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EDITORIAL COMMENT

Patent Foramen Ovale Science

Keeping the Horse in Front of the Cart*

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Compared with a prevalence of 25% in the general population, the higher prevalence of patent foramen ovale (PFO) in cryptogenic stroke (CS) patients has led to the intuitive conclusion that PFO is a risk factor for CS (1). However, distinguishing truly culpable PFOs from the innocent bystanders has been difficult. Some have advocated closure for just about any PFO (2), an approach which subjects people (many are not yet "patients" with any PFO-related neurological or other clinical syndrome) to procedural and device-related risks. This clearly puts the cart before the horse. PFO closure for secondary stroke prevention continues to be controversial even after 3 published randomized clinical trials (3–5). Primary stroke prevention with PFO closure is entirely unstudied.

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For some, PFO interventions have become an acceptable part of the routine armamentarium for secondary stroke prevention well before the resolution of many issues that make this a confusing and complicated subject. Patient selection, nonstandard diagnostic testing and CS definition, and devices with different safety profiles bedevil doctors looking after these patients. The observational, nonrandomized data from the last decade were biased in favor of showing a benefit from device closure. Device studies more often included patients without stroke (and so likely lower "recurrence" rates than a CS population), failed to use validated screening tools for outcome ascertainment, failed to require neurologist involvement, and did not require neuroimaging (6). Compared to the observational data, the recently completed PFO closure trials showed higher recurrent stroke rates in the device groups (probably due to better outcome ascertainment) and lower recurrent stroke rates in the medically treated patients (probably due to better selection of lower-risk CS populations). One clear message from the trials is that the natural history of PFO-related stroke is relatively benign compared with other stroke categories. If PFO closure works, it will only be in carefully selected patients with a high risk of PFO-related recurrence in whom a device with a low risk of device-related complications is safely deployed. Therefore, even if the consensus is that PFO closure is helpful, there will still be some PFOs that are better left alone.

Of course, those of us interested in winning the cerebrovascular war would like to prevent the first stroke rather than fight only after the initial battle is already lost. Device closure was widely applied in secondary prevention efforts before the science was available to confirm that the right patients were being treated and that they benefited in a statistically meaningful way (6). For primary stroke prevention, PFO closure is not yet widely offered, so we have the opportunity to keep the horse of science firmly in front of the cart of practice. Otherwise, PFO closure may be considered, and used, in the general asymptomatic population, where 25% of people may be unscientifically, and unnecessarily, turned into patients.

In this issue of the *Journal*, Di Tullio et al. (7) present data from the Northern Manhattan Study (NOMAS) that attempt to fill in gaps in knowledge about harm from PFO in the general population. It is just this sort of study that will inform physicians' and patients' decisions about what, if anything, to do about an incidentally discovered PFO.

Their paper uses prospectively collected data from an ongoing population-based study. They recruited 1100 people over 39 years old, stroke free, and living in northern Manhattan between 1993 and 1999. All subjects underwent baseline transthoracic echocardiography with saline contrast injection. PFO prevalence was 14.9%. All participants underwent annual protocol-required neurological follow-up and were assessed for cerebrovascular symptoms. Follow-up was impressive, with data available for 98% of subjects at 10 years. A subpopulation (n = 360) had magnetic resonance imaging (MRI) scans to assess for radiologically apparent but clinically silent infarcts. Subjects in the substudy were 55 years old and older when it was conducted (2003 to 2008). After a mean of 11 years, the incidence of first ever stroke was 9.2% in the PFO group and 10.3% in those without PFO. The adjusted hazard ratio for PFO was 1.10 (95% confidence interval [CI]: 0.64 to 1.91). Similarly, the hazard ratio of PFO for clinically silent but radiologically apparent stroke was not significant at 1.15 (95% CI: 0.50 to 2.62).

How can PFO be a risk factor for stroke (1) but not show up in this population study?

First, subjects had PFO status determined by a diagnostic test (transthoracic echocardiography) which has a sensitivity of approximately 50%. The very low prevalence of PFO in their population (14.9%) belies this fact. Some in the non-PFO group, therefore, must have been harboring one. The argument that only the "less significant" PFOs were missed follows the logic that large shunts are more dangerous. This is intuitive but unproven and even contrary to some data that suggest recurrence is predicted by smaller shunts (8,9).

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Second, although PFO-associated strokes do occur in older patients (10), the PFO proportion of all strokes falls considerably as competing stroke mechanisms (e.g., atrial fibrillation, atherosclerosis, lacunar disease) become more prevalent with age (11). The transition point from a young stroke patient to an old one is unclear but is probably in the mid-40s (12). The population in this study (mean age = 68 years old) was not young. Conventional vascular diseases likely "drowned out" the PFO-associated risk that might have been detectable in a study of younger subjects. The unusually high prevalence of hypertension in this cohort (>60%) increases this concern. As additional support for the contamination of non–PFO-related stroke mechanisms, hypertension was significantly, and not surprisingly, associated with silent stroke in the MRI substudy. It has never been suggested that hypertension and PFO synergistically increase stroke risk, so the more conventional hypertension-related pathologies must have been involved.

For years, the NOMAS team has produced very high quality studies. Except for the issues described above, we have no concerns with the protocol or study conduct. The neuroimaging and follow-up were exemplary. Studies of this type are needed. Unfortunately these data do not settle this issue. If a population at risk from their PFOs is going to be identified before their first stroke, it needs to be done in people who are in their 20s and 30s (and perhaps 40s), with PFO status defined by transesophageal echocardiography or transcranial Doppler and perhaps also described in detail beyond present/absent, and with or without atrial septal aneurysm. A focus on asymptomatic subpopulations that may be at higher risk of a first-ever stroke, for example, those with migraine with aura (13), obstructive sleep apnea (14), and silent infarcts (15), is likely to increase the success of the next population-based study.

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