Current PFO and Migraine Trials

With the recent troubles concerning MIST, where do we go from here?

BY BRIAN WHISENANT, MD

Numerous investigators have reported a dramatic reduction or elimination of migraine burden in patients with a history of cryptogenic stroke undergoing transcatheter patent foramen ovale (PFO) closure. The Migraine Intervention with StarFlex Technology (MIST) trial was designed to verify the ability of PFO closure to eliminate migraines in a prospective, randomized, and blinded fashion. However, MIST failed to meet both its primary endpoint of complete resolution of migraine headaches in patients with PFOs closed with the StarFlex device (NMT Medical, Boston, MA), as well as the secondary endpoint of a 50% reduction in migraine days with PFO closure when compared with a sham procedure. The MIST investigators and an accompanying editorial point out the many shortcomings of the MIST trial, which may explain its failure to demonstrate the predicted benefit.[1,2] The MIST II trial of PFO closure in migraine has ceased enrolling patients secondary to slow enrollment. The ongoing PREMIUM (Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the Amplatzer [AGA Medical Corporation, Plymouth, MN] PFO Occluder Compared to Medical Management) and ESCAPE (Effect of Septal Closure of Atrial PFO on Events of Migraine with Premere [St. Jude Medical, St. Paul, MN]) trials are rumored to have poor enrollment and may be subject to some of the limitations of the MIST trial. Questions persist regarding trial design and appropriate patient populations for next-generation PFO migraine trials.

Given the invasive nature of PFO closure, future studies of PFO must balance inherent procedural risks with potential patient-derived benefits. Potential benefit is a function of both the likelihood of success as well as severity of disease. Success may be maximized by studying patients with provocative hypothesis-generating data such as observational studies of efficacy or increased frequency of right-to-left shunting. Patients at risk for stroke or with debilitating headaches stand to derive greater clinical benefit than patients with rare episodic migraine. This article provides a framework for designing appropriate clinical trials of PFO closure for the relief of migraine.

THE PREVALENCE AND MORBIDITY OF MIGRAINE

Migraine is a disabling and potentially dangerous disease with inadequate medical therapy. Migraine affects 12% to 13% of adults and is associated with marked work-related disability, direct and indirect costs, and reduced health-related quality of life.[3-7] Many patients with episodic migraine develop frequent and debilitating headache syndromes including chronic or transformed migraine, chronic daily headache, and medication overuse headache.[8] Multiple medications are used for both prophylaxis as well as rescue symptoms. Although prophylactic medications reduce headache frequency, many migraine patients experience persistent symptoms that are refractory to medications.[4] Medications used for migraine prophylaxis are also associated with undesirable side effects and adverse reactions. The majority of patients who have episodic migraine and other migraine-associated headaches reject prophylactic medications.[9,10]

Decreasing migraine burden may decrease the risk of stroke and subclinical abnormal brain MRI findings. Migrainous infarction and migraine-triggered seizure are rare but well described.[11] Multiple studies have demonstrated an increased risk of stroke and brain abnormalities in migraineurs, particularly in young women who experience migraine with aura.[12-16] Women who experience migraine headaches and also take oral contraceptives experience a nearly ninefold increased incidence of stroke compared with the general population (Table 1).[17]

TABLE 1. MIGRAINE AS A RISK FACTOR FOR SUBCLINICAL BRAIN LESIONS			
	Control (N=140)	Migraine Without Aura (N=134)	Migraine With Aura (N=161)
Posterior circulation infarct	1 (0.7%)	3 (2.2%)	13 (8.1%)
Adapted from Kruit MC. JAMA. 2004;28;291:427-434.[19]			

A disproportionate number of patients who have experienced cryptogenic stroke also have migraine with aura.[18] MRI evidence of posterior circulation infarction may be found in 8.1% of patients with migraine with aura (Table 2).[19] Subclinical MRI abnormalities may be found in a majority of migraineurs but seem to have no association with right-to-left shunting.[20] Iron deposition in periventricular white matter correlates to migraine frequency.[21]

OBSERVATIONS REGARDING PFO AND MIGRAINE

Observational studies uniformly report improved or eliminated migraine symptoms after PFO closure (Table 3).[22-30] The observation of migraine improvement is supported by studies demonstrating marked increased frequency of PFO in patients who have migraine with aura,[1,31,32] as well as an increased frequency of migraines in patients with right-to-left shunting.[33,34] There is a clear association between PFO and cryptogenic stroke,[35-37] and patients with both migraine and stroke have larger shunts than patients with migraine without stroke.[38] Migraine may be triggered by the injection of agitated saline in patients with right-to-left shunts.[39] Skeptics note that the associations between PFO and migraine and between PFO and stroke do not prove causation. Observational data are inherently limited by the placebo effect, and the retrospective nature of the observational studies regarding migraine resolution after PFO closure is subject to bias. Although some investigators have advocated transcatheter PFO closure in migraine patients to reduce stroke and headache based on existing observational data,[40] this potential can only be validated in randomized, blinded, and sham-controlled trials.[41]

THE MIST, PREMIUM, AND ESCAPE TRIALS

Several randomized, blinded, and sham-controlled studies were initiated to test the hypothesis that closing PFOs will eliminate or improve migraine headaches. The UK-based MIST trial was the first randomized, blinded, sham-controlled study of PFO closure to prevent migraine headaches.[1] Preliminary MIST results were presented during the spring 2006 American College of Cardiology meetings, and the final results were published in the February 2008 issue of *Circulation*. The MIST II

TABLE 2. RISK OF ISCHEMIC STROKE IN PEOPLE WITH MIGRAINE: SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONAL STUDIES	
	Relative Risk
Migraine (any)	2.16
Migraine with aura	2.88
Migraine without aura	1.83
Migraine among women <45 y	2.76
Migraine + oral contraceptives	8.72
Adapted from Etminan M. BMJ 2005;330:54-55.[17]	

(clinicaltrials.gov identifier NCT00283738), PREMIUM, and ESCAPE (clinicaltrials.gov identifier NCT00267371) trials were designed and initiated in the US shortly after the initial presentation of the MIST trial. Given the frequency of migraines and prevalence of PFOs in the migraine population, it has been estimated that 10 million migraineurs could be candidates for PFO closure in the US. Government regulatory bodies and physicians judiciously questioned the safety and wisdom of embarking on a clinical trial pathway that, if successful, could lead to widespread intracardiac deployment of devices with little procedural or long-term safety data. A clinical trial pathway was developed with the goal of maximizing the risk:benefit ratio by limiting enrollment to patients disabled by migraine and refractory to medications. The MIST 2 trial was recently halted by the sponsor secondary to poor enrollment. PREMIUM and ESCAPE are also rumored to be hampered by extraordinarily slow enrollment with unclear prospects for completion.

MIST failed to meet both its primary endpoint of complete resolution of migraine headaches in patients closed with the StarFlex device, as well as a secondary endpoint of a 50% reduction in migraine days when PFO closure was compared with a sham procedure. The MIST patients receiving devices also experienced complications including tamponade and retroperitoneal bleed. When the MIST trial preliminary results were initially presented at the American College of Cardiology meeting in the spring of 2006, a statistically significant reduction in the secondary endpoint of 50% reduction in migraine days

TABLE 3. MIGRAINE EFFECT OF TRANSCATHETER PFO CLOSURE, PUBLISHED RETROSPECTIVE OBSERVATIONS

Investigator	Year	No. of Patients	Migraine (%)	Resolved (%)	Improved (%)
Wilmshurst et al[22]	2000	37	57	48	38
Morandi et al[23]	2003	17	100	29	59
Post et al[24]	2004	66	39	84	Not reported
Schwerzmann et al[25]	2004	215	22	Not reported	83
Azarbal et al[26]	2005	89	42	60	16
Reisman et al[27]	2005	162	35	56	14
Kimmelsteil et al[28]	2007	41	100	Not reported	83
Dubiel et al[30]	2007	191	24	24	63
Total		808	35	41	40

after PFO closure was reported. The MIST II, PREMIUM, and ESCAPE trials were designed to validate the endpoint of 50% reduction in migraine days by elevating it to a primary endpoint. In light of the MIST publication and recognition of the failure to achieve significance in the 50% reduction of headache days, sponsors must critically analyze the MIST trial, why it failed, and the assumptions upon which ongoing and future trials are based.

The MIST investigators and the accompanying editorial[2] offer several hypotheses for the difference between the lack of clinical benefit in the MIST trial compared with observational reports of PFO closure. Possible explanations include insufficient statistical power, frequent and undefined residual shunts, an early sampling period after PFO closure with incomplete closure and inadequate placebo washout, and inaccurate PFO screening methodology. The PREMIUM and ESCAPE trials have been carefully designed and may not be subject to these

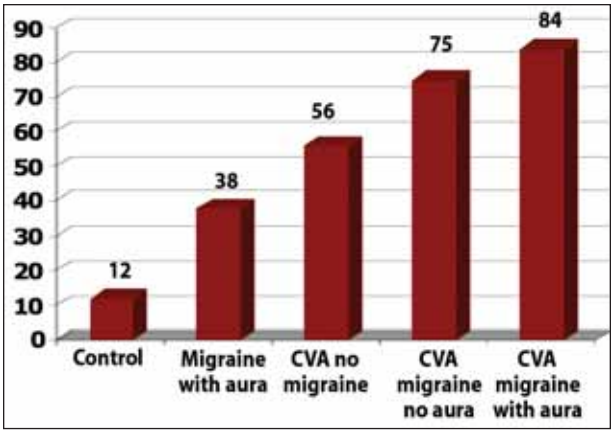

Figure 1. Relation of atrial shunts to migraine in patients with ischemic stroke and peripheral emboli. CVA, cerebral vascular accident. Adapted from Wilmshurst P. Am J Cardiol. 2006;98:831-833.[43]

shortcomings. The PREMIUM and ESCAPE trials have received the direction, support, energy, and investment of numerous thoughtful neurologists, cardiologists, and industry professionals. Enrollment difficulties are related to both the trial structure as well as restrictive enrollment criteria. Enrollment in these trials should be facilitated through changes in the protocol, such as allowing for PFO screening prior to migraine diaries and through relaxation of inclusion/exclusion criteria.

EPISODIC, REFRACTORY, AND COMPLEX MIGRAINE POPULATIONS

The MIST investigators noted that patients who have severe and refractory migraines, particularly if associated with chronic frequent headache, depression, or other comorbidities, may prove less amenable to treatment than those with mild or moderate migraine. The diagnosis and classification of severe and refractory headache patients as migraineurs compared with transformed headache, medication overuse headache, and chronic daily headache involves art in addition to science, and often includes overlapping diagnoses that may not be distinguished in patient diaries.[8,42] The MIST exploratory analysis excluded two patients who experienced more than 28 headache days per month. This headache pattern is by definition inconsistent with episodic migraine, further demonstrating the complex nature of patients who have demonstrated refractoriness to medication. The MIST population, consisting of patients with severe, refractory headaches, was selected to justify the risk of an invasive procedure. However, if this population is less likely to benefit from PFO closure, the risk:benefit ratio may be inadvertently increased.

The severe and refractory population is also different from the cryptogenic stroke and decompression illness populations in whom a beneficial effect of PFO closure for headache has been observed. In fact, stroke patients

TABLE 4. COMPARISON AMONG ONGOING TRIALS OF PFO CLOSURE FOR THE TREATMENT OF MIGRAINES AND A SUGGESTED FUTURE TRIAL

	PREMIUM	MIST II	ESCAPE	Suggested Trial
Device (Company)	Amplatzer	Biostar (NMT Medical)	Premere	n/a
Inclusion	Refractory to medications	Refractory to medications	Refractory to medications	Stroke, TIA, or migraine with focal neurologic deficit
Exclusion	Stroke, TIA	Stroke, TIA	Stroke, TIA	Refractory to medications

were excluded from the MIST trial and are excluded from ongoing PFO/migraine studies. Wilmshurst et al reported a greater shunt prevalence in patients with stroke and migraine with aura than in those with migraine with aura but no stroke (84% vs 38.1%; *P*<.001) (Figure 1).[43] If shunt prevalence indicates the contribution of shunting to disease, then shunting plays the greatest role in patients with stroke and migraine with aura. Patients with a history of stroke or transient ischemic attack (TIA) not only constitute the population that initially generated the hypothesis of PFO closure to diminish migraine symptoms but also may be most likely to benefit from PFO closure given the frequency of PFO in this population and the additional potential benefit of stroke prevention.

Two arguments are commonly offered against studying the effect of PFO closure on episodic migraine in patients who have experienced stroke, TIA, or decompression illness. The first relates to the risk of PFO closure in episodic migraine patients. The second relates to the ability to enroll patients in such a trial. Patients with a history of cryptogenic stroke presumed due to paradoxical embolism through a PFO have an excessive risk of recurrent neurologic events including stroke and may be most deserving of PFO closure. However, the CLOSURE I and RESPECT trials of PFO closure in patients who have experienced TIA or stroke have demonstrated the reluctance of these patients to be enrolled in a sham-controlled protocol. If one accepts the view of migraine on a continuum with stroke, it may be possible to define an intermediate risk group of migraine patients who experience focal neurologic deficits, are at increased risk of stroke, and would allow themselves to be randomized in a sham-controlled fashion. This population may include those commonly referred to as "complex migraine" in whom the distinction with TIA may be difficult. The role of PFO closure to prevent recurrent neurologic symptoms in migraine patients in addition to relieving headaches warrants additional investigation (Table 4).

The potential risk:benefit ratio may be further minimized by identifying those patients at higher risk for recurrent stroke from an anatomical perspective. Excessive right-to-left shunting including atrial septal aneurysms seems to convey an increased risk of recurrent neurologic events.[38,44] People with abnormal MRIs may also be considered.

CONCLUSION

Despite observational studies suggesting diminished migraine symptoms after PFO closure, the only completed study designed to test this hypothesis in a prospective randomized fashion demonstrated no benefit. Ongoing randomized trials are facing low enrollment and are enrolling severe refractory headache patients unlike the episodic migraine patients with cryptogenic stroke in whom benefit was first observed and reported. The ongoing possibility that PFO closure will diminish migraine episodes and reduce the risk of stroke in migraineurs demands additional investigation. The potential benefit of closing PFOs will be maximized and justified by identifying patients who are highly symptomatic with migraine with aura, in whom stroke may be prevented, and who are most likely to respond to therapy. Additional observational studies of the effect of PFO closure in migraine should include detailed characterization of headaches. Additional research regarding the frequency of PFO in patients with chronic migraine, chronic daily headache, and severe refractory migraine may help define patient populations most likely to benefit from PFO closure. ■

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