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EDITORIAL COMMENT

PFO Device Closure Despite Thrombophilia

The Need for Good Observational Studies*

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For those of us who take care of patients with patent foramen ovale (PFO)-associated conditions, the field is complicated, as in many areas of medicine, by questions that will never be answered by randomized clinical trial data. One of these dilemmas is what to do with a patient who has a predilection for developing blood clots with a condition of thrombophilia. Although the blood-clotting predisposition may have led to the thrombus, which paradoxically crossed through the PFO passageway to the brain, if we place a foreign body device in the left atrium to close the PFO, could that not in itself become a nidus for thrombosis and future systemic embolization? These patients were purposefully excluded from the randomized clinical trials of prior stroke and migraine, because it was believed that these individuals were more likely to develop new strokes, even if the PFO were closed; this would prejudice the results of the trials. Thus, we are left to make clinical decisions as best as we can on the basis of observational studies.

In this issue of *JACC: Cardiovascular Interventions*, Abrahamyan et al[1] have added to the literature on PFO closure in patients who have underlying thrombophilia.[1] The presence of thrombophilia was defined by an abnormal blood test result of protein C, protein S, antithrombin, anticardiolipin antibodies, lupus anticoagulant, factor V Leiden, and prothrombin gene mutation. Between 1999 and 2017, 669 patients underwent percutaneous PFO closure. Of these, 26% had thrombophilia, and 98% of the subjects underwent device closure for secondary prevention of stroke from an otherwise unidentified etiology. Over an 11.6-year follow-up period, there was no difference in recurrent stroke rates between those who had thrombophilia and the group that did not (mean recurrent stroke rate 0.8% per 100 patient-years). The investigators should be commended for their thorough reporting on this topic, including the meticulous aggregation of prior observational studies that have been performed on the thrombophilia population (see Supplemental Tables A and B in their Supplemental Appendix).

A prothrombotic condition that was not examined in this study is the presence of estrogen-related hormone therapy. In our experience at UCLA, 50% of women who presented with PFO-associated stroke were using birth control pills or hormone replacement therapy at the time of the stroke.[2] Once these medications are stopped after a patient has had a stroke, it is not clear whether the PFO needs to be closed. With cessation of the thrombophilia-inciting estrogen, it is possible that the patient would not have another thrombotic event. This has never been tested in a prospective clinical trial. These patients, however, were included in randomized clinical studies, which may have lessened the risk of the control group. In general, lower risk patients were included in the trials because the high-risk patients often refused to participate and wanted their PFOs closed, which was possible at the time because there were available devices that were approved by the U.S. Food and Drug Administration. This made trial enrollment very difficult and lowered the risk profile of the control

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group. I suspect that almost all strokes that are associated with birth control pills arise from paradoxical embolism mediated through a PFO. This also has never been tested in a clinical trial, because the gynecology community has not included PFO screening in its clinical trials of birth control pills. Similarly, I suspect that most strokes that are seen in patients with migraine, especially migraine with aura, are due to an associated PFO, which permits the passage not only of a venous thrombus but also of vasoactive substances that may trigger migraine attacks.[3]

The likelihood of forming a thrombus on a device also depends on the type of device and its material characteristics. The CardioSEAL device, which is no longer manufactured, appeared to have a higher predilection to form clots on fabric made of polyester.[4] However, the currently available closure devices in the United States, the Amplatzer (Nitinol weave with Dacron patch) and Cardioform (Nitinol springs covered with expanded polytetrafluoroethylene) formats do not appear to be thrombogenic. The findings of Abrahamyan et al reinforces previous findings that even patients who have various thrombophilic predispositions tolerate these devices very well, with no evidence of thrombus formation. On the basis of the accumulation of these observational studies (but not randomized clinical trials), there is no reason not to close a PFO for paradoxical embolic stroke for those individuals who have these prothrombotic conditions.

Any discussion of PFO and stroke should include a clarification of the distinction between stroke and transient ischemic attack (TIA). In several of the studies summarized in Supplemental Table A, recurrent events were combined if they were adjudicated as stroke or TIA, with the assumption that a TIA is an embolic event. However, it is clinically impossible to distinguish between a TIA and a complex migraine, because both present with a transient neurologic deficit and normal findings on brain magnetic resonance imaging. It is probable that many of these recurring suspected TIAs were actually complex migraines and not thrombotic events. Interpreting any study with regard to PFO needs to separate those subjects who had magnetic resonance imaging-documented stroke from those who had subsequent transient neurologic events due to presumed TIA.

Also relevant to a discussion of PFO closure is the recognition that there will be a new randomized clinical trial of PFO closure for migraine in patients who respond to thienopyridine $P2Y_{12}$ inhibitors, called RELIEF (Gore® Cardioform Septal Occluder Migraine Clinical Study; NCT04100135). Nevertheless, other less prevalent conditions associated with PFO will probably never be assessed in randomized clinical trials, such as the association of PFO and altitude illness, sleep apnea, unexplained hypoxemia and exercise desaturation, platypnea-orthodeoxia, and decompression sickness. Another intriguing connection with PFO is the possible association with some cases of coronary artery spasm, angina, and sudden death. Similar to Abrahamyan et al's study of thrombophilia, we will be dependent on meticulous observational studies to help guide our best clinical judgment for these conditions.

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REFERENCES

1. Abrahamyan L, Schmidt ACS, Dharma C, et al. Short and long-term outcomes in patients with thrombophilia undergoing transcatheter closure of patent foramen ovale. *J Am Coll Cardiol Intv*. 2023;16:1360–1366.

2. Kar S, Noureddin N, Aboulhosn J, Mahmzi Y, Coluzzi A, Tobis J. Percutaneous closure of patent foramen ovale or atrial septal defect in the presence of thrombophilia. *J Struct Heart Dis*. 2017;3(5):135–140.

3. Mojadidi MK, Kumar P, Mahmoud AN, et al. Pooled analysis of PFO occluder device trials in patients with PFO and migraine. *J Am Coll Cardiol*. 2021;77(6):667–676.

4. Anzai H, Child J, Natterson B, et al. Incidence of thrombus formation on the CardioSEAL and the Amplatzer interatrial closure devices. *Am J Cardiol*. 2004;93:426–431.

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