Patent Foramen Ovale and Stroke

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This review summarizes the current state of knowledge about the relationship of patent foramen ovale (PFO) with ischemic stroke. Initial sections discuss the studies that identified this association. Subsequent sections discuss the detection techniques for PFO and other variables that may cause a PFO to be a conduit of paradoxical embolization. Finally, a section is devoted to summarizing the studies that assessed the strategies for preventing recurrent ischemic events in patients with PFO.

Cryptogenic Stroke and PFO

In ~40% of patients with acute ischemic stroke, the cause remains undefined. PFO is a hemodynamically insignificant interatrial communication present in >25% of the adult population. During fetal life, because the lungs do not receive blood flow, blood returning to the right atrium is shunted through a PFO to the left atrium. Postnatally, PFO closes spontaneously in ~75% of the population. However, in a portion of adults, by maintaining a direct communication between the right- and left-sided circulation, PFO can serve as a conduit for paradoxical embolization.

In 1877, Cohnheim described the association of PFO with stroke in a young woman with cerebral arterial embolism. However, it has been difficult to diagnose PFO in vivo until the development of echocardiography and its ability to image the interatrial shunting with an injection of saline contrast. With the use of contrast echocardiography, a strong association of cryptogenic stroke with PFO has become evident in patients <55 years of age (Table 1).

Because stroke occurs more frequently in older population, with only 3% of cerebral infarctions occurring in patients <40 years of age, the number of stroke patients with PFO ≥40 years of age is much larger than in the younger patients. Several studies reported the association of PFO with cryptogenic stroke in older patient populations. However, this has not been seen in other studies (Table 1). Therefore, although the association between cryptogenic stroke and PFO is established among the younger population, it is not clearly established in the older population. This also has been substantiated in a meta-analysis of studies relating to atrial abnormalities and stroke.

In support of PFO as a conduit for paradoxical embolization, there are occasional case reports demonstrating venous thrombi trapped in a PFO in patients with central or systemic embolization. Nevertheless, other possible mechanisms of stroke cannot be excluded. Given that a PFO can be a tunnel-like structure with possibly a stagnant area of flow, in situ thrombus formation may occur. Also, patients with PFO may be susceptible to atrial arrhythmias with possible intra-atrial thrombus formation, leading to stroke.

Detection of PFO

Contrast Echocardiography

Transthoracic (TT) echocardiography and transesophageal (TE) echocardiography with saline contrast injection are widely used to detect PFO. A PFO is judged to be present if any microbubble is seen in the left-sided cardiac chambers within 3 cardiac cycles from the maximum right atrial opacification. Figure 1 demonstrates the appearance of microbubbles in the left-sided cardiac chambers after the venous injection of contrast material in TT imaging. Injection is performed with and without the Valsalva maneuver. Coughing during injection may increase the sensitivity for detecting PFO over that achieved by the Valsalva maneuver. Use of harmonic imaging with TT echocardiography and contrast injection may also increase the sensitivity of PFO detection. Saline contrast injection can be performed while imaging the heart with a TE probe. Again, PFO is judged to be present with the visualization of microbubbles in the left atrium within 3 cardiac cycles from the right atrial opacification. Figure 2 demonstrates the passage of microbubbles from the right atrium into the left atrium through PFO as demonstrated by TE echocardiography.

Location of the contrast material injection can influence the chance of detecting a PFO. Contrast material injected into the lower extremities has a higher chance of crossing a PFO because the flow from the inferior vena cava is directed toward the fossa ovalis as it enters the right atrium. Doppler color-flow detection of a PFO is possible with TE; however, this technique may not be as sensitive as contrast injection.

Transcranial Doppler in PFO Detection

Paradoxical embolization through a PFO is considered to be a mechanism for stroke associated with a PFO. In support, direct demonstration of embolism through a PFO to the cerebral circulation has been demonstrated. Figure 3 demonstrates the baseline flow pattern obtained by transcranial Doppler (TCD) in the middle cerebral artery and that seen after saline contrast injection in a patient with a PFO. However, detection of microbubbles in the cerebral circula-
tion by TCD does not necessarily imply the presence of a PFO. Any right-to-left shunt such as that resulting from ventricular septal defect or intrapulmonary shunt may result in the detection of microbubbles in the cerebral circulation by TCD. As a result, TCD cannot identify the site of right-to-left shunt, whereas TT or TE studies provide this information.21,22 Several studies performed contrast TT, TE, and TCD imaging in the same patient group to compare the sensitivity of the techniques (Table 2).23–30 The TE contrast study is the most sensitive diagnostic test available for detecting a PFO, followed by TCD and TT contrast studies (P<0.001 for TE versus TT and for TCD versus TT contrast studies).

Quantification of Size and Shunt
There are several methods to quantify the size of a shunt. The number of microbubbles can be counted with TT echocardiography.4 The Doppler signal across the mitral valve can also be quantified.31 Similarly, the number of microbubbles can be counted with TE studies.32,33 With TCD, high-intensity transient signals also can be quantified.34,35 However, any of these methods will be variable because of differences in the amount of bubbles injected, speed with which they are injected, and variations in blood flow pattern in cardiac chambers.36–38 Alternatively, anatomic size of a PFO can be measured by TE echocardiography (Figure 2). Measurement from a vertical plane view in TE studies correlates well with that by the invasive balloon method,39 which in general relates to the amount of shunt.32 However, a PFO is inherently a 3D structure with dynamic opening and closing, as well as a channel-like structure in some patients that makes it difficult to describe the size in 1 dimension.
Factors Associated With Paradoxical Embolization

Atrial Anatomy

Size of a PFO

As shown in Table 3, the prevalence of a PFO in autopsy studies is \( \approx 26\% \). Given the high prevalence of PFO in the general population and the variability in PFO size, its size may be an important factor in determining the importance of an individual PFO to act as a conduit for paradoxical embolization. With contrast TT echocardiography, TE echocardiography, or TCD imaging, or during cardiac catheterization, patients with presumed paradoxical embolization appear to have larger PFOs compared with those in control groups. In the recent PFO in Cryptogenic Stroke Study (PICSS), it also has been shown that large PFOs were significantly more prevalent among cryptogenic stroke patients compared with those with known cause of stroke. Additionally, stroke patients with larger PFOs have brain imaging findings suggestive of an embolic mechanism, and PFO size may be an independent risk factor for recurrent cerebrovascular events.

Atrial Septal Aneurysm

Atrial septal aneurysm (ASA) is a redundancy of the interatrial septum detected most commonly by TT or TE studies. On TE study, it is typically defined as >10-mm protrusion beyond the plane of the septum into the left or right atrium. Although the definition varies somewhat in different series, the prevalence in the general population is estimated with TT imaging to be only 0.23% (Table 4). A considerably higher prevalence of 4.6% is noted among those referred for TE echocardiography, most likely because of the higher sensitivity of the TE technique for imaging the septal area and the selection bias for patients referred for TE echocardiography (Table 4).

The prevalence of ASA is greater among patients with embolic events. It is also well known that ASA is associated with PFO, with \( \approx 60\% \) of patients with ASA having a PFO (Table 4). Additionally, the PFOs seen in the presence of ASA tend to be large compared with those seen without associated ASA. Thus, the association of ASA with embolic events is likely based on the high prevalence of large PFOs. Because an ASA is usually highly mobile, protruding from right to left atrium, it is unlikely that a thrombus forms in the ASA itself. This is corroborated by a rare finding of thrombus associated with ASA in a large series of patients.

Eustachian Valve and Chiari’s Network

The eustachian valve is a membrane-like structure in the right atrium, a remnant of the right valve of the sinus venosus that directs blood flow from the inferior vena cava to the fossa ovalis area in the fetus. Among adults, a eustachian valve can cause a significant right-to-left shunt in the presence of an interatrial communication by altering the blood flow pattern. Prominent eustachian valve is also more commonly found among patients with presumed paradoxical embolism than in control patients. The presence of Chiari’s network and filamentous strands in the right atrium is also associated with the presence of PFO.

<table>
<thead>
<tr>
<th>TABLE 2. Comparison of Techniques for PFO Detection</th>
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<tbody>
<tr>
<td>Study</td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Teague and Sharma(^{23})</td>
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<tr>
<td>Di Tullio et al(^{24})</td>
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<tr>
<td>Jauss et al(^{25})</td>
</tr>
<tr>
<td>Kamik et al(^{26})</td>
</tr>
<tr>
<td>Job et al(^{27})</td>
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<tr>
<td>Klitzsch et al(^{28})</td>
</tr>
<tr>
<td>Nemec et al(^{29})</td>
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<tr>
<td>Di Tullio et al(^{30})</td>
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<tr>
<td>Total</td>
</tr>
</tbody>
</table>
atrial anatomic variants that can promote flow from the inferior vena cava toward the PFO may increase the chance of paradoxical embolization beyond that associated with PFO size.

**Hemodynamics**

In addition to the atrial anatomic variables, hemodynamic alterations play a major role in determining the chances of paradoxical embolization. Although transiently higher right atrial pressure can occur during normal cardiac cycle, cardiac lesions more consistently elevating right atrial pressure will increase the chance of right-to-left shunt. As a result, paradoxical embolization is often reported in patients with pulmonary embolism. Similarly, patients with right ventricular infarction or severe tricuspid regurgitation or those on a mechanical left ventricular assist device have an increased right-to-left shunt through a PFO. Although a right-sided pressure elevation can increase the flow across PFO, left-sided pressure elevation will decrease it.

**Venous Thrombus and Hypercoagulable State**

For paradoxical embolization to occur, a source of thrombus is needed. A significant stroke can result from an arterial occlusion by an embolus as small as 1 mm in diameter. A greater prevalence of deep venous thrombus is observed in one study in patients with cryptogenic stroke compared with a control group. However, several other studies do not corroborate this finding. More recently, pelvic vein thrombi are reported to be found more frequently in young patients with cryptogenic stroke compared with those with more defined causes of stroke. Pelvic veins and abdominal veins are not studied routinely in patients with cryptogenic stroke and PFO, and these areas may harbor thrombus. Finding of a venous thrombus strengthens the possible role of PFO as a conduit for paradoxical embolization and will affect treatment strategy. Patients with a tendency toward venous thrombus formation may be exposed to a higher chance of paradoxical embolization in the presence of PFO. Several studies report a higher frequency of prothrombotic states such as G20210A and factor V Leiden mutations in patients with cryptogenic stroke and PFO. A recent study demonstrates a higher recurrent event rate in older cryptogenic stroke patients with PFO compared with similarly aged cryptogenic stroke patients without PFO. This may be due in part to the presence of occult thrombi in older patients compared with the younger patients.

In summary, variation in PFO size, right atrial anatomy, hemodynamic conditions, and potential source of an available thrombus all play a part in influencing the chances of paradoxical embolization.

### Recurrent Stroke Prevention

Possible treatment modalities to prevent recurrent events among stroke patients with a PFO include medical treatment with warfarin or antiplatelet agents, percutaneous PFO closure, and surgical PFO closure. In this section, recurrent event rates from the available outcome studies are summarized. Recurrent event rates are estimated from published studies in MedLine since 1990. The number of subjects, mean age, and follow-up time are obtained for each publication. If there are duplications of patient population in studies, only one is included or, to the extent possible, correction in numbers is made. Inclusion criteria are (1) presumed paradoxical embolic events without obvious cause, including cryptogenic stroke, transient ischemic attack (TIA), or other embolic arterial events such as peripheral embolism; (2) documented PFO on echocardiography, either TT or TE; and (3) original manuscript available in English.

For the purpose of creating a summary table, all-cause mortality is included in the table. Thus, when discrepancies in the number exist in some of the cells compared with the published manuscript, it is due to the difference in the criteria used for end points. The number of events in each study was summed to obtain the total number of events. Similarly, the total time at risk was determined by summing the number of subjects multiplied by the mean follow-up time for each study. Event rates were calculated as the ratio of the total number of events to the total years of follow-up divided by 100 to yield event rates per 100 patient-years. The 95% CI for

### Table 4. Prevalence Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>ASA Patients</th>
<th>Prevalence, %</th>
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<tbody>
<tr>
<td>Prevalence of ASA by TT study</td>
<td></td>
<td></td>
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<tr>
<td>Hanley et al&lt;sup&gt;90&lt;/sup&gt;</td>
<td>80/36,200</td>
<td>0.22</td>
</tr>
<tr>
<td>Gallet et al&lt;sup&gt;90&lt;/sup&gt;</td>
<td>10/4840</td>
<td>0.21</td>
</tr>
<tr>
<td>Longhini et al&lt;sup&gt;91&lt;/sup&gt;</td>
<td>23/4000</td>
<td>0.57</td>
</tr>
<tr>
<td>Bewick and Montagu&lt;sup&gt;92&lt;/sup&gt;</td>
<td>6/4700</td>
<td>0.12</td>
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<tr>
<td>Wolf et al&lt;sup&gt;93&lt;/sup&gt;</td>
<td>12/724</td>
<td>1.7</td>
</tr>
<tr>
<td>Belkin et al&lt;sup&gt;94&lt;/sup&gt;</td>
<td>36/6979</td>
<td>0.5</td>
</tr>
<tr>
<td>Brand et al&lt;sup&gt;95&lt;/sup&gt;</td>
<td>35/3500</td>
<td>1.0</td>
</tr>
<tr>
<td>Roudant et al&lt;sup&gt;96&lt;/sup&gt;</td>
<td>44/62,540</td>
<td>0.08</td>
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<td>Katayama et al&lt;sup&gt;97&lt;/sup&gt;</td>
<td>26/2074</td>
<td>1.2</td>
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<tr>
<td>Oneglia et al&lt;sup&gt;98&lt;/sup&gt;</td>
<td>38/4031</td>
<td>0.94</td>
</tr>
<tr>
<td>Schneider et al&lt;sup&gt;99&lt;/sup&gt;</td>
<td>20/12,137</td>
<td>0.16</td>
</tr>
<tr>
<td>Total</td>
<td>330/141,725</td>
<td>0.23</td>
</tr>
</tbody>
</table>

| Prevalence of ASA by TE Study |
| Schneider et al<sup>99</sup> | 23/765 | 3.0 |
| Schreiner et al<sup>100</sup> | 7/340 | 2.1 |
| Zabalgoitia et al<sup>101</sup> | 20/199 | 10 |
| Pearson et al<sup>102</sup> | 32/410 | 7.8 |
| Mirode et al<sup>103</sup> | 32/751 | 4.2 |
| Total | 114/2465 | 4.6 |

| PFO prevalence among patients with ASA |
| Mügge et al<sup>104</sup> (TE echo) | 106/195 | 54 |
| Hanley et al<sup>105</sup> (TE echo) | 24/49 | 49 |
| Schneider et al<sup>106</sup> (TE echo) | 17/22 | 77 |
| Zabalgoitia-Reyes et al<sup>107</sup> (TE echo) | 17/20 | 85 |
| Pearson et al<sup>108</sup> (TE echo) | 20/29 | 69 |
| Silver et al<sup>109</sup> (autopsy) | 8/16 | 50 |
| Mattioli et al<sup>110</sup> (TE echo) | 39/44 | 89 |
| Burger et al<sup>111</sup> (TE echo) | 18/32 | 56 |
| Homma et al<sup>112</sup> (TE echo) | 44/69 | 64 |
| Total | 293/476 | 62 |
the pooled event rates was determined by assuming that observed events followed the Poisson distribution. For the studies of the effect of medical therapy on stroke recurrence or TIA, homogeneity of event rates was assessed using Cochran’s Q test after excluding the single study with 13 subjects and no events. A significant lack of homogeneity was not detected for either recurrent stroke (Q=4.35, $P=0.74$) or TIA (Q=6.89, $P=0.44$). Similar tests of homogeneity were not performed for percutaneous closure or surgery because of the small number of events. Tables are made that include number of patients in the study, mean age, and mean follow-up in months. In terms of the end points, stroke, any-cause death, TIA, stroke or death, stroke or TIA, and stroke death or TIA are included. A similar summary, but with somewhat different criteria, has been recently published.104

**Medical Therapy**

A total of 943 patients are considered in the analysis (Table 5).33,54,105–111 The mean age of the patients is 45 years; mean duration of follow-up is 33 months. Medications used include both warfarin and aspirin. There were 15 deaths (any cause), 14 strokes, and 82 TIA patients is 46 years; the mean duration of follow-up is 18 months. There is variable use of warfarin or antiplatelet agents after closure. There were 4 deaths, 4 strokes, and 32 TIA patients. The annual rate of stroke is 1.98% (95% CI, 1.48 to 2.60) and of stroke or death is 3.12% (95% CI, 2.32 to 4.11). Individual studies demonstrate variable recurrent event rates. This is due in part to the difference in the age of subjects; younger cryptogenic stroke patients with PFO have a significantly lower event rate compared with the older cryptogenic stroke patients with PFO.103 Only one study randomized patients to warfarin or aspirin therapy.54 In this study, there is no difference in event rates between those with and without PFO on medical therapy. When patients treated with warfarin are compared with those treated with aspirin, there is no significant difference, although the study is not adequately powered for this purpose.

Some studies identified the combination of ASA and PFO as a predisposing factor for increased recurrent event rates, whereas another has not.79,106,110 Major bleeding risk from medical therapy, particularly from the use of warfarin, is estimated at 1% to 2% annually and minor bleeding risk 10% to 20%, higher in those on warfarin compared with aspirin.112,113

**Percutaneous Closure of PFO**

Because PFO represents a repairable lesion, interest in closing them is high. Currently, the most commonly used devices in the United States are the Amplatzer PFO Occluder (AGA Medical) and CardioSEAL (NMT Medical) devices.114,115 The Amplatzer device is made of self-expanding nickel-titanium alloy wire mesh with double disks that contain inner polyester fabric patches. The CardioSEAL device is constructed from a low-profile nickel-cobalt alloy framework shaped like an umbrella to which a knitted polyester fabric is attached. Under the Humanitarian Device Exemption (HDE) program of the US Food and Drug Administration (FDA), these devices are approved for use in patients with recurrent cryptogenic stroke caused by presumed paradoxical embolism through a PFO who have failed therapeutic dosage of oral anticoagulants.

Using the same criteria as for Table 5, Table 6 shows the event rates in patients undergoing percutaneous PFO closure.53,116–126 Again, when overlap in patient population occurs, only one study appears in Table 6 or the numbers are adjusted. A total of 1430 patients are considered in the analysis. Of note, some of the studies include patients receiving a device other than an Amplatzer or a CardioSEAL, and many of studies are performed outside the United States where the devices can be clinically used. The mean age of the patients is 46 years; the mean duration of follow-up is 18 months. There is variable use of warfarin or antiplatelet agents after closure. There were 4 deaths, 4 strokes, and 32 TIA patients. The annual rate of stroke is 0.19% (95% CI, 0.05 to 0.49) and of stroke or death 1.15% (95% CI, 0.46 to 2.37).

Complications from device implantation include major complications such as death, major hemorrhage, cardiac tamponade, and fatal pulmonary emboli. These occur in $\approx1.5\%$ of the patients.104 Minor complications such as atrial arrhythmias, device arm fractures, device embolization, de-

**TABLE 5. Summary Table of Medical Therapy Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Age, y</th>
<th>Follow-Up, mo</th>
<th>Stroke, n</th>
<th>Death, n</th>
<th>TIA, n</th>
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<th>Stroke or TIA, n</th>
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<td>27</td>
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<tr>
<td>Mas and Züber106</td>
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<td>Cujec and Mainra108</td>
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<td>Nedeltchev et al111</td>
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<td>59</td>
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<td>Events per 100 patient-years</td>
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<td>...</td>
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<td>95% CI</td>
<td>...</td>
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<td>1.48–2.60</td>
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<td>1.71–2.89</td>
<td>2.32–4.11</td>
<td>3.43–5.01</td>
<td>3.78–5.94</td>
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</table>
vice thrombosis, ECG changes, and AV fistula formation are reported in 7.9%.\textsuperscript{104} Thrombus formation on the device may depend largely on the device used.\textsuperscript{127} PFO represents a potential space, bordered by 2 overlapping membranes, some with tunnel-like anatomy. “PFO-specific” devices may simplify closure in the future, and there are a variety of newer devices and methods conceptualized and tested to close a PFO. These include anatomically fitting devices, staplers, and tissue glues.

**Surgical Closure of PFO**

Table 7 shows the event rates in surgically treated patients with PFO.\textsuperscript{128–132} A total of 161 patients are considered in this analysis. The mean age of the patients is 43 years, and the mean duration of follow-up is 22 months. There were 2 deaths, 1 stroke, and 11 TIA. The annual rate of stroke is 0.34\% (95\% CI, 0.01 to 1.89) and of stroke or death is 0.85\% (95\% CI, 0.10 to 3.07). However, the number of patients in this analysis is small, and with the advent of percutaneous closure devices, the surgical approach is no longer widely used. Even with the use of a minimally invasive approach,\textsuperscript{133} it is very likely that the surgical approach will be replaced by percutaneous approaches.

**Comparison of Modalities and Current Trials**

Although Tables 5 through 7 demonstrate summary outcome measures for the different treatment approaches, there are no direct randomized comparisons of treatment modalities. In a collective analysis, there are no convincing data to indicate that the presence of PFO increases recurrent events in medically treated patients.\textsuperscript{134} Whether PFO closure decreases the event rate further remains unanswered. Some analyses suggest possible superiority of percutaneous closure compared with medical therapy.\textsuperscript{135}

Using our tables, we compared medical therapy with percutaneous closure, with stroke or stroke and TIA as end points. For both comparisons, percutaneous closure gives lower event rates compared with medical therapy.
Because PFO is commonly found in normal populations, we need to identify a subset of cryptogenic stroke patients who are likely to have experienced paradoxical embolization. Various factors need be considered such as atrial anatomic variation (PFO size, ASA, eustachian valve anatomy), hemodynamic parameters, presence of venous thrombus identified through higher-sensitivity tests such as lower extremity/abdominal/pelvic MRI, and the presence of hypercoagulable genetic variables. The presence of any of these findings increases the chance of PFO contributing to stroke. As such, tests to define these parameters are necessary. Currently, the superiority of one method over another for recurrent event prevention remains undefined. Randomized studies comparing medical and percutaneous closure approaches are underway, but large patient enrollment is necessary because of the low event rate in the younger patients. At this juncture, for those meeting enrollment criteria, participation in ongoing studies is recommended. For those requiring therapeutic decision, once the likelihood of individual PFO association with ischemic event is determined, the choice of therapy needs be tailored to an individual patient’s lifestyle and preference. Meanwhile, as the complication rate from device implantation decreases and simpler devices are developed with reliability further demonstrated, the threshold for percutaneous closure is likely to decline. Patients should also be updated periodically on the developments in this field and reassured that lifelong anticoagulation (for those placed on warfarin) may not be necessary.

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