Percutaneous Closure of Patent Foramen Ovale in Patients With Paradoxical Embolism

Long-Term Risk of Recurrent Thromboembolic Events

Stephan Windecker, MD; Andreas Wahl, MD; Tushar Chatterjee, MD; Ali Garachemani, MD; Franz R. Eberli, MD; Christian Seiler, MD; Bernhard Meier, MD

Background—Patients with a patent foramen ovale (PFO) and paradoxical embolism are at risk for recurrent thromboembolic events. This study investigated the long-term risk of recurrent thromboembolic events in patients with PFO and paradoxical embolism after percutaneous PFO closure.

Methods and Results—Since 1994, a total of 80 patients with PFO and at least 1 paradoxical embolic event (transient ischemic attack [TIA], cerebrovascular accident [CVA], peripheral embolism) have undergone percutaneous PFO closure with 5 different devices. There were 30 women and 50 men, with a mean age of 52 ± 12 years. Sixty patients had only a PFO, whereas 20 patients had both a PFO and an atrial septal aneurysm. The implantation procedure was successful in 78 patients (98%). During 5 years of follow-up (mean, 1.6 ± 1.4 years; range, 0.1 to 5.0 years), the actuarial annual risk to suffer a recurrent thromboembolic event was 2.5% for TIA, 0% for CVA, 0.9% for peripheral emboli, and 3.4% for the combined end point of TIA, CVA, or peripheral embolism. A postprocedural shunt was a predictor of recurrent paradoxical embolism (RR, 4.2; 95% CI, 1.1 to 17.8; \( P = 0.03 \)). The risk for recurrent thromboembolic events in patients with both atrial septal aneurysm and PFO was not significantly increased compared with patients with only PFO (RR, 1.0; 95% CI, 0.2 to 4.7; \( P = 0.95 \)).

Conclusions—Percutaneous PFO closure appears to be a promising technique in the prevention of recurrent systemic thromboembolism in patients with a PFO after a first event. Prospective studies comparing percutaneous PFO closure with antithrombotic medications or surgery must define its therapeutic value.

Key Words: foramen ovale • stroke • embolism

A patent foramen ovale (PFO) has been increasingly recognized as a mediator of paradoxical embolism, allowing passage of air, thrombus, and fat, with their subsequent systemic sequelae. Several case-control studies using contrast echocardiography established a strong association between cryptogenic stroke and the presence of PFO in young adults <55 years old. The relationship is less well defined in older age groups. Patients with PFO and paradoxical embolism are also at increased risk for recurrent thromboembolic events, with a combined cerebrovascular accident (CVA) and transient ischemic attack (TIA) rate of 3.4% to 3.8% per year. A large PFO size and presence of an atrial septal aneurysm (ASA) have been identified as morphological characteristics of PFO portending a high risk for paradoxical embolism.

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The probability of PFO being the mediator of paradoxical embolism prompted the quest for a therapeutic and preventive strategy in affected patients. Surgical PFO closure has proved feasible, but the results have been mixed with respect to stroke prevention. Promising results of percutaneous PFO closure were initially reported by Bridges et al. who used the clamshell device in a sizeable cohort of patients with presumed paradoxical embolism. The present study prospectively assessed the long-term risk for recurrent thromboembolic events after percutaneous PFO closure with a variety of devices in 80 consecutive patients with paradoxical embolism during a follow-up period of up to 5 years.

Methods

Patient Population

Since April 1994, 80 patients with PFO and at least 1 documented thromboembolic event have undergone percutaneous PFO closure according to a study protocol approved by the local Ethics Committee. A thromboembolic event was considered to be due to paradoxical embolism when the following criteria were met: (1) presence of PFO with or without ASA with spontaneous or provokable right-to-left shunt during contrast transesophageal echocardiography, (2) clinically and neuroradiologically confirmed ischemic stroke or symptoms of TIA with neuroradiologically identified intracranial
ischemic or clinically and radiologically verified extracranial peripheral thromboembolism, and (3) exclusion of any identifiable cause for the thromboembolic event other than the PFO. All patients gave written informed consent to participate in the study before the procedure.

**Implantation Procedure**

Venous access was gained via the right femoral vein, and the PFO was passed under fluoroscopic guidance with a 6F multipurpose catheter. With a standard 0.035-in exchange wire, the multipurpose catheter was exchanged for a 6F to 14F transseptal sheath. The PFO occluder was delivered through the transseptal sheath and placed within the PFO under fluoroscopic guidance according to device-specific implantation recommendations. Before the release of the PFO occluder, device position was checked by right atrial contrast angiography to delineate the atrial septum. Transesophageal echocardiography was performed only during the first 3 procedures. At the end of the procedure, the transseptal sheath was removed, and hemostasis was achieved by manual compression. A transthoracic contrast echocardiographic examination was performed within 24 hours of percutaneous PFO closure. All patients were treated with aspirin 100 mg once daily for 3 to 6 months, at which time the medication was stopped unless required for another indication.

**Follow-Up Evaluation**

At baseline before implantation and at 6 months after percutaneous PFO closure, a transesophageal contrast echocardiographic study with aerated colloid solution injected into the antecubital vein was performed. Any recurrent thromboembolic events, including TIA, CVA, or peripheral embolus, were considered primary endpoints of the study. All patients were followed up prospectively for up to 5 years (range, 0.1 to 5 years). Patients with suspected thromboembolic recurrence were reexamined by a neurologist, and whenever possible, an imaging study, ie, MRI, CT, or angiography of the region of interest, was repeated. As of the most recent contact, all patients were subjected to a structured interview addressing recurrence of thromboembolism, current health status, and quality of life. No patient was lost to follow-up.

**Definitions**

ASA was diagnosed when the interatrial septum was abnormally redundant, with an excursion of >10 mm into the right or left atrium. TIA was defined as a transient neurological deficit lasting ≤24 hours with complete resolution of symptoms. CVA was defined as any new neurological deficit lasting >24 hours. Peripheral embolism was defined as ischemia in any end organ other than the brain caused by reduced blood flow in a particular artery and objectively documented by Doppler flow, CT, MRI, or angiographic imaging. Procedural complications were defined as any adverse event that occurred within 24 hours of PFO occluder implantation.

**Statistical Analysis**

Continuous variables were expressed as mean ± SD. Nominal variables were compared by χ² analysis and paired continuous variables by a 2-sided, paired t test. Statistical significance was assumed at a value of P < 0.05. Actuarial analysis of freedom from recurrent thromboembolic events was calculated according to the Kaplan-Meier method. Average annual event rates were calculated according to the formula 1−[(1−P)²]−1, where P equals the cumulative event rate at n years of follow-up. The log-rank test was used for univariate analysis of independent variables (age, sex, procedural complications, postprocedural shunt, or device type) on the rate of recurrence. Estimates of the relative risk (RR) and 95% CIs for each independent variable were obtained by proportional hazards regression analysis.

**Results**

**Short-Term Results and Periprocedural Complications**

Patient demographics are summarized in Table 1. The implantation procedure was successful in 78 patients (98%).

<table>
<thead>
<tr>
<th>Table 1. Patient Demographics</th>
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<tbody>
<tr>
<td><strong>Clinical Characteristics</strong></td>
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<tr>
<td>No.</td>
</tr>
<tr>
<td>Age, y</td>
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<tr>
<td>Sex, female/male, n (%)</td>
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<tr>
<td>Atrial septal anatomy, n (%)</td>
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<tr>
<td>PFO only</td>
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<tr>
<td>PFO and ASA</td>
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<tr>
<td>Thromboembolic index event, n (%)</td>
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<tr>
<td>CVA</td>
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<tr>
<td>TIA</td>
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<tr>
<td>Peripheral embolism</td>
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<tr>
<td>Follow-up period, y, mean (range)</td>
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</table>

There were 8 procedural complications (10%), which are summarized in Table 2 and described below. In 1 patient, the procedure was aborted before device delivery because of laceration of the femoral artery during venous puncture with an ensuing retroperitoneal hematoma. This required surgical revision, at which time the PFO was closed surgically. In another patient with PFO and a large ASA, an Amplatzer occluder embolized into the pulmonary artery 12 hours after the procedure. The device was retracted percutaneously into the femoral vein with an Amplatzer retrieval basket and from there removed by local incision. Repeat PFO closure was not attempted. Thus, in 2 patients, the implantation procedure failed.

One patient suffered an intraprocedural CVA, presumably due to air embolism through the transseptal sheath during device delivery. The clinical manifestations of aphasia and mild right hemiparesis completely resolved within 48 hours, at which time the patient was discharged home. When a reversed buttoned device was used, embolization of the counteroccluder into the pulmonary artery occurred in 2 patients. It was retrieved percutaneously. The occluding umbrella remained in the correct position, and therefore,

<table>
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<th>Table 2. Implantation Procedure</th>
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<tr>
<td><strong>Implantation Characteristics</strong></td>
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<tr>
<td>Procedural success</td>
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<tr>
<td>Periprocedural complications (total)</td>
</tr>
<tr>
<td>Embolization of part of the device</td>
</tr>
<tr>
<td>1 Amplatzer device</td>
</tr>
<tr>
<td>2 Buttoned devices</td>
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<tr>
<td>Intraprocedural CVA (lasting &lt; 48 hours)</td>
</tr>
<tr>
<td>1 PFO-STAR device</td>
</tr>
<tr>
<td>Cardiac tamponade (treated percutaneously)</td>
</tr>
<tr>
<td>1 PFO-STAR device</td>
</tr>
<tr>
<td>Retroperitoneal hematoma</td>
</tr>
<tr>
<td>1 Buttoned device</td>
</tr>
<tr>
<td>Embolization of air (with transient symptoms)</td>
</tr>
<tr>
<td>1 PFO-STAR device</td>
</tr>
<tr>
<td>1 CardioSEAL device</td>
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</table>

Values are n (%).
placement of a second device was not necessary. Perforation of the right atrium with an 11F Mullins sheath resulted in a pericardial effusion with cardiac tamponade requiring needle pericardiocentesis in 1 patient who was orally anticoagulated. Embolization of air into the systemic circulation was responsible for transient inferior ST-segment elevations in 1 patient and visual disturbances in another patient during implantation of a PFO Star device.

A total of 5 different device types were implanted. There were no obvious differences in the incidence of intraprocedural complications, residual shunts, or recurrent thromboembolic events relative to the implanted device (Table 3).

Recurrent Paradoxical Embolism
During a mean follow-up period of 1.6±1.4 years (range, 0.1 to 5 years), 8 recurrent thromboembolic events were encountered in 78 patients with an implanted device. These comprised 6 TIAs, no CVAs, and 2 peripheral emboli. One patient suffered a recurrent peripheral embolus into the left leg requiring urgent percutaneous embolectomy 1.6 years after percutaneous PFO closure. At transesophageal echocardiography, a significant residual shunt was discovered, which was closed by implantation of a second device. Another patient suffered a TIA and a peripheral embolus simultaneously 0.6 years after PFO closure, with occlusion of the left popliteal artery. No residual shunt was found at transesophageal echocardiography, but the patient subsequently underwent surgical removal of the device with suture closure of the PFO. This patient suffered another TIA 7 months after surgery. There were no cardiac deaths, deaths due to device complications, or fatal strokes during the observation period. The actuarial rates of event-free survival for recurrent TIA, CVA, or the combined end point of TIA, CVA, or peripheral embolism are displayed in Figure 1. The average annual recurrence rates were 2.5% for TIA, 0% for CVA, 0.9% for peripheral emboli, and 3.4% for the combined end point during the observation period. The risk of recurrence was highest during the first year after percutaneous PFO closure, with no further events beyond 2 years after percutaneous PFO closure (Table 4).

Prognostic Variables
An analysis of clinical predictors for recurrent paradoxical embolism after percutaneous PFO closure is summarized in

<table>
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<th>TABLE 3. PFO Occluder Devices</th>
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<tbody>
<tr>
<td>Device</td>
</tr>
<tr>
<td>Buttoned device</td>
</tr>
<tr>
<td>PFO-STAR</td>
</tr>
<tr>
<td>Amplatzer</td>
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<tr>
<td>Angel-wings</td>
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<tr>
<td>Septal occluder</td>
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</table>

Table 5. Sex or older age (>55 years) did not influence the risk of recurrent thromboembolism. The occurrence of intraprocedural complications had no measurable influence on the risk of recurrence.

Patients were stratified according to atrial septal anatomy into those with only PFO and those with both PFO and ASA (Figure 2, Table 5). During 5 years of follow-up, there was no statisti- cally significant difference in the annual risk of recurrent TIA (PFO only, 1.8%, versus PFO and ASA, 4.1%, P=0.7), recurrent CVA (PFO only, 0%, versus PFO and ASA, 0%), recurrent peripheral emboli (PFO only, 1.3%, versus PFO and ASA 0%, P=0.4), and the combined end point (PFO only, 3.1%, versus PFO and ASA, 4.1%, P=0.95).
between patients with only PFO and patients with both PFO and ASA.

Complete PFO closure as assessed by color flow imaging and/or bubble contrast injection under Valsalva maneuver was achieved in 57 patients (73%), and a residual right-to-left shunt of some degree was present in 21 patients (27%). The presence of a residual shunt after percutaneous PFO closure as assessed by contrast echocardiography was a predictor for recurrent thromboembolic events with a relative risk of 4.2 (95% CI, 1.1 to 17.8; \(P=0.03\)). The average annual rates of recurrence of the combined end point TIA, CVA, or peripheral embolism were 6.8% in patients with versus 2.1% in patients without a postprocedural shunt (Figure 3).

**Discussion**

**Present Study**

The present study, based on 128 patient-years, demonstrates that percutaneous PFO closure can be performed with a success rate of \(>95\%\) and a periprocedural complication rate of 10% by use of a variety of PFO occluder devices. At up to 5 years of follow-up, the average annual rates of recurrent thromboembolic events were comparable to previously published data on medical\(^{12,13}\) and surgical\(^{19,20,25,26}\) treatment of PFO. The presence of a postprocedural shunt was a predictor of recurrent thromboembolic events. This not only emphasizes the importance of achieving complete PFO closure but also suggests that PFO is indeed the mediator of paradoxical embolism in this patient population.

The limitation of recurrent events to the first 2 years after percutaneous PFO closure is of note. On one hand, the recurrence rate appears to be rather high during the first year after the procedure. This may be due to device-related problems, but it also is in keeping with recent observations from other stroke series, ie, the Oxfordshire Community Stroke Project\(^{23}\) and the Northern Manhattan Stroke Study,\(^{27}\) in which the risk for recurrence was highest during the first year after stroke. This raises the question of whether a more intensive antithrombotic regimen than 100 mg of aspirin should be recommended after percutaneous PFO closure. A limitation in the interpretation of the restriction of recurrence to the first 2 years after percutaneous PFO closure is that the mean follow-up period of our study was 1.6±1.4 years (median, 1.4 years). As detailed in Table 4, only 24 patients (31%) had a follow-up period of 3 years, 14 patients (18%) of 4 years, and 7 patients (9%) of 5 years. Therefore, recurrent events >2 years after device implantation cannot be excluded with longer durations of follow-up in a larger patient cohort.

The mean age of our patient population was 52±12 years, which is \(\approx 10\) years older than that of other series of PFO and paradoxical embolism.\(^{12,13}\) The association of PFO with cryptogenic stroke is less conclusively established in the elderly, with some studies confirming the association between PFO and cryptogenic stroke\(^{6,7,9,10}\) and others failing to show this link.\(^{8,28}\) Although it appears that other causes of stroke predominate in the elderly, the careful exclusion of known causes of stroke should minimize the inclusion of nonqualifying elderly patients. This is reflected in the observation of our study that older age (>55 years old) was not predictive of recurrent thromboembolic events.

**TABLE 5. Risk Ratios for Recurrence of Paradoxical Embolism**

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
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<tbody>
<tr>
<td>Male sex</td>
<td>0.9</td>
<td>0.2–3.8</td>
</tr>
<tr>
<td>Age &gt;55 years</td>
<td>1.3</td>
<td>0.3–5.4</td>
</tr>
<tr>
<td>Procedural complications</td>
<td>2.4</td>
<td>0.3–19.8</td>
</tr>
<tr>
<td>ASA</td>
<td>1.0</td>
<td>0.2–4.7</td>
</tr>
<tr>
<td>Postprocedural shunt</td>
<td>4.2</td>
<td>1.1–17.8</td>
</tr>
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</table>

**Figure 2.** Actuarial freedom from combined end point of recurrent TIs, CVA, and peripheral embolism stratified according to atrial septal anatomy (PFO only versus PFO and ASA). ▲ indicates patients with only PFO; ▼, patients with PFO and ASA.

**Figure 3.** Actuarial freedom from combined end point of recurrent TIs, CVA, or peripheral embolism stratified according to presence or absence of a residual shunt after percutaneous PFO closure. ▲ indicates patients without and ▼ patients with a postprocedural shunt.
lism after percutaneous PFO closure. Another finding of our study is that the coexistence of an ASA with PFO did not result in a higher recurrence rate of paradoxical embolism after percutaneous PFO closure. This is in contrast to the spontaneous course, in which the presence of an ASA in addition to PFO signifies a high-risk population. Cabanes et al.\textsuperscript{10} reported that the relative risk of suffering a cryptogenic stroke was 4 times higher in patients with PFO and 33 times higher in patients with both PFO and ASA than in control subjects. The results of our study suggest that the high-risk population of patients with both PFO and ASA might derive a particularly high benefit from percutaneous PFO closure. However, this conclusion is subject to inclusion of more patients with a longer duration of follow-up.

**Previous Studies of Percutaneous PFO Closure**

Bridges et al.\textsuperscript{21} reported their experience of percutaneous PFO closure with the clamshell device in 36 patients (mean age, 39 years). The implantation procedure was successful in all patients, and complete closure as assessed by echocardiography was achieved in 28 patients. During follow-up (mean, 8 months; range, 1 to 24 months), there were no recurrent CVAs or arterial embolisms, but 4 patients experienced transient focal deficits. One patient was retrospectively thought to be wrongly classified as having paradoxical embolism. The mean time to recurrence was 5.5 months.

Ende et al.\textsuperscript{29} summarized data on 10 patients (mean age, 40 years) undergoing percutaneous PFO closure with the buttoned device. Implantation was successful in 9 of 10 patients. Embolization of the counteroccluder into the left atrium was encountered in 1 patient, who subsequently underwent surgical closure. A residual shunt was noted in 4 patients at 1 month of follow-up, with subsequent closure by 6 to 12 months after the procedure. During a mean follow-up of 32 months in 9 patients, no recurrent neurological events were observed.

In a multicenter study\textsuperscript{10} using the atrial septal defect occlusion system (ASDOS) device for percutaneous PFO closure, only 1 of 46 patients (mean age, 44 years) with PFO and paradoxical embolism suffered a recurrent TIA 7 months after the procedure.

The early complication rate of the present study (8 patients, 10%) is high and asks for improvement. The underlying mechanisms for the complications encountered are (1) embolization of the device, (2) air embolism during device delivery, and (3) a learning curve in performing the procedure with different device designs. The buttoned device in particular poses a risk for embolization because of its potential for unbuttoning. Furthermore, anatomic variations such as a floppy atrial septum set the stage for device embolization. Air embolism during device delivery is a risk for intraprocedural stroke and myocardial infarction. It requires meticulous care for air evacuation at each step of the implantation procedure. Finally, as with any new technical method, there is a learning curve for each operator. However, the complication rate appears comparable to other studies. Specifically, Bridges et al.\textsuperscript{21} using the clamshell device, reported a reversible brachial plexus injury in 1 of 36 patients (2.8%); Ende et al.\textsuperscript{29} described embolization of the counteroccluder of the buttoned device into the left atrium requiring percutaneous removal in 1 of 10 patients (10%); and Sievert et al.\textsuperscript{30} using the ASDOS device for both PFO and atrial septal defect closure, acknowledged embolization of the device in 2 patients (1%), pericardial effusion in 6 patients (3%), thrombus formation in 9 patients (6%), and infection in 2 patients (2%).

**Other Treatment Modalities**

Other treatment modalities for patients with PFO and presumed paradoxical embolism include medical treatment with either antiplatelet or antithrombin drugs and surgical PFO closure.

Comess et al.\textsuperscript{24} described 33 patients with PFO and presumed paradoxical embolism who were followed up for 18 months and had a recurrent event rate of 16% per year (combined end point of TIA and CVA). In 132 patients <60 years old with PFO and cryptogenic stroke, Mas et al.\textsuperscript{12} retrospectively analyzed the risk of recurrence during a mean follow-up period of 23 months during treatment with either aspirin (250 to 500 mg/d) or oral anticoagulation (target INR, 2 to 3). The average annual rate of recurrence was 1.2% for CVAs and 3.4% for the combined end point of TIA and CVA. Patients with both PFO and ASA had an average annual rate of recurrent stroke of 4.4%. Similar recurrence rates on medical treatment were reported from the Lausanne Stroke Registry.\textsuperscript{13} Ninety-two patients with PFO and cryptogenic stroke were treated with aspirin (250 to 500 mg/d), whereas 37 patients were treated with oral anticoagulation (target INR, 2.0 to 3.0). Eight patients were switched to aspirin after 3 months of oral anticoagulation. The average annual recurrence rate was 1.9% for CVA and 3.8% for the combined end point of TIA and CVA during a follow-up period of 3 years, with no statistically significant difference between the 2 antithrombotic drug regimens. A multicenter study in the United States funded by the NIH is currently investigating the effect of medical treatment on stroke recurrence in such patients by randomly assigning patients to either aspirin or anticoagulant therapy.

Surgical closure of PFO in patients with paradoxical embolism has been reported by Homma et al.\textsuperscript{20} who followed up 28 patients (mean age, 41 years) with PFO and cryptogenic stroke after surgical PFO closure by open thoracotomy. One recurrent ischemic stroke and 3 recurrent TIAs were observed, amounting to an actuarial recurrence rate of 20% at 13 months. This is in contrast to a series of 59 patients with a mean age of 42 years undergoing surgical closure by either open thoracotomy (n=44) or minimally invasive thoracotomy (n=15) reported by Ruchat et al.\textsuperscript{26} Except for 1 perioperative TIA, no further recurrent thromboembolic events were observed during a mean follow-up of 36 months.

**Limitations**

The following limitations apply to our study. (1) The patient population is a selected cohort referred to our center for percutaneous PFO closure and may differ from other published series. (2) The diagnosis of paradoxical embolism rests on presumptive assumptions. Most probably, PFO is not the sole mediator of thromboembolic events in patients selected according to the criteria used, and an alternative cause may become
apparent only during follow-up. (3) A weakness of this study is
the use of 5 different devices. Although our study did not find an
obvious difference in clinical outcome relative to the device
type, this is probably due to insufficient case numbers in each
device group. There are important differences between the
devices used that may be clinically relevant. For example, the
incidence of postprocedural shunt, which correlates with recur-
rence of thromboembolic events, was higher in patients with the
buttoned device. (4) The PFO comes in many, as yet underes-
timated, anatomic phenotypes, ranging from small pinhole
openings over large tunnel-shaped structures to small atrial
septal defects with aneurysms and different degrees of redundant
intratiaíre tissue. This study does not address which device best
fits different anatomic subsets.

Conclusions
Percutaneous PFO closure appears to be a promising new
technique in the prevention of recurrent systemic thromboem-
bolism in patients with a PFO after a first event. Prospective
studies comparing percutaneous PFO closure with antithrom-
botic medications or surgery must define its therapeutic value.

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