Patent Foramen Ovale and Recurrent Stroke: Closure is the Best Option: Yes

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Patent foramen ovale (PFO), a common congenital cardiac anomaly in the general population, is more prevalent among patients with stroke <50 years of age, especially patients with “cryptogenic” stroke. That a PFO can serve as a conduit for brain emboli is not in dispute. Right-to-left shunting is easily demonstrated on echocardiography with agitated saline. If the bubbles (ie, emboli) can get from the right heart to the left heart, they can get to the brain.

Although warfarin has been the “conventional” medical therapy for patients with PFO and transient ischemic attack (TIA) or stroke, there are few data to support its routine use and associated risk of bleeding. In a French study, the 2-year risk of stroke or TIA was not increased in patients with cryptogenic stroke and a PFO alone treated with aspirin, but was increased from 4.7% to 8.0% in patients with PFO and atrial septal aneurysm. In the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), PFO was more prevalent among patients with cryptogenic stroke, but there was no significant difference in the 2-year rate of stroke and death in patients with or without PFO (14.3% versus 12.7%). There was also no significant difference whether PFO patients were treated with warfarin or aspirin. Unfortunately, while suggesting that the risk of recurrent stroke in patients with cryptogenic stroke and PFO is low even with aspirin, except perhaps in patients with atrial septal aneurysm, definitive conclusions cannot be drawn from available studies because the patient numbers are too small.

The advent of percutaneous devices has made PFO closure an increasingly attractive alternative option. Open-heart surgery is now done infrequently for simple PFO closure. At the Cleveland Clinic we have closed 300 PFOs percutaneously in the past 2 years and about 10000 have been closed worldwide. Percutaneous PFO closure has a very low serious complication rate (<1%). Long-term durability of available devices also appears excellent, with a 5-year failure rate of <1%.

One of the persuasive arguments for PFO closure is the avoidance of long-term warfarin. Warfarin carries a 1% per year risk of significant hemorrhage, no small consideration especially in younger patients. Of course, the issue of long-term warfarin risk becomes moot if aspirin works just as well. After percutaneous PFO closure, patients are treated with aspirin indefinitely and with clopidogrel usually for 6 months.

In the United States, percutaneous PFO closure is permitted under an FDA Humanitarian Device Exemption (HDE). The specific HDE wording for the CardioSEAL® device is instructive:

“The CardioSEAL Septal Occlusion System is indicated for the closure of a patent foramen ovale (PFO) in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a patent foramen ovale and who have failed conventional drug therapy. Cryptogenic stroke is defined as a stroke occurring in the absence of potential phanerogenic cardiac, pulmonary, vascular or neurological sources. Conventional drug therapy is defined as a therapeutic INR on oral anticoagulants.”

Aside from the word phanerogenic, the HDE poses 2 dilemmas: first, how to define “recurrent cryptogenic stroke,” and, second, defining warfarin as the “conventional drug therapy.” Both concepts may be outdated. The modern definition of stroke includes diffusion-weighted MRI–positive TIA—as many as 75% of clinical TIA lasting >1 hour have an abnormal diffusion-weighted MRI. A recurrent true TIA also poses a treatment dilemma since that is how many patients with a PFO end up on long-term warfarin in the first place. If a TIA warrants warfarin, why not close the PFO? A TIA simply signifies that the paradoxical embolism lysed; what about the next time?

Many patients are psychologically crippled by their PFO and prefer simply to have it closed. Certainly patients who meet the HDE criteria should undergo percutaneous PFO closure. However, the HDE definition of “recurrent stroke” should include MR-positive TIA. Personally, I would also close the PFO for a recurrent TIA. Percutaneous PFO closure should also be considered as the initial treatment in patients with cryptogenic stroke or TIA requiring long-term warfarin. On the basis of available data, this would include patients with a brisk right-to-left shunt and patients with an atrial septal aneurysm.
septal aneurysm. The truth is, however, that whether percutaneous PFO closure is worse than, equivalent to, or superior to warfarin or aspirin alone (to say nothing of combination therapy or other agents) in patients with cryptogenic stroke and PFO is unknown. That is why 2 FDA-approved multicenter trials of percutaneous PFO closure versus medical therapy alone are about to get under way. For patients with first TIA or first stroke presumably due to a PFO, I therefore confidently recommend percutaneous PFO closure but only if the patient is randomized to the device arm within one of these clinical trials. Otherwise, a “hole” will always remain in our stroke prevention knowledge base.

References

Where’s the Evidence?
Several small, uncontrolled studies have suggested a relationship between PFO and stroke. Recent data, however, indicate that these studies may overestimate the association. In one study, PFOs were found in 20.8% of 519 randomly selected asymptomatic community-based controls compared with 16.5% of 158 patients referred for evaluation of cryptogenic stroke, demonstrating no increase in the prevalence of PFO among patients with stroke compared with a random nonhospitalized reference population.

Only 2 prospective multicenter studies of substantial size have evaluated the stroke recurrence risk in patients with PFO. These studies provide the best data for guiding the management of patients with PFO and ischemic cerebrovascular events.

The French PFO-ASA Study Group evaluated 216 young patients (aged 18 to 55, mean age 40) with PFO and cryptogenic stroke and compared them with 304 cryptogenic stroke patients without PFO. All patients were extensively screened for alternative stroke etiologies, including coagulation testing and transesophageal echocardiography. Treatment consisted of aspirin (300 mg) in all cases. In this study, patients with PFO alone had a nonsignificantly lower stroke risk than those without a PFO at 4-year follow-up (2.3% PFO[+] versus 4.2% PFO[-]). Only patients with both PFO and an atrial septal aneurysm (ASA) experienced an increased risk of stroke (15.2% at 4 years; odds ratio 4.17, range 1.47 to 11.84).

The second major study was the PFO in Cryptogenic Stroke Study (PICSS). PICSS was a substudy of the Warfarin Aspirin Recurrent Stroke Study (WARSS) and evaluated 630 older (age range 30 to 85, mean 59) patients with PFO and stroke who underwent transesophageal echocardiography in a blinded fashion. The majority of strokes in PICSS were cryptogenic (42%) or lacunar (39%). Patients were randomized to aspirin (325 mg) or warfarin (INR 1.7 to 2.2). In this study, the rate of recurrent stroke or death in patients with PFO was not significantly different, regardless of treatment (Figure). Moreover, the recurrence risk was not significantly different from that observed in patients without PFO. Among patients with cryptogenic stroke (n = 265), the stroke or death rate was about 50% lower in warfarin treated patients, although this difference did not reach statistical significance (Figure). The presence of a PFO, however, did not influence this lower rate of stroke recurrence on warfarin, which was
9.5% in patients with PFO and 8.3% in patients without PFO. Of interest, larger PFOs were associated with a lower, not higher, overall rate of recurrent stroke or death (18.5% with small PFOs versus 9.5% with large PFOs), in contradiction to the common belief that larger septal defects should be associated with higher stroke risk. In the PICSS, the coexistence of PFO and ASA did not increase stroke risk as in the French PFO-ASA study. These findings question the causal relationship between PFOs and stroke in most patients.

Are We Doing the Right Studies?
Despite these data, several closure trials have been initiated. Unfortunately, design issues may make the results difficult to interpret. For example, some studies include primarily younger patients who have had only a single neurological event. Since the best information show a very low stroke recurrence rate in this population, these studies may have difficulty demonstrating a difference between treatments. In one study, the end point includes both TIA and strokes. Given the subjective nature of TIA, their inclusion as an end point could be particularly problematic in a trial in which adequate blinding cannot be achieved due to the invasive nature of the therapy. This trial also allows enrollment of patients with TIA, risking the dilution of treatment effects, as well as subjecting individuals to potentially unnecessary therapy. Moreover, it is unclear whether a reduction in transient ischemic events is sufficient justification to perform an invasive procedure, especially if a reduction in the firmer end points of stroke or death is not detected. This latter possibility is of particular concern given that such trials are probably underpowered to detect significant differences in these hard end points alone.

Finally, at least one proposed closure trial is an “equivalency study” in which a positive result will be declared if the recurrent event rate for the device is no worse than that of “best medical therapy.” Because the “best medical therapy” is unknown and will not be standardized, the results of these trials will be difficult to interpret. Moreover, given the extremely low rate of stroke seen in the French PFO-ASA study and the uncertain effects of medical therapy found in PICSS, equivalency seems an inappropriate criterion by which to judge success.

The assumed association between PFO and stroke may be analogous to that between mitral valve prolapse and stroke reported over the last decade. While early studies suggested an association between mitral valve prolapse and stroke, a number of subsequent investigations failed to confirm this relationship. One can image the harm that might have occurred if an invasive treatment to “fix” the mitral valve had been available at that time.

In summary, it is imperative that before embarking on a trial of PFO closure appropriate studies be designed to better characterize who is at sufficient risk to warrant interventional therapy. While it is likely that such a population exists, the challenge is to identify this group before exposing them to an invasive treatment.

References

**KEY WORDS:** foramen ovale, patent

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**PICSS Two-Year Stroke or Death Rate**

![Graph showing PICSS two-year stroke or death rate.](image-url)
With the increasing use of transesophageal echocardiography as a diagnostic tool in ischemic stroke, where no obvious pathogenetic mechanism is evident, clinicians are more frequently faced with the finding of patent foramen ovale (PFO) as a possible or likely cause. For example, in a 45-year-old woman with cryptogenic stroke and a large PFO, with spontaneous right-to-left shunt and atrial septal aneurysm (ASA), what should be the preferred management strategy? Further, what about optimal treatment in a similar case with PFO, without spontaneous shunting or atrial septal aneurysm, but a second clinical event and despite best medical therapy (whatever that is)?

Both our protagonists present reasonable arguments for percutaneous device closure (in some), clinical trials, or better definition of high-risk subsets before designing trials of device closure. There is clearly controversy concerning the precise criteria for high-risk PFO patients, with one major observational study suggesting that the presence of an associated aneurysm may significantly increase stroke risk. It should also be noted that the risk diminishes with age, so much so that it appears to be negligible in stroke-aged patients. Clearly, if one accepts causality, no optimal medical therapy has been identified and warfarin may be no better than aspirin. However, although it should be noted that this finding was based on a carefully planned substudy of the Warfarin-Aspirin Recurrent Stroke Study (WARSS), the mean age of the 203 patients with PFO was 58 years, an age where the overall risk was likely to have been low. Indeed, research in Melbourne suggests that PFO is not a risk factor for cerebral ischemia in those >50 years. What about the risks and benefits of percutaneous device closure? Like other interventional methods such as carotid artery stenting, there have been significant technological advances in device closure and recent reports indicate quite low complication rates.

What is our practice while awaiting level I evidence concerning medical therapy versus closure in patients with PFO? We would use standard antiplatelet therapy in a patient with a PFO alone, without spontaneous shunting and a first event. Conversely, for patients with a spontaneous right-to-left shunt and an associated ASA, we would consider device closure by an experienced interventionalist. Ideally, we would prefer to randomize patients in the latter group and other presumed high-risk patients to either device closure or medical therapy, but our centers are currently not involved in such a trial. Closure of this issue is required!

### References
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