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EDITORIAL COMMENT

PFO and Migraine

The Blind Leading the Blinded*

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"There's something happening here.
What it is ain't exactly clear."
—Buffalo Springfield (1)

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 (2), discussed in this issue of the *Journal*, was designed to test a hypothesis that originated with observations of migraine improvement following PFO closure performed for a variety

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of nonheadache indications (3-5). "Blind" cardiologists, lacking specialist understanding of migraine, began to investigate PFO closure for migraine headache relief with modest insight into likely responsive populations. Neurologists joined the effort, but similarly with modest insight into mechanisms and responsive populations. As transcatheter PFO closure is an invasive procedure, presumably with risks beyond those of medications, a conservative approach was selected for this early trial, limiting enrollment to those with few options. The PREMIUM trial thus restricted inclusion to those who continued to experience 6 to 14 migraine days/month despite failing at least 3 migraine preventative medications. The PREMIUM trial represents a tremendous collaborative effort of cardiologists and neurologists to test a hypothesis of PFO closure for the prevention of episodic migraine, refractory to medications.

The primary PREMIUM efficacy endpoint, a responder rate defined as a 50% reduction in migraine attacks per month between baseline and months 10 to 12, was achieved in 38.5% of patients randomized to device and 32% of those randomized to control, which failed to achieve statistical superiority ($p = 0.32$). As the point estimate favored the device and the sample size yielded an overall power of 80%, it is possible that a larger sample size may have detected a statistically significant, albeit modest benefit of PFO closure regarding this primary endpoint. Nevertheless, the primary conclusion of the PREMIUM trial is that PFO closure did not significantly reduce headache frequency among patients with episodic migraine refractory to multiple medications.

The refractory episodic population studied in the PREMIUM trial posed numerous challenges. Identifying and recruiting patients who continued to experience 6 to 14 migraine days/month despite failure of 3 medications proved to be highly challenging. The investigators and sponsor must be congratulated for persevering for 7 years to randomize 230 subjects. Difficult enrollment lead to a trial design with borderline power and discouraged refining inclusion criteria for hypothetical predictors of success, such as prominent aura. Few therapies directed at refractory migraine have achieved success, particularly when studied in a prospective, randomized, and controlled fashion (6). Although a 50% responder rate such as that used in the PREMIUM trial is a commonly used endpoint for pharmacological prevention of episodic migraine, the PREMIUM trial's secondary endpoint of a statistically significant reduction in the number of headache days is a commonly used primary endpoint for less-responsive populations including chronic migraine (>15 migraine days/month), and may be an appropriate endpoint for a medication refractory population (7). The PREMIUM trial should be considered a failure not of the PFO migraine

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hypothesis, but rather of the selected episodic and medication refractory population.

Secondary PREMIUM endpoints support the hypothesis that PFO closure benefits a minority of migraine patients, and suggest a need to further investigate populations who are more likely to benefit from PFO closure than the medication refractory population. Although control patients had 2 fewer migraine days/month, which represented a 25% reduction from the baseline of 8 migraine days/month, PFO closure patients experienced 3.4 fewer migraine days/month, which represented a 47% reduction from the baseline rate of 7.2 migraine days/month ($p = 0.025$). This was driven by 8.5% (10 of 117) of PFO closure patients benefitting with complete cessation of migraine attacks compared with 1.0% (1 of 103) in the control arm ($p = 0.01$).

Several additional observations support a cryptic connection between PFOs and migraines. Migraineurs seem to have an increased incidence of right-to-left shunts (8). Transcatheter atrial septal defect closure and injection of agitated saline have been reported to precipitate migraine (9,10). Atrial myxomas seem to be associated with migraines (11).

Prior studies have suggested prominent aura as a predictor of headache reduction following PFO closure (12). Further narrowing the PREMIUM population to those with prominent aura would have dramatically lengthened enrollment time. Alternatively, patients experiencing frequent headache accompanied by prominent aura were evaluated as a secondary endpoint. Ultimately, 49% (19 of 39) of patients with frequent aura responded with >50% reduction in migraine days compared with 23% (9 of 40) of control subjects ($p = 0.015$). Among 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 ($p = 0.04$). Aura stands as a likely predictor of benefit.

Consistent with recent published data demonstrating the safety of PFO closure (13), the PREMIUM trial demonstrated the Amplatzer PFO occluder (St. Jude Medical, St. Paul, Minnesota) to be safe. Procedure-related complications, including atrial fibrillation, hematomas, and transient hypotension, were observed in 2.9% of patients randomized to PFO closure and were self-limited. This assurance of safety should allow investigators to select a future study population based on the likelihood of benefit while considering patient perspectives with shared decision making, rather than reserving PFO closure as a therapy of last resort in a refractory population.

Migraine remains among the most debilitating chronic diseases, destroying the lives of otherwise healthy men and especially women during years that otherwise may be the most productive and rewarding. Medications are highly effective for many patients, but disabling side effects and limited efficacy leave a large treatment gap (14). PFO closure in the PREMIUM trial failed to significantly reduce headache frequency among patients with episodic migraine refractory to multiple medications. Pharmacological and lifestyle interventions remain the mainstay of migraine prevention, and PFO closure cannot be considered a viable alternative therapy for routine clinical practice. However, the PREMIUM trial was hobbled by enrolling a ubiquitous group of patients experiencing headache with the single commonality of being refractory to multiple medications. Consistent with prior studies, secondary endpoints suggested a dramatic benefit for a small segment of patients. PFO closure is not a cure for migraine to be applied broadly, but may be an important therapy for some. Given the tremendous unmet need of additional migraine prevention therapies, the safety of PFO closure, and ongoing observations of migraine improvement in some patients, future research must focus on removing the blinders and identifying those who may be most responsive to PFO closure.

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