A patent foramen ovale (PFO) is common and found in nearly 25% of healthy individuals. The majority of patients with PFO remain asymptomatic and they are not at increased risk for developing a stroke. The presence of PFO, however, has been found to be higher in patients with cryptogenic stroke, suggesting there may be a subset of patients with PFO who are indeed at risk for stroke. Paradoxical embolization of venous thrombi through the PFO, which then enter the arterial circulation, is hypothesized to account for this relationship. Although aerated-saline transesophageal echocardiography is the gold standard for diagnosis, aerated-saline transthoracic echocardiography and transcranial Doppler are often used as the initial diagnostic tests for detecting PFO. Patients with cryptogenic stroke and PFO are generally treated with antiplatelet therapy in the absence of another condition for which anticoagulation is necessary. Based on the findings of 3 large randomized clinical trials, current consensus guidelines do not recommend percutaneous closure, though this is an area of controversy. The following review discusses the relationship of PFO and cryptogenic stroke, focusing on the epidemiology, pathophysiological mechanisms, diagnostic tools, associated clinical/anatomic factors and treatment. (Circ J 2016; 80: 1665–1673)

Key Words: Paradoxical embolism; Patent foramen ovale (PFO); Stroke

The foramen ovale is an important fetal structure that closes after birth in most individuals and remains open as a patent foramen ovale (PFO) in approximately 25% of the healthy population. In these individuals, bypass of the pulmonary circulation via shunting from the right-sided venous circulation to the left-sided arterial circulation is possible. Although most patients with PFOs are completely asymptomatic, reports from the late 1800s by Cohnheim and Litten described cases of patients who were found to have the triad of deep venous thrombosis (DVT), PFO and systemic embolization. They hypothesized that the PFO enabled bypass of a venous thrombosis to the systemic arterial circulation, a process now termed paradoxical embolization. Since those initial observations, additional studies have demonstrated a strong association between the presence of PFO and cryptogenic stroke in young patients. In addition to its association with stroke, PFO has also been implicated in platypnea-orthodeoxia, decompression illness, myocardial infarction, obstructive sleep apnea, and migraine headaches.

This review will focus on the relationship between PFO and stroke, discussing the embryology, epidemiology, association, mechanisms, diagnostic methods, associated anatomic factors and management strategies.

**Embryology**

The right and left atria begin as a single chamber and separation begins with growth of the septum primum from the roof of the common atrium. As the septum primum grows downward, fenestrations form in its superior portion. The fenestrations coalesce into a single orifice that becomes the foramen secundum. The septum secundum then forms via involution of the ventrocranial wall and overlaps with the foramen secundum. The septum secundum does not close fully and an oval-shaped opening remains, which becomes the foramen ovale. Prior to birth, the fetus is dependent on the maternal circulation for oxygenation, as the immature fetal lungs do not yet participate in oxygen exchange. As such, the foramen ovale (as well as the ductus arteriosus), enables shunting of blood away from the pulmonary circulation. At birth, when the neonate’s lungs begin to participate in oxygen exchange, there is a precipitous drop in the pulmonary vascular resistance and there is reversal of flow through both the foramen ovale and ductus arteriosus. In approximately 75% of individuals, the foramen ovale closes within a few years while in the remaining others, it stays open permanently as a PFO.

**Epidemiology**

The prevalence of PFO in the healthy adult population ranges from 15% to 25% on echocardiography and 15–35% on autopsy studies. Observational and autopsy studies have showed that the prevalence of detected PFOs is lower in older patients and that detected PFOs in older individuals tend to be larger. Those studies, however, may be confounded by selection and detection bias because none of the longitudinal studies have demonstrated that individual PFOs change in size. The prevalence of PFOs is equal among men and women, though there may be race-ethnic differences.
Cryptogenic Stroke and PFO

A stroke is considered cryptogenic when a cause has not been identified. Depending on the classification system, cryptogenic strokes account for almost 30% of cases and are more common in younger patients.13 Multiple studies have demonstrated an association between PFO and cryptogenic stroke.6,11,23,25,26 Attributing an initial stroke to the presence of a PFO can be challenging, given the multiple other causes of stroke combined with the high prevalence of PFOs in the general population. The Risk of Paradoxical Embolism (RoPE) study helped address this issue.24 In this patient-level meta-analysis, nearly 3,000 patients from 12 independent studies were included and the following factors were found to be associated with the detection of a PFO: younger age, radiographic evidence of a cortical infarct and absence of traditional vascular risk factors (hypertension, diabetes, prior history of stroke/transient ischemic attack (TIA) and smoking). The data suggested that the fewer traditional risk factors that were present, the more likely that the stroke was caused by a PFO. Importantly, it also demonstrated that the more likely the stroke was caused by the PFO, the lower the risk for recurrent stroke.

Although it has been well established that a PFO is associated with cryptogenic stroke, it is important also to note that studies following patients with PFO without stroke have not shown them to be at an increased risk of developing an ischemic stroke.22,25,26 These observations suggest, therefore, that the development of stroke in patients with PFO is likely multifactorial with contributions from other factors. Although the main hypothesized pathophysiological explanation is that of paradoxical embolism, the exact causative mechanism remains controversial.27 Other possible mechanisms for the association between PFO and stroke have been proposed. It is well established that atrial fibrillation (AF) and atrial flutter are risk factors for stroke and several studies have suggested that the risk for recurrence in patients with PFO and cryptogenic stroke may be related to the subsequent development of these atrial arrhythmias.28 This mechanism, however, remains uncertain as the results from the CRYSTAL AF study showed that subsequent development of AF (at 3 years) in patients with cryptogenic stroke was not related to the presence of PFO.29

In addition to a connection with atrial arrhythmias, recent proteomic profiling studies have demonstrated differences in protein expression in patients with PFOs with and without stroke and have also shown that PFO closure results in alterations in cholesterol handling, thereby providing additional alternative mechanisms.30,31

Detection

Although PFO was initially a diagnosis that was made at the time of autopsy, it can now be detected non-invasively using ultrasound. Contrast transcranial Doppler (TCD) and transcranial Doppler (TCD) allow for the physiologic identification of PFOs through detection of microbubbles in the left-sided circulation that in the absence of a PFO are filtered out by the pulmonary circulation.32,33 Neither of these techniques, however, are able to localize the level of shunting. The third method, contrast transesophageal echocardiography (TEE), allows for direct anatomic visualization of shunting across a PFO and is considered the gold standard for diagnosis.3

Aerated-saline TTE is commonly used for initial evaluation for PFO. In order to perform this test, intravenous access is obtained and aerated saline is injected. While visualizing the entire heart (either apical or subxiphoid view), aerated saline (which appears echobright) is first seen filling the right atrium (RA) and right ventricle. If microbubbles are seen on the left side of the heart within 3 cardiac cycles, this is considered a positive test for evidence of intracardiac shunting. Occasionally in the presence of rapid pulmonary transit (as can be seen with pulmonary arteriovenous malformations), microbubbles can appear on the left side of the heart after 5 cardiac cycles. In normal individuals without intracardiac shunting or rapid pulmonary transit, microbubbles are filtered by the lungs and are not seen on the left side. Given that the distinction between intracardiac shunting and rapid pulmonary transit is made based upon the time of microbubble appearance, distinguishing between these entities can be challenging. If no shunting is seen at rest, repeat injections are performed after release of the strain phase of the Valsalva maneuver or coughing, and imaging is again acquired. The purpose of these maneuvers is to transiently increase right-sided filling pressures, which can improve the ability to detect intracardiac shunting.34 Although early studies demonstrated a sensitivity of close to 50%,35,36 more contemporary studies have indicated that it has increased to 80–90%, an improvement that is likely related to technical improvements in imaging quality.37,38 Given the reduced sensitivity, it is not surprising, therefore, that the estimated prevalence...
of PFOs in the general population when TTE is used is approximately 15% as compared with 24% with TEE. TCD is a noninvasive and reproducible assessment of cerebral blood flow that when coupled with use of aerated-saline injection is also often used in the initial evaluation for PFO. In this technique, the ultrasound probe is placed over the temporal window and insonation of the middle cerebral artery is performed. Aerated saline is then injected into a peripheral vein. In the presence of a right-to-left shunt, microbubbles bypass the pulmonary circulation and are detected on Doppler assessment of the middle cerebral artery. Quantification of shunting is possible through counting of the number of microbubble signals. Detection of right-to-left shunting can be improved through imaging in multiple positions and with maneuvers that transiently increase right-sided pressures, maneuvers that are more easily performed with TCD. Similar to TTE, the detection of microbubbles indicates only the presence of right-to-left shunting. Although early detection and large quantity of microbubbles can be helpful in suggesting an intracardiac source of shunting, no consensus standardization has been established and distinguishing between intracardiac shunting and intrapulmonary shunting can still be difficult. When comparing TCD with contrast-enhanced TTE for detection of PFO, a recent meta-analysis suggested it to be more sensitive but less specific. Similar to TTE, the detection of microbubbles indicates only the presence of right-to-left shunting. Although early detection and large quantity of microbubbles can be helpful in suggesting an intracardiac source of shunting, no consensus standardization has been established and distinguishing between intracardiac shunting and intrapulmonary shunting can still be difficult. When comparing TCD with contrast-enhanced TTE for detection of PFO, a recent meta-analysis suggested it to be more sensitive but less specific.

Although both TCD and contrast-enhanced TTE provide the direct visualization of the PFO opening and measurement of the separation height between the septum primum and septum secundum (Figure 1). The shunting of blood can sometimes be visualized directly by color Doppler (Figure 2). Oftentimes, however, diagnosis requires injection of aerated saline via a peripheral vein. The interatrial septum is visualized in the mid-esophageal bicaval view. PFO is diagnosed with the appearance of microbubbles in the left atrium and they can often be seen traversing the PFO (Figure 3). This assessment is performed both at rest and with maneuvers that result in increased right atrial pressure such as coughing or the Valsalva maneuver. If initially negative, this can be repeated with multiple injections, which has been shown to improve the sensitivity. In contrast to TTE and TCD, direct visual assessment of the pulmonary veins can often be used to better...
the observation that the rate of strokes in asymptomatic individuals is no different than in patients without PFOs means it is likely that a multifactorial model exists whereby additional factors need to be present in order for paradoxical embolization to occur. This section will discuss several factors that may be associated with paradoxical embolization, including PFO size, and the presence of other anatomic features, including ASA, prominent Eustachian valve, Chiari network and hypercoagulability.

PFOs have a wide variability in size and autopsy studies have demonstrated that the mean diameter is 4.9 mm and ranges from 1 to 19 mm. This differs from sizing defined by TEE, which defines PFO size as the maximal height of separation between the septum primum and secundum. There are conflicting reports regarding the relationship of PFO size and the development of cryptogenic stroke, with early studies suggesting that larger PFOs are associated with cryptogenic stroke, but observations from the RoPE database showing no relationship.

Along these same lines, other characteristics, including the physiologic shunt size (determined by the quantity of bubbles that cross the PFO) and the presence of shunting at rest, have also been inconclusive, with some showing an increased risk of stroke and stroke recurrence, and others showing no relationship.

ASA is a redundancy of the atrial septum that results in significant movement (>10 mm from the plane of the septum or >15 mm of total excursion) (Figure 4). ASAs are more commonly observed in patients with stroke than in the general population. PFOs are found in approximately 60% of patients with cryptogenic stroke and ASA as compared with approximately 30% of patients with cryptogenic stroke but no ASA. In the same study, larger PFOs were more commonly seen in those with ASA as compared with those without ASA.

In addition to the hypothesis that the presence of ASA may help facilitate paradoxical embolization through a PFO, it has also been shown that the presence of ASA alone is associated with left atrial dysfunction and may serve as another mechanism by which ASA may be related to stroke. It is not yet clear how the presence of ASA affects the risk of cryptogenic stroke, and further studies are required.

A prominent Chiari network and Eustachian valve are commonly seen in patients with PFO and stroke. Both structures distinguish between PFO and intrapulmonary shunting. It is important to note that although TEE is considered the gold standard for diagnosis, it is a semi-invasive test that is generally performed with conscious sedation. Because of this, it can often be difficult for patients to perform the Valsalva maneuver or to cough and as such, may lead to rare false-negative results. Although multiple studies have demonstrated the safety of aerated-saline injections, the rare development of transient neurological symptoms has been reported.

**Factors Associated With PFO and Cryptogenic Stroke**

The main hypothesized pathophysiologic mechanism relating PFO and cryptogenic stroke is that of paradoxical embolization. Although there is a clear association between PFO and cryptogenic stroke, the observation that the rate of strokes in asymptomatic individuals is no different than in patients without PFOs means it is likely that a multifactorial model exists whereby additional factors need to be present in order for paradoxical embolization to occur. This section will discuss several factors that may be associated with paradoxical embolization, including PFO size, and the presence of other anatomic features, including ASA, prominent Eustachian valve, Chiari network and hypercoagulability.

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Along these same lines, other characteristics, including the physiologic shunt size (determined by the quantity of bubbles that cross the PFO) and the presence of shunting at rest, have also been inconclusive, with some showing an increased risk of stroke and stroke recurrence, and others showing no relationship.

ASA is a redundancy of the atrial septum that results in significant movement (>10 mm from the plane of the septum or 15 mm of total excursion) (Figure 4). ASAs are more commonly observed in patients with stroke than in the general population. PFOs are found in approximately 60% of patients with cryptogenic stroke and ASA as compared with approximately 30% of patients with cryptogenic stroke but no ASA. In the same study, larger PFOs were more commonly seen in those with ASA as compared with those without ASA.

In addition to the hypothesis that the presence of ASA may help facilitate paradoxical embolization through a PFO, it has also been shown that the presence of ASA alone is associated with left atrial dysfunction and may serve as another mechanism by which ASA may be related to stroke. It is not yet clear how the presence of ASA affects the risk of cryptogenic stroke in the setting of PFO, if at all, and further studies are required.

A prominent Chiari network and Eustachian valve are commonly seen in patients with PFO and stroke. Both structures
are remnants of the embryologic right valve of the sinus venosus that directs blood preferentially through the foramen ovale in utero. The Chiari network is a mobile web-like structure that typically extends from the junction of the inferior vena cava (IVC) and RA and attaches to the upper wall of the RA or the septum (though it can also be fenestrated) (Figure 5). The Eustachian valve extends anteriorly from the IVC-RA junction and unlike the Chiari network typically does not attach at other sites (Figure 6). Although the mechanism for the association between these structures, PFO and stroke is not clear, they have been shown to direct blood flow from the IVC towards the PFO, which, in the setting of a lower extremity DVT, may help facilitate paradoxical embolization.65

In order for paradoxical embolism to occur, there must be a source of thrombus in addition to a PFO. Both lower extremity and pelvic DVT have been reported in patients with cryptogenic stroke and PFO.56,57 In 1 study, when compared with patients with known etiology for stroke, the rates of pelvic DVT in cryptogenic stroke were higher (20% vs. 4%),58 though another more recent study showed no differences in the rates of DVT.59 In addition, studies have shown that the prevalence of the otherwise rare May-Thurner syndrome (an anatomic vascular variant that predisposes towards development of DVT) in patients with cryptogenic stroke and PFO is approximately 6–8%.60,61 Despite these conflicting results, pelvic vein thrombosis may still be an important source of thrombi in patients with cryptogenic stroke and DVT.

Hypercoagulable states have been implicated as additional risk factors for cryptogenic stroke in patients with PFO. Two of these, the prothrombin G20210A mutation and Factor V Leiden, have been most strongly linked to the development of cryptogenic stroke in the setting of a PFO.62,63 though results are inconsistent.64 Polymorphisms in APOCIII, a lipoprotein that is critical in triglyceride metabolism and is associated with increased cardiovascular risk,65 have been reported in patients with cryptogenic stroke and PFO as well.66 Antiphospholipid antibodies were not found to be a risk factor however.66 Although not specifically linked with cryptogenic stroke, traditional risk factors for DVT, including prolonged immobility, malignancy and use of oral contraceptives, to name only a few,67 are likely to also be potential risk factors for paradoxical embolization in the setting of a PFO.

### Medical Therapy

Currently, it is recommended that patients with cryptogenic stroke and PFO be treated with antiplatelet therapy (in the absence of another indication for anticoagulation).68 Because it is hypothesized that these strokes are caused either by paradoxical embolism or embolism of in situ atrial thrombi, it seems logical that some type of antithrombotic therapy would be of benefit. Although there is no direct evidence supporting use of antiplatelet therapy in patients with PFO and stroke over no therapy, given the safety and well-demonstrated benefit of these agents in the treatment of stroke in general, it remains the standard of care for the subset of patients with stroke and PFO.68

Because of the role that paradoxical embolization may play in the pathogenesis of stroke in patients with PFO, it has been hypothesized that anticoagulation may be of benefit in these patients. There is, however, limited data comparing antiplatelet therapy with anticoagulation in these patients. PICSS (PFO in Cryptogenic Stroke Study) was a sub-study of a large, randomized control trial of warfarin vs. aspirin for secondary stroke prevention.69 The study compared dose-adjusted warfarin (targeting an internal normalized ratio of 2–3) with aspirin 325 mg daily in those with cryptogenic stroke and PFO. Of the 630 stroke patients included in the original trial, 98 had both cryptogenic stroke and PFO; 42 of the 98 patients were treated with warfarin and the remaining 56 were treated with aspirin. There was no difference in the primary endpoint (recurrent stroke or death) at 2 years between the 2 groups.

A very small (44 patients), single-center randomized controlled trial compared dose-adjusted warfarin (targeting an international normalized ratio of 2–3) with aspirin (240 mg daily) in patients with PFO and cryptogenic stroke. There were no significant differences between the 2 groups in the primary endpoint (ischemic stroke, TIA or death), though the study was underpowered to fully detect such a difference.

Given the small numbers in the previously discussed studies (in addition to others), meta-analyses have been performed, with some favoring warfarin therapy70 and others demonstrating no benefit of anticoagulation over antiplatelet therapy.71 Although there is currently no evidence to suggest a benefit of warfarin over aspirin, the lack of adequately powered studies

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**Table 1. Summary of the Randomized Controlled Trials Evaluating Percutaneous Closure of Patent Foramen Ovale**

<table>
<thead>
<tr>
<th>Device</th>
<th>Closure 1</th>
<th>PC Trial</th>
<th>RESPECT</th>
</tr>
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<tbody>
<tr>
<td>Design</td>
<td>909 patients randomized to medical therapy (aspirin, warfarin or both at physician discretion) vs. closure Follow-up 2 years</td>
<td>414 patients randomized to medical therapy (70% antiplatelet, 30% anticoagulation) vs. closure Follow-up 4 years</td>
<td>980 patients randomized to medical therapy (antiplatelet 75%, anticoagulation 25%) vs. closure Follow-up 2.5 years</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Composite of stroke/TIA at 2 years, death from any cause in the first 30 days or death from neurologic causes between 31 days and 2 years</td>
<td>Composite of death, nonfatal stroke, TIA, embolism</td>
<td>Recurrent stroke or death</td>
</tr>
<tr>
<td>Results</td>
<td>No differences in closure vs. medical therapy: - Primary endpoint (5.5% vs. 6.8%) - Recurrent stroke (2.9% vs. 3.1%)</td>
<td>No difference in closure vs. medical therapy: - Primary endpoint (5.2% vs. 3.4%) - Recurrent stroke (2.4% vs. 0.4%)</td>
<td>Total 25 primary endpoints occurred, all nonfatal strokes</td>
</tr>
<tr>
<td></td>
<td>No procedural deaths</td>
<td>No differences in bleeding or atrial fibrillation</td>
<td>Intention-to-treat analysis showed no difference between closure vs. medical therapy (0.66 events per 100 patient-years vs. 1.38 events per 100 patients-years, HR=0.49, P=0.08)</td>
</tr>
<tr>
<td></td>
<td>Increased risk of atrial fibrillation in the closure group over the medical therapy group (5.7% vs. 0.7%, P&lt;0.001)</td>
<td></td>
<td>As-treated analysis showed benefit of closure (HR=0.27, P=0.007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No difference in atrial fibrillation</td>
</tr>
</tbody>
</table>

HR, hazard ratio; TIA, transient ischemic attack.
leaves this as an area of uncertainty. However, given the low risk of stroke recurrence and the well-established increased bleeding risk of warfarin over aspirin, antiplatelet therapy is likely to be favored in most patients with PFO and cryptogenic stroke. Treatment with novel oral anticoagulants (NOACs) in this population is intriguing, given their lower bleeding risk when compared with warfarin. Studies evaluating their use in the cryptogenic stroke population are underway and may provide additional insight into the optimal medical therapy for these patients.

Advances in catheter-based techniques have made PFO closure an attractive treatment option. Percutaneous closure is highly effective, with >90% success rate and a low rate of adverse events (<5%). It can often be performed as a same-day procedure and patients are generally maintained on antiplatelet therapy for at least 6 months (and often indefinitely). Three randomized clinical trials comparing percutaneous PFO closure vs. medical therapy have been performed (Table 1). The first was CLOSURE I, which was a multicenter trial that randomized 909 patients to percutaneous closure with the STARFlex device (NMT Medical) or medical therapy (specific treatments were left to the discretion of the treating provider). The primary endpoint was a composite of stroke or TIA during 2 years of follow-up, death from any cause during the first 30 days or death from neurologic causes between 31 days and 2 years. There were no significant differences in the primary endpoint, recurrent stroke or TIA. The majority of recurrent strokes in both groups were caused by mechanisms unrelated to the PFO (87% in the closure group and 76% in the medical group). Although there were no procedural deaths in the closure group, there was a 3% risk of major vascular procedural complication. In addition, the rate of AF in the closure group was significantly higher (5.7% in the closure group vs. 0.7%, P<0.001).

The other 2 randomized clinical trials of percutaneous PFO closure were the PC Trial and the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial, both of which used the Amplatzer PFO Occluder (St. Jude Medical Inc). The PC trial randomized 414 patients with cryptogenic stroke, TIA or peripheral thromboembolism to PFO closure or medical therapy. The choice of medical therapy was left to the discretion of the treating provider, though it was specified that patients must be on at least 1 antithrombotic agent. The primary endpoint was a composite of death, nonfatal stroke, TIA or peripheral embolism. The mean follow-up was similar (4.1 years in the closure group, 4 years in the medical therapy group). There were no differences in the primary outcome, or TIA.

The RESPECT trial was a multicenter study that randomized 980 patients to PFO closure or medical therapy. Specific medical therapy was, again, left to the discretion of the treating provider, but 75% of the patients received ≥1 antiplatelet medication and the remaining 25% received warfarin. The primary endpoint was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke or early death after randomization. In the intention-to-treat analysis, there was a non-statistically significant trend towards a reduction in the primary outcome with closure (9 events in the closure group vs. 16 in the medical therapy group, hazard ratio 0.49, 95% confidence interval (CI) 0.22–1.11, P=0.08). There were higher rates of dropout in the medical therapy group vs. the closure group, resulting in a significant difference in follow-up observation (1.375 years in the closure group vs. 1.184 years in the medical therapy group, P=0.009). In a prespecified as-treated analysis, however, there was a reduction in the primary outcome with closure.

### Table 2. Summary of Meta-Analyses Evaluating Percutaneous Closure of Patent Foramen Ovale

<table>
<thead>
<tr>
<th>Studies favoring PFO closure</th>
<th>Studies against PFO closure</th>
</tr>
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<tbody>
<tr>
<td>Khan et al, 2013⁷⁸</td>
<td>Kitsios et al, 2013⁹³</td>
</tr>
<tr>
<td>· Pooled results showed benefit of PFO closure over medical therapy for intention-to-treat (HR=0.67, P=0.05), per-protocol (HR=0.62, P=0.03) and as-treated (HR=0.61, P=0.03) cohorts</td>
<td>· No significant reduction in recurrent stroke with PFO closure (StarFlex+Amplatzer PFO Occluder combined AND Amplatzer PFO Occluder alone) over medical therapy</td>
</tr>
<tr>
<td>Rengifo-Moreno et al, 2013⁹⁹</td>
<td>Udell et al, 2014⁸¹</td>
</tr>
<tr>
<td>Kent et al, 2016⁸⁵</td>
<td>Spencer et al, 2014⁸⁴</td>
</tr>
<tr>
<td>· No difference in unadjusted primary outcome (stroke, TIA, death)</td>
<td>· No significant reduction in recurrent stroke with PFO closure over medical therapy (2.1% vs. 3.6%, RR=0.61, P=0.34)</td>
</tr>
<tr>
<td>· Closure favored over medical therapy for recurrent stroke, both unadjusted (HR=0.58, P=0.044) and adjusted (HR=0.58, P=0.044)</td>
<td>· No differences between closure with StarFlex or Helex device closure over medical therapy</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio; RR, relative risk; TIA, transient ischemic attack.
outcome in the closure group (5 events in the closure group vs. 14 events in the medical therapy group, hazard ratio 0.27, 95% CI 0.1–0.75, P=0.007). The difference between these 2 analyses was a result of non-adherence to the protocol in each group. It is possible that confounding factors could have introduced bias into this analysis; however, it is important to note that 3 of the 9 events in the closure group occurred in patients who did not actually receive a device. One event occurred after randomization but prior to PFO closure, the second event occurred in a patient who decided not to undergo PFO closure and the third event occurred in a patient who underwent unanticipated coronary artery bypass surgery and surgical PFO closure. The rate of serious adverse events was similar in both groups (23% in the closure group vs. 21.6% in the medical therapy group, P=0.65). Procedure or device-related serious adverse events occurred in 21 patients (4.2%) in the closure group and the rates of AF were not significantly different (3% in the closure group, 1.5% medical therapy group, P=0.13).

One of the challenges in evaluating therapies for cryptogenic stroke and PFO is that the risk of recurrent stroke/TIA is quite low in this population. Although these 3 randomized controlled trials failed to demonstrate stroke reduction with PFO closure in the intention-to-treat analyses, it has been hypothesized that larger trials may have been necessary in order to fully detect the benefit of PFO closure. Addressing this, the multiple meta-analyses using published aggregate data have been conflicting (Table 2). Recently, a meta-analysis was performed using individual patient-level data that enabled standardization across all 3 studies, as well as more detailed statistical assessment. The primary endpoint was the composite of stroke, TIA or death and the secondary endpoint was recurrent stroke. There was no statistical difference between the closure group and the medical therapy group in the primary endpoint (1.5% vs. 2.3%, P=0.517); however, the difference became significant after adjusting for covariates (P=0.0491).

There was a significant difference in the secondary endpoint of recurrent stroke (0.7% in the closure group vs. 1.3% in the medical therapy arm) in both the unadjusted analysis (P=0.04) and the covariate-adjusted analysis (P=0.04). The number needed to prevent 1 ischemic stroke over 2.5 years was 67. Given that the average age of the patients in these trials was 45, it has been argued that the most appropriate time frame is 15–20 years, and based on this data would reduce the number needed to treat to 11 and 8, respectively, a number that is 3% in the closure group, 1.5% medical therapy group, P=0.13.

Based on the 3 randomized clinical trials, the 2014 American Heart Association and American Stroke Association guidelines recommend against closure of PFO in crypto
genetic stroke. The most recent patient-level meta-analysis attempted to address the main criticism of the randomized trials (mainly, the low event rate) while providing a rigorous standardized approach to handling data from the 3 separate trials and provides possible evidence in favor of PFO closure. The last remaining randomized trial evaluating PFO closure in patients with cryptogenic stroke has recently completed enrollment but the results have not yet been published. Of note for all these trials, long-term monitoring for AF was not performed and NOACs were not yet available. Newer trials addressing these 2 issues are needed to fully assess efficacy of percutaneous closure over medical therapy.

Conclusions

PFO is more commonly found in patients with cryptogenic stroke than in the normal population. The mechanism of stroke in this setting is thought to be paradoxical embolization. Although it can be challenging to attribute a stroke to a PFO, the RoPE score can be helpful in making this distinction. Given that the rate of stroke in asymptomatic patients with PFO is no different than in those without stroke, it is likely that other risk factors (eg, ASA, Chiari network, prominent Eustachian valve, anatomic and physiologic PFO size and hypercoagulable states) need to be present in order for stroke to occur. Current guidelines recommend use of antiplatelet medications in all patients with cryptogenic stroke and PFO and, based on the 3 randomized clinical trials, against PFO closure. Despite these recommendations, however, there is likely a subset of patients who would benefit from anticoagulation and/or percutaneous closure. Given that the majority of patients with cryptogenic stroke caused by a PFO are young and otherwise healthy with few remaining expected life years, a recurrent stroke has the potential to be a particularly life-changing event. It is imperative to take into account the relative effect of a recurrent event for that particular patient and balance that with the potential benefits and risks of the intervention (both in the selection of pharmacologic therapy and the decision of whether or not to pursue percutaneous closure). Further studies clarifying patient groups for whom device closure is beneficial need to be performed.

References


