



Late Results After Percutaneous Closure of Patent Foramen Ovale for Secondary Prevention of Paradoxical Embolism Using the Amplatzer PFO Occluder Without Intraprocedural Echocardiography

Effect of Device Size

Andreas Wahl, MD,* Tony Tai, MD,* Fabien Praz, MD,* Markus Schwerzmann, MD,* Christian Seiler, MD,* Krassen Nedeltchev, MD,† Stephan Windecker, MD,* Heinrich P. Mattle, MD,† Bernhard Meier, MD*

Bern, Switzerland

Objectives We sought to assess the safety and clinical efficacy of patent foramen ovale (PFO) closure under fluoroscopic guidance only, without intraprocedural echocardiography.

Background Percutaneous PFO closure has been shown to be safe and feasible using several devices. It is generally performed using simultaneously fluoroscopic and transesophageal or intracardiac echocardiographic guidance. Transesophageal echocardiography requires sedation or general anesthesia and intubation to avoid aspiration. Intracardiac echocardiography is costly and has inherent risks. Both lengthen the procedure. The Amplatzer PFO Occluder (AGA Medical Corporation, Golden Valley, Minnesota) can be safely implanted without echocardiographic guidance.

Methods A total of 620 patients (51 ± 12 years; 66% male) underwent PFO closure using the Amplatzer PFO Occluder for secondary prevention of presumed paradoxical embolism. Based on size and mobility of the PFO and the interatrial septum, an 18-mm device was used in 50 patients, a 25-mm device in 492, and a 35-mm device in 78.

Results All procedures were successful, with 5 procedural complications (0.8%): 4 arteriovenous fistulae requiring elective surgical correction, and 1 transient ischemic attack. Contrast transesophageal echocardiography at 6 months showed complete closure in 91% of patients, whereas a minimal, moderate, or large residual shunt persisted in 6%, 2%, and 1%, respectively. During a mean follow-up period of 3.0 ± 1.9 years (median: 2.6 years; total patient-years: 1,871), 5 ischemic strokes, 8 transient ischemic attacks, and no peripheral emboli were reported. Freedom from recurrent ischemic stroke, transient ischemic attack, or peripheral embolism was 99% at 1 year, 99% at 2 years, and 97% at 5 years.

Conclusions The Amplatzer PFO Occluder affords excellent safety and long-term clinical efficacy of percutaneous PFO closure without intraprocedural echocardiography. (J Am Coll Cardiol Intv 2009; 2:116–23) © 2009 by the American College of Cardiology Foundation

From the Departments of *Cardiology and †Neurology, University Hospital, Bern, Switzerland. Prof. Meier receives a research grant from and serves on the Speakers' Bureau of AGA Medical, Golden Valley, Minnesota. Drs. Tai and Praz contributed equally to this paper.

Manuscript received September 16, 2008; accepted September 29, 2008.

The association of patent foramen ovale (PFO) with cryptogenic stroke has been repeatedly confirmed (1,2) after being independently reported by Lechat et al. (3) and Webster et al. (4) in 1988. A systematic review of case-control studies (1) established a strong association between PFO alone (odds ratio [OR]: 5.0; 95% confidence interval [CI]: 2.4 to 10.4) and especially of PFO associated with atrial septal aneurysm (ASA) (OR: 23.3; 95% CI: 5.2 to 103.2) in young adults (<55 years) with cryptogenic

See page 124

stroke compared with nonstroke controls. More recently, this observation was extended to adults >55 years, with a significantly higher prevalence of PFO alone (28.3% vs. 11.9%; OR: 2.9; 95% CI: 1.7 to 5.0; $p < 0.001$) as well as of PFO associated with ASA (15.2% vs. 4.4%; OR: 3.9; 95% CI: 1.8 to 8.5; $p < 0.001$) among patients with cryptogenic stroke compared with those with a known stroke cause (5). Percutaneous PFO closure has been shown to be safe and feasible using a variety of devices (6–11), and its clinical efficacy for secondary prevention of paradoxical embolism appeared favorable when compared with medical treatment (12–14). The reported success rates varied between 90% and 100%, with complication rates between 0% and 10%. Complete PFO closure was reported in 51% to 100% of patients, and the yearly recurrence rates of ischemic strokes and transient ischemic attacks (TIA) varied between 0% and 3.4%. Important differences were observed between the devices used (11,15,16). Initial device-related complications inflicted by large delivery systems, device dislodgment and embolization, structural failure, thrombus formation (17), and inability to reposition or remove the device were reduced by improvements in device design. Anatomic and

physiologic differences between PFOs and atrial septal defects led to the development of devices specifically designed for percutaneous PFO closure. The Amplatzer PFO Occluder (APFO) (AGA Medical Corporation, Golden Valley, Minnesota) is a self-expanding double-disk device manufactured from 0.005-inch nitinol wire with a polyester fabric patch sewn into both disks (Fig. 1). It is fully recoverable and repositionable as long as it is attached to its delivery cable (18). In contrast to the Amplatzer Septal Occluder, the left atrial disk is smaller than the right (except for the so-called cribriform models), and a thin and flexible waist connects the 2 retention disks. Percutaneous PFO closure is generally performed using simultaneous fluoroscopic and transesophageal echocardiographic (TEE) (9,10,16) or intracardiac echocardiographic (ICE) (19, 20) guidance. Whereas TEE requires sedation or general anesthesia and intubation to avoid aspiration, ICE is costly and has inherent risks. Moreover, both imaging modalities considerably lengthen the procedure.

Methods

Patients. Between November 1998 and December 2006, 620 patients underwent percutaneous PFO closure for secondary prevention of presumed paradoxical embolism using the APFO. An embolic event was considered to be due to paradoxical embolism when the following criteria were fulfilled: the presence of PFO with or with-

Abbreviations and Acronyms

APFO = Amplatzer PFO Occluder

ASA = atrial septal aneurysm

CI = confidence interval

ICE = intracardiac echocardiography

OR = odds ratio

PFO = patent foramen ovale

TEE = transesophageal echocardiography

TIA = transient ischemic attack

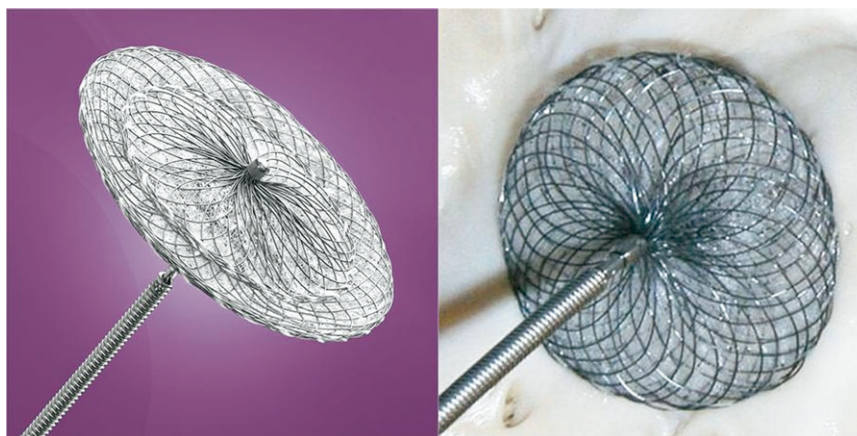


Figure 1. Amplatzer PFO Occluder

Amplatzer PFO Occluder (left) placed in a cadaver heart (right), seen from the right atrium. Courtesy of AGA Medical. PFO = patent foramen ovale.

out ASA with spontaneous or inducible interatrial right-to-left shunt during contrast TEE, clinically and/or radiologically confirmed ischemic stroke, TIA, or peripheral embolism, and exclusion of any other obvious cardiac, aortic, or cerebrovascular cause. The procedure was approved by the local ethics committee, and patients gave written informed consent.

Echocardiography. The diagnosis of PFO and ASA was based on contrast TEE, with aerated colloid solution injected into an antecubital vein at the end of a vigorous and sustained Valsalva maneuver. We defined PFO as a flaplike opening in the atrial septum secundum, with the septum primum serving as a 1-way valve allowing for permanent or transient right-to-left shunt. We diagnosed ASA as an abnormally redundant interatrial septum with an excursion of >10 mm into the right or left atrium and a diameter at the base of the aneurysm of at least 15 mm (21). 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) (4). To unequivocally demonstrate the presence of a PFO, care was taken to document the actual passage of contrast bubbles through the rent, but this was not possible in all cases.

APFO. The APFO was commercially available in 3 sizes, with the dominant right atrial disk measuring 18, 25, or 35 mm, and the left atrial disk measuring 18, 18, and 25 mm, respectively. It can be constrained within an 8-F (9-F for the largest model) delivery system and reassumes its double-disk shape upon release.

Percutaneous PFO closure. The interventions were performed under local anesthesia and fluoroscopic guidance only (7). Intraprocedural guidance by TEE (9,10,16) or ICE (19,20) was not used in any case. However, all patients had undergone TEE prior to the intervention for initial diagnosis of PFO. After venous access was gained via the right femoral vein, the PFO was crossed under fluoroscopic guidance in the anteroposterior view either by a standard length normal 0.035-inch guidewire alone or with the help of a catheter, typically a 6-F multipurpose catheter. Initially, a J-tip was used to ensure passage through the largest hole in case there were several. In some cases (small PFO), the tip had to be straightened for passage of the defect. Balloon sizing was not used. Indeed, the maximal opening of the flaplike PFO is not instrumental for the success of closure. Moreover, there is a finite risk of the measuring balloon tearing the thin septum primum (22). A 25-mm device was selected for all cases, save those with particularly low mobility (18 mm) or extremely long tunnel (35 mm). In 5% of cases, the initial device had to be exchanged for a larger device during the procedure because of suboptimal anchoring (negative Pacman sign) (Fig. 2) (23). The device was

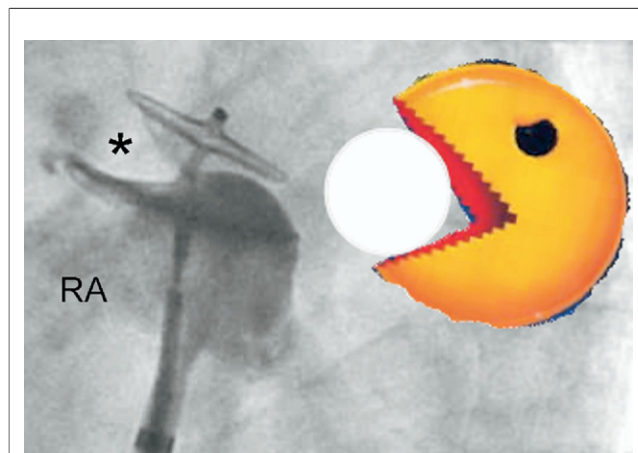


Figure 2. Pacman Sign for Angiographic Assessment of Correct Device Position

The Pacman sign (23) illustrated with the proper projection of the device during a hand injection of contrast medium into the right atrium (RA). The septum secundum (*) represents the dot the device (represented by Pacman) is biting into.

prepared before introducing the sheath to keep the indwelling time of the sheath short. To avoid air aspiration, the obturator of the sheath was pulled back while the guidewire remained in the left atrium or a pulmonary vein. This avoids wedging of the end hole against the wall and allows the blood to follow the receding obturator, filling the void rather than air being sucked in from the outside. The loader was connected to the sheath with the device peeking out a few millimeters, lateral to the patient's thigh, well below the heart level. The APFO was then pushed with the delivery cable to the tip of the sheath positioned in the left atrium. The left atrial disk was deployed and gently pulled back against the atrial septum under fluoroscopic guidance in a left anterior oblique projection. To deploy the right atrial disk, tension was maintained on the delivery cable while further withdrawing the delivery sheath. After aspiration of the air from the sheath, a right atrial contrast angiography by a hand injection through a sidearm of the delivery sheath delineated the atrial septum. The so-called Pacman sign (23) (Fig. 2) refers to the aspect of the device on fluoroscopy that should be achieved before release. Seen in perfect profile, the cranial halves of the left and right atrial disks should appear like open jaws biting into the thick septum secundum, reminding one of the arcade game figure Pac-Man about to gobble up a dot. Upon verification of correct position, the APFO was released by unscrewing the delivery cable in counterclockwise fashion. The transseptal sheath was then used for a final contrast medium injection. The contrast can be followed through to the levo-phase to also delineate the left atrial contour and disk placement. Finally, the sheath was removed and hemostasis achieved by light manual compression, often done by the patient himself.

Patients were released to full physical activity a few hours after the procedure. A transthoracic contrast echocardiography was performed within 24 h of percutaneous PFO closure to document correct and stable device position. Acetylsalicylic acid 100 mg once daily for 6 months and clopidogrel 75 mg once daily for 1 to 6 months were prescribed for antithrombotic protection.

Follow-up evaluation. The outcome after the intervention was prospectively assessed for up to 8 years. A contrast TEE was repeated 6 months after percutaneous PFO closure. In case of a significant residual shunt, a repeat TEE at 1 year was recommended. If the shunt persisted at that time, implantation of a second device was recommended. Thereafter, patients underwent structured telephone interviews, addressing recurrent embolic events, device-related problems, and health status at regular intervals. Follow-up information was available for all patients, but 19 patients (3%) were eventually lost to follow-up. Death and recurrent ischemic stroke, TIA, or peripheral embolism were considered end points. Patients with suspected recurrent cerebrovascular events were re-examined by a neurologist, and a new imaging study of the brain (computed tomography or magnetic resonance imaging) was performed.

Statistical analysis. Continuous variables are expressed as mean \pm 1 standard deviation, and were compared by a 2-sided, unpaired *t* test. Categorical variables are reported as counts and percentages and were compared by chi-square analysis. Estimates for freedom from the composite of recurrent TIA, stroke, and peripheral embolism were obtained using the Kaplan-Meier method. The log-rank test was used for univariate analysis of independent predictors of recurrence. Estimates of the hazard ratio (HR) and 95% confidence intervals for each independent variable were obtained by proportional hazard regression analysis. Statistical significance was assumed with a *p* value <0.05 . All data were analyzed by SPSS software version 15.0.1 (SPSS Inc., Chicago, Illinois).

Results

In-hospital outcome. Demographic data are summarized in Table 1. All implantation procedures were successful (Table 2). There were 5 procedural complications (0.8%): 4 arteriovenous fistulae at the puncture site requiring elective surgical closure (2 in patients with concomitant coronary angiography) and 1 TIA with visual symptoms (immediately after PFO closure). There were no in-hospital deaths, and none of the procedural complications resulted in long-term sequelae. Total procedure time, including incidental coronary angiography (24) in 439 patients (71%), and ad hoc percutaneous coronary intervention in 44 (7%), was 40 ± 21 min (median: 36 min). Total fluoroscopy time was 7.3 ± 6.6 min (median: 5.5 min). In the 181 patients undergoing PFO closure only, the total procedure time amounted

Table 1. Baseline Clinical Characteristics

Patients	620
Age, yrs	51 \pm 12 (median: 53)
Male	377 (66%)
Height, cm	173 \pm 9
Weight, kg	76 \pm 15
Atrial septal anatomy	
Left atrial size, mm	37 \pm 6
Associated atrial septal aneurysm	207 (33%)
Cardiovascular risk factors	
Arterial hypertension	198 (32%)
Diabetes mellitus	26 (4%)
Smoking history	188 (30%)
Total cholesterol, mmol/l	5.2 \pm 1.1
Embolic index event	
Ischemic stroke	358 (58%)
Transient ischemic attack	228 (37%)
Peripheral embolism	34 (5%)
Number of clinically apparent prior embolic events	
1	429 (69%)
2	101 (16%)
3	25 (4%)
4 or more	63 (10%)

Values are n (%) or mean \pm SD.

to only 25 ± 12 min (median: 22 min), and the fluoroscopy time was 3.8 ± 2.5 min (median: 3.1 min). Patients with small occluders (18 and 25 mm; *n* = 542 patients) had similar complication rates (0.7% vs. 1.3%; *p* = 0.62) compared with patients with large occluders (35 mm; *n* = 78). Patients with an associated ASA (*n* = 207; 33%) had similar complication rates (1.4% vs. 0.5%; *p* = 0.21) compared with patients with an isolated PFO (*n* = 413; 66%). Patients ≥ 55 years (*n* = 264; 43%) and <55 years (*n* = 356; 57%) also had similar complication rates (1.1% vs. 0.6%; *p* = 0.43). Transthoracic contrast echocardiography after the Valsalva maneuver within 24 h of percutaneous PFO closure (performed in all patients) detected a residual shunt in 11% of patients.

Late echocardiographic outcome. Complete PFO closure as assessed by contrast TEE (performed in 94% of patients) after the Valsalva maneuver at 6 months was achieved in 91% of patients, whereas a minimal, moderate, or large residual shunt persisted in 6%, 2%, or 1% of patients, respectively (Fig. 3). Patients with 18- and 25-mm devices (*n* = 542) had considerably fewer residual shunts compared with patients with 35-mm devices (*n* = 78), that is, 7% versus 27%, respectively (*p* < 0.001) (Fig. 4). Older (≥ 55 years; *n* = 264; 43%) and younger (<55 years; *n* = 356) patients had similar residual shunt rates (9% vs. 9%; *p* = 0.92). Patients with PFO and an associated ASA (*n* = 207; 33%) had higher residual shunt rates than patients with an isolated PFO (*n* = 413; 67%), that is, 13% versus 7%,

Table 2. Implanted Amplatzer PFO Occluder Devices

Device Size	Patients	Atrial Septal Aneurysm	Baseline PFO-Mediated Shunt	Procedural Complications	Residual Shunt (Contrast TEE at 6 Months)	Recurrent Embolism	Cumulative Follow-Up (Patient-Yrs)
18-mm	50	20%	4% grade 1 16% grade 2 80% grade 3	0	7%	1	157
25-mm	492	31%	2% grade 1 18% grade 2 80% grade 3	0.8%	7%	11	1,395
35-mm	78	58%	3% grade 1 14% grade 2 83% grade 3	1.3%	27%	1	319
Total	620	33%		0.8%	9%	13	1,871

PFO = patent foramen ovale; TEE = transesophageal echocardiography.

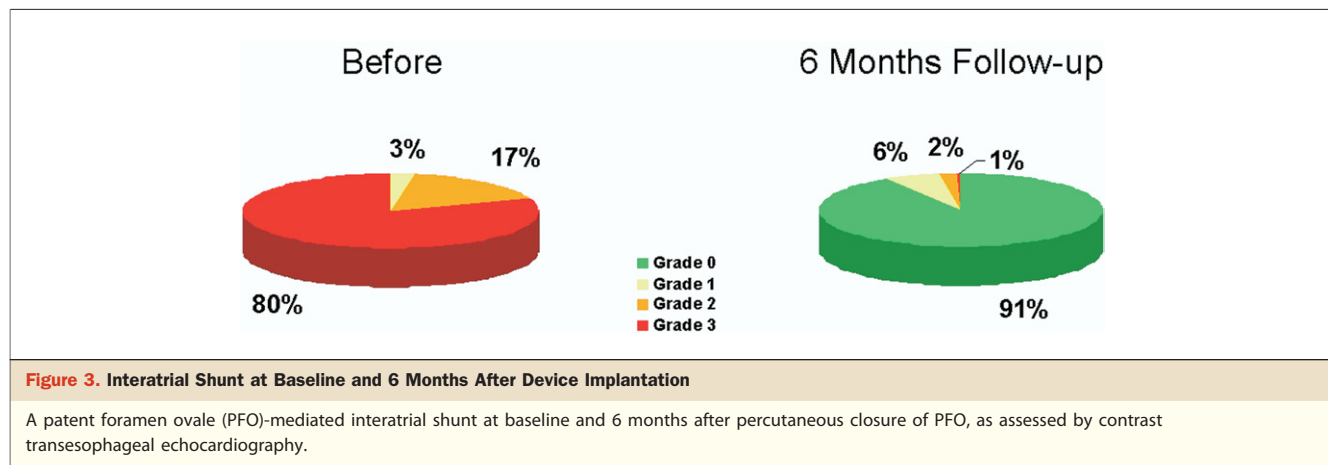
respectively ($p < 0.05$). At 6-month follow-up, contrast TEE examination showed a thrombus on the device in 3 asymptomatic patients (0.5%). One patient (25-mm APFO) had a tiny thrombus on the left atrial disk, which remained unchanged after 4 months of oral anticoagulation. One patient (35-mm APFO) had a small thrombus on the left atrial disk, which resolved after 3 months of oral anticoagulation. Another patient had a 20×7 mm thrombus adherent to the right atrial disk (35-mm APFO) that resolved after 6 months of oral anticoagulation. Ten months after cessation of oral anticoagulants, TEE showed a recurrent right atrial thrombus, which resolved once again after oral anticoagulant therapy during 6 months, without further recurrences. The last echocardiography at the 7-year follow-up was normal.

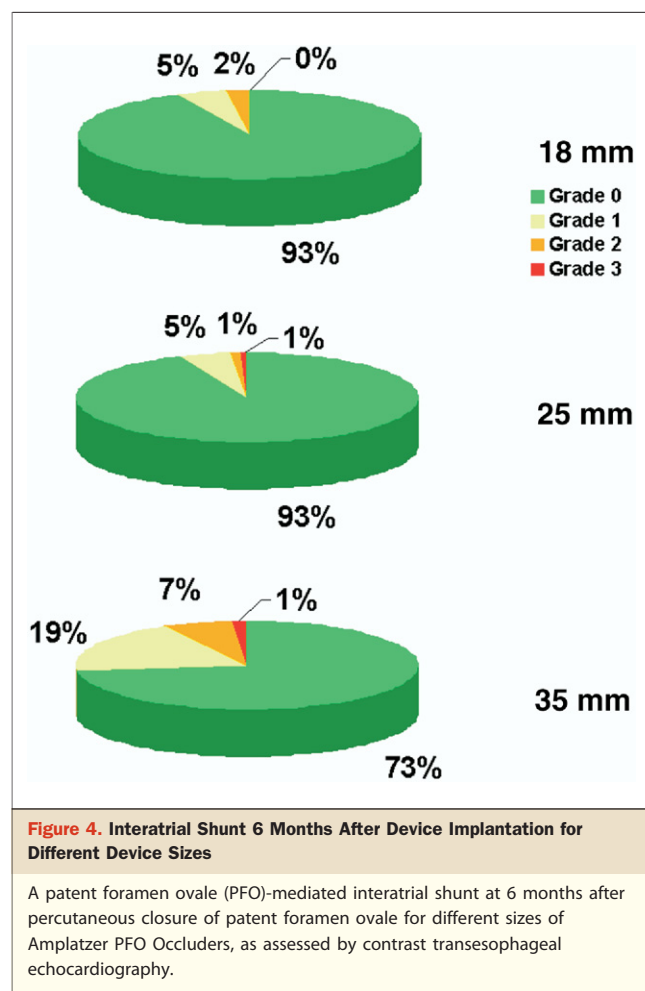
A total of 8 patients (1.3%), 4 of them with an ASA, with 1 18-mm and 7 25-mm devices in place, underwent implantation of a second device (1 APFO 18-mm and 7 APFO 25-mm) due to a significant residual shunt. In all of these patients, TEE showed the initial closure device in the correct position, but a residual shunt in the region of the former PFO. No periprocedural complications occurred during the second intervention. After implantation of the

second device, complete closure was finally achieved in 6 of 8 patients (75%), with persistence of a mild and a moderate residual shunt in 1 patient each.

In a patient with a PFO grade III associated with a large ASA, TEE 2 years after implantation of an APFO 35-mm device (performed due to persistence of a residual shunt after 6 months) disclosed a new tiny atrial septal defect at the lower rim of the device, probably corresponding to an erosion of the interatrial septum due to the wear and tear of the ASA undulating incessantly between the right and left disk of the device. In another patient, routine TEE 6 months after implantation of an APFO 25-mm device showed a completely occluded PFO, but a new small atrial septal defect was seen at the lower rim of the device. In both cases, these iatrogenic small atrial septal defects were successfully closed using a 25-mm APFO (25). There were no further device-related complications, in particular no dislocations or erosions of the free atrial walls.

Late outcome. During 3 ± 1.9 years of follow-up (median: 2.6 years; total patient-years: 1,871), 9 deaths (3 accidents, 2 cancer, 2 ventricular fibrillation, 1 infection, 1 coma due to prolonged hypoglycemia), none of them related to recurrent





embolic events; 5 ischemic strokes, 8 TIAs and no peripheral emboli were reported. Symptomatic paroxysmal atrial fibrillation was documented in 10 cases only (1.6%; mean age: 61 years; range: 51 to 74 years) but was not specifically looked for in all patients. Freedom from the composite end point of recurrent ischemic stroke, TIA, or peripheral embolism was 99% at 1 year, 99% at 2 years, and 97% at 5 years, respectively (Fig. 5). The presence of multiple clinical embolic events prior to PFO closure was a risk factor for recurrence (HR: 4.9; 95% CI: 1.5 to 15.9; $p = 0.008$). On the other hand, male gender was associated with less recurrent events (HR: 0.2; 95% CI: 0.1 to 0.8; $p < 0.03$). Contrary to previously reported findings by our group in a smaller cohort with different devices (7,8,11), a residual right-to-left shunt after transcatheter treatment of PFO was not a predictor of recurrent events (HR: 0.9; 95% CI: 0.1 to 6.7; $p = 0.89$). Older age (≥ 55 years), the presence of an ASA associated with the PFO, arterial hypertension, diabetes mellitus, smoking status, family history, hypercholesterolemia, device size, and procedural complications did not adversely affect the outcome either.

Discussion

This study is the largest series of patients with presumed paradoxical embolism treated at a single center and with one of the longest follow-ups reported to date to investigate the safety, feasibility, and long-term clinical efficacy of percutaneous PFO closure using the APFO. Moreover, the procedure was performed without intraprocedural echocardiography in all patients. To our knowledge, there is only 1 large study reporting mid-term results after percutaneous PFO closure using mostly APFO (20). In the study of Onorato et al. (20), 248 of 256 patients received an APFO, which was successfully implanted in all cases. Onorato et al. (20) used ICE in 69% of cases, and TEE in 31%. Procedure and fluoroscopy times were markedly longer than in our study, at 57 ± 21 min and 9.5 ± 5 min, respectively.

Our study confirms the safety and feasibility of percutaneous PFO closure with the APFO using the simple technique described in the Methods section in a large series. The complication rate was 0.8%, and none of the complications had a connection to the omission of ultrasound guidance. In contrast, the use of ICE would have compounded the risk for puncture site problems accounting for all but 1 complication. Complete PFO closure could be achieved in 91% of patients, and even 93% in patients with smaller devices (18- and 25-mm). During long-term follow-up, the risk of recurrent events after transcatheter treatment of PFO with or without associated ASA was $<1\%$ per year. Of note, recurrent embolic events occurred up to 5.3 years after PFO closure, which is considerably longer than the 8 months reported by Braun et al. (16). The excellent clinical

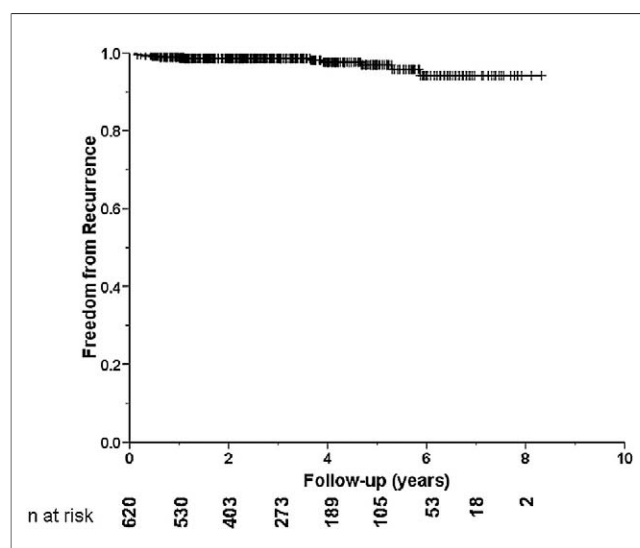


Figure 5. Freedom From Recurrent TIA, Ischemic Stroke, and Peripheral Embolism

Freedom from the composite end point of recurrent transient ischemic attack (TIA), ischemic stroke, or peripheral embolism after percutaneous closure of patent foramen ovale.

efficacy compares favorably with medical treatment (26). Long-term device-related events (3 thrombi and 2 erosions of the interatrial septum) were rare, and none had clinical sequelae. These are important safety findings for an interventional treatment of a condition that has a low annual event rate in natural history.

In patients with both PFO and ASA, who constitute a high-risk population with a 3- to 5-fold increased risk for recurrent embolic events than for patients with PFO alone (1), secondary prevention with acetylsalicylic acid alone has been found to be insufficient (27). In this series, an ASA associated with PFO had no influence on device success or on the risk of periprocedural complications or recurrent events. However, it was associated with an increased residual shunt rate. Moreover, this series confirmed that percutaneous PFO closure is equally safe, feasible, and efficacious in selected older (≥ 55 years) (28) and younger patients. Indeed, the association between PFO alone and PFO with ASA with cryptogenic stroke has been recently extended to adults >55 years (5), and the elderly who have the highest risk (29,30) of paradoxical embolism should not be denied a simple preventive treatment. The uncontested association of PFO and stroke renders the consideration of the PFO as a stroke cause only in cryptogenic strokes illogical. In older people, the diagnosis of cryptogenic stroke is rare, due to a high prevalence of stroke-associated disorders. Notwithstanding, a PFO per se might be more dangerous in them than in younger people due to the increasingly high prevalence of venous thrombosis associated with age (30).

Transcatheter treatment of patients with cryptogenic stroke and PFO has been shown to be safe and feasible using a variety of occlusion devices, mostly with (9,10,16,28) but also without intraprocedural echocardiographic guidance (7,8,31). Routine TEE guidance provides little additional information to what can be gleaned from a hand injection of contrast medium (23) in a profile-adjusted view (Fig. 2). Because TEE is poorly tolerated by supine patients, it comes at the cost of sedation or general anesthesia, including intubation to virtually exclude the risk of bronchial aspiration. This considerably lengthens the procedure. Although ICE (19,20) is a costly alternative that is more comfortable for the patient, it increases the invasive risk (additional vascular access, second rigid, and unguided intravenous catheter, with potential complications including development of arteriovenous fistulae at the puncture site, air embolism through the introducer, cardiac perforation, and bacterial entry). In this large series of PFO closure without intraprocedural TEE or ICE guidance, the device success was 100%, and the 5 periprocedural complications (0.8%) were unrelated to the presence or absence of echocardiography. Although this series did not include a control group with echocardiographic guidance, these rates compare favorably with the published experience. Indeed, in studies using echocardiographic guidance, the complication rates

reported varied between 0% and 9% (6,9,10,16,20,28). With respect to closure rates, this study showed that larger devices, selected for larger shunts in the presence of an ASA, were associated with considerably higher residual shunt rates. However, this nonrandomized comparison was biased in favor of smaller devices (e.g., only 30% of patients receiving an 18- or 25-mm device had an associated ASA vs. 58% for 35-mm devices; $p < 0.001$). Although larger devices are easier to implant and preferred by most operators in case of larger PFOs or associated ASAs, there is more concern about the risk of impairment or erosion of adjacent structures. Smaller devices more snugly fit into the fossa ovalis. However, they are intrinsically more likely to embolize or to only partially cover a slitlike PFO or a cribriform septum primum.

Study limitations. Because both PFO and cryptogenic stroke are prevalent conditions, they may coexist without causal relation in certain patients. Percutaneous PFO closure in patients with falsely PFO-related strokes will not influence recurrent embolic events, a circumstance likely to contribute to the small recurrence rate despite successful PFO closure in our and other series. Nonetheless, these patients will be protected against true paradoxical embolism. It has to be emphasized that the true therapeutic efficacy of percutaneous PFO closure as an adjunct or alternative to medical treatment can only be ascertained by randomized studies. While we wait for those studies, it is time to shift the term “cryptogenic” in stroke patients to beyond the exclusion of a PFO. A PFO is a reason for stroke, not more but not less.

Reprint requests and correspondence: Prof. Bernhard Meier, Swiss Cardiovascular Center Bern, University Hospital, 3010 Bern, Switzerland. E-mail: bernhard.meier@insel.ch.

REFERENCES

1. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000;55: 1172-9.
2. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002;105: 2625-31.
3. Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988;318:1148-52.
4. Webster MW, Chancellor AM, Smith HJ, et al. Patent foramen ovale in young stroke patients. *Lancet* 1988;2:11-2.
5. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med* 2007;357:2262-8.
6. Bridges ND, Hellenbrand W, Latson L, Filiano J, Newburger JW, Lock JE. Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. *Circulation* 1992;86:1902-8.
7. Windecker S, Wahl A, Chatterjee T, et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. *Circulation* 2000;101:893-8.

8. Wahl A, Meier B, Haxel B, et al. Prognosis after percutaneous closure of patent foramen ovale for paradoxical embolism. *Neurology* 2001;57:1330-2.
9. Martin F, Sanchez PL, Doherty E, et al. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Circulation* 2002;106:1121-6.
10. Braun MU, Fassbender D, Schoen SP, et al. Transcatheter closure of patent foramen ovale in patients with cerebral ischemia. *J Am Coll Cardiol* 2002;39:2019-25.
11. Wahl A, Krumsdorf U, Meier B, et al. Transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale for prevention of recurrent paradoxical embolism in high-risk patients. *J Am Coll Cardiol* 2005;45:377-80.
12. Khairy P, O'Donnell CP, Landberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* 2003;139:753-60.
13. Windecker S, Wahl A, Nedeltchev K, et al. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. *J Am Coll Cardiol* 2004;44:750-8.
14. Wohrle J. Closure of patent foramen ovale after cryptogenic stroke. *Lancet* 2006;368:350-2.
15. Schwerzmann M, Windecker S, Wahl A, et al. Percutaneous closure of patent foramen ovale: impact of device design on safety and efficacy. *Heart* 2004;90:186-90.
16. Braun M, Glied V, Boscheri A, et al. Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow-up results of three different device occluder systems. *Eur Heart J* 2004;25:424-30.
17. Krumsdorf U, Ostermayer S, Billinger K, et al. Incidence and clinical course of thrombus formation on atrial septal defect and patent foramen ovale closure devices in 1,000 consecutive patients. *J Am Coll Cardiol* 2004;43:302-9.
18. Han YM, Gu X, Titus JL, et al. New self-expanding patent foramen ovale occlusion device. *Catheter Cardiovasc Interv* 1999;47:370-6.
19. Koenig P, Cao QL, Heitschmidt M, Waight DJ, Hijazi ZM. Role of intracardiac echocardiographic guidance in transcatheter closure of atrial septal defects and patent foramen ovale using the Amplatzer device. *J Interv Cardiol* 2003;16:51-62.
20. Onorato E, Melzi G, Casilli F, et al. Patent foramen ovale with paradoxical embolism: mid-term results of transcatheter closure in 256 patients. *J Interv Cardiol* 2003;16:43-50.
21. Pearson AC, Nagelhout D, Castello R, Gomez CR, Labovitz AJ. Atrial septal aneurysm and stroke: a transesophageal echocardiographic study. *J Am Coll Cardiol* 1991;18:1223-9.
22. Bonvini RF, Sigwart U, Verin V. Interatrial septum rupture during balloon measurement of a patent foramen ovale in a young patient presenting cryptogenic stroke. *Catheter Cardiovasc Interv* 2007;69:274-6.
23. Meier B. Pacman sign during device closure of the patent foramen ovale. *Catheter Cardiovasc Interv* 2003;60:221-3.
24. Wahl A, Praz F, Seiler C, Windecker S, Meier B. Clinical relevance of coronary angiography at the time of percutaneous closure of a patent foramen ovale. *Catheter Cardiovasc Interv* 2007;70:641-5.
25. Meier B. Iatrogenic atrial septal defect, erosion of the septum primum after device closure of a patent foramen ovale as a new medical entity. *Catheter Cardiovasc Interv* 2006;68:165-8.
26. Homma S, Sacco RL. Patent foramen ovale and stroke. *Circulation* 2005;112:1063-72.
27. Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med* 2001;345:1740-6.
28. Kiblawi FM, Sommer RJ, Levchuck SG. Transcatheter closure of patent foramen ovale in older adults. *Catheter Cardiovasc Interv* 2006;68:136-42.
29. Meier B. Patent foramen ovale, guilty but only as a gang member and for a lesser crime. *J Am Coll Cardiol* 2006;47:446-8.
30. Anderson FA Jr., Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991;151:933-8.
31. Bijl JM, Ruygrok PN, Hornung TS, Wilson NJ, West T. Percutaneous closure of patent foramen ovale. *Intern Med J* 2005;35:706-10.

Key Words: atrial septal aneurysm ■ patent foramen ovale ■ cerebral ischemia ■ embolism ■ secondary stroke prevention.