Is closure recommended for patent foramen ovale and cryptogenic stroke?

**Patent Foramen Ovale and Cryptogenic Stroke: To Close or Not to Close?**

**Closure: What Else!**

Stephan Windecker, MD; Bernhard Meier, MD

A 39-year-old mother of 2 teenage boys complained of severe migraine with aura for >10 years. Otherwise healthy, she suffered an ischemic stroke that rendered her permanently aphasic. Diagnostic evaluation revealed no evidence of atherosclerosis of the carotid arteries or plaques of the ascending aorta and the aortic arch. The ECG showed normal sinus rhythm, and the patient denied any history of palpitations or arrhythmias. Echocardiography documented normal ventricular function without wall motion abnormalities or evidence of thrombus and normal-appearing valves but a large patent foramen ovale (PFO). The most likely clinical diagnosis is stroke due to paradoxical embolism. The patient’s neurologist recommended PFO closure. However, guidelines regarding PFO closure from professional societies remain ambiguous because of insufficient evidence regarding therapeutic measures (Table 1).1,2

**Response by Messé and Kasner p 1998**

Stroke is the third leading cause of mortality and the most important cause of serious, long-term disability in developed countries.3 The presented case is testimony to the sad sequelae of stroke that may deprive someone permanently of speech, an emotional and mental tragedy. A classic etiology is not found in up to 40% of ischemic strokes despite an extensive diagnostic evaluation. This is referred to as cryptogenic stroke, a term that strangely ignores the role of the PFO.4 The foramen ovale is an opening in the atrial septum secundum, with the septum primum functioning as a 1-way valve allowing right-to-left shunt during in utero development. The postnatal decrease in right atrial pressure results first in functional followed by anatomic closure in the ensuing months. Autopsy studies show that fusion of the 2 septae fails to occur in ≈1 of 4 people.5 This is referred to as PFO and represents the most common congenital abnormality.6 Paradoxical embolism via a PFO has been documented as a stroke mechanism,7–10 and therapeutic measures aimed at secondary prevention intend to eliminate thrombus formation or its embolization.11–14 In the United States, nearly 800 000 strokes occur yearly, of which 10% to 40% are presumed to be cryptogenic (according to the old definition that does not take into account the PFO). Of these, 50% of patients have a PFO.3 Accordingly, 40 000 to 160 000 of strokes may be attributable to PFO per annum.

**Association by Chance or Cause-and-Effect Relationship**

Part of the controversy surrounding percutaneous PFO closure relates to the fact that paradoxical embolism is rarely a...
proven diagnosis but rather one of suspicion.13 The question of whether the presence of a PFO in the context of cryptogenic stroke represents an association by chance or a true cause-and-effect relationship remains. The problem of association versus causation arises frequently in biomedical research, and epidemiologists have developed a set of criteria that, when fulfilled, support a true cause-and-effect relationship (Table 2). They are discussed below.15,16

### Consistency and Strength of the Association

The association of PFO with cryptogenic stroke was independently reported by Lechat et al18 and Webster et al19 in 1988. Although some studies, such as a case-control study from Olmsted County conducted during 1993–1997, were unable to reproduce these results,17 other reports, such as the prospective PFO in Cryptogenic Stroke Study (PICSS)18 as well as a systematic review of available case-control studies, strongly support the association between PFO and the risk of cryptogenic stroke.19 The latter established an association between PFO alone (odds ratio [OR], 5.0; 95% CI, 2.4 to 10.4) and PFO with atrial septal aneurysm (OR, 23.3; 95% CI, 5.2 to 103.2) in young adults (aged <55 years) with cryptogenic stroke compared with controls without stroke. More recently, this observation was extended to older adults (aged ≥55 years) with a significantly higher prevalence of PFO alone (28.3% versus 11.9%; OR, 2.9; 95% CI, 1.7 to 5.0; *P*<0.001) as well as PFO associated with atrial septal aneurysm (15.2% versus 4.4%; OR, 3.9; 95% CI, 1.8 to 8.5; *P*<0.001) among patients with cryptogenic stroke compared with those with known stroke cause.10 Multivariate analysis adjusted for age, plaque thickness, presence of coronary artery disease, and hypertension identified PFO as an independent risk factor of cryptogenic stroke in both younger and older patients (Figure 1). Although competing sources of stroke become more prevalent with increasing age, the risk of paradoxical embolism may also increase because of a higher predisposition to venous thromboembolism.

### Biological Plausibility and Temporal Sequence of Events

PFO being the mediator of cryptogenic stroke is biologically plausible because numerous case reports have provided evidence of thrombus trapped within the PFO (Figure 2), supporting paradoxical embolism as a pathophysiological mechanism.7,20–23 Data from the Stroke Prevention Assessment of Risk in a Community study established an interatrial shunt via PFO as the only source of embolism in the majority of patients with atrial septal aneurysm,24 suggesting paradoxical embolism as the principal mechanism of atrial septal aneurysm–related embolic events, whereas atrial septal aneurysm without PFO (absence of a right-to-left shunt) was shown to portend no particular risk for recurrent cerebrovascular events.25 More recently, the term *economy class stroke syndrome* was coined after the observation of ischemic stroke in patients with PFO in the absence of alternative stroke causes shortly after long-distance airplane flights.26 Further evidence in support of PFO-mediated paradoxical embolism comes from an observational study of 139 patients suffering from major pulmonary embolism, whose clinical outcome was stratified according to presence or absence of PFO.27 Patients with PFO were more likely to die (44% versus 13%; *P*=0.02) and to suffer from stroke (13% versus 2%; *P*=0.02) or peripheral embolism (15% versus 0%; *P*=0.01), and PFO emerged as an independent predictor of mortality. The higher frequency of pelvic vein thrombosis in stroke patients with PFO (20%) than in those with known stroke cause (4%) within 2 days of the onset of symptoms is also suggestive of

### Table 1. Guidelines From Professional Societies1,2

<table>
<thead>
<tr>
<th>American Academy of Neurology</th>
<th>American College of Chest Physicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFO</td>
<td>Insufficient evidence to determine the superiority of aspirin or warfarin for prevention of recurrent stroke or death (level I), but risks of minor bleeding are possibly greater with warfarin (level C); there is insufficient evidence regarding the effectiveness of surgical or percutaneous PFO closure (level II)</td>
</tr>
<tr>
<td>PFO alone</td>
<td>...</td>
</tr>
<tr>
<td>PFO and ASA</td>
<td>...</td>
</tr>
<tr>
<td>PFO with DVT or PE</td>
<td>At least 3 months of anticoagulation recommended</td>
</tr>
</tbody>
</table>

ASA indicates atrial septal aneurysm; DVT, deep vein thrombosis; and PE, pulmonary embolism. Data derived from Albers et al and Messé et al.2

### Table 2. Criteria in Favor of a Cause-and-Effect Relationship

Consistency of association: has the association been repeatedly observed by different investigators?

Strength of association: how strong is the effect (relative risk)?

Biological plausibility: does the association make sense, and can it be explained pathophysiologically?

Temporality: does exposure precede adverse outcome?

Biological gradient: does a dose-response relationship exist?

The demonstration of a strong and consistent association, evidence of biological plausibility, a notable risk of recurrent events, and detection of a biological gradient, ie, a dose-response relationship suggest causation rather than association by chance alone. Modified from Grimes and Scholz18 with permission from Elsevier. Copyright 2004.

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References:

thrombi crossing the PFO to cause paradoxical embolism. These studies not only suggest paradoxical embolism as biologically plausible disease mechanism but also lend support to the temporal sequence of events with the trigger preceding the disease manifestation. Further evidence in favor of the biological plausibility of paradoxical embolism comes from an observational study of 202 patients with transvenous pacing leads, in whom the presence of intracardiac shunts was associated with a 2-fold increased risk of systemic embolism during follow-up. Similarly, for patients with deep venous thrombosis or pulmonary embolism, the relative risks of stroke during the first year after the thrombotic event were increased 2.2-fold and 2.9-fold compared with controls in a population-based study, suggesting the possibility of paradoxical embolism in selected patients.

**Biological Gradient**

There is good evidence that the size of a PFO correlates with the risk of cryptogenic stroke. The mean size of a PFO has been found to be larger in patients with cryptogenic stroke than in controls without stroke. Similarly, the size of PFO as assessed by the amount of microbubbles crossing with the Valsalva maneuver has been found to be larger in patients with cryptogenic stroke than in controls without stroke. Moreover, the presence of a right-to-left shunt at rest has been reported to be more prevalent in patients with cryptogenic stroke than in controls. Finally, some studies have shown an increased risk of recurrence in patients with a residual shunt after percutaneous PFO closure compared with patients in whom complete PFO closure was achieved.

The most striking evidence for a biological gradient comes from the consistent observation of an increased stroke risk in patients with PFO and associated atrial septal aneurysm compared with those with PFO alone. The French PFO/atrial septal aneurysm study showed a risk of recurrent stroke or transient ischemic attack (TIA) at 4 years of 0% in patients with atrial septal aneurysm without PFO, 5.6% in patients with PFO alone, and 19.2% in patients with both PFO and atrial septal aneurysm (Figure 3). It has been noted that the extent of the interatrial septal deviation correlates with the anatomic size of a PFO. Not the atrial septal aneurysm per se but the size of the associated PFO appears responsible for the increased predisposition to paradoxical embolism in patients with PFO and associated atrial septal aneurysm. Accordingly, a risk continuum that increases progressively with PFO size is more plausible than a dichotomous classification with PFOs representing a low risk and PFOs associated with atrial septal aneurysm representing a high risk of stroke (Figure 3).

The evidence reviewed above provides support of a consistent and strong association between PFO and cryptogenic support, its biological plausibility, and the presence of a biological gradient. In the aggregate, these data have established PFO as independent risk factor for cryptogenic stroke similar to other established risk factors such as hypertension, diabetes, and hypercholesterolemia. Paradoxical embolism is the pathophysiological mediator. The likely cause-and-effect relationship between PFO and the risk of stroke strongly supports the hypothesis that percutaneous PFO closure addresses the very cause of paradoxical embolism.
The risk of recurrence in patients with PFO and cryptogenic stroke determines the therapeutic value of interventions (medical treatment or PFO closure) aimed at secondary prevention. Observational studies in this patient population undergoing medical treatment with either antiplatelet therapy or oral anticoagulation reported a risk of recurrent stroke or TIA ranging from 3.4% to 12% during the first year.\(^\text{12,18,34-44}\) Homma and Sacco\(^\text{38}\) recently summarized the results of 9 studies of medical treatment in 943 cryptogenic stroke patients and observed an annual risk of recurrent stroke or TIA of 4.9% (95% CI, 3.8% to 5.0%) and of recurrent stroke or death of 5.9%). Of note, in trials with both antiplatelet therapy and anticoagulation, the risk of recurrence appeared lower with the latter. Because the risk of stroke in the normal population is estimated to be \(\approx 1\)% per year, and PFO is an independent risk factor for stroke in the absence of alternative causes,\(^\text{39,40}\) a therapeutic intervention to lower this risk further appears justified particularly because the best alternative prevention, permanent oral anticoagulation, is not only cumbersome but carries a substantial risk for bleeding.

Mas and coworkers\(^\text{25}\) reported on the clinical outcome of 581 patients with cryptogenic stroke stratified according to the presence or absence of various atrial septal abnormalities, who were treated with acetylsalicylic acid 300 mg per day. The risk of recurrent stroke or TIA at 4 years was 6.2% in patients without atrial septal abnormality, 5.6% in patients with PFO alone, and 19.2% in patients with both PFO and atrial septal aneurysm. The authors concluded that patients with a PFO alone were at low risk for recurrence comparable to those without atrial septal abnormality, but patients with both PFO and atrial septal aneurysm were insufficiently protected by antiplatelet therapy alone, requiring other preventive strategies, ie, percutaneous PFO closure. Of note, patients without atrial septal abnormalities had significantly more competing stroke risk factors, such as arterial hypertension, smoking, or hypercholesterolemia, than patients with PFO, possibly camouflaging the PFO inherent risk. Finally, in light of the low rate of recurrence in patients with PFO alone, it cannot be excluded that percutaneous PFO closure would be able to further reduce events in these patients.

In the prospective PICSS,\(^\text{18}\) a substudy of the Warfarin-Aspirin Recurrent Stroke Study (WARSS),\(^\text{45}\) 630 patients were solicited to undergo transesophageal echocardiography for detection of PFO. During follow-up to 2 years, the presence of PFO was not found to adversely affect the rate of recurrent stroke or death (14.8% versus 15.4%; hazard ratio=0.84; 95% CI, 0.62 to 1.48). However, only 42% of patients included in this study had suffered a cryptogenic stroke as opposed to stroke of known etiology. Therefore, it comes as no surprise that PFO was only an “innocent bystander” in the majority of patients. Along this line, patients included into PICSS differed from typical cryptogenic stroke patients, as evidenced by older age, a higher proportion of arterial hypertension, and diabetes (Table 3).\(^\text{18,25,46}\) Moreover, clinical outcome was worse in the PICSS population, with a rate of recurrent stroke and TIA of 20.4% at 2 years compared with an event rate of only 1.8% in patients with PFO alone and of 4.0% in patients with PFO and associated atrial septal aneurysm in the French PFO/atrial septal aneurysm study.\(^\text{25}\) The higher event rate is likely related to the higher burden of atherosclerosis in the PICSS population. Finally, rates of recurrent stroke or death at 2 years were 9.5% and 17.9% for cryptogenic stroke patients with PFO receiving warfarin or acetylsalicylic acid, respectively (relative risk=0.52; 95% CI, 0.16 to 1.67; \(P=0.3\)). Although not statistically 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-treated or acetylsalicylic acid–treated patients, respectively, in the entire PICSS cohort. Given the small patient population and the low level of anticoagulation achieved with warfarin (mean

### Table 3. Differences in Clinical Characteristics Between Various Studies of Medical Treatment in Patients With PFO and Stroke

<table>
<thead>
<tr>
<th>Patients</th>
<th>Wahl et al(^\text{46})</th>
<th>Mas et al(^\text{25})</th>
<th>PICSS(^\text{18})</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>825</td>
<td>581</td>
<td>630</td>
</tr>
<tr>
<td>Age, y</td>
<td>50±13</td>
<td>40±11</td>
<td>59±12</td>
</tr>
<tr>
<td>Male gender</td>
<td>58%</td>
<td>53%</td>
<td>55%</td>
</tr>
<tr>
<td>Associated atrial septal aneurysm</td>
<td>29%</td>
<td>18%</td>
<td>21%</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>32%</td>
<td>9%</td>
<td>60%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5%</td>
<td>3%</td>
<td>28%</td>
</tr>
<tr>
<td>Smoking history</td>
<td>31%</td>
<td>44%</td>
<td>29%</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>...</td>
<td>2%</td>
<td>15%</td>
</tr>
<tr>
<td>Obesity</td>
<td>...</td>
<td>19%</td>
<td>49%</td>
</tr>
</tbody>
</table>
international normalized ratio=2.0), therapeutic superiority of oral anticoagulation over acetylsalicylic acid cannot be excluded.

On the basis of these 2 studies, the American Academy of Neurology concluded that there is no difference in the risk of recurrence after cryptogenic stroke between patients with and without PFO. However, this conclusion is premature and potentially inaccurate because the risk of recurrence was compared with patients with cryptogenic stroke without PFO and not with the general population. Accordingly, it cannot be excluded that patients with cryptogenic stroke without PFO have an as yet unidentified increased risk of recurrence independent of the PFO.

**Benefit-Risk Considerations of Secondary Preventive Measures**

Secondary prevention of paradoxical embolism by either medical treatment or percutaneous PFO closure has to be weighed in the context of the respective risks and benefits in any individual patient. Although medical treatment lacks the risk of an interventional procedure, it is associated with adverse effects, most notably an increased risk of bleeding. Thus, major bleeding amounted to 1.5 to 2.2 per 100 patient-years in the prospective PICSS and WARSS trials with no significant differences between acetylsalicylic acid and oral anticoagulation. Although a low-frequency event, major bleeding has been shown to portend a poor prognosis and oral anticoagulation because of the frequent need for international normalized ratio monitoring, interference with dietary intake, and fear of bleeding. Finally, medical treatment may be contraindicated under certain circumstances such as pregnancy, which is encountered at times in this predominantly young patient population.

In contrast, medical treatment is no longer necessary in patients undergoing percutaneous PFO closure as soon as complete occlusion has been ascertained and the substrate for paradoxical embolism eliminated. However, percutaneous PFO closure imposes a risk of periprocedural complications. A recent summary of 11 studies with 1970 patients treated with percutaneous PFO closure revealed TIsAs in 0.2%, tamponade in 0.3%, device embolization in 1.1%, and puncture site problems in 1.5% of cases. Of note, there were no instances of death, myocardial infarction, stroke, or any other adverse event with long-lasting sequelae. A systematic review of percutaneous PFO closure reported minor complications in 7.9% of cases, including minor bleeding, atrial arrhythmias, transient atrioventricular node block, device arm fractures, device embolization with successful catheter retrieval, asymptomatic device thrombosis, symptomatic air embolism, and vascular access site problems, as well as major complications in 1.5% of cases, including cardiac tamponade, need of surgical intervention, pulmonary embolism, or blood transfusions. Death was reported only in a single case.

Thrombus formation on the device surface is of concern after percutaneous PFO and atrial septal defect closure because it may be associated with thromboembolic complications and may necessitate device removal. However, the risk appears to depend on the antithrombotic regimen and to be lower with dual antiplatelet therapy than oral anticoagulation. Moreover, thrombus formation has been reported to be device specific and is exceedingly low (<0.5%) in newer-generation devices. Although free wall device erosion resulting in cardiac tamponade has been described as a rare complication (0.1%), this observation pertains largely to patients with atrial septal defects and large device diameters rather than patients with PFO. New-onset atrial fibrillation has been reported in 7% to 15% of patients undergoing percutaneous PFO closure. Most episodes of atrial fibrillation are transient and occur during the first 4 weeks after device implantation, and usually sinus rhythm is restored spontaneously or after pharmacological or electric cardioversion. Comparing the incidence of atrial fibrillation between patients undergoing percutaneous PFO closure and patients with stroke of other etiology, another study found no difference between the groups (15% versus 17%; P=NS) and concluded that the presence of an occluder device is not an independent predictor of this arrhythmia. Aortic regurgitation after percutaneous PFO closure has been reported in a single study. It was mild in 90% of cases. The neighborhood of the atrial septum to the aortic root with the potential to distort the local anatomy of the valve as well as tissue overgrowth has been put forward as a potential explanation of this phenomenon.

**Comparison of Medical Treatment With Percutaneous PFO Closure**

Studies assessing medical treatment and percutaneous PFO closure encompass observational single-arm studies, comparative registries, and a systematic review of case series, whereas none of the prospective, randomized clinical trials has completed enrollment to date. Wöhrl recently summarized clinical outcome as reported in 8 studies comprising 998 patients treated...
medically and 12 studies with 2016 patients who underwent percutaneous PFO closure. The annual rate of stroke or TIA was lower after percutaneous PFO closure (1.3%; 95% CI, 1.0% to 1.8%) compared with medically treated patients (5.2%; 95% CI, 4.4% to 6.2%) and comparable to event rates of patients without PFO.

Our group compared clinical outcome of 308 patients with cryptogenic stroke and PFO, who were either treated medically (158 patients) or underwent percutaneous PFO closure (150 patients). Patients undergoing percutaneous PFO closure had a larger right-to-left shunt and were more likely to have suffered >1 cerebrovascular event, whereas there were no differences regarding age or other, major cardiovascular risk factors. Four-year event rates of death, stroke, or TIA (8.5% versus 24.3%; P=0.05; 95% CI, 0.23% to 1.01%) and of recurrent stroke or TIA (7.8% versus 22.2%; P=0.08; 95% CI, 0.23% to 1.11%) showed a strong although nonsignificant trend in favor of percutaneous PFO closure (Figure 4A). Of note, the difference became significant when percutaneous PFO closure was compared with antiplatelet therapy alone (8.5% versus 28.3%; P=0.03). In addition, patients with complete occlusion of PFO (Figure 5A) and those with >1 cerebrovascular event at baseline (Figure 5B) were at lower risk for recurrent stroke or TIA after percutaneous PFO closure compared with medically treated patients (7.3% versus 33.2%; P=0.01; 95% CI, 0.08% to 0.81%; and 6.5% versus 22.2%; P=0.04; 95% CI, 0.14% to 0.99%, respectively). The higher efficacy in patients suffering from recurrent cerebrovascular events suggests a high-risk group characterized by inadequate protection with medical treatment alone and potentially a higher prevalence of paradoxical embolism because of the selection process of repetitive events. The achievement of complete PFO closure appears of particular importance in light of the aforementioned findings, a goal that can be reached in >95% of patients with newer-generation devices. Schuchlenz et al reported clinical outcome of 280 consecutive patients treated with either antiplatelet therapy (n=66), oral anticoagulation (n=47), or percutaneous PFO closure (n=167) (Figure 4B). There were no significant differences regarding age or cardiovascular risk factors, although patients undergoing PFO closure had a larger PFO at baseline. A total of 33 patients (12%) suffered a recurrent cerebrovascular event during a mean follow-up of 2.6 years, and the annual rate of recurrent TIA or stroke was lowest after percutaneous PFO closure (0.6%) compared with both oral anticoagulation (5.6%; hazard ratio=0.06; 95% CI, 0.12 to 0.29; P<0.001) and antiplatelet therapy (13%).

Percutaneous PFO closure may be a particularly valuable treatment option in patients with PFO and associated atrial septal aneurysm. One study compared clinical outcome after device closure between patients with both PFO and atrial septal aneurysm (n=141) and those with PFO alone.
Table 4. Status of Randomized Clinical Trials Comparing Medical Treatment With Percutaneous PFO Closure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Device</th>
<th>End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC (NCT 00166257)</td>
<td>400/410</td>
<td>Amplatzer</td>
<td>Death, CVA, PE</td>
</tr>
<tr>
<td>RESPECT PFO</td>
<td>NA/500</td>
<td>Amplatzer</td>
<td>Death, CVA</td>
</tr>
<tr>
<td>CLOSURE 1</td>
<td>725/1600 (900*)</td>
<td>Starflex</td>
<td>Death/neurological death</td>
</tr>
<tr>
<td>CARDIA STAR</td>
<td>NA/500</td>
<td>Cardia</td>
<td>NA/500</td>
</tr>
</tbody>
</table>

RESPECT indicates Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; NA, not applicable; CVA, cerebrovascular accident; PE, pulmonary embolism; CLOSURE 1, Evaluation of the STARRflex Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale (PFO); and CARDIA STAR, A United States Randomized Clinical Trial of the CARDIA STAR Patent Foramen Ovale Closure System.

*Recent revision of protocol.

Device implantation success and the rate of residual shunt as assessed by transesophageal echocardiography 6 months after the procedure were similar for both groups. At 4 years of follow-up, the rate of recurrent stroke, TIA, or peripheral embolism amounted to 5.1% and 6.0% in groups. At 4 years of follow-up, the rate of recurrent stroke, TIA, or peripheral embolism amounted to 5.1% and 6.0% in patients with and without associated PFO (hazard ratio = 0.4; 95% CI, 0.3 to 2.3; P = 0.70). Accordingly, device closure in patients with both PFO and atrial septal aneurysm lowered the rate of recurrence to those of patients with PFO alone (5.0% versus 6.1% at 4 years; P = 0.70), which was considerably lower than the 19.2% rate at 4 years reported in the French PFO/atrial septal aneurysm study.

A systematic review of case series compared clinical outcome of 10 studies with 1355 patients who underwent percutaneous PFO closure and 6 studies comprising 895 patients treated medically. The annualized rates of stroke (0.4% versus 3.1%; OR = 0.14; 95% CI, 0.06 to 0.4; P < 0.001), TIA (1.4% versus 2.6%; OR = 0.56; 95% CI, 0.3 to 1.1; P < 0.07), and stroke or TIA combined (1.9% versus 5.8%; OR = 0.33; 95% CI, 0.2 to 0.5; P < 0.001) were significantly lower after percutaneous PFO closure compared with medical treatment.

The results of the aforementioned studies have to be interpreted in light of limitations intrinsic to registry comparisons such as lack of randomization and therefore selection bias, confounding by unmeasured characteristics, lack of data monitoring and independent event adjudication, and differences in definitions, outcome measures, and their assessment. Moreover, the inclusion of TIA in the assessment of clinical outcome in the aforementioned studies may have inflated event rates and therefore differences between both treatment options. The diagnosis of TIA is less specific than that of stroke because of the lack of objective imaging and serum markers and may be clouded by patients with migraine rather than TIA. However, short of the results of randomized clinical trials, the aforementioned studies represent the best available evidence to date and show a consistent pattern in favor of percutaneous PFO closure. Unfortunately, investigator- and industry-initiated prospective randomized controlled trials comparing percutaneous PFO closure with medical treatment have been hampered by slow enrollment (Table 4), which may be the source of selection bias. Because most high-risk patients are currently treated by percutaneous PFO closure outside of randomized clinical trials because of either patient or physician preference, trial results may largely depend on low-risk patients diminishing a potential difference in clinical events between the therapeutic options.

Conclusions

Available evidence and common sense strongly favor causation rather than association between PFO and the risk of stroke, with paradoxical embolism being the pathophysiological mediator. Therefore, PFO has been accepted as an independent risk factor for stroke in the absence of other causes, which applies to young but also older patient groups with a significantly higher prevalence of venous thrombosis. The restriction to otherwise cryptogenic strokes is a historical oxymoron and should be dropped. Percutaneous PFO closure represents a valuable treatment option, particularly in high-risk patients, because it addresses the very cause of paradoxical embolism by elimination of the right-to-left shunt conduit, thus avoiding long-term medical therapy. Data from observational studies, registry comparisons, and systematic reviews of case series consistently show lower event rates after percutaneous PFO closure than medical treatment. Moreover, antiplatelet therapy with acetylsalicylic acid has been found to be insufficient in patients with large PFOs and/or associated atrial septal aneurysm, requiring alternative therapeutic strategies, among them percutaneous PFO closure. Device closure is invasive, leaving an implant behind. However, the procedure can be accomplished in a few minutes, with minimal suffering or risk and no postinterventional restrictions of any kind. Available evidence at this time therefore favors percutaneous PFO closure, and it appears likely that the latter at least will not be inferior to medical treatment. The findings of these observational studies require confirmation in ongoing, prospective randomized clinical trials before this therapy can be approved by regulatory agencies and finds its justification in guidelines of professional societies.

Disclosures

Dr Windecker reports having received lecture and consultant fees from AGA Medical (Minneapolis, Minn) and St Jude Medical (Minneapolis, Minn). Dr Meier reports having received lecture and consultant fees from AGA Medical (Minneapolis, Minn) and St Jude Medical (Minneapolis, Minn) and research support from AGA Medical for the randomized Patent Foramen and Cryptogenic Embolism trial.

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Response to Windecker and Meier

Steven R. Messé, MD; Scott E. Kasner, MD

Windecker and Meier argue that the association between patent foramen ovale (PFO) and stroke is strong and therefore closing the PFO is the logical solution. Although we strongly agree that percutaneous PFO closure needs to be tested for secondary stroke prevention, we are concerned that this is another hypothesis that could very well be destroyed by ugly facts. Logical assumptions and best intentions do not amount to safety and efficacy. Numerous seemingly reasonable interventions, including hormone replacement therapy, bypass procedures for carotid occlusion, and, most recently, coronary angioplasty for stable coronary artery disease, all had biological plausibility and had varying degrees of low-level evidence to support them, until definitive randomized studies proved that they were ineffective and/or harmful. PFO closure could easily go the same way. Moreover, recommending invasive procedures to patients without firm evidence results in a major credibility gap with the public if that practice is eventually discredited. Off-label closure of PFO has greatly limited enrollment of patients in ongoing randomized controlled trials and could undermine their generalizability if subjects at high risk are systematically excluded. Furthermore, the data supporting risk factors (ie, atrial septal aneurysm or large PFO) are inconsistent across the existing studies and are weak at best. High-level evidence for PFO management is desperately needed, so that clinicians can choose the optimal management strategy for their patients. Off-label and off-protocol closure needs to stop. Clinicians and payors must demand scientific integrity. Windecker and Meier also believe that antithrombotic medications are not required after successful PFO closure. Stopping antithrombotic medication assumes that right-to-left shunting is the only possible mechanism for the stroke, despite the fact that PFO is found in ≈25% of the healthy population and could be an “innocent bystander” in many cases. Notably, Windecker and Meier were coauthors on the article describing that 15% of patients who underwent PFO closure had atrial fibrillation detected 3 to 6 months afterward. Given the potential for alternative causes of stroke and the high incidence of atrial fibrillation, PFO closure patients warrant antiplatelet medication at a minimum. Current guidelines recommend antithrombotic therapy for all, and withholding standard effective secondary prevention therapy after stroke seems to defy logic and best intentions. PFO closure plus medical therapy needs to be proven superior to medical therapy alone before this invasive approach can be justified as appropriate clinical care.
Stephan Windecker and Bernhard Meier

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