JACC: CARDIOVASCULAR INTERVENTIONS VOL. 2, NO. 5, 2009

ISSN 1936-8798/09/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2008.12.015

Percutaneous Device Closure of Patent Foramen Ovale in Patients With Presumed Cryptogenic Stroke or Transient Ischemic Attack

The Mayo Clinic Experience

Monique A. Ford, MD,* Guy S. Reeder, MD,* Ryan J. Lennon, MS,†
Robert D. Brown, MD,‡ George W. Petty, MD,‡ Allison K. Cabalka, MD,§
Frank Cetta, MD,*§ Donald J. Hagler, MD*§

Rochester, Minnesota

Objectives We sought to determine safety, recurrence rates, and novel risk factors for recurrence in patients with cryptogenic stroke/transient ischemic attack (TIA) after patent foramen ovale closure.

Background Patent foramen ovale closure in patients with cryptogenic stroke/TIA remains highly controversial. There are limited data on long-term recurrence rates and their predictors in these patients.

Methods The records of all patients who underwent patent foramen ovale device closure between December 2001 and June 2006 were reviewed. Patients were seen for clinical follow-up at 3 months then followed annually via telephone. Primary end points were recurrent stroke/TIA. Kaplan-Meier methods were used to estimate recurrent event rates. Cox regression analysis was used to identify risk factors for recurrences.

Results There were 352 patients with cryptogenic stroke (n = 225) or TIA (n = 118) with a mean age of 53.4 years. The procedural complication rate was 3.4%. Recurrent events occurred in 8 patients: 7 strokes and 2 TIA, 1 patient had 2 recurrent strokes. The recurrence rate was 0.6% and 2.1% for stroke and 0.3% and 0.7% for TIA at 1 and 4 years, respectively. The combined end point of recurrent stroke/TIA occurred at a rate of 0.9% and 2.8% at 1 and 4 years, respectively. Risk factors for recurrences were 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). Residual shunt and atrial septal aneurysm were not associated with recurrences.

Conclusions Patent foramen ovale device closure is safe and is associated with a low recurrence of stroke/TIA. Factors associated with recurrence are thrombophilia and elevated intracardiac pressures. (J Am Coll Cardiol Intv 2009;2:404–11) © 2009 by the American College of Cardiology Foundation

From the Divisions of *Cardiovascular Diseases, †Biostatistics, ‡Neurology, and §Pediatric Cardiology, Mayo Clinic College of Medicine, Rochester, Minnesota. Funded by the Division of Cardiovascular Diseases, Mayo Clinic Rochester, Minnesota.

Manuscript received December 9, 2008, accepted December 21, 2008.

Stroke remains the third leading cause of death, and in 2004, caused 1 of every 16 deaths in the U.S. Cryptogenic strokes comprise between 20% and 40% of ischemic strokes (1). In the Rochester Epidemiology Project, the total age- and sex-adjusted incidence rate for cryptogenic ischemic stroke subtypes was 52 per 100,000 population (2). Patent foramen ovale (PFO) is detected in up to 24% in healthy individuals on transesophageal echocardiography (TEE) studies (3). The prevalence of PFO in patients with cryptogenic stroke is significantly higher, with estimates ranging from 30% up to 70% (4–7), suggesting an etiologic role.

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Direct documentation of embolization through a patent PFO is rare (8–10) so there remains considerable debate about the role of PFO in stroke/transient ischemic attack (TIA). Although several studies established strong associations between the PFO and cryptogenic stroke/TIA (5,6,11–13), not all (14,15) substantiate this association.

There has been dramatic increase in percutaneous PFO closure in recent years (16), but there are at present no data from randomized trials in this field. However, observational data show reduced episodes of cryptogenic stroke/TIA after PFO closure (17–19). The objectives of the present study were to systematically review our experience with transcatheter device closure of PFO in selected patients with cryptogenic stroke/TIA with regard to procedural safety and efficacy, measure recurrent event rates, and identify risk factors for these recurrent events.

Methods

We reviewed the Mayo Clinic Rochester PFO database for patients who underwent percutaneous device closure of PFO for cryptogenic stroke/TIA between December 2001 and June 2006. Patients were referred from external institutions or internal referrals from neurologists and other colleagues. Baseline characteristics, procedural details, complications, and follow-up data were reviewed for all patients. Patients were included only if their qualifying neurologic event was a documented ischemic stroke or TIA. All patients gave written informed consent for inclusion in the study, and the Mayo Foundation Institutional Review Board approved the study.

Definitions. Patent foramen ovale was defined as the presence of a typical flaplike interatrial communication with interatrial shunting during echocardiography detected by color flow imaging or intravenous injections of agitated saline at rest or with provocative maneuvers such as cough or Valsalva (14). Right-to-left atrial shunting was diagnosed if micro bubbles were observed to cross the defect into the left atrium within 3 to 5 cardiac cycles after injection (3). Atrial septal aneurysm (ASA) was diagnosed if part or all of the atrial septum exhibited aneurysmal dilation protruding at least 1.5 cm beyond the plane of the atrial septum or if there was phasic excursion during the cardiorespiratory cycle exceeding 1.5 cm and if the base of the aneurysmal protrusion was at least 1.5 cm in diameter (20).

We defined ischemic stroke as the acute onset (minutes to hours) of a focal neurologic deficit persisting more than 24 h, with computed tomography (CT) or magnetic resonance imaging (MRI) documentation and caused by altered circulation to a limited region of the cerebral hemispheres, brainstem, or cerebellum. Patients were excluded if findings on CT or MRI showed evidence of intracerebral hemorrhage or some other nonischemic cause for the presenting symptoms. Transient ischemic attack was defined as a neurologic deficit lasting <24 h attributed to focal cerebral ischemia (21). We used the TOAST (Trial of Org 10172 in Acute Stroke Treatment) definition for cryptogenic stroke as the presence of a stroke in a patient with no likely etiology determined despite an extensive evaluation (22). We excluded patients whose qualifying event was peripheral embolization such as renal or retinal emboli as their only embolic event.

Abbreviations and Acronyms

ASA = atrial septal aneurysm
CT = computed tomography
IQR = interquartile range
MRI = magnetic resonance imaging
PFO = patent foramen ovale
TEE = transesophageal echocardiography
TIA = transient ischemic attack
TTE = transthoracic echocardiography

Pre-procedure evaluation. All patients underwent comprehensive neurology evaluation by a neurologist. A diagnosis of cryptogenic stroke or TIA was made only after extensive evaluation excluded any secondary causes. Patients underwent neurology consultation with imaging: brain CT and/or MRI. Some patients had additional imaging including magnetic resonance angiography of the head and neck or cerebral angiography. Patients also underwent thrombophilia screens with hematology consultations for any abnormal findings and cardiac Holter monitoring to screen for cardiac arrhythmias.

All patients had transthoracic echocardiography (TTE) and TEE with color Doppler flow and agitated saline contrast at rest and with Valsalva maneuver for identification of PFO and right-to-left shunting. Patients were not excluded based on resting PFO size or degree of shunting as long as some right-to-left shunt was observed. Patients with an identified cause of stroke such as intracardiac thrombus, vegetation, significant carotid or vertebral artery abnormality, or other embolic source were excluded. The clinical decision to proceed with PFO closure was made in conjunction with the neurologist involved in the patient's care.

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Implantation procedure. We previously described the procedure of percutaneous PFO device closure (23). Briefly, patients presented to the cardiac catheterization laboratory after an overnight fast. Femoral venous sheaths were placed and intravenous heparin was administered. Hemodynamic right heart catheterization was performed. Under TEE (n = 60) or intracardiac echocardiographic (n = 292) guidance, the PFO was visualized. The stretched PFO diameter was then measured using a low pressure, compliant sizing balloon to facilitate appropriate device sizing.

Patients received either the Amplatzer ASD (AGA Medical Corporation, Plymouth, Minnesota) or the CardioSEAL (NMT Medical Inc., Boston, Massachusetts) septal occluder device. If device placement was judged suboptimal, the device was withdrawn and repositioned or a new device was placed. Patients were observed in hospital overnight and dismissed the following day after a TTE demonstrated normal device position and no pericardial effusion. All patients received aspirin 81 to 325 mg after the procedure. At the discretion of the operator, some patients received clopidogrel 75 mg for 1 month after the procedure. Warfarin was usually not used unless there was an indication for anticoagulation such as in those patients with thrombophilia who received warfarin for 6 months after device closure.

Follow-up evaluation. Patients returned for follow-up at approximately 3 months after the procedure and underwent a limited history, examination, and TTE with agitated saline contrast, at rest and with the Valsalva maneuver, to determine presence of any residual shunt. All patients were then called yearly to complete a standardized telephone questionnaire (Online Appendix) for surveillance of recurrent events. Patients were followed at other junctures at the discretion of their primary providers. All subsequent echocardiograms performed at our institution for follow-up of persistent shunts or for other indications were also reviewed.

Evaluation of recurrent events. Patients were evaluated for the occurrence of the pre-specified primary end points of recurrent stroke and/or TIA. Pertinent external clinical records were obtained for the adjudication process as necessary. All post-procedure events were audited by the author panel by review of hospital and clinical records. Questionable events were adjudicated by a neurologist (R.D.B. and G.W.P.) who reviewed clinical records and neurologic imaging (brain CT or MRI). Only definite recurrent strokes and TIA were included in the analysis. All patients with recurrent events also underwent TTE or TEE to check for a cardiac source of embolism, device position, or residual shunt.

Statistical analysis. Continuous variables were expressed as mean ± SD unless otherwise indicated. Discrete variables are summarized as frequency and percentage. Survival estimates, such as recurrent thromboembolic events during follow-up were calculated using Kaplan-Meier methods. Cox regression analysis was used to calculate hazard ratios and identify risk factors for recurrent events. We considered p values <0.05 to be statistically significant.

Results

Between December 2001 and June 2006, 441 patients at Mayo Clinic Rochester underwent percutaneous transcatheter device closure of PFO for events presumed secondary to paradoxical embolization. Thirty-eight patients did not give consent for review of their records so were not included; 51 patients were excluded because their qualifying event was not stroke or TIA. The study population consisted of the remaining 352 patients.

Baseline characteristics. There were 208 males and 144 females (Table 1). The mean age of the population was 53.4 years (median: 54 years, range: 19 to 84 years). There were 225 patients (63.9%) who had stroke, 118 patients (33.5%) with TIA, and 9 patients with both as their qualifying event. Fourteen patients had a history of peripheral embolism along with their qualifying stroke or TIA. All patients had echocardiographic right-to-left shunt, either at rest or after Valsalva release. Atrial septal aneurysm was diagnosed in 83 (23.6%) of patients. None were noted to contain thrombus.

Procedural results. The mean intracardiac pressures are shown in Table 1. The mean unstretched PFO size was 5.8 ± 3.4 mm, and the mean stretched diameter at procedure was 11.3 ± 3.8 mm. We successfully deployed 352 devices (100% procedural success). Procedural success was defined as deployment of a device with disks on either side of the PFO flap with no or minimal residual shunt without impingement of adjacent cardiac structures. An Amplatzer septal occluder device was used in 348 of the 352 procedures and a CardioSEAL occluder was deployed in 4 patients. The mean device size was 14.1 ± 4.2 mm.

Procedural complications were defined as those occurring during the PFO procedure and up to the patient's dismissal from hospital, usually within 24 h. Complications occurred in 12 patients: 7 males and 5 females (3.4%) and included atrial flutter (n = 2), atrial fibrillation, protamine reaction, vasovagal reaction, retroperitoneal bleed, pericardial tamponade, transient diplopia, vascular complications, and transient generalized erythema. Development of complications was not related to age or gender. There were no procedural deaths and no patient required a surgical procedure.

Follow-up. The mean follow-up was 37 months (interquartile range [IQR]: 25 to 49 months) with a maximum follow up of 6 years. Of the total study population, 89% were contacted within 1 year of retrieval of the follow-up data, 95% were contacted within 18 months, and 98% within 2 years.

Residual shunt. At the first post-discharge echocardiogram (median duration from closure: 98 days, IQR: 86 to 120 days), residual shunt was detected in 21 (6.6%) patients. At the last follow-up echo (median duration

Table 1. Baseline Characteristics (N = 352)

Mean age, yrs	53.4 (19.0–84.0)
Male	208 (59.1)
Female	144 (40.9)
Aspirin	252 (72)
Clopidogrel	80 (22.8)
Warfarin	157 (44.7)
HTN	130 (36.9)
Diabetes mellitus	25 (7.1)
Oral contraceptives	15 (4.3)
Hyperlipidemia	146 (41.6)
Smoking	
Current	31 (8.8)
Former	80 (24)
Atrial septal aneurysm	83 (23.6)
Intracardiac thrombus	0
Baseline right-to-left shunt grade	
Minimal	86 (36.4)
Moderate	107 (45.3)
Severe	41 (17.4)
Coagulation screen	293 (89.6)
Protein C deficiency	14 (4.3)
Protein S deficiency	11 (3.4)
Factor V Leiden	14 (4.3)
Lupus anticoagulant	3 (0.9)
Anticardiolipin antibodies	9 (2.8)
Brain computed tomography	152 (43.2)
Brain MRI	266 (75.6)
Cerebral angiogram	24 (6.8)
Carotid ultrasound	88 (25)
24-h Holter	129 (36.7)
Qualifying event	
Stroke	234 (66.5)
TIA	127 (36.1)
Mean right atrial pressure, mm Hg	6 (0–20)
Mean left atrial pressure, mm Hg	9 (3–22)
Right ventricular systolic pressure	29 (20–52)
Pulmonary artery systolic pressure, mm Hg	27 (13–53)
Unstretched PFO diameter, mm	5.8 (1.0–16.0)
Stretched PFO diameter, mm	11.3 (3.0–22.0)

Variables expressed as mean (range) or n (%).
HTN = hypertension; MRI = magnetic resonance imaging; PFO patent foramen ovale; TIA = transient ischemic attack.

from closure: 129 days, IQR: 92 to 472 days), residual shunt remained in 15 (4.3%). Overall, residual shunt was present at any time during follow-up in 27 (8.5%) patients. Follow up shunt data was not available in 34 patients. None of the patients with residual shunts at last follow-up had recurrent events.

Deaths. There were 16 deaths during follow-up, none of which were due to device complications or recurrent neurological ischemic events (Table 2).

Anticoagulant use. Follow-up medication data was available in 351 of 352 (99.7%) cases. There were 145 (41%) patients on warfarin, 117 (33%) on clopidogrel, and 327 (93%) who were on aspirin after the procedure.

Recurrent events. There were 8 recurrent events in 7 patients (2.3%). There were 7 strokes and 2 TIA with 1 patient having 2 recurrent strokes. There were no peripheral embolizations. The first recurrent stroke occurred 163 days after the procedure in a patient whose qualifying event was stroke. At the time of the recurrent event, TEE was performed in 6 patients and 1 patient had TTE. No intracardiac thrombus, device dislodgement, or residual shunt was detected in any patient with a recurrent event. Two patients had an event before their first follow-up. Of the remaining 6 patients, 5 (83%) were on warfarin, 3 (50%) were on clopidogrel, and 5 (83%) were on aspirin after device closure and before their recurrent neurologic event.

The recurrence rate at 1 year was 0.6% for stroke and 0.3% for TIA. At 4 years, the recurrence rate for stroke was 2.1% and 0.7% for TIA (Figs. 1A and 1B). The recurrence rate for the combined end point of recurrent stroke or TIA was 0.9% at 1 year and 2.8% at 4 years (Fig. 1C). Although there was a steady annual event rate, the overall risk during follow-up was very low. Using hazard ratio (HR) analysis, factor V Leiden mutation (HR: 9.9, $p < 0.001$), protein S deficiency (HR: 3.1, $p = 0.014$), and elevated pulmonary artery pressure (HR: 1.12, $p = 0.009$) were statistically associated with recurrent events (Table 3). Notably, recurrent events were not significantly related to initial PFO size, presence of ASA, or device type. No patient with a recurrent event had a residual shunt or intracardiac or device thrombus.

Table 2. Patient Deaths During Follow-Up

Patient #	Time Between PFO Closure and Death (days)	Cause of Death
1	47	Acute renal failure, cardiogenic shock, staphylococcal pneumonia
2	122	Right-sided congestive heart failure, primary biliary cirrhosis
3	281	Squamous cell carcinoma of the ovary
4	654	Ventricular fibrillation arrest
5	264	Acute coronary syndrome
6	292	Acute respiratory distress syndrome
7	1,500	Esophageal and lung cancer
8	303	Liver cancer
9	269	Bladder cancer
10	549	Central nervous system lymphoma
11	24	Aspiration pneumonia
12	21	Bladder cancer
13	747	Myocardial infarction
14	33	Lung cancer
15	6	Died before consent to review records obtained
16	148	Renal failure, idiopathic cardiomyopathy

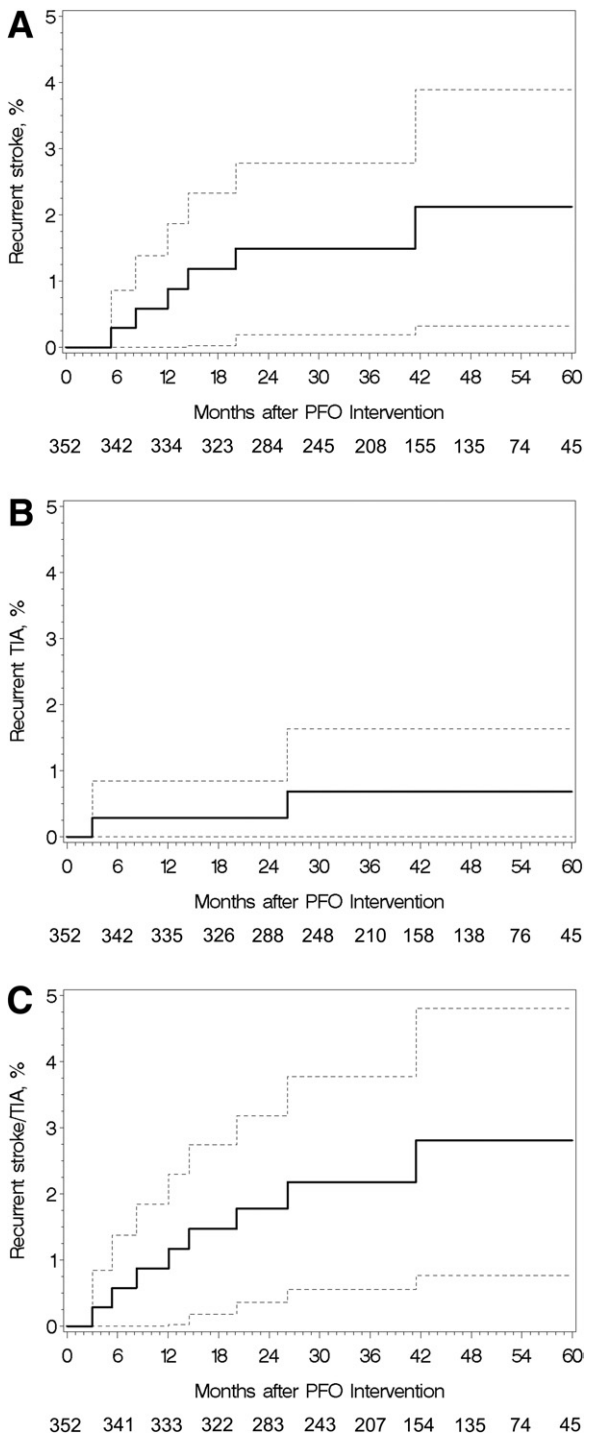

Figure 1. Recurrent Stroke/TIA After PFO Device Closure

(A) Recurrent stroke after patent foramen ovale (PFO) device closure was 0.6% at 1 year and 2.1% at 4 years. **(B)** The rate of recurrent transient ischemic attack (TIA) after percutaneous device PFO closure was 0.3% at 1 year and 0.7% at 4 years. **(C)** The rate of the combined end point of recurrent ischemic stroke/TIA after PFO closure was 0.9% at 1 year and 2.8% at 4 years. **Dashed lines** represent 95% confidence limits.

Discussion

We reviewed our experience with percutaneous PFO closure in 352 patients with cryptogenic stroke or TIA. The major findings of this study are: 1) PFO device closure is effective and safe with a complication rate of 3.4% with no complications causing long-term deficits or death; 2) a small proportion of patients (2.3%) have recurrent events (stroke/TIA) after PFO closure; 3) the recurrent stroke/TIA rate is very low; 4) thrombophilia and elevated pulmonary pressures increase the risk of recurrent thromboembolic events; and 5) neither ASA nor residual shunt was associated with recurrent events.

Complications. Our complication rate was 3.4%, which is considerably lower than previously reported (23), and most complications were minor. The only serious complication, tamponade, occurred in 1 patient and was immediately recognized and treated with pericardiocentesis in the catheterization laboratory and did not recur. Wahl et al. (24) had a complication rate of 2.5% in over 500 consecutive patients.

Recurrent events. The rates of recurrent events in our study population are lower than the rates of recurrent stroke and TIA in general population studies of stroke patients. In the Heart Disease and Stroke Statistics 2007 Update (25), 13% of men and 22% of women between 40 to 69 years experience a recurrent stroke within 5 years of the first event, whereas in patients age 70 years and older, 23% of men and 28% of women have recurrent strokes.

It is exceedingly difficult to identify a control group of patients with PFO and recurrent cryptogenic strokes who do not undergo intervention. Results of 2 systematic reviews (17,18) encompassing 21 publications of medical or catheter therapy for PFO are shown in Table 4. These observational data, overlapping to some extent, summarize the knowledge base from 1985 to 2005 regarding secondary prevention of embolic events with either medical therapy or catheter closure. Although outcomes are reported differently, figures can be considered roughly equivalent to a 1-year risk of recurrent event. Our recurrence rates for stroke or TIA of less than 1% at 1 year are significantly lower than those associated with medical therapy in these studies (3.8% to 12%).

Atrial septal aneurysm. Atrial septal aneurysm was not a risk factor for recurrence in this study but has been suggested to increase the risk of stroke in patients with PFO. In a meta-analysis by Overell et al. (12), the odds ratio was 4.96 for PFO with ASA versus 1.83 for PFO only. Cabanes et al. (26) reported a relative risk of cryptogenic stroke 33 times higher than controls for both PFO and ASA versus a 4-fold increase with PFO only. In a study by Mas et al. (7), there was a 4-fold higher risk of recurrent stroke in patients with both PFO and ASA than in those patients with no defect or with PFO alone. Other studies have not shown such an

Table 3. Risk Factors for Recurrent Stroke/TIA After PFO Device Closure

Variable	No Event (n = 344)	Event (n = 8)	HR (95% CI)	p Value
Age, yrs	53.3 ± 13.2	57.0 ± 18.7	1.02 (0.97–1.08)	0.43
Male	203 (59)	5 (63)	1.15 (0.27–4.80)	0.85
Aspirin	248 (73)	4 (50)	0.36 (0.09–1.43)	0.15
Clopidogrel	77 (22)	3 (38)	2.02 (0.48–8.44)	0.34
Warfarin	154 (45)	3 (38)	0.67 (0.16–2.84)	0.59
Hypertension	125 (36%)	5 (63)	3.00 (0.72–12.5)	0.13
Hyperlipidemia	141 (41)	5 (50)	1.43 (0.41–4.95)	0.57
Diabetes mellitus	24 (7)	1 (13)	2.33 (0.28–19.0)	0.43
Oral contraceptives	15 (4)	0		0.99
Smoking status				
Former	76 (23)	2 (25)	0.94 (0.19–4.64)	0.64
Current	17 (5)	0		
Atrial septal aneurysm	81 (27)	2 (25)	0.96 (0.19–4.76)	0.96
Normal coagulation screen	288 (90)	5 (63)	0.19 (0.05–0.81)	**0.025**
Protein C deficiency	13 (4)	1 (13)	3.11 (0.38–25.3)	0.29
Protein S deficiency	9 (3)	2 (25)	12.2 (2.42–61.1)	**0.002**
Factor V Leiden	12 (4)	2 (25)	7.42 (1.49–36.8)	**0.014**
Lupus anticoagulant	3 (1)	0		0.99
Anticardiolipin antibodies	9 (3)	0		1.00
Mean right atrial pressure, mm Hg	6.2 ± 3.3	7.5 ± 2.4	1.11 (0.90–1.37)	0.34
Mean left atrial pressure, mm Hg	8.7 ± 3.5	12.3 ± 6.0	1.27 (0.95–1.69)	0.10
Right ventricular systolic pressure, mm Hg	28.4 ± 7.7	34.1 ± 5.8	1.09 (1.00–1.19)	**0.048**
Pulmonary artery pressure, mm Hg	26.9 ± 6.4	33.4 ± 5.4	1.12 (1.03–1.22)	**0.009**
Pulmonary capillary wedge pressure, mm Hg	9.7 ± 4.2	11.7 ± 4.9	1.09 (0.94–1.26)	0.25
Stretched PFO diameter, mm	11.0 ± 3.7	13.2 ± 3.8	1.16 (0.95–1.41)	0.15
Device size	14.1 ± 4.2	14.8 ± 3.9	1.04 (0.88–1.22)	0.66

Bold values are statistically significant.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

association (18,19,27). One proposed mechanism by which ASA could increase stroke risk is by in situ thrombosis. We did not observe thrombus in any of the 83 patients with ASA. In addition, the constant mobility of the ASA observed by echocardiography would reduce the likelihood of development of in situ thrombosis.

Residual shunt. Unlike other published reports (19), we did not find residual shunts in any patient who had a recurrent event. In fact, 90% of residual shunts detected by contrast echocardiography at the first 3-month follow-up visit spontaneously closed by 255 days after the procedure. Most shunts were tiny and often only noted with Valsalva release. We do not recommend aggressive attempts to obliterate tiny residual shunts detected at early follow-up with additional device deployment because they often close spontaneously without affecting outcome. The lack of association of residual shunt with recurrent events is puzzling. It could be postulated that incomplete endothelialization of the Amplatzer device could allow some tiny residual intradevice bubble shunting while preventing paradoxical embolization of larger thrombi. Alternatively, neurologic events at follow-up (and including the index event) may represent, in some patients, a process totally unrelated to the PFO.

Table 4. Secondary Prevention of Cryptogenic Stroke With PFO: Results of 2 Systematic Reviews From 1985 to 2003

Investigator (Ref. #) Years	Therapy	N	Stroke (%)	TIA (%)	Stroke/TIA (%)
Homma et al. (15)* 1990–2005	Medical	943	1.98	2.24	4.22
	Catheter closure	1,430	0.19	1.52	1.62
Khairy et al. (18)† 1985–2003	Medical	895	—	—	3.8–12
	Catheter closure	1,355	—	—	0–4.9

*Events reported as percentage per 100 patient-years (15). †Events reported as percentage of recurrent at 1 year (18).
Abbreviations as in Table 1.

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Thrombophilia and recurrent events. Five patients with recurrent events had a thrombophilia: heterozygous factor V Leiden (n = 2), protein C deficiency (n = 1), and protein S deficiency (n = 2). The presence of factor V Leiden mutation or protein S deficiency imparted a significant risk of recurrent stroke/TIA (HR: 7.4 and 12.2, respectively).

In patients with PFO, thrombophilic states may increase the occurrence of venous clots that can paradoxically embolize to the systemic circulation. In fact, in a recent case-control matched study, thrombophilia predisposed patients with PFO to cryptogenic strokes (HR: 2.8) (28). Based on these observations, we would recommend that patients with PFO and thrombophilias be strongly considered for chronic oral anticoagulation after device closure. Further studies are needed to extend this recommendation for primary stroke prophylaxis in such patients. However, after PFO closure, the mechanism would be less clear but may include device or in situ thrombosis. We did not observe device thrombus in patients with recurrent events in this study but not all patients had TEE performed.

Intracardiac pressures and recurrent events. Patients with recurrent stroke/TIA had higher mean intracardiac pressures than those who did not have recurrent events even though pressures were still within the normal range (Table 2). Patients with elevated right-sided pressures have a higher right-to-left pressure gradient, which, under the right circumstances, could facilitate systemic embolization. Several investigators have described strokes occurring during Valsalva maneuvers (29). Perhaps higher pressure is a marker of increased stroke risk by association with factors such as diastolic dysfunction rather than being a direct causal factor. However, in the entire study population, the right-sided pressures were only minimally elevated (mean right atrial pressure: 6.2 ± 3.3 mm Hg, mean right ventricular systolic pressure: 28.4 ± 7.7 mm Hg, mean pulmonary artery systolic pressure: 26.9 ± 6.4 mm Hg) so the clinical significance of this finding is unclear.

Study limitations. The retrospective nonrandomized nature of this highly selected study population may not be representative of the general population at risk. The small numbers of recurrent events make it difficult to absolutely define the true treatment effect of PFO device closure. Clinically silent cerebral ischemic episodes would not have been detected. Exhaustive efforts were taken to exclude patients with strokes from other identifiable causes, and we believe our study population is a good representation of truly cryptogenic stroke/TIA patients. The likelihood of ascertainment bias with unreported recurrent events is low because all patients had complete and extensive follow-up. The absence of a similarly selected control population (patients presenting to our institution with cryptogenic stroke with PFO without closure during this time frame) is a major limitation. Ongoing randomized trials will provide such a group and hopefully a similar cohort of cryptogenic stroke patients will be enrolled.

Percutaneous device closure of PFO in patients with cryptogenic stroke or TIA is safe with a 3.4% procedural complication rate at our institution. The combined recurrence rate of stroke/TIA was 0.9% at 1 year and 2.8% at 4 years. Thrombophilia and increased intracardiac pressures were risk factors for recurrent events after PFO device closure. We found no association between recurrent events and residual shunting or ASA. The majority of residual shunts spontaneously close within a year. We await the results of randomized clinical trials to accurately quantify the effect of PFO device closure on recurrent cryptogenic strokes/TIA as compared with medical therapy. Until such trials are completed, we believe our results support PFO closure for cryptogenic stroke in carefully selected patients.

Acknowledgment
The authors are grateful to Darlene Cooper for her expert assistance with data collection and patient follow-up.

Reprint requests and correspondence: Dr. Guy S. Reeder, Cardiovascular Diseases, 200 First Street SW, Rochester, Minnesota 55905. E-mail: Reeder.Guy@mayo.edu.

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Key Words: patent foramen ovale ■ cryptogenic stroke ■ transient ischemic attack.

APPENDIX

For the text of the phone follow-up and the written questionnaire, please see the online version of this article.