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Comparison of Medical Treatment With Percutaneous Closure of Patent Foramen Ovale in Patients With Cryptogenic Stroke

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OBJECTIVES The purpose of this study was to compare the efficacy of medical treatment with percutaneous closure of patent foramen ovale (PFO).

BACKGROUND Patients with cryptogenic stroke and PFO are at risk for recurrent cerebrovascular events.

METHODS We compared the risk of recurrence in 308 patients with cryptogenic stroke and PFO, who were treated either medically (158 patients) or underwent percutaneous PFO closure (150 patients) between 1994 and 2000.

RESULTS Patients undergoing percutaneous PFO closure had a larger right-to-left shunt ($p < 0.001$; 95% confidence interval [CI] 1.38 to 3.07) and were more likely to have suffered more than one cerebrovascular event ($p = 0.03$; 95% CI 1.04 to 2.71). At four years of follow-up, percutaneous PFO closure resulted in a non-significant trend toward risk reduction of death, stroke, or transient ischemic attack (TIA) combined (8.5% vs. 24.3%; $p = 0.05$; 95% CI 0.23 to 1.01), and of recurrent stroke or TIA (7.8% vs. 22.2%; $p = 0.08$; 95% CI 0.23 to 1.11) compared with medical treatment. Patients with more than one cerebrovascular event at baseline and those with complete occlusion of PFO were at lower risk for recurrent stroke or TIA after percutaneous PFO closure compared with medically treated patients (7.3% vs. 33.2%; $p = 0.01$; 95% CI 0.08 to 0.81, and 6.5% vs. 22.2%; $p = 0.04$; 95% CI 0.14 to 0.99, respectively).

CONCLUSIONS Percutaneous PFO closure appears at least as effective as medical treatment for prevention of recurrent cerebrovascular events in cryptogenic stroke patients with PFO. It might be more effective than medical treatment in patients with complete closure and more than one cerebrovascular event. (J Am Coll Cardiol 2004;44:750–8) © 2004 by the American College of Cardiology Foundation

The etiology of ischemic stroke remains unknown in up to 40% of patients despite an extensive diagnostic evaluation, and it is referred to as cryptogenic (1). The association of patent foramen ovale (PFO) with cryptogenic stroke initially observed by Lechat et al. (2) and Webster et al. (3) has been confirmed in a recent meta-analysis of case-control studies (4) and in the prospective Patent foramen ovale In

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Cryptogenic Stroke Study (PICSS) (5). Patients with cryptogenic stroke related to PFO are at risk for recurrence despite medical treatment (5–8), a risk that is particularly pronounced in patients with PFO and associated atrial septal aneurysm (7,9,10). Paradoxical embolism via a PFO has been implied to be the most likely stroke mechanism (11), and therefore therapeutic measures for secondary prevention are intended to eliminate thrombus formation, paradoxical embolization, or both.

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Percutaneous PFO closure is a catheter-based technique using atrial septal occlusion devices. It was initially advocated for prevention of recurrent stroke in 1992 (12), and safety and feasibility have been addressed in several studies (12–19). However, the therapeutic efficacy of percutaneous PFO closure as an adjunct or alternative to medical treatment in cryptogenic stroke patients with PFO is unknown. This non-randomized study compares the risk of recurrent cerebrovascular events in patients with cryptogenic stroke and PFO who underwent percutaneous PFO closure or received medical treatment alone.

METHODS

Patients. We identified all patients with transient ischemic attack (TIA) or ischemic stroke, who were admitted to our university hospital stroke center between January 1994 and August 2000. The diagnosis of ischemic stroke was based on the symptoms and signs of a suddenly occurring neurologic deficit, and the corresponding findings on computed tomography or magnetic resonance imaging scans. Transient ischemic attack was defined as a focal neurologic deficit resolving completely within 24 h. Doppler and color Duplex

Abbreviations and Acronyms

CI = confidence interval
PFO = patent foramen ovale
PICSS = Patent foramen ovale In Cryptogenic Stroke Study
RR = risk ratio
TIA = transient ischemic attack

examination of the extracranial carotid, the vertebral and basal intracranial arteries, electrocardiography, and contrast transesophageal echocardiography were performed in all patients. The cerebrovascular event was considered the result of paradoxical embolism if the following conditions were met: 1) presence of PFO with or without atrial septal aneurysm with spontaneous or provocable right-to-left shunt as assessed by transesophageal echocardiography; 2) clinically and radiologically confirmed ischemic stroke or TIA; and 3) exclusion of any other identifiable cardiac, aortic, or cerebrovascular cause. After excluding patients without a PFO or with a concurrent etiology for the cerebrovascular event, 308 patients were classified as having suffered a cryptogenic stroke presumably related to PFO. Percutaneous PFO closure was performed in 150 patients, whereas 158 patients were treated medically. The individual treatment decision was based on patient and physician preference.

Transesophageal echocardiography and diagnosis of paradoxical embolism. The diagnosis of PFO and atrial septal aneurysm was based on contrast transesophageal echocardiography with an aerated colloid solution injected into an antecubital vein at the end of a Valsalva maneuver in all patients. Patent foramen ovale was defined as flap-like opening in the atrial septum secundum, with the septum primum serving as a one-way valve allowing for permanent or transient right-to-left shunt. Atrial septal aneurysm was diagnosed as abnormally redundant interatrial septum with an excursion of ≥10 mm into the right or left atrium and a base span of at least 15 mm (20). Spontaneous or provoked right-to-left shunt was semiquantitatively graded according to the amount of bubbles detected in the left atrium after crossing the interatrial septum on a still frame: grade 0 = none, grade 1 = minimal (1 to 5 bubbles), grade 2 = moderate (6 to 20 bubbles), and grade 3 = severe (>20 bubbles) (3).

Medical treatment. Patients assigned to medical treatment were treated with a vitamin K antagonist or antiplatelet therapy at the discretion of the attending neurologist. Coumadin was adjusted to a target international normalized ratio of 2.0 to 3.0; acetylsalicylic acid was prescribed at a mean dose of 233 ± 83 mg/day, and clopidogrel at a dose of 75 mg/day.

Percutaneous PFO closure. The procedure was performed under local anesthesia and fluoroscopic guidance as described previously (15). Six different device types were utilized according to availability at different time points, including the Amplatzer PFO Occluder (n = 54), PFO STAR (n = 42), Sideris buttoned device (n = 27), Angel Wing device (n = 10), Amplatzer ASD Occluder (n = 9), and CardioSEAL (n = 8). Patients were treated with acetylsalicylic acid 100 mg once daily for six months for antithrombotic protection until full device endothelialization. A contrast transesophageal echocardiography was repeated six months after percutaneous PFO closure to assess for a residual shunt after endothelial overgrowth. Medical treatment was discontinued in 93 of 150 patients after six months. Fifty-seven patients continued medical treatment with acetylsalicylic acid 100 mg once daily owing to a residual shunt (26 patients) or presence of mild coronary artery disease as assessed by coronary angiography (31 patients).

Follow-up evaluation. All family physicians and patients were subjected to a structured interview addressing recurrence of cerebrovascular events, rehospitalizations, and device- or medication-related problems. Death, recurrent ischemic stroke, TIA, or peripheral embolism were considered adverse events. Patients with suspected recurrent cerebrovascular events were reexamined by a neurologist, and an imaging study of the brain was repeated. Follow-up information was available for all patients at some point in time, but two patients in the medical treatment group and three patients in the percutaneous PFO closure group were subsequently lost to follow-up as a result of address changes. Patients gave informed consent, and the study was approved by the local ethics committee.

Statistical analysis. Continuous variables are expressed as mean ± 1 SD and were compared by a two-sided, unpaired *t* test. Categorical variables are reported as counts and percentages and were compared by chi-square analysis. The Kaplan-Meier survival analysis was used to assess the risk of recurrent events. The log-rank test was used to compare the cumulative incidence curves between the treatment groups. Predictors of recurrent events according to treatment assignment were analyzed by a Cox proportional hazards model. Statistical significance was assumed with a p value <0.05. All data were analyzed with the use of SPSS software (version 10.0, SPSS Inc., Chicago, Illinois).

RESULTS

The two groups were comparable with respect to age, gender, cardiovascular risk factors, and associated atrial septal aneurysm (Tables 1 and 2). Patients who underwent percutaneous PFO closure were more likely to have suffered more than one cerebrovascular event before inclusion in the study (p = 0.03; risk ratio [RR] 1.68; 95% confidence interval [CI] 1.04 to 2.71) and had a larger right-to-left shunt at baseline (p < 0.001; RR 2.01; 95% CI 1.38 to 3.07).

Table 1. Baseline Clinical Characteristics

	Percutaneous PFO Closure (n = 150)	Medical Treatment (n = 158)	Oral Anticoagulants (n = 79)	Antiplatelet Agents (n = 79)
Age (yrs)	50 ± 12	51 ± 13	51 ± 13	51 ± 14
Male gender	80 (53%)	92 (58%)	45 (57%)	47 (59%)
Follow-up (yrs)	2.1 ± 1.6	2.4 ± 1.9	2.4 ± 1.8	2.4 ± 2.0
Cardiovascular risk factors				
Arterial hypertension	42 (28%)	50 (32%)	21 (27%)	29 (37%)
Diabetes mellitus	6 (4%)	14 (9%)	6 (8%)	8 (10%)
Smoking	49 (33%)	51 (33%)	25 (32%)	26 (33%)
Total cholesterol (mmol/dl)	5.5 ± 1.2	5.8 ± 1.3	5.6 ± 1.4	6.0 ± 1.0
Cerebrovascular index event				†
Transient ischemic attack	53 (35%)	40 (25%)	10 (13%)	30 (38%)
Ischemic stroke	97 (65%)	118 (75%)	69 (87%)	49 (62%)
Number of previous cerebrovascular events		*		
Mean number of events	1.8 ± 1.1	1.5 ± 1.0	1.5 ± 0.9	1.5 ± 1.0
More than one event	59 (39%)	44 (29%)	24 (30%)	20 (25%)

*p = 0.03 versus percutaneous PFO closure. †p < 0.001 versus oral anticoagulants.
PFO = patent foramen ovale.

Medical treatment. Oral anticoagulation with the vitamin K antagonist coumadin was initially used in 79 patients, whereas 79 patients were treated with antiplatelet therapy (acetylsalicylic acid in 77 patients and clopidogrel in 2 patients). Baseline clinical and echocardiographic characteristics stratified according to type of medical treatment are summarized in Tables 1 and 2. Patients treated with oral anticoagulants had more frequently suffered an ischemic stroke as the cerebrovascular index event and a higher prevalence of PFO-associated atrial septal aneurysm than patients treated with antiplatelet drugs. In 26 patients, oral anticoagulants were substituted with acetylsalicylic acid after a mean of 12 ± 11 months. No major bleeding complications were observed during follow-up. Nine patients discontinued antithrombotic therapy because of malcompliance.

Percutaneous PFO closure. Percutaneous PFO closure was successful in 148 patients (99%) and failed in 2 patients. Periprocedural complications were observed in nine patients (6%), and they included embolization of the device in four patients, air embolism in three patients, and vascular access site problems in two patients. There were no procedural deaths, no requirement for open-heart surgery, and none of the procedural complications resulted in long-term sequelae. Complete PFO closure as assessed by transesophageal echocardiography at six months was achieved in 83% of patients, whereas a small, moderate, or large shunt persisted in 10%, 3%, or 4% of patients, respectively.

Recurrent events. Outcome events during a mean follow-up of 2.3 ± 1.7 years are summarized in Tables 3 through 5. Three deaths, 7 ischemic strokes, and 14 TIAs were observed in the medical treatment group, compared with 1 death, 2 ischemic strokes, and 7 TIAs in the percutaneous PFO closure group. In the medical treatment group, one stroke and five TIAs were encountered with oral anticoagulation, six strokes and six TIAs with antiplatelet treatment, and three TIAs in patients who had discontinued antiplatelet therapy. No peripheral embolic events were encountered during follow-up in either group.

At four years of follow-up, percutaneous PFO closure showed a non-significant trend toward a lower risk in the combined end point of death, stroke, or TIA (8.5% vs. 24.3%; p = 0.05; RR 0.48; 95% CI 0.23 to 1.01) (Fig. 1) when compared with medical treatment. There was no significant difference in the risk of recurrent stroke or TIA between percutaneous PFO closure and medical treatment (7.8% vs. 22.2%; p = 0.08; RR 0.51; 95% CI 0.23 to 1.11)

Table 2. Baseline Echocardiographic Characteristics

	Percutaneous PFO Closure (n = 150)	Medical Treatment (n = 158)	Oral Anticoagulants (n = 79)	Antiplatelet Agents (n = 79)
Atrial septal anatomy				†
PFO only	113 (75%)	123 (78%)	55 (70%)	68 (86%)
PFO and atrial septal aneurysm	37 (25%)	35 (22%)	24 (30%)	11 (14%)
Interatrial right-to-left shunt		*		
Small	5 (3%)	17 (11%)	4 (5%)	13 (16%)
Moderate	26 (17%)	44 (28%)	23 (29%)	21 (27%)
Large	119 (80%)	97 (61%)	52 (66%)	45 (57%)
Left atrial size (mm)	36 ± 6	36 ± 5	37 ± 5	36 ± 6

*p = 0.001 versus percutaneous PFO closure. †p = 0.01 versus oral anticoagulants.
PFO = patent foramen ovale.

Table 3. Recurrent Events

	Events		Probability of Event at 4 Years*			
	PFO Closure	Medical Treatment	PFO Closure	Medical Treatment	Hazard Ratio (95% CI)†	p Value‡
Entire patient cohort	150	158				
Recurrent death, stroke, or TIA	10	24	8.5%	24.3%	0.48 (0.23–1.01)	0.05
Death	1	3	0.7%	2.7%	0.33 (0.03–3.22)	0.32
Recurrent stroke or TIA	9	21	7.8%	22.2%	0.51 (0.23–1.11)	0.08
Recurrent stroke	2	7	2.1%	7.6%	0.36 (0.08–1.74)	0.19
Recurrent TIA	7	14	5.9%	15.8%	0.58 (0.23–1.44)	0.23
Patients with complete PFO occlusion after percutaneous PFO closure	122	158				
Recurrent stroke or TIA	5	21	6.5%	22.2%	0.37 (0.14–0.99)	0.04
Patients with more than one cerebrovascular event at baseline	59	44				
Recurrent stroke or TIA	4	11	7.3%	33.2%	0.26 (0.08–0.81)	0.01

*Probabilities of events were derived from Kaplan-Meier analyses. †Hazard ratios and 95% confidence intervals were derived from Cox regression analyses. ‡p values were calculated with the log-rank test.
CI = confidence interval; PFO = patent foramen ovale; TIA = transient ischemic attack.

(Fig. 2) in the overall study group. Outcome was not different comparing treatment with oral anticoagulants and antiplatelet drugs (Table 4). Although there were no differences in outcome between percutaneous PFO closure and oral anticoagulation, the combined end point of death, stroke, or TIA was significantly lower after percutaneous PFO closure than with antiplatelet therapy (8.5% vs. 28.3%; p = 0.03; RR 0.43; 95% CI 0.20 to 0.94) (Table 4).

Univariate predictors of recurrent stroke or TIA according to treatment assignment are summarized in Figure 3. Patients with complete PFO occlusion after percutaneous PFO closure had a significantly lower risk of recurrent stroke or TIA than medically treated patients (6.5% vs. 22.2%; p = 0.04; RR 0.37; 95% CI 0.14 to 0.99) (Fig. 4). Similarly, patients with more than one cerebrovascular event at baseline, had a significantly lower risk of recurrent stroke or TIA after percutaneous PFO closure than medically treated patients (7.3% vs. 33.2%; p = 0.01; RR 0.26; 95% CI 0.08 to 0.81) (Fig. 5). There were no significant differences in the risk of recurrent events between treatment groups with respect to gender, older age, previous stroke, arterial hypertension, smoking, hypercholesterolemia, diabetes, or associated atrial septal aneurysm.

DISCUSSION

There is considerable evidence that PFO is not only associated but the cause of ischemic stroke in cryptogenic stroke patients. First, PFO-mediated paradoxical embolism is pathophysiologically plausible, and thrombus trapped within the PFO has been documented iteratively (21–23). Second, larger PFO size has been associated with a higher recurrence rate, suggesting a dose-response relationship (24–28). Third, the higher frequency of deep venous thrombosis in stroke patients with PFO supports the concept of thrombi crossing the PFO to cause paradoxical embolism (29–32). Fourth, the Stroke Prevention Assessment of Risk in a Community study (9) suggested paradoxical embolism as the principal mechanism of stroke in patients with PFO and associated atrial septal aneurysm,

Table 4. Recurrent Events Stratified According to Treatment

	Probability of Event at 4 Years*					
	PFO Closure	Oral Anticoagulants	Antiplatelet	p Value OAC vs. Asp	p Value Closure vs. OAC	p Value Closure vs. ASP
Recurrent death, stroke, or TIA	8.5%	13.3%	28.3%	0.47	0.32	0.03
Death	0.7%	0%	3.9%	0.24	0.58	0.16
Recurrent stroke or TIA	7.8%	19.3%	25.4%	0.74	0.25	0.07
Recurrent stroke	2.1%	1.8%	10.2%	0.30	0.82	0.11
Recurrent TIA	5.9%	17.8%	16.9%	0.74	0.24	0.29
Patients with more than one cerebrovascular event at baseline						
Recurrent stroke or TIA	6.5%	17.9%	42.6%	0.33	0.18	0.005

*Probabilities of events were derived from Kaplan-Meier analyses; p values were calculated with the log-rank test.
Asp = acetylsalicylic acid; OAC = oral anticoagulation; PFO = patent foramen ovale; TIA = transient ischemic attack.

Table 5. Individual Recurrent Events Grouped by Treatment Allocation

	Age	Gender	ASA	RF (n)	Previous TIA (n)	Previous Strokes (n)	Time of Event	Type of Event	Antithrombotic Treatment at Time of Event	Shunt Grade*
Medical treatment group										
1	39	F	yes	4	1	0	48 months	TIA	Oral anticoagulants	2
2	56	M	no	3	0	1	73 months	TIA	Oral anticoagulants	3
3	67	M	no	2	1	0	42 months	Minor cryptogenic stroke	Acetylsalicylic acid	3
4	54	M	no	0	4	1	9 months	TIA	Oral anticoagulants	3
5	42	M	no	4	0	1	3 months	Minor cryptogenic stroke	Acetylsalicylic acid	3
6	35	F	no	0	2	0	3 months	TIA	Oral anticoagulants	3
7	42	M	no	1	1	1	4 months	Fatal road traffic accident	Acetylsalicylic acid	3
8	55	F	no	2	0	1	17 months	Minor cryptogenic stroke	Acetylsalicylic acid	3
9	55	F	no	1	1	1	7 months	TIA	Acetylsalicylic acid	3
10	62	M	yes	3	0	1	48 months	TIA	Acetylsalicylic acid	3
11	15	F	no	0	0	1	33 months	TIA	Acetylsalicylic acid	1
12	68	F	yes	3	0	1	34 months	TIA	Oral anticoagulants	2
13	55	M	no	1	1	0	36 months	TIA	Discontinued	3
14	77	M	yes	1	0	1	33 months	TIA	Acetylsalicylic acid	2
15	31	M	no	1	3	0	32 months	TIA	Acetylsalicylic acid	1
16	64	M	no	4	0	1	22 months	Sudden cardiac death, known CAD	Acetylsalicylic acid	2
17	74	M	yes	1	0	2	28 months	Major cryptogenic stroke	Acetylsalicylic acid	3
18	77	M	no	0	4	0	12 months	TIA	Acetylsalicylic acid	2
19	52	M	no	3	4	0	26 months	Minor cryptogenic stroke	Acetylsalicylic acid	2
20	33	M	no	1	1	1	17 months	Minor cryptogenic stroke	Acetylsalicylic acid	3
21	53	F	no	0	0	1	7 months	Fatal lung cancer	Discontinued	3
22	74	F	no	1	4	0	3 months	TIA	Discontinued	2
23	41	M	no	0	1	1	13 months	TIA	Discontinued	1
24	37	F	no	1	0	2	1 month	Minor cryptogenic stroke	Oral anticoagulants	3
										Residual Shunt Grade
PFO closure group										
1	41	M	no	2	0	1	8 months	TIA	Acetylsalicylic acid (residual shunt)	1
2	47	F	no	1	2	6	3 weeks	TIA	Acetylsalicylic acid (per protocol)	2
3	74	M	yes	2	0	1	22 months	TIA (large vessel; hypesthesia right arm; new large plaque at carotid bifurcation)	Acetylsalicylic acid (associated CAD)	None
4	61	F	no	0	1	0	12 months	TIA (microangiopathic; internuclear ophthalmoplegia)	None	None
5	74	M	no	2	1	2	6 months	TIA	Acetylsalicylic acid (per protocol and associated CAD)	None

Continued on next page

Table 5 Continued

	Age	Gender	ASA	RF (n)	Previous TIA (n)	Previous Strokes (n)	Time of Event	Type of Event	Antithrombotic Treatment at Time of Event	Shunt Grade*
6	59	M	no	2	1	1	6 months	TIA	Acetylsalicylic acid (residual shunt)	1
7	24	M	no	0	0	1	20 months	Minor cryptogenic stroke	None	None
8	39	F	no	3	0	1	3 days	Minor cryptogenic stroke	Acetylsalicylic acid (per protocol)	1
9	64	M	no	1	0	1	4 months	Fatal road traffic accident	Acetylsalicylic acid (per protocol)	None
10	45	F	no	1	2	3	10 months	TIA	None	None

*Shunt grade: 1 = small, 2 = moderate, 3 = severe.
ASA = atrial septal aneurysm; CAD = coronary artery disease; PFO = patent foramen ovale; RF = cardiovascular risk factors; TIA = transient ischemic attack.

Figure 1. Probability of death, recurrent stroke, or transient ischemic attack stratified for medical treatment **(continuous line)** and percutaneous patent foramen ovale (PFO) closure **(dashed line).**

whereas atrial septal aneurysm without PFO (absence of a right-to-left shunt) has been shown to portend no particular risk for recurrent cerebrovascular events (10). Accordingly, PFO closure has been proposed as a logical therapeutic approach for secondary prevention of cerebrovascular events (12,33).

Although several observational studies have reported the long-term outcome after medical treatment (5–8,10) and percutaneous (12–19) or surgical (34–36) PFO closure, this is the first study to compare percutaneous PFO closure with medical treatment for prevention of recurrent cerebrovascular events in patients with cryptogenic stroke and PFO. Percutaneous PFO closure was as effective as medical treatment in the overall study group. It was significantly better than medical treatment in the prevention of recurrent cerebrovascular events in two subgroups: patients with complete PFO occlusion after the intervention and patients with more than one cerebrovascular event at baseline.

The superiority of percutaneous PFO closure when compared with medical treatment in patients with complete

Figure 2. Probability of recurrent stroke or transient ischemic attack stratified for medical treatment **(continuous line)** and percutaneous patent foramen ovale (PFO) closure **(dashed line).**

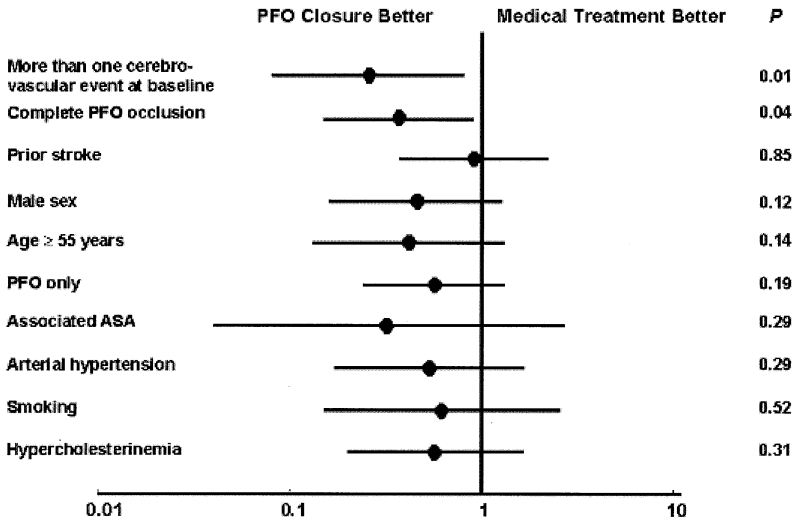

Figure 3. Risk ratios according to treatment assignment in subgroups. PFO = patent foramen ovale; ASA = atrial septal aneurysm.

PFO occlusion is in line with our previously reported finding that complete compared with incomplete PFO occlusion results in a significantly lower risk of recurrence in patients undergoing percutaneous PFO closure (15,16). This observation lends further support to paradoxical embolism being the prevalent mechanism for cerebrovascular events in this patient group. Furthermore, it highlights that complete PFO occlusion is desirable for therapeutic efficacy in patients undergoing percutaneous PFO closure, a goal which can be achieved in >90% of patients with the most recent devices (17,18).

The higher efficacy of percutaneous PFO closure compared with medical treatment in patients with more than one cerebrovascular event indicates that these patients represent a high-risk population. Indeed, these patients suffered recurrent cerebrovascular events despite medical treatment, suggesting inadequate protection by medical treatment alone. The fact that previous events were more frequent in patients who underwent percutaneous PFO closure enhances the results in favor of the interventional group. So does the larger PFO size in the interventional group, another established risk factor for recurrence (24–28).

Event rates between medical treatment and percutaneous PFO closure appeared to separate only after two years of follow-up. One explanation for this observation is the intention to treat analysis of our study. Thus, patients with incomplete PFO closure (17%) were included in the overall percutaneous PFO closure group. Because the device becomes fully protective only after complete endothelialization has ensued, a residual shunt during the initial months after device implantation may predispose to recurrent events despite antithrombotic therapy. This observation is validated by the early separation of cerebrovascular event rates in patients with complete PFO closure compared with the medical treatment group (Fig. 4). Another explanation for the more pronounced separation after two years of follow-up could be non-compliance with medical treatment in patients in the medical treatment group.

The benefits of percutaneous PFO closure in our study were associated with a certain risk of procedural complications, albeit without any long-term sequelae, and with the

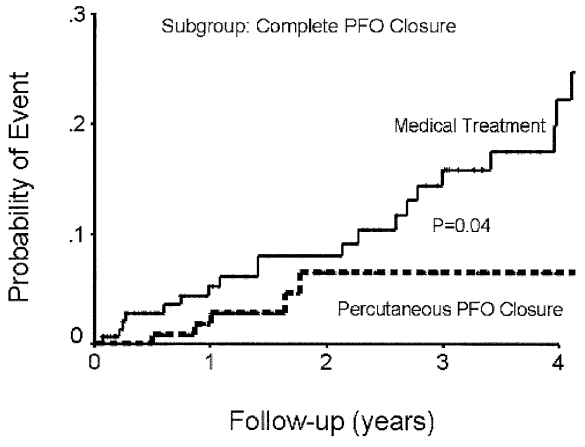

Figure 4. Probability of recurrent stroke or transient ischemic attack stratified for medical treatment **(continuous line)** and percutaneous patent foramen ovale (PFO) closure **(dashed line)** in the subgroup of patients with complete PFO occlusion.

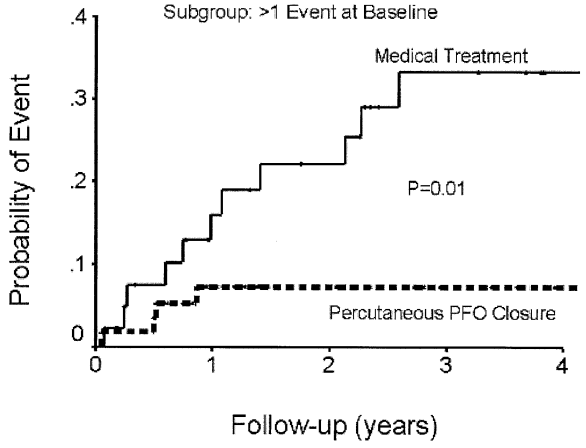

Figure 5. Probability of recurrent stroke or transient ischemic attack stratified for medical treatment **(continuous line)** and percutaneous patent foramen ovale (PFO) closure **(dashed line)** in the subgroup of patients with more than one cerebrovascular event at baseline.

incremental cost of the procedure and the device. Ultimate proof of paradoxical embolism being the principal stroke mechanism in such patients and of the superiority of percutaneous PFO closure over medical treatment will have to await the results of prospective, randomized trials such as the Percutaneous Closure of Patent Foramen Ovale and Cryptogenic Embolism trial initiated by our group (16).

Mas et al. (10) recently reported on the clinical outcome of 581 patients (mean age 42 years) with cryptogenic stroke, who were treated with acetylsalicylic acid 300 mg/day and followed for up to 4 years. The risk of recurrent stroke or TIA at four years was 5.6% in patients with PFO alone, 19.2% in patients with both PFO and atrial septal aneurysm, 0% in patients with atrial septal aneurysm alone, and 6.2% in patients without atrial septal abnormality. The authors concluded that patients with both PFO and atrial septal aneurysm are at substantial risk for recurrence requiring additional preventive strategies beyond treatment with acetylsalicylic acid alone, whereas patients with a PFO alone are at low risk for recurrence comparable to those patients without atrial septal abnormality. It has been hypothesized, however, that a large PFO rather than the associated atrial septal aneurysm was responsible for the high recurrence rate in this study (37). We did not observe a significant difference in recurrence rates with respect to the additional presence of atrial septal aneurysm between the medical treatment and percutaneous PFO closure group in our study. However, this subgroup represented only one-fourth of the entire cohort, and a potential difference in clinical outcome might have become apparent with a larger patient group and during longer follow-up. Thus, patients with PFO and associated atrial septal aneurysm deserve further investigation with respect to the role of percutaneous PFO closure in addition to medical treatment. Despite the low recurrence rate in patients with PFO alone as reported by Mas et al. (10), it cannot be excluded that percutaneous PFO closure reduces further events even in these patients. Notably, patients without atrial septal abnormalities had significantly more competing stroke risk factors, such as arterial hypertension, smoking, or hypercholesterolemia, than PFO patients, possibly camouflaging the PFO risk.

In the prospective PICSS (5), the presence of PFO was reported not to have an adverse impact on recurrent cerebrovascular events regardless of PFO size and presence of an atrial septal aneurysm. However, only 42% of patients included in this study had suffered a cryptogenic stroke as opposed to stroke of known etiology, that is, large vessel (11%), lacunar (39%), other determined cause (4%), or conflicting mechanism (4%). Therefore, it comes as no surprise that PFO was only an innocent bystander in the majority of patients. Notwithstanding, the investigators were able to reproduce the previously documented association of PFO with cryptogenic stroke as well as a higher prevalence of large PFOs in cryptogenic stroke patients than in control subjects of known stroke cause. The recurrent stroke and death rates at two years were 9.5% and 17.9% for cryptogenic stroke patients with PFO receiving warfarin or acetylsalicylic acid, respectively (RR 0.52, 0.16 to 1.67, $p = 0.3$). Although not significant, this corresponds to a 48% event reduction in favor of warfarin and contrasts with the event rates of 16.5% and 13.2% for warfarin or acetylsalicylic acid treated patients, respectively, in the entire PICSS cohort of PFO patients. However, a similar 49% event reduction in favor of warfarin was observed in cryptogenic stroke patients without PFO, implying a PFO-independent but possibly anticoagulation-responsive stroke mechanism.

The recurrent event rates in our study were similar to those in the PICSS patient group (5) but higher than those reported by Mas et al. (10), suggesting important baseline differences with respect to age, cardiovascular risk factors, and number of previous cerebrovascular events. However, patients in our study were diagnosed and treated according to identical criteria established by a team of neurologists and cardiologists at a single institution, thus minimizing case-to-case variations. Because of the overall low recurrence rate of stroke, the cost and small risk of device implantation must be carefully weighed against the potential therapeutic benefit.

Study limitations. The following limitations apply to our study. The most important limitation is the nonrandomized study design, which may confound the results and introduce bias. However, short of randomized trials which are not expected to be completed within the near future, these data provide important preliminary results relevant to this patient population. The diagnosis of PFO-mediated paradoxical embolism is presumptive, and therefore PFO and cryptogenic stroke may coexist without causal relationship in certain patients. Percutaneous PFO closure in such patients will not influence recurrent cerebrovascular events, a circumstance contributing to the small recurrence rate despite successful PFO closure in our and other series. Percutaneous PFO closure was performed using six different device types employed during different time periods. Current devices for percutaneous PFO closure achieve complete PFO occlusion in $>95\%$ of cases and are associated with complications in $<1\%$ of cases (18). This improvement in device performance might have a positive impact on clinical outcome in the future. Discontinuation of antithrombotic treatment in the medical treatment group could be an important confounder of the presented data. Thus, it cannot be excluded that a considerable portion of patients in the medical treatment group actually did not take antithrombotic treatment at all. However, the limitation of noncompliance with medical treatment applies to everyday clinical practice and does not affect the overall finding of our study.

CONCLUSIONS

Percutaneous PFO closure appears at least as effective as medical treatment for prevention of recurrent cerebrovascular events in cryptogenic stroke patients related to PFO. Percutaneous PFO closure may be more effective than medical treatment in patients with complete PFO closure and more than one cerebrovascular event.

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