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Long-Term Experience and Outcomes With Transcatheter Closure of Patent Foramen Ovale

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Objectives This study sought to examine the frequency of indications for and the immediate and long-term clinical outcomes of transcatheter closure of patent foramen ovale (PFO).

Background Transcatheter PFO closure is commonly performed for several indications, including cryptogenic stroke, despite conflicting data regarding the efficacy of this intervention.

Methods We report the outcomes of 800 consecutive patients (52% male, 50 ± 14 years of age) who underwent PFO closure at our institution after multidisciplinary evaluation over a 16-year period.

Results Indications for closure included cryptogenic cerebrovascular event (94%), hypoxemia (2%), peripheral embolism (3%), and migraine headaches (2%). Procedural success was 99% with effective closure obtained in 93% of patients. At a mean follow-up of 42.7 ± 33.4 months, 21 patients suffered a recurrent ischemic neurologic event (12 strokes, and 9 transient ischemic attacks) for an incidence rate of 0.79 events per 100 person-years and freedom from recurrent events of 91.6% at 10 years. There was no device-based difference in the rate of recurrent ischemic neurologic events ($p = 0.82$). Only Eustachian valve prominence (hazard ratio: 9.04; 95% confidence interval: 2.07 to 39.44; $p = 0.0034$) was associated with recurrent neurologic events.

Conclusions Transcatheter PFO closure is safe and feasible in patients with several clinical indications. The long-term efficacy of this intervention in patients with paradoxical embolism appears superb in this observational study. Carefully selected patients with features suggestive of paradoxical embolism are the most likely to benefit from PFO closure and should be the focus of future investigation. (J Am Coll Cardiol Intv 2013;6:1176–83) © 2013 by the American College of Cardiology Foundation

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The clinical implications of patent foramen ovale (PFO) have been unclear and have driven substantial debate within the field of cardiovascular medicine. The most commonly feared consequence of PFO is a paradoxical embolism resulting in a neurologic event or peripheral embolism (1–6), but PFO has also been associated with the platypnea-orthodeoxia syndrome, hypoxemia, decompression sickness in divers, and migraine headaches (3,7–15). Although no percutaneous transcatheter device is currently approved in the United States for PFO closure, the off-label use of atrial septal defect closure devices for PFO closure has been widespread (16). We and others have shown that transcatheter PFO closure is a safe intervention that is associated with favorable short- and intermediate-term outcomes (17); however, the efficacy of transcatheter PFO closure has been questioned due to conflicting clinical data (14–21). In contrast to substantial favorable observational data (14–17,21), 3 randomized controlled trials assessing PFO closure for secondary prevention of cryptogenic ischemic neurologic events each failed to meet their primary efficacy endpoint (18–20). However, results of secondary and subgroup analyses favoring PFO closure in addition to several challenges in trial execution have introduced further uncertainty to the field. The present study seeks to report the long-term clinical outcomes of patients with PFO who underwent transcatheter closure at the Massachusetts General Hospital.

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Methods

Patient population. A total of 800 adult patients underwent transcatheter PFO closure from January 1, 1995 to May 20, 2010, at the Massachusetts General Hospital. All patients were identified to have a PFO by transthoracic or transesophageal echocardiography with color Doppler and agitated saline injection to assess for intracardiac shunting. Only patients undergoing repeat PFO closure for residual shunting were excluded from this analysis.

In the event of a suspected paradoxical embolism, PFO closure was performed only after thorough evaluation and multidisciplinary discussion. Such patients underwent brain magnetic resonance imaging, Holter or event monitoring, assessment of extracranial cerebrovascular disease either by angiography or Doppler ultrasonography, thrombophilia testing (proteins C and S, antithrombin III, lupus anticoagulant, anticardiolipin antibodies, homocysteine, and factor V Leiden), and pelvic magnetic resonance venography to screen for May-Thurner anatomy. Patients were also independently evaluated by specialists in cardiology, hematology, vascular medicine, and neurology; they were ultimately jointly discussed at a weekly PFO committee meeting. The committee would consider the appropriateness of transcatheter closure on the basis of the perceived likelihood that the clinical event was PFO-related, the risk of recurrent thromboembolic event, the presence of inciting events such as prolonged travel, immobility, or hormonal therapy, and the ability of the patient to receive anticoagulation therapy. Patients with substantial competing risk factors for recurrent thromboembolic events, such as atrial fibrillation or advanced vascular disease, were largely treated conservatively and not closed.

Echocardiographic assessment. All patients underwent transthoracic and/or transesophageal echocardiographic evaluation prior to PFO closure. Intracardiac right-to-left shunting suggestive of PFO was characterized by the appearance of microbubbles in the left atrium within 3 beats of right atrial opacification at rest or with release of the Valsalva maneuver. The severity of shunt was categorized as follows: 0 = none/trace, <3 microbubbles in the left atrium; 1 = small, indicating the presence of 3 to 9 microbubbles in the left atrium; 2 = moderate, indicating 10 to 30 microbubbles in the left atrium after administration of agitated saline; and 3 = large, >30 microbubbles in the left atrium after administration of agitated saline (17). Atrial septal aneurysm was defined as >10 mm excursion of the aneurysm beyond the plane of the atrial septum. A hypermobile atrial septum was defined as hypermobility that did not meet the criteria for atrial septal aneurysm. Eustachian valve prominence was prospectively reported at the discretion of the attending echocardiographer.

Abbreviations and Acronyms

CI = confidence interval(s)
HR = hazard ratio(s)
PFO = patent foramen ovale
TIA = transient ischemic attack

Transcatheter PFO closure procedure. PFO were percutaneously closed using the Amplatzer Septal Occluder, the Amplatzer Multifenestrated Septal Occluder "Cribiform" device (St. Jude Medical, Inc., St. Paul, Minnesota), CardioSEAL/STARFlex Septal Occlusion system (NMT Medical, Inc., Boston, Massachusetts), the HELEX Septal Occluder (W. L. Gore and Associated, Inc., Flagstaff, Arizona), the Premere PFO closure device (St. Jude Medical, Inc.), or the Sideris buttoned septal occlusion device (Custom Medical Devices, Amarillo, Texas) under fluoroscopic and echocardiographic guidance. Either transesophageal echocardiography or intracardiac echocardiography was used for intraprocedural guidance. Patients were systemically anticoagulated during the PFO closure procedure with intravenous heparin with a goal activated clotting time of 200 to 220 s. Patients were also treated with intravenous antibiotics, either cefazolin or vancomycin, during the procedure and for 24 h thereafter.

Antithrombotic and anticoagulant therapy. Patients received aspirin (81 or 325 mg daily) and/or clopidogrel (75 mg daily)

at the discretion of the operator. Patients requiring short- or long-term anticoagulation with warfarin for other causes, such as deep venous thrombosis or pulmonary embolism, were maintained on heparin or low molecular weight heparin while undergoing warfarin loading. Patients with a hypercoagulable state, a single thromboembolic event, and a reversible risk factor for clotting were anticoagulated with warfarin for 3 months after PFO closure and then switched to aspirin therapy. Those with 2 or more thromboembolic events and thrombophilia were prescribed life-long warfarin anticoagulation.

Clinical and echocardiographic follow-up. All patients received a transthoracic echocardiogram after closure and prior to hospital discharge. Patients were then seen in follow-up at 4 to 6 weeks, 6 months, and annually for 5 years after PFO closure almost uniformly by the interventional cardiologist. Transthoracic echocardiography was performed at each visit to assess for residual shunt or other device-related abnormality. Patients with any recurrent neurologic symptoms underwent neurological evaluation by a specialist, and when necessary, the appropriate neurologic imaging study. For the purpose of this study, attempts were made to contact patients no longer being followed by our practice by phone or electronic medical records were reviewed to identify clinical events. The Massachusetts General Hospital panel of the Partners Human Research Committee approved all research activities.

Statistical analysis. Patient characteristics, including demographics, medical history, imaging and serologic test results, and procedural data were retrospectively collected. Data are presented either as mean ± SD or median (interquartile range). Between-group comparisons were made using Fisher exact test for categorical variables or unpaired Student *t* test for continuous variables. Because of the low event rate, multivariable regression analyses were not conducted. Kaplan-Meier survival analysis was used to assess the absolute risk of events after transcatheter PFO closure and between-group comparisons made using the log-rank test. All tests were 2-tailed with significance accepted at the $p < 0.05$. Statistical analyses were performed with SAS (version 9.2, SAS Institute, Inc., Cary, North Carolina) and JMP (version, 9, SAS Institute, Inc.).

Results

Patient characteristics. A total of 800 patients were included in this analysis, with a mean age of 50 ± 14 years. The cohort was 52% male and 93% white in race (Table 1). Due to our selection process for transcatheter PFO closure, the frequency of cardiovascular risk factors was relatively low with hypertension present in 245 (31%), dyslipidemia in 276 (35%), diabetes in 48 (6%), and current smoking in 75 (9%) patients. A hypercoagulable state was identified in 227 (28%) patients. Antiphospholipid syndrome and lipoprotein(a) were the most frequent, identified in 83 (10%) and 78 (10%) patients, respectively. May-Thurner anatomy was documented in 85 (11%) patients.

Table 1. Baseline Characteristics (N = 800)

Age, yrs	50 ± 14
Male	418 (52)
Race	
White	746 (93)
Black	16 (2)
Hispanic	29 (4)
Asian	9 (1)
Hypertension	254 (31)
Dyslipidemia	276 (35)
Diabetes	48 (6)
Atrial fibrillation	9 (1)
Smoking	
Current	75 (9)
Former	201 (25)
Family history of CVD	82 (10)
Migraine headaches	114 (14)
Deep vein thrombosis	10 (1)
May-Thurner anatomy	88 (11)
Hypercoagulable state	
Antithrombin III deficiency	17 (2)
Protein S deficiency	30 (4)
Protein C deficiency	7 (1)
Antiphospholipid syndrome	83 (10)
Prothrombin gene mutation	22 (3)
Factor V Leiden	27 (3)
Lipoprotein (a)	78 (10)
HIT	3 (0)
Indications for PFO Closure	
Cerebrovascular events	
Stroke	564 (71)
TIA	131 (16)
Multiple events	54 (7)
Hypoxemia	18 (2)
Peripheral embolism*	22 (3)
Migraine headaches	12 (2)
Other	2 (0)
PFO Anatomic Features	
Direction of shunt	
Right to left	694 (87)
Left to right	55 (7)
Bi-directional	51 (6)
Shunt condition	
Rest only	119 (15)
Valsalva only	232 (29)
Both	449 (56)
Interatrial septal mobility	
Atrial septal aneurysm	203 (25)
Hypermobility	139 (17)
Eustachian valve	11 (1)

Values are mean ± SD or n (%). *3 patients suffered peripheral emboli and stroke.
CVD = cardiovascular disease; HIT = heparin-induced thrombocytopenia; PFO = patent foramen ovale; TIA = transient ischemic attack.

Transcatheter PFO closure was performed predominantly in patients who had suffered cerebrovascular event(s) felt to be due to a paradoxical embolism (Table 1). Of these 749 patients with neurologic events, 564 experienced a stroke, 131 a transient ischemic attack (TIA), and 54 multiple neurologic events. Closure of PFO was also performed for hypoxemia in 18 (2%) patients, peripheral embolic events in 22 (3%), and migraine headaches in 12 (2%). Peripheral embolic events, defined as emboli to the coronary, renal, splenic, and retinal arteries, occurred concurrently with a neurologic event in 3 patients. Patients who underwent transcatheter PFO closure solely for migraine headaches were treated within clinical trials.

The majority of patients had right-to-left shunting documented on echocardiographic assessment (87%), although some patients possessed PFO that were stretched open and allowed for either bidirectional (6%) or left-to-right shunting (7%) (Table 1). An atrial septal aneurysm was identified in 203 (25%) patients, hypermobile atrial septum in 139 (17%), and a prominent Eustachian valve in 11 (1%) patients.

Procedural outcomes. Of 800 patients, 794 (99%) underwent successful transcatheter PFO closure, one of which required multiple devices. Effective closure was obtained in 737 (93%). Of these, 303 (38%) patients received the Amplatzer Cribiform device, 178 (22%) the Amplatzer Atrial Septal Occluder, 47 (6%) the Gore Helex Septal Occluder, 228 (29%) the Cardioseal or STARFlex Occlusion System, 35 (4%) the Sideris buttoned septal occlusion device, and 2 (0%) the Premere Septal Occluder. We found no significant difference in the rate of effective PFO closure among devices ($p = 0.17$) (Table 2). In 6 patients, transcatheter PFO closure was unsuccessful. A PFO could not be identified in 2 of these patients. Anatomic features precluded safe device deployment in 3 patients. The last patient suffered damage to the tricuspid valve during retrieval of an embolized device. The procedure was consequently aborted, and the patient referred for surgical tricuspid valve repair and PFO closure.

One procedural death occurred due an aortic dissection and tamponade. Four additional patients experienced tamponade. Device embolization occurred in 4 patients, 1 of which required surgery as previously described. A procedural TIA occurred in 1 patient and a deep venous thrombosis in another (Table 3).

Long-term clinical outcomes. Over a mean follow-up of 42.7 ± 33.4 months (median: 37.1 months, interquartile range: 16.2 to 59.9 months; 2,666 person-years), a recurrent ischemic cerebrovascular event occurred in 21 (2.8%) patients, 12 (1.6%) of which were strokes and 9 (1.2%) were TIA (Table 3). Thus, the cumulative incidence rate of recurrent cerebrovascular events (ischemic stroke or TIA) was 0.79 events per 100 person-years. When limited solely to patients referred for ischemic stroke or multiple neurologic events, 7 (1.1%) and 10 (1.6%) patients experienced a recurrent TIA and stroke, respectively (0.79 events per 100 person-years).

At 5- and 10-year follow-up, 96.7% and 91.5% of patients, respectively, were free of recurrent ischemic neurologic events (Fig. 1A). Freedom from recurrent ischemic neurologic events, procedural or neurologic death was comparably high (Fig. 1B). In exploratory analyses, we found that only the detection of a Eustachian valve on transthoracic echocardiography (hazard ratio [HR]: 9.04; 95% confidence interval [CI]: 2.07 to 39.44; $p < 0.0034$) (Table 4) was significantly associated with the occurrence of cerebrovascular event after PFO closure. Notably, the 3 patients with prominent Eustachian valves who suffered a recurrent event had persistent residual shunt after PFO closure. There was no significant difference in the rate of neurologic events between closure devices (log-rank $p = 0.82$) (Fig. 1C).

Reintervention was performed in 38 (5%) patients for substantial persistent shunt in 3 patients, concomitant atrial septal defect in 2 patients, and device embolization in 3 patients (Table 3). Of these 38 patients, 4 underwent surgical reintervention. The rate of reintervention was 5.7% at 5 years and 9.3% at 10 years (Fig. 2). Rates of reintervention significantly differed by device type with increased

Table 2. Frequency of Atrial Septal Occlusion Device Use and Associated Residual Shunting

		Shunt Severity				
		Effective Closure				
	Total	None/Trace	Mild	Moderate	Severe	p Value
Overall	794*	677 (85)	59 (7)	27 (3)	30 (4)	
Amplatzer Cribiform	303 (38)	258 (85)	20 (7)	8 (3)	17 (6)	0.17
Amplatzer ASO	178 (22)	151 (85)	13 (7)	10 (6)	4 (2)	
Gore Helex	47 (6)	38 (81)	3 (6)	3 (6)	3 (6)	
Cardioseal/STARFlex	228 (29)	200 (88)	18 (8)	6 (3)	4 (2)	
Sideris	35 (4)	29 (83)	4 (11)	0 (0)	2 (6)	
Premere	2 (0)	1 (50)	1 (50)	0 (0)	0 (0)	

Values are n or n (%). *One patient received multiple devices.
ASO = atrial septal occluder.

Table 3. Short- and Long-Term Outcomes After Transcatheter PFO Closure

Procedural success	793 (99)
30-day outcomes	
Death	0.1 (1/793)
Stroke	0.0 (0/793)
Recurrent	0.0 (0/749)
De novo	0.0 (0/749)
TIA	0.1 (1/793)
Recurrent	0.1 (1/749)
De novo	0.0 (0/44)
Device embolization	0.5 (4/793)
Tamponade	0.6 (5/793)
DVT	0.1 (1/793)
Long-term outcomes	
Neurologic death	0.5 (4/793)
Stroke	1.5 (12/793)
Recurrent	1.6 (12/749)
De novo	0.0 (0/44)
TIA	1.2 (10/793)
Recurrent	1.2 (9/749)
De novo	2.3 (1/44)
Redo	5.0 (38/793)
Transcatheter	4.0 (34/793)
Surgical	0.5 (4/793)

DVT = deep venous thrombosis; other abbreviations as in Table 1.

need of redo procedures with the Gore Helex device, many of which were early generation devices, and with the Sideris device (p = 0.006) (Table 5).

Four patients died of neurologic causes in addition to the previously described procedural death (Table 3). One patient suffered a stroke and died within 2 months of PFO closure. The patient was found to have a left ventricular thrombus and marantic endocarditis in the setting of adenocarcinoma of the lung. Another patient died of a stroke approximately 1 year after PFO closure in the setting of advanced lung cancer. A third patient suffered a subarachnoid hemorrhage. The last patient presented with a hemorrhagic stroke.

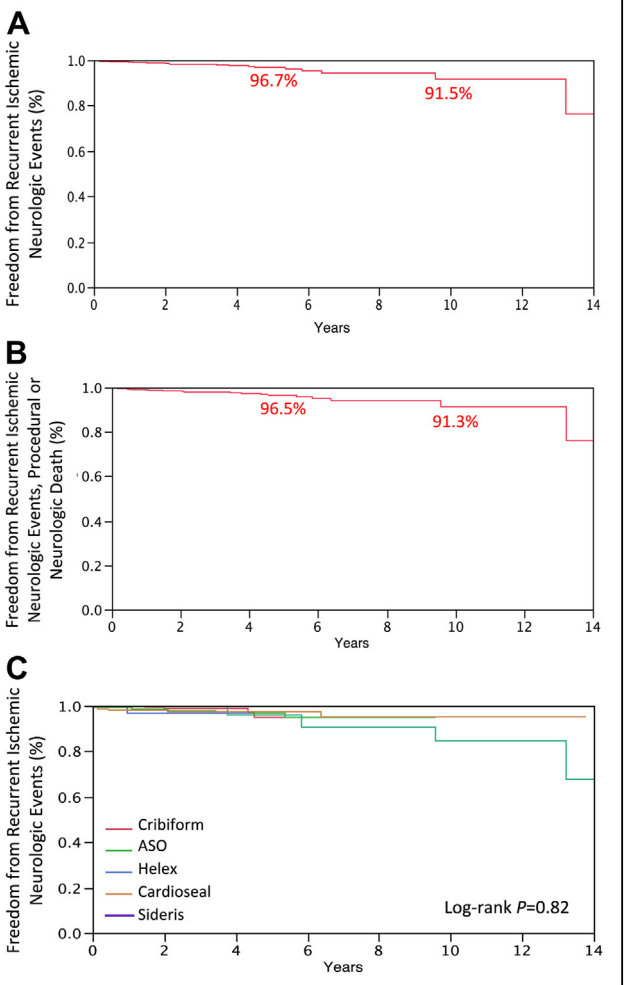

Figure 1. Long-Term Clinical Outcomes After Transcatheter PFO Closure

Kaplan-Meier curves depict the probability of freedom from recurrent ischemic neurologic events **(A)** within subjects with previous cryptogenic stroke **(B)**. Probabilities for freedom from recurrent ischemic neurologic events are depicted at 5- and 10-year follow-up. Stratification by device type revealed no significant difference in the rates of recurrent ischemic neurologic events between the closure devices (log-rank p = 0.82) **(C)**. ASO = atrial septal occluder; PFO = patent foramen ovale.

Discussion

The present study adds to substantial evidence that transcatheter closure of PFO is a feasible and safe technique (13–17,22–24). We add to the existing literature by establishing within a large and diverse cohort of patients the excellent long-term outcomes following transcatheter PFO closure and the breadth and relative frequency of indications for which patients are referred for this controversial procedure. Secondary prevention for cryptogenic neurologic events in patients found to have a PFO is overwhelmingly the most common reason for PFO closure, although the technique is considered for patients with peripheral emboli, migraine headaches, and hypoxemia as well.

The efficacy of transcatheter PFO closure, however, remains quite controversial, especially in regard to secondary stroke prevention (25,26). Considerable evidence from a multitude of small observational studies suggest superb preventative efficacy of PFO closure for recurrent events. Two recent meta-analyses reviewed data from approximately 50 observational studies including almost 9,000 patients (16,21). Both studies found the cumulative rate of recurrent stroke or TIA to be 0.8 events per 100 person-years with PFO closure versus approximately 5 events per 100 person-years with medical therapy. These results are comparable to our results (0.79 events per 100 person-years) as well as

Table 4. Unadjusted Relationship Between Clinical Factors and Ischemic Cerebrovascular Events After Transcatheter PFO Closure

	Hazard Ratio	95% Confidence Interval	p Value
Age, yrs	1.02	0.98–1.05	0.35
Male	2.21	0.84–5.80	0.11
Hypertension	2.08	0.86–5.04	0.11
Dyslipidemia	1.69	0.70–4.10	0.24
Diabetes	1.45	0.96–10.95	0.72
Smoking status			
None	Referent		
Current	0.93	0.20–4.48	0.93
Former	1.87	0.72–4.86	0.2
Family history of CVD	0.36	0.05–2.69	0.32
Migraine headaches	1.28	0.29–5.71	0.75
Hypercoagulable state	1.79	0.73–4.39	0.2
PFO anatomic features			
Direction of shunt			
Right to left	Referent		
Left to right	2.11	0.61–7.36	0.24
Bi-directional	1.58	0.36–6.98	0.55
Shunt condition			
Rest only	Referent		
Valsalva only	0.54	0.14–2.06	0.37
Both	0.88	0.28–2.78	0.82
Interatrial septal mobility			
Atrial septal aneurysm	0.59	0.17–2.02	0.4
Hypermobility	0.72	0.21–2.44	0.59
Eustachian valve	9.04	2.07–39.44	0.0034
Residual shunt severity			
None/Trace	Referent		
Mild	3.16	0.92–10.87	0.07
Moderate	None		
Severe	None		

Hazard ratios could not be calculated for May-Thurner or atrial fibrillation due to lack of events.
Abbreviations as in Table 1.

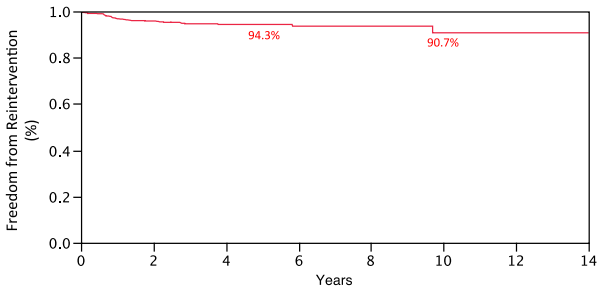

Figure 2. Freedom From Reintervention

Kaplan-Meier curve depicts the probability of freedom from reintervention after transcatheter patent foramen ovale closure. Probabilities for freedom from reintervention are depicted at 5- and 10-year follow-up.

those from the recently reported RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial (0.66 events per 100 person-years) and PC (Percutaneous versus Medical Treatment in Patients with Cryptogenic Embolism) trial (1.06 events per 100 person-years), but are in stark contrast to results of the CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale) trial (2.6 events per 100 person-years) (18–20).

Several factors have been hypothesized to account for the high event rates in the CLOSURE I trial (16,25,27). First, the CLOSURE I trial exclusively used the STARFlex Septal Closure System for PFO closure. This device, which is no longer in production, has been associated with higher rates of atrial fibrillation and in situ thrombosis than other atrial septum occlusion devices (28,29). Whereas such differences may lead to higher event rates with the STARFlex device, our experience suggests no such difference for recurrent neurovascular events. However, it is notable that we obtained 96% effective closure with the NMT Medical devices compared with only 86% effective closure in the CLOSURE I trial. The greater likelihood of effective closure in our hands may simply be due to our ability to choose the best device for a given patient's PFO anatomy, a freedom that is not available with clinical trials. Alternatively, our extensive experience with the NMT Medical devices in 29% (228 of 800) of cases may have contributed to the favorable results. Regardless, such a high prevalence of residual shunt within CLOSURE I may contribute to the relatively high event rate observed in the closure group within the trial. Second, of the 23 patients with recurrent cerebrovascular events in the device arm of the CLOSURE I trial, 20 (87%) were felt not to be due to a PFO-mediated paradoxical embolism. Although some of these recurrent events were device- or procedure-related, the presence of subcortical lacunar infarctions, aortic arch atheroma, and vasculitis in many of these trial participants suggest that rigorous attempts to exclude patients with alternative causes of stroke were unsuccessful. Third, evidence is emerging that the diagnosis of TIA within the CLOSURE I trial was

Table 5. Rates of Redo Transcatheter PFO Closure by Device Type (N = 793)

Overall	38 (5.0)	p = 0.006
Amplatzer Cribiform	9 (3.0)	
Amplatzer ASD	9 (5.1)	
Gore Helex	6 (12.8)	
Cardioseal/STARFlex	9 (4.0)	
Sideris	5 (14.3)	
Premere	0 (0.0)	

Values are n (%) with percentage within device type.
ASD = atrial septal defect; PFO = patent foramen ovale.

nonspecific and possibly represented alternate clinical entities (30). Thus, the use of previous TIA as an inclusion criterion and within the primary endpoint likely contaminated both the study population and endpoint determination, making it more difficult to demonstrate efficacy of PFO closure.

Similar challenges have plagued the RESPECT and PC trials and might have contributed to their failures to meet primary efficacy endpoints (19,20). Despite demonstrating large point estimates for relative risk reduction of recurrent ischemic strokes, both trials suffered from low event rates, patient crossover, difficult study recruitment, and underpowered analyses. The widespread availability of off-label atrial septal defect closure devices for PFO closure likely contributed to each of these issues by providing a treatment option for high-risk patients outside of clinical trials and for those assigned to medical therapy within trials (19,20,31). As opposed to the CLOSURE I and PC trials, the RESPECT trial did not use TIA as an inclusion criterion or clinical endpoint and mandated neuroradiographic confirmation of clinical events (18–20). With such stringent criteria, Carroll et al. (19) demonstrated a large, although not significant, 51% reduction in the primary composite endpoint of nonfatal or fatal ischemic stroke or early death (HR: 0.49; 95% CI: 0.22 to 1.11) within the intention-to-treat cohort. Notably, 3 recurrent strokes in the device arm of the trial occurred in patients that had not received transcatheter PFO closure; evaluation of the as-treated cohort demonstrated a marked reduction in the risk of recurrent ischemic neurologic events with PFO closure (HR: 0.27; 95% CI: 0.10 to 0.75; $p = 0.007$) (19). An important lesson from both RESPECT and PC was that the trend toward benefit with PFO closure was not apparent within the first 2 years after randomization (19,20). The negative results in CLOSURE I may consequently be in part due to a short follow-up period (18).

We suspect that the low rate of recurrent events observed here is at least partly due to our efforts to identify those patients likely to have suffered a PFO-mediated event. We subject all patients with a suspected paradoxical embolism to independent evaluation by cardiology, neurology, and hematology, and by vascular medicine in the event of a deep venous thrombosis or May-Thurner. On completion of an extensive evaluation, a decision for or against PFO closure is jointly made by the specialists largely on the basis of the likelihood that the index event was PFO-related. This process has led to denial for PFO closure in approximately 20% to 25% of referred patients, and its success is evident in the low prevalence of cardiovascular risk factors within our study cohort (only 6% with diabetes mellitus and 9% smokers).

We found that the detection of a prominent Eustachian valve on transthoracic echocardiography significant predicts recurrent events. Limited data exist regarding the risk attributable to a prominent Eustachian valve with PFO (32,33). Rigatelli et al. (32) demonstrated a markedly elevated risk of recurrent paradoxical embolisms with prominent Eustachian valve or Chiari network (odds ratio: 7.8; 95% CI: 4.1 to 15; $p < 0.001$) versus PFO alone. A prominent Eustachian valve was identified in approximately 40% of patients by intracardiac echocardiography in the study, compared with only 10 (1%) patients here. We suspect that differences in the sensitivity of echocardiographic techniques led to this discrepancy. In fact, Rigatelli et al. (32) report less frequent detection of the Eustachian valve by transesophageal echocardiography. These data suggest that only the largest Eustachian valves are likely to be detected by transthoracic echocardiography and that this anatomic feature may identify those PFO patients at greatest risk of paradoxical embolism. The impact of this anatomic variant after PFO closure logically should depend on the presence of residual shunt. Here, all patients with prominent Eustachian valves that suffered a recurrent event also had residual shunting across the interatrial septum.

Study limitations. This is a retrospective study of highly selected patients that may differ from those in other published series and randomized trials. In addition, a small number of recurrent events after PFO closure limited our ability to identify predictive variables. In this regard, our analyses identifying Eustachian valve prominence and residual shunt severity as predictors of neurologic events should be considered hypothesis-generating and will need confirmation. Furthermore, Eustachian valve prominence was defined and reported at the discretion of the attending echocardiographer during routine clinical care. Future studies using strict definitions are needed to assess the clinical impact of this anatomic variant. Whereas our clinical follow-up was comparable to that described in recent clinical trials, we did not implement systematic methods of screening for atrial fibrillation or recurrent neurologic events after PFO closure. Patients were routinely referred for neurologic assessment for new or recurrent neurologic symptoms, but this was performed at the discretion of the interventional cardiologist. Lastly, we do not currently possess formal clinical assessments of migraine severity after PFO closure.

Conclusions

Transcatheter closure of PFO is a safe and feasible therapy for patients with PFO. Consistent with evidence from recent randomized controlled trials, the recurrence rate for ischemic neurologic events is remarkably low after PFO closure. Carefully selected patients with features suggestive of paradoxical embolism are the most likely to benefit from PFO closure and should be the focus of future investigations. In addition, our analysis suggests Eustachian valve prominence is a significant predictor of recurrent embolic events after PFO closure. Further efforts are needed to

confirm these findings and to definitively establish the clinical role of PFO closure.

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