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Patent foramen ovale and stroke: To close or not to close?

Patent foramen ovale (PFO) is common, with the prevalence being approximately 20% in individuals younger than 50 years. This congenital cardiac anomaly has been found in many referral-based studies to be more common in young patients with cryptogenic stroke than in stroke of known cause. Parodoxical embolism via right-to-left shunt is the presumed mechanism of cryptogenic stroke in patients with PFO.[1]

The diagnosis of PFO is made by either contrast transthoracic or transesophogeal echocardiography during Valsalva maneuver. Transcranial Doppler can also be used to identify paradoxical emboli in the middle cerebral artery.

PFO is considered the most common identified cause of stroke in patients younger than 50 years. However, recent data have called into question the relationship between PFO and cryptogenic ischemic stroke in the population at large, as well as the notion that paradoxical embolism through PFO is a common cause of cryptogenic ischemic stroke.[2]

EPIDEMIOLOGY: REFERRAL-BASED VS POPULATION-BASED STUDIES

In the PFO in Cryptogenic Stroke Study (PICSS),[1] which included 630 patients with stroke, PFO was present in 39.2% of patients with cryptogenic stroke and 29.9% of those with noncryptogenic stroke. The 2-year cumulative risk of recurrent stroke and death was not significantly different between patients with and patients without PFO in the overall study population or in the subset with cryptogenic stroke.

Large PFOs with rapid right-to-left shunting are thought to pose a greater stroke risk than small PFOs. However, in PICSS, the lowest rate of recurrent stroke or death at 2 years was observed in patients with large PFOs (9.5%) compared with patients with small PFOs (18.5%) or no PFO (15.4%).

PFO with atrial septal aneurysm may confer an especially high risk of recurrent stroke. In a study of 581 patients with an ischemic stroke, Mas et al found that PFO alone was associated with a risk of recurrent stroke of 2.3% at 4 years, whereas patients with both PFO and an atrial septal aneurysm had a rate of recurrent stroke of 15.2% and patients with neither had a rate of 4.2%.[3]

Whereas the previously mentioned data that identified PFO as a risk factor for cryptogenic stroke were obtained in referral-based populations, the most recent data, from a population-based study, found no such link between PFO and the risk of cryptogenic stroke or transient ischemic attack (TIA).[2] In this case-control study, Petty et al found no association between PFO or large PFOs and cryptogenic or noncryptogenic stroke, and they suggest that such associations found previously were the result of referral bias.[2]

TREATMENT: MEDICAL THERAPY OR CLOSURE?

The best option for treating patients with PFO and previous stroke or TIA is controversial.

Medical therapy: Evidence is weak

Traditionally, warfarin has been the medical therapy of choice, although evidence to support its routine use is weak and the risk of bleeding with warfarin in this patient population has not been established. In the subgroup of patients in PICSS with PFO and cryptogenic stroke, those treated with warfarin had better outcomes (fewer deaths or recurrent strokes) at 2 years than those treated with aspirin (9.5% vs 17.9%), but because of the small sample size (n = 98), the difference failed to achieve statistical significance (P = .28).[1] Although these data suggest that the risk of death and recurrent stroke in patients with cryptogenic stroke and PFO is low even with aspirin treatment, except possibly in patients with atrial septal aneurysm, drawing a definitive conclusion is not possible because of the small number of patients.

Closure: Evidence plagued by small numbers

The alternative to medical therapy is PFO closure.

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Before the advent of percutaneous closure devices, this decision meant open heart surgery, with its inherent risks. Endovascular devices obviate the need for open heart surgery, which is now performed infrequently for PFO closure. The evidence for efficacy of endovascular closure of PFO comes mostly from case series, and the numbers of patients included in such series are even smaller than those in PICSS **(Table 1)**.[4]

A variety of PFO occluder devices has been used **(Table 1)**, all with reasonable safety. These devices appear to reduce the long-term risk of stroke and TIA, although prospective clinical studies are lacking.

The complication rates and the rates of recurrent events associated with medical therapy and endovascular therapy were compared in a systematic review by Khairy et al.[5] Ten studies of transcatheter closure and six studies of medical therapy were included in the review, with a total of 2,250 patients. A tremendous amount of variability was observed in the rates of recurrent events and complications in these studies. The 1-year rate of recurrent events ranged from 3.8% to 12.0% with medical therapy, and from 0% to 4.9% with transcatheter closure. Major complications occurred at a rate of about 1% per year with warfarin therapy. In the studies of percutaneous closure, the rate of major complications was 1.5% and the rate of minor complications was 7.9%.

Several limitations to the review by Khairy et al are evident.[5] In the studies of medical therapy, treatment was not uniform, as some patients received antiplatelet therapy and others were treated with warfarin. In addition, in those treated with warfarin, there was significant variation in the targets for the International Normalized Ratio (INR). Further, the patients included in these studies were dissimilar to a typical PFO population; they were older, were more likely to be men, and had a higher prevalence of diabetes and smoking. There was also significant selection bias in the studies of catheter closure, and significant variation in the postimplant pharmacologic therapy.

Thus, the available nonrandomized studies suggest a low stroke recurrence rate with either warfarin (and in selected patients with aspirin) or endovascular closure, but the numbers are small. Randomized clinical trials are needed to firmly establish the best stroke prevention therapy for PFO.

FDA INDICATION FOR PERCUTANEOUS CLOSURE

For the past 6 years the US Food and Drug Administration (FDA) has permitted percutaneous closure of PFOs under a Humanitarian Device Exemption (HDE). Two PFO closure devices—the Amplatzer PFO Occluder and the CardioSEAL Septal Occlusion System—have been approved via the HDE process, based on observational data from fewer than 100 patients with each device. The indication specific to the CardioSEAL Septal Occlusion System is worded as follows:

> The CardioSEAL Septal Occlusion System is indicated for closure of a PFO in patients with recurrent cryptogenic stroke due to presumed paradoxical embolus through the PFO who have failed medical 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. The effectiveness of this device in this indication has not been demonstrated.[6]

The HDE for PFO closure does not include TIA, a first stroke, migraine, or failed antiplatelet therapy.

Because the subset of patients who qualified for PFO closure under the HDE has increased beyond 4,000 per year (the HDE limit), the FDA recently asked US PFO device manufacturers to review their existing HDE. Effective October 2006, both NMT Medical, Inc., and AGA Medical Corporation have voluntarily withdrawn their PFO HDE. As a result, there is no longer any FDA-approved indication for

TABLE 1
Comparison of short-term and periprocedural complications between PFO occluder devices

Device	Total (n = 80)	Procedural complications (n = 8)	Residual shunt (n = 21)	Recurrence of paradoxic embolism* (n = 8)
Buttoned device	28	3	11	2
PFO-STAR	19	3	5	1
Amplatzer occluder	14	1	3	2
Angel-wings occluder	10	0	1	2
CardioSEAL	9	1	1	1
Septal occluder	9	1	1	1
P value		0.74	0.26	0.71

* Comprised six transient ischemic attacks and two peripheral emboli.
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PFO closure in patients with stroke or TIA. This means that PFO closure must now be done under an Investigational Device Exemption within a clinical trial. Alternatively, some interventionalists may elect to insert devices not specifically approved for PFO ("off-label" use).

Ongoing clinical trials

Three studies of PFO closure to prevent recurrent stroke are ongoing.

In CLOSURE I (Trial to Evaluate the Safety and Efficacy of the STARFlex® Septal Closure System Versus Best Medical Therapy in Patients With a Stroke and/or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale), patients with a recent (≤ 6 months) diagnosis of stroke and/or TIA due to a presumed paradoxical embolism through a PFO are being randomized to PFO closure using the STARFlex septal occlusion system or best medical therapy. The goal is to enroll 1,600 patients and follow them for 2 years. The primary end point is the incidence of recurrent stroke/TIA.

The Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT PFO) is randomizing patients with cryptogenic stroke, defined as an acute focal neurological deficit presumed due to focal ischemia, to PFO closure with the Amplatzer PFO Occluder or medical management (antiplatelet or anticoagulant therapy). The primary end points are recurrent nonfatal stroke, periprocedural death, or fatal stroke.

The PC-Trial is a randomized trial comparing PFO closure using the Amplatzer PFO Occluder with best medical management in patients with cryptogenic embolism (mostly cryptogenic stroke). The recommended medical management is warfarin for 6 months followed by antiplatelet therapy. The goal is to enroll 410 patients and follow them for 5 years with primary end points of death, nonfatal stroke, and peripheral embolism.

Enrollment in these studies has been slow for various reasons. Physician and patient bias toward a particular treatment has deterred physicians from entering patients into the trials. Many interventionalists have already accepted that PFO closure is a superior strategy despite an absence of randomized data, whereas neurologists appear to favor medical therapy. Local referral patterns in which patients with PFO are referred directly to the catheterization laboratory, because the procedure is reimbursed, may bypass knowledgeable neurologists and represent another roadblock to enrolling patients.

The FDA has publicly recognized the problem of off-label use of devices in a large number of patients who do not meet HDE criteria, and has admitted that this practice has interfered with completion of important clinical trials.[7] Because of these difficulties, a variety of alternatives to the traditional randomized clinical trial is under discussion with the FDA.

CONCLUSION

Stroke can occur due to paradoxical embolism through a PFO, but the absolute risk is low. Nonrandomized case series suggest a low stroke recurrence rate in patients with PFO who are treated with either warfarin, aspirin, or endovascular device closure. Whether any of these treatments is superior for preventing recurrent stroke is unknown since there has never been a randomized trial comparing any therapy in patients with PFO and stroke. Currently, there is no FDA-approved indication for PFO device closure although many PFOs are closed "off-label" using devices approved for other heart conditions. The only way out of this PFO treatment dilemma is to enroll patients into one of the several ongoing randomized clinical trials.

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