather than the culprit trigger of the neurovascular events.

CONCLUSIONS

In this pooled analysis of individual participant data from the 2 randomized trials using the Amplatzer PFO Occluder to treat patients with migraine headache, PFO closure plus medical therapy, compared with medical treatment, was associated with significant mean reductions in migraine days and migraine attacks. Additionally, PFO closure was associated with a 9% chance of complete headache cessation compared with 1% in control subjects. PFO closure did not show a significant benefit in responder rate. Both PREMIUM and PRIMA had larger than expected reductions of migraine in the medically treated control populations. The results of this pooled analysis, which increased the power of the 2 trials, warrant a reevaluation of PFO closure in treating episodic migraine, especially migraine with frequent aura.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Closure of PFO with the Amplatzer PFO Occluder can reduce the burden of migraine attacks compared with medication therapy.

TRANSLATIONAL OUTLOOK: Additional studies are needed to validate catheter-based PFO closure for management of patients with migraine, identify patients best suited to this approach, and clarify the mechanism responsible for the treatment effect.

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