

## EDITORIAL COMMENT

# Patent Foramen Ovale: Closing Arguments\*

Mark Reisman, MD

Seattle, Washington

The unsettling diagnosis of “cryptogenic” stroke presents both patient and physician with a variety of potential pathophysiologic culprits of uncertain clinical significance. During the last decade patent foramen ovale (PFO), previously considered to be a highly prevalent but benign congenital anomaly is more frequently insinuated into the differential diagnosis of stroke/transient ischemic attack (TIA). Despite the fact that at the time of the index event there are often “no witnesses” or identifiable accomplices (e.g., deep vein thrombosis, intratunnel clot), there is emerging circumstantial evidence that implicates a PFO. The conundrum we face is knowing who should receive a septal closure device and who should be treated medically. Retrospective PFO closure studies have demonstrated high procedural success, low complications, and favorable long-term outcomes. However, controversy remains in the absence of randomized clinical data as to the optimal management of these often young, active, and otherwise healthy patients, who are disabled from a stroke or have had a TIA and fear a subsequent event.

See page 404

In this issue of *JACC: Cardiovascular Interventions*, Ford et al. (1) identified the PFO as the culprit, after other potential sources of TIA or stroke were ruled out. Thus, a diagnosis of exclusion was used for clinical decision-making and definitive treatment with a closure device. The study showed a low incidence of major complications, an excellent closure rate adjudicated by transthoracic echocardiogram (TTE) and a very low recurrence rate of stroke or TIA (2.8% at 4 years). Recurrence of stroke/TIA was significantly higher in those with elevated pulmonary artery pressure (hazard ratio [HR]: 1.12,  $p = 0.009$ ), elevated right ventricular pressure (HR: 1.09,  $p = 0.04$ ), factor V Leiden

mutation (HR: 7.42,  $p = 0.014$ ), and protein S deficiency (HR: 12.2,  $p = 0.002$ ). In this area of clinical uncertainty, should these results be used to guide therapy and should PFO closure be considered the standard of care?

The demographic data are similar to other reports of PFO closure, with patients younger than traditionally seen in stroke populations (mean age 53.4 years) and an absence of a clearly identifiable cause (2–4). The relatively low percentage of patients that underwent carotid ultrasound (25%) and Holter monitor evaluation (36%) was somewhat surprising. Additional information would have been helpful to thoroughly evaluate the mechanistic role of the PFO, such as lower extremity venous duplex (5) and travel history within the weeks preceding the event. (6). Furthermore, knowledge of the presence or absence of migraine headaches (7) would have enhanced the evaluation, since migraine has been associated with a high incidence of venous thrombosis (8) as well as PFO and stroke.

The decision to proceed with PFO closure in this study depended only on the clinical presentation and the presence of the PFO defect. Right to left shunts were confirmed on the basis of TTE and transesophageal echocardiography (TEE) in all patients: 17% had a severe shunt, 45% had a moderate shunt, and 36% had a minimal shunt. The ability to predict stroke/TIA on the basis of shunt size remains controversial (9–11). More importantly, the determination of the magnitude of the shunt varies significantly depending on the method of detection. Among the available modalities, Power M-mode transcranial Doppler is the most sensitive, followed by TEE, and TTE is the least sensitive (12). Intravascular volume status, location of venous injection of agitated saline (upper vs. lower extremity), and the ability to perform an adequate Valsalva maneuver plays a significant role in detection and reproducibility. Furthermore, differentiating PFO diameter size from right to left shunt magnitude can be valuable, because our group observed that small anatomical PFOs can conduct a disproportionately high volume across the atrial septum (12).

It is critical to recognize that all PFOs are not created equal. The image of a small probe patent PFO seen in surgical texts rarely resembles the morphology of PFOs we observed in patients referred for PFO closure evaluation. For example, PFOs with coexisting atrial septal aneurysms represent an important morphological feature. Although a misnomer, these often extremely redundant septum primums have large excursions between atria, can be associated with long or short tunnels (overlap between septum secundum and primum), and have been linked in several studies with a high risk of recurrent stroke in medically treated patients (13–15). Atrial septal aneurysm was present in 23% of the sample in the Ford et al. (1) study, which is consistent with other reports (2,16). The prevalence of structures such as Chiari’s network, a congenital remnant of the right valve

\*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology. Dr. Reisman is on the advisory boards of Coaptus Inc. and Ovalis Inc., and has received research grants from NMT Inc. and Coherex Medical Inc.

From the Swedish Heart and Vascular Institute, Seattle, Washington.

of the sinus venosus, were not reported, but may have clinical significance in increasing stroke risk (17).

After PFO closure, the presence of a residual shunt seen at a median follow-up of 129 days was 4.3%. This is lower than seen in many reports and might reflect the insensitivity of TTE (2,18). Transthoracic echocardiography has been shown to be one-half as sensitive as TEE in shunt detection (12). Another explanation might be the use of the Amplatzer septal occluder. Using the Amplatzer septal occluder for PFO closure might at first glance be counterintuitive, because it is designed for treatment of a hole in the atrial septum (atrial septal defect) and not a flap as seen in PFO. The high closure rate demonstrated in this study may be a result of the central disc of the device plugging the tunnel. Thus, this device might have advantages over PFO devices that are designed with left and right "clamshells" with a connecting pin that sits within the tunnel. In addition, single time point analysis might be subject to error. In our experience we have seen both a reduction as well as an increase in residual shunt in late follow-up (2). These disparities might be due to the effect of tissue growth over the device, misalignment (subtle migration), or device retraction.

Recurrent events occurred in eight patients (2.3%), 7 strokes and 2 TIAs. Following the event, transesophageal echocardiography was performed in 6 patients, and 1 patient had a TTE. There were no findings of intracardiac thrombus, device dislodgement, or residual shunts. Two patients had an event before first follow-up. Of the remaining 6 patients, 5 (83%) were taking warfarin, 3 (50%) were taking clopidogrel, and 5 (83%) were taking aspirin, after device closure and before the recurrent neurologic event. Therefore, they were maximally medically managed. The combined end point of stroke and TIA was 0.9% and 2.8% at 1 and 4 years, respectively. This recurrence rate is low and compares favorably to many of the nonrandomized studies looking at medical therapy (19,20). The majority of events occurred in the first 2 years after closure, an outcome consistent with other studies (21). This result is important, because the recently completed CLOSURE I study comparing PFO closure with medical therapy has a primary end point of stroke or TIA at the 2-year timeframe. Interestingly, none of the patients with residual shunts had recurrent events, which is consistent with the data of Harms et al. (2). One could speculate that, by changing the architecture of the tunnel and having large baffles on each side of the septum, there is a consequential reduction in size and/or load of cerebral embolization.

Atrial septal aneurysm did not increase the risk of recurrence after device placement. The abatement of the atrial septal aneurysm risk of recurrent stroke by PFO devices was shown in this trial as in others (2) and is encouraging, because atrial septal aneurysm might carry the highest risk of primary and repeat neurologic events.

Five of the patients with recurrent events had thrombophilia. Factor V Leiden mutation and protein S deficiency were statistically significant risk factors for recurrent stroke/TIA. However, these results should be interpreted cautiously due to the large variance observed (confidence intervals 1.49 to 36.8 and 2.42 to 61.1, respectively). Whether PFO closure provides additional embolic protection for these patients beyond that conferred by warfarin remains unclear. Conversely, whether the closure device promotes thrombosis and emboli should be considered.

Elevations of right ventricular systolic and pulmonary artery pressures were also found to be significant predictors of recurrent neurologic events. Reconciling this in a closed PFO is challenging. The pressures were only minimally elevated, making the clinical significance unclear. Additional studies should evaluate and attempt to corroborate these findings.

In summary, the questions that arise from this study are provocative and warrant further investigation. It is imperative that, in the absence of randomized clinical data that support superiority or an approved indication for device implantation, cardiologists and neurologists continue to collaborate to define patients with the highest likelihood of benefiting from PFO closure. The paper by Ford et al. (1) takes us one step closer.

---

**Reprint requests and correspondence:** Dr. Mark Reisman, Director, Cardiovascular Research, Swedish Heart and Vascular Institute, 550 17th Avenue, Suite 630, Seattle, Washington 98122. E-mail: mark.reisman@swedish.org.

---

## REFERENCES

1. Ford MA, Reeder GS, Lennon RJ, et al. Percutaneous device closure of patent foramen ovale in patients with presumed cryptogenic stroke or transient ischemic attack: the Mayo Clinic experience. *J Am Coll Cardiol Intv* 2009;2:404-11.
2. Harms V, Reisman M, Fuller CJ, et al. Outcomes after transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Am J Cardiol* 2007;99:1312-5.
3. Wahl A, Praz F, Stinimann J, et al. Safety and feasibility of percutaneous closure of patent foramen ovale without intra-procedural echocardiography in 825 patients. *Swiss Med Wkly* 2008;138:567-72.
4. Spies C, Timmermanns I, Reissmann U, van Essen J, Schrader R. Patent foramen ovale closure with the Intrasept occluder: complete 6-56 months follow-up of 247 patients after presumed paradoxical embolism. *Catheter Cardiovasc Interv* 2008;71:390-5.
5. Cramer SC, Maki JH, Waitches GM, et al. Paradoxical emboli from calf and pelvic veins in cryptogenic stroke. *J Neuroimaging* 2003;13:218-23.
6. Heckmann JG, Stadter M, Reulbach U, Duetsch M, Nixdorff U, Ringwald J. Increased frequency of cardioembolism and patent foramen ovale in patients with stroke and a positive travel history suggesting economy class stroke syndrome. *Heart* 2006;92:1265-8.
7. Dalla Volta G, Guindani M, Zavarise P, Griffini S, Pezzini A, Padovani A. Prevalence of patent foramen ovale in a large series of patients with migraine with aura, migraine without aura and cluster headache, and relationship with clinical phenotype. *J Headache Pain* 2005;6:328-30.

8. Schwaiger J, Kiechl S, Stockner H, et al. Burden of atherosclerosis and risk of venous thromboembolism in patients with migraine. *Neurology* 2008;71:937-43.
9. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002;105:2625-31.
10. Anzola GP, Morandi E, Casilli F, Onorato E. Does transcatheter closure of patent foramen ovale really "shut the door?" A prospective study with transcranial Doppler. *Stroke* 2004;35:2140-4.
11. Goel SS, Tuzcu EM, Shishehbor MH, et al. Morphology of the patent foramen ovale in asymptomatic versus symptomatic (stroke or transient ischemic attack) patients. *Am J Cardiol* 2009;103:124-9.
12. Spencer MP, Moehring MA, Jesurum J, Gray WA, Olsen JV, Reisman M. Power m-mode transcranial Doppler for diagnosis of patent foramen ovale and assessing transcatheter closure. *J Neuroimaging* 2004;14:342-9.
13. Mas JL, Zuber M. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. *Am Heart J* 1995;130:1083-8.
14. Wahl A, Krumsdorf U, Meier B, et al. Transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale for prevention of recurrent paradoxical embolism in high-risk patients. *J Am Coll Cardiol* 2005;45:377-80.
15. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med* 2007;357:2262-8.
16. Slavin L, Tobis JM, Rangarajan K, Dao C, Krivokapich J, Liebeskind DS. Five-year experience with percutaneous closure of patent foramen ovale. *Am J Cardiol* 2007;99:1316-20.
17. Rigatelli G, Cardaioli P, Dell'Avvocata F, et al. The association of different right atrium anatomical-functional characteristics correlates with the risk of paradoxical stroke: an intracardiac echocardiographic study. *J Interv Cardiol* 2008;21:357-62.
18. Taaffe M, Fischer E, Baranowski A, et al. Comparison of three patent foramen ovale closure devices in a randomized trial (Amplatzer versus CardioSEAL-STARflex versus Helex occluder). *Am J Cardiol* 2008;101:1353-8.
19. Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* 2003;139:753-60.
20. Windecker S, Wahl A, Nedeltchev K, et al. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. *J Am Coll Cardiol* 2004;44:750-8.
21. Benbassat J, Bauml R. Variability in duration of follow up may bias the conclusions of cohort studies of patients with patent foramen ovale. *Eur J Neurol* 2008;15:909-15.

---

**Key Words:** closure ■ cryptogenic stroke ■ patent foramen ovale ■ stroke ■ TIA.