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Editorial Comment

Patent Foramen Ovale and Migraine Headaches: The Saga Continues

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The accompanying article by Bartorelli and colleagues from Milan entitled: ''Sustained Long-Term Benefit of PFO Closure on Migraine''[1], continues the debate about the association of migraine headaches with right to left shunting of blood, most commonly occurring with patent foramen ovale (PFO). In this well written article, the authors document the higher than expected incidence of migraine (25% versus the expected 12% in the general population) in 305 consecutive patients who presented with cryptogenic stroke with abnormal brain imaging by MRI. The PFO was closed with an Amplatzer PFO occluder, which is available in Europe, but is only obtainable in the United States if the patient participates in one of the randomized controlled trials (RCT) for stroke (RESPECT) or migraine (PREMIUM). This study extends our knowledge base because the follow-up is moderately long (mean of 28 ± 27 months) and they document that those people who had initial benefit in reduction of migraine headache, have persistent long-term relief from their migraine symptoms. Overall, 89% of the 77 patients with migraine had sustained relief: 46% of the patients claimed that their migraines ceased after the PFO was closed, and an additional 43% had a reduction (>50%) in the frequency and severity of their migraine symptoms. Only 10% of patients claimed they had no change in their migraines.

In one sense, this article is just another observational testimonial that is consistent with other single center experiences already documented in the literature. None of these studies prove causality between PFO and migraines, only a RCT can do that; but the length of follow-up and the documentation that the relief from migraines is sustained should be encouraging news for patients, researchers, and industry personnel who have a stake in this debate. The disappointing results of the MIST Trial still leave lingering questions and doubt about this field. Bartorelli's report highlights several differences between the observational studies and the MIST Trial:

1. These studies were performed with different devices. The Amplatzer PFO occluder is a more effective device for occluding the right to left shunt through the atrial septum. The CardioSEAL/StarFLEX has a 14% residual large shunt. In addition, the CardioSEAL has a higher rate of thrombus formation on the device (7–22%), with a 3.5% incidence of recurrent stroke. The Amplatzer device has an extremely low rate of thrombus formation and close to 0% recurrent stroke rate.
2. These studies were done on different populations. Bartorelli's study and most of the observational studies were performed on patients who had cryptogenic stroke. The MIST trial appropriately targeted patients with severe migraine with aura. Even if we accept the accusation that up to 35% of subjects in the MIST trial had a large residual shunt, there were many people who had effective closure with the StarFLEX device, and yet only 3/73 people (4%) had complete relief of their migraine compared with 46% with the Amplatzer PFO occluder. We still do not have a sufficient answer to this paradox.

Will Bartorelli's results presage the results of the PREMIUM Trial? This is the only current randomized trial of PFO closure for severe debilitating migraine headache using the Amplatzer PFO occluder. Similar to Bartorelli's population, the PREMIUM Trial is enrolling migraineurs with or without aura. Although migraineurs with aura have a higher likelihood of having a PFO, it is important to note that both groups of patients responded well to PFO closure in his report. For those physicians in the United States who use the

Conflict of interest: Dr. Tobis is on the steering committee for the PREMIUM Trial.

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cribriform Amplatzer ASD device to close PFOs off-label, you should note the report by Sorenson et al. [2] which documents that the residual shunt rate is higher for the cribriform device compared with an Amplatzer ASD occluder (and we believe this effectiveness is also true of the PFO occluder), and so we can not extrapolate the results of different devices. (By the way, this would also be true of the stroke trials; the results of CLOSURE 1 with the StarFlex device may not presage the ultimate results of the RESPECT Trial which uses the Amplatzer PFO occluder, or the REDUCE Trial testing the Gore-Helex device.)

What if PFO closure only works to eliminate or reduce migraine frequency in patients with cryptogenic stroke or those who have white matter lesions on MRI, but, as seen in the MIST Trial, is not effective for subsets of patients with severe migraines, despite the observational data to the contrary? PFO closure might still be beneficial to prevent stroke in this population. If 20% of all people have a PFO, and cryptogenic stroke accounts for 20–40% of all ischemic strokes, then the approximate risk for a stroke in someone with a PFO is 1 in 1000 per year. People with migraine have a 2-fold increased risk of having a stroke and we presume that almost all of this is due to the presence of a PFO and paradoxical embolism. If that person with migraine takes birth control pills, the risk of stroke increases 8X; if she also smokes, the risk is 15X. So perhaps these people only need to take aspirin and they will reduce their risk similar to having a StarFlex device. But if there are other devices out there that are more effective with a lower complication rate, I am optimistic that ultimately it will be demonstrated that PFO closure with an optimal device will reduce migraines as well as the risk for potential paradoxical embolus and stroke.

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