

# Patent Foramen Ovale in Cryptogenic Stroke

## Current Understanding and Management Options

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**T**here is increasing interest in the association between patent foramen ovale (PFO) and documented stroke of unknown cause, commonly referred to as cryptogenic stroke. We reviewed the literature and, on the basis of the available data, designed a diagnostic and treatment algorithm for patients with PFO and cryptogenic stroke. Patent foramen ovale is relatively common in the general population, but its prevalence is higher in patients with cryptogenic stroke. Importantly, paradoxical embolism through a PFO should be strongly considered in young patients with cryptogenic stroke. There is no consensus on the optimal management strategy, but treatment options include antiplatelet agents, warfarin sodium, percutaneous device closure, and surgical closure. High-risk features in the patient's history (ie, temporal association between Valsalva-inducing maneuvers and stroke, coexisting hypercoagulable state, recurrent strokes, and PFO with large opening, large right-to-left shunt, or right-to-left shunting at rest, and a coexisting atrial septal aneurysm) should prompt PFO closure.

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Recent studies have suggested a strong association between patent foramen ovale (PFO) and cryptogenic stroke. Treatment options have included warfarin sodium, antiplatelet agents, and surgical or percutaneous device closure. Specific treatment recommendations have been made based on patient characteristics (eg, age, hypercoagulable state, and history of stroke) and morphologic features of the interatrial communication (eg, size of PFO and associated atrial septal aneurysm). However, there remains a lack of consensus regarding the optimal management strategy. The main purpose of this review is to construct a practical diagnostic and treatment algorithm for patients with PFO and cryptogenic stroke based on current understanding of the cause-effect relationship.

lished between 1966 and August 2002. The keywords used in the search were *patent foramen ovale, atrial septal aneurysm, paradoxical embolism, cryptogenic stroke, and ischemic stroke*. We also reviewed the references in articles identified in the MEDLINE search to identify additional articles for inclusion. The articles that we included documented the prevalence of PFO in the general population and the association of PFO and cryptogenic stroke. We emphasized reports that looked into patient clinical characteristics and morphologic characteristics of the atrial septum that are associated with risk of stroke recurrence, as well as articles that addressed treatment options for paradoxical embolism.

### METHODS

Using MEDLINE, we searched the English-language medical literature for articles pub-

### DATA SYNTHESIS

#### Prevalence of PFO in the General Population

In an autopsy study of 965 normal hearts from patients with no history of cardioembolic events, the prevalence of probe-PFO was 27%.<sup>1</sup> There was no difference

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between men and women, regardless of age (men, 26.8%; women, 27.6%). For the entire group, the mean size of the probe-PFO was approximately 5 mm. Probe-PFO prevalence decreased with each decade of life (approximately 30%, 25%, and 20% for age groups 1-29 years, 30-79 years, and  $\geq 80$  years, respectively), but PFO size increased with each decade of life (mean diameter: first decade, 3.4 mm; tenth decade, 5.8 mm). Other autopsy studies showed similar results.<sup>2-4</sup> This apparent paradox has been attributed to spontaneous closure of PFOs, particularly smaller ones, and stretching of the fossa ovalis with age.<sup>1</sup>

A similar prevalence of PFO was observed in the Stroke Preven-

tion: Assessment of Risk in a Community (SPARC) study, in which 588 randomly selected, healthy adult residents of Olmsted County, Minnesota, who were older than 45 years, underwent transesophageal echocardiography (TEE) and carotid ultrasonography to identify potential risk factors for stroke.<sup>5</sup> These included the presence of PFO, atrial septal aneurysm (ASA), valve strands, and atherosclerosis of the aorta or carotid arteries. The prevalence  $\pm$  SE of PFO was 25.6%  $\pm$  1.9%. Of the 148 subjects with PFO, 68 (46%) had defects that were 1 mm or larger, 84 (57%) had shunts at rest, and 136 (92%) had shunts after straining or coughing. The prevalence of ASA was low (2.2%  $\pm$  0.6%) and half of the subjects with ASA had concomitant PFO. Overall PFO prevalence was similar for men and women. In contrast to the findings from autopsy studies,<sup>1,2</sup> PFO prevalence was stable across all age groups and for both sexes.

#### Association of PFO and Stroke

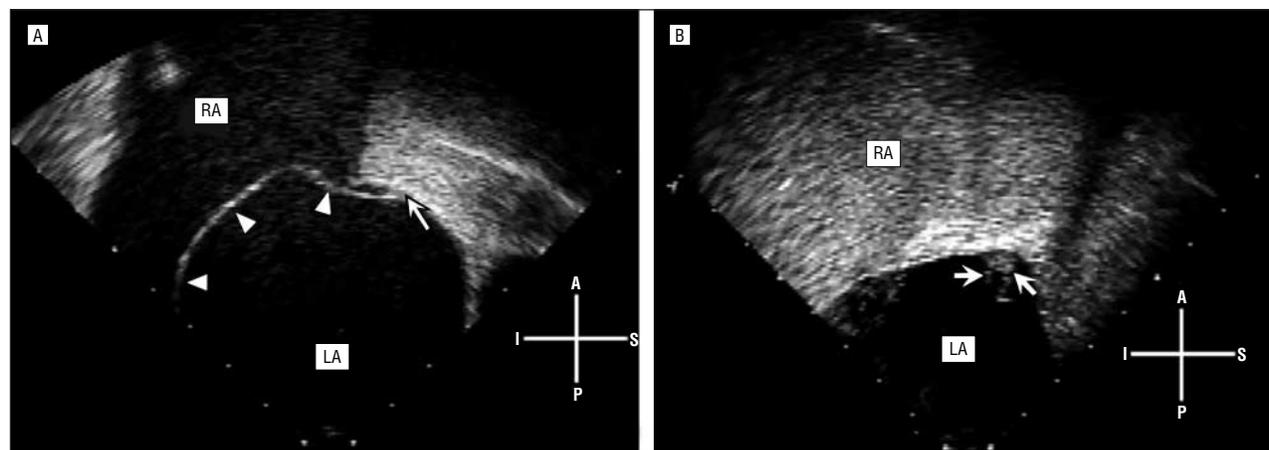
The high prevalence of PFO in the general population notwithstanding, the clinical significance of PFO in patients with stroke remains unclear. Stroke has a wide range of causes (**Table 1**). Atrial fibrillation or advanced atherosclerotic disease (of small and large vessels) is the underlying cause in most individuals older than 50 years.<sup>5-10</sup> In contrast, idiopathic cardioembolic and nonatherosclerotic arteriopathies,

such as reversible vasoconstriction, arterial dissection, and fibromuscular dysplasia, are the more common causes of stroke in younger patients (particularly in those  $< 35$  years old).<sup>11,12</sup> Moreover, in 35% to 40% of all strokes in all age groups, the cause of stroke is unknown; such strokes commonly are referred to as cryptogenic.<sup>13-17</sup> A meta-analysis of retrospective studies evaluating the association of PFO with stroke showed that patients younger than 55 years who sustained a cryptogenic stroke had a PFO prevalence that was 6 times greater than that of patients with other forms of stroke.<sup>18</sup> In addition, a recent prospective study found a significantly ( $P < .02$ ) higher prevalence of PFO in patients with cryptogenic stroke compared with patients with stroke of known cause.<sup>19</sup>

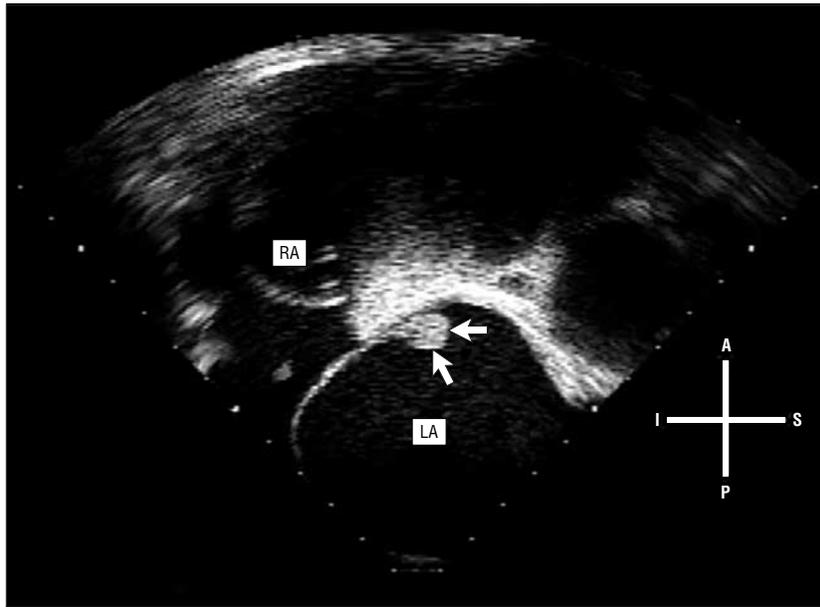
Current data, therefore, suggest a cause-effect association between PFO and an as yet undetermined percentage of cryptogenic strokes. The presumed mechanism is the migration of a thrombus, or less commonly fat or air,<sup>20</sup> from the venous side of the circulation (eg, lower extremity veins and right atrium) to the left atrium via a PFO, with subsequent systemic embolization, an event commonly referred to as "paradoxical embolism." This can occur when right atrial pressure exceeds left atrial pressure (**Figure 1**). It also can occur because of flow momentum, with blood flow moving from the inferior vena cava, across the eustachian valve, and through the PFO, such as in normal fetal circulation.

**Table 1. Causes of and Predisposing Factors in Stroke and Transient Ischemic Attack**

Atherosclerosis (of small or large vessels)
Thrombotic diathesis
Factor V Leiden mutation
Prothrombin 20210 mutation
Antiphospholipid antibodies
Protein C deficiency
Protein S deficiency
Antithrombin III deficiency
Autoimmune disease
Vasculitis
Severe migrainous attack
Cardioembolic conditions
Atrial fibrillation or flutter
Dilated cardiomyopathy
Valvular lesions (eg, vegetations)
Atrial or ventricular mass or thrombus
Atherosclerosis of the thoracic aorta
Paradoxical embolism



**Figure 1.** Transesophageal echocardiogram (long-axis view) showing right atrial inflow. A, Atrial septum (arrowheads) and foramen ovale (arrow) are visible. B, Contrast bubbles (arrows) pass into left atrium (LA) through a patent foramen ovale. RA indicates right atrium.



**Figure 2.** Transesophageal echocardiogram showing a thrombus (arrows) passing from right atrium (RA) to left atrium (LA) through a patent foramen ovale.

In patients with no underlying cardiopulmonary disease, mean left atrial pressure exceeds right atrial pressure. However, right atrial pressure may exceed left atrial pressure during normal inspiration or after release of Valsalva maneuvers such as coughing or straining. In 76 healthy volunteers, a transthoracic echocardiographic study using a well-established, agitated saline contrast technique found that the prevalence of right-to-left shunting through a PFO was 5% when subjects were at rest and 18% when subjects performed a Valsalva maneuver.<sup>21</sup> In the SPARC study, the prevalence of right-to-left shunting increased from 14% in subjects at rest to 23% with performance of maneuvers (release of Valsalva maneuver and cough) that increased the right atrial pressure by increasing venous return.<sup>5</sup> Acute pulmonary embolism is the most common cause of right-to-left shunting through a PFO. Pulmonary embolism may cause pulmonary hypertension, which in turn can result in markedly elevated right atrial pressure. The incidence of paradoxical embolism in patients with acute pulmonary embolism has been estimated to be as high as 60%.<sup>22</sup> Right ventricular infarction or acute respiratory failure are other causes of a sudden elevation in right atrial pressure.

Patients, however, rarely report that a Valsalva maneuver immediately preceded a cardioembolic event.<sup>23,24</sup> Moreover, a venous thrombus in transit to the left atrium is rarely detected.<sup>23-25</sup> Thus, the cause of stroke in a patient with a PFO can only be presumed to be paradoxical embolism unless there is actual visualization of an entrapped thrombus through the PFO (**Figure 2**).<sup>26</sup>

Findings that argue against the association between PFO and cryptogenic stroke include the high prevalence of PFO in all subtypes of stroke<sup>27</sup> and the low likelihood of finding a source of thrombus for paradoxical embolism in stroke patients with PFO (**Table 2**).<sup>23-25,30-33</sup> In addition, small (<1-2 mm) clots that are beyond the resolution of TEE transducers may be missed, and migration or lysis of clots can occur before diagnostic imaging has been performed. These confounding factors underscore the difficulties in establishing a cause-effect relationship between PFO and paradoxical embolism.

#### Prognostic Implications for Patients With PFO

Retrospective studies have identified clinical and echocardiographic markers of increased risk for initial and recurrent stroke. These include a large PFO opening,<sup>34,35</sup> large

**Table 2. Reasons for Inconsistent Findings Among Studies of Patent Foramen Ovale (PFO) and Cryptogenic Stroke**

Selection bias
Variability in subject age
Differences in stroke subtype definitions
Methodologic differences in PFO detection
Acquisition of imaging data by nonblinded personnel
PFO detection limitations
Poor or inconsistent performance of Valsalva maneuver
Sonographer inexperience
Increased left atrial pressure leading to decreased detection of right-to-left atrial shunting <sup>28</sup>
Nonprotocolized detection <sup>29</sup>

right-to-left shunting, right-to-left shunting at rest, presence of an ASA, and acute pulmonary embolism (**Table 3**).

Atrial septal aneurysm, originally described by Silver and Dorsey,<sup>43</sup> is present if the base of the aneurysmal protrusion measures at least 1.5 cm in diameter and there is either a fixed protrusion of the fossa ovalis at least 1 to 1.5 cm into an atrium or phasic excursion of the fossa ovalis throughout the cardiorespiratory cycle exceeding 1.5 cm from the plane of the atrial septum (**Figure 3**).<sup>44,45</sup> The prevalence of PFO in patients with ASA ranges approximately from 50% to 80%.<sup>39,44,45</sup> Atrial septal aneurysm alone has been found in up to 28% of patients with cryptogenic stroke.<sup>14</sup> The combination of PFO and ASA was associated with a 33-fold higher risk of cryptogenic stroke in one study<sup>14</sup> and a 15% risk of stroke recurrence within 4 years in younger patients (age <55 years) with cryptogenic stroke in another study.<sup>46</sup> However, these markers of increased risk have been questioned on the basis of data from the recent PFO in Cryptogenic Stroke Study (PICSS), which demonstrated that neither PFO diameter or degree of shunt nor concomitant ASA was associated with an increased risk of stroke recurrence or death on 2-year follow-up.<sup>19</sup> However, the PICSS patients were older (mean ± SD age, 59 ± 12 years), and other atherosclerotic or vascular mechanisms may have been responsible for their strokes.

**Table 3. Clinical and Morphologic Features Associated With Recurrent Paradoxical Embolic Events**

**History**

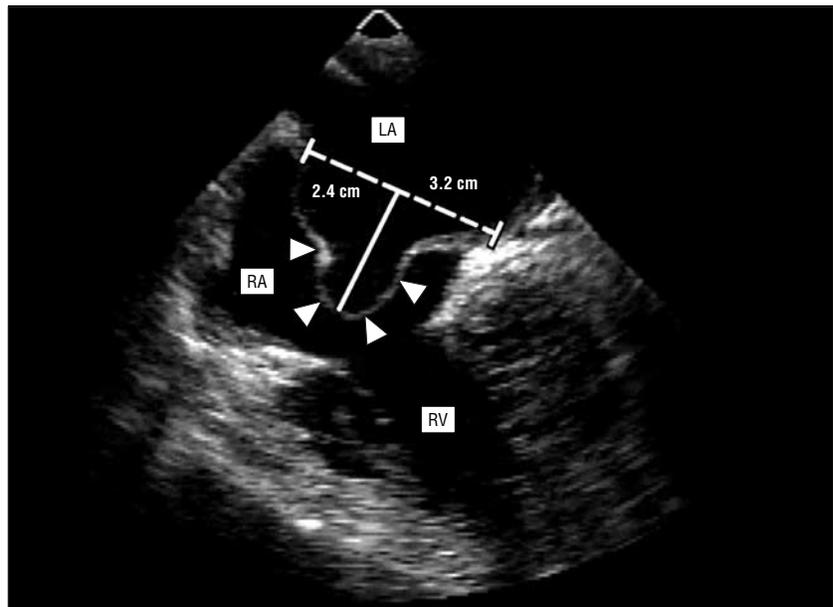
- Valsalva maneuver preceding the cerebrovascular ischemic event<sup>36</sup>
- Coexisting cause of stroke (in particular, hypercoagulable state)<sup>31</sup>
- Multiple strokes or events (in particular, those involving *different* signs and symptoms)<sup>36</sup>
- Patent foramen ovale characteristics
  - Large opening
  - Large right-to-left shunting (defined on the basis of number of contrast microbubbles seen on echocardiographic study of the left atrium after full opacification of the right atrium)<sup>34,35,37</sup>
- Right-to-left shunting at rest<sup>38</sup>
- Presence of an atrial septal aneurysm<sup>29,39-42</sup>

**Methods of PFO Detection**

Transesophageal echocardiography is superior to transthoracic echocardiography for the diagnosis of a PFO and delineation of its morphologic details. Hence, TEE is regarded as the imaging procedure of choice in adult patients with suspected paradoxical embolism.<sup>47,48</sup> For the detection of right-to-left shunting across a PFO, agitated saline contrast medium is typically injected into a peripheral vein during the strain phase of the Valsalva maneuver and the atrial septum is imaged during the release phase of this maneuver. If the clinical suspicion is high, but a right-to-left interatrial shunt cannot be detected by injecting agitated saline contrast medium into a peripheral vein, the femoral vein should be used.<sup>49</sup> Eustachian valve baffling of the agitated saline contrast medium injected through the femoral vein tends to facilitate its movement across the PFO. Transcranial Doppler is an alternative method for detecting a PFO and is considered by some to be superior to the use of 2-dimensional echocardiographic imaging of the atrial septum after intravenous injection of saline contrast medium.<sup>50</sup>

**Treatment Options**

Currently accepted treatment options for patients with PFO and cryp-



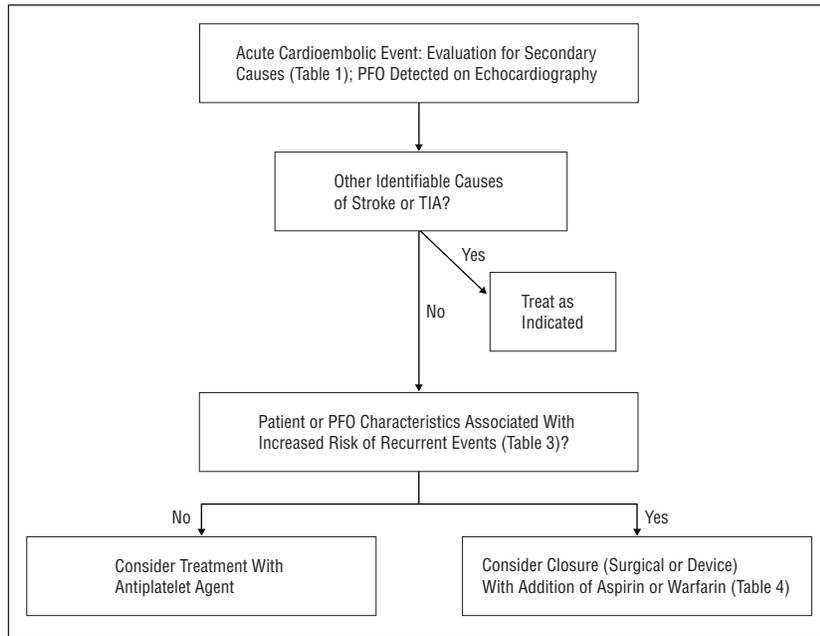
**Figure 3.** Transesophageal echocardiogram (4-chamber view) showing atrial septal aneurysm (arrowheads), atrial septal aneurysm base measuring 3.2 cm, and aneurysm excursion measuring 2.4 cm. LA indicates left atrium; RA, right atrium; and RV, right ventricle.

togenic stroke include antiplatelet agents (usually aspirin, clopidogrel, or dipyridamole), warfarin sodium, direct surgical closure, and percutaneous device closure. A meta-analysis of 5 retrospective studies showed that direct surgical closure was superior to medical treatment (warfarin or antiplatelet therapy) in preventing recurrent neurologic events (odds ratio [OR], 0.27; 95% confidence interval [CI], 0.11-0.66), but this finding was mainly due to its superiority over antiplatelet therapy (OR, 0.36; 95% CI, 0.04-3.09).<sup>51</sup> Warfarin was superior to antiplatelet agents (OR, 0.37; 95% CI, 0.23-0.6) and comparable to surgical closure (OR, 1.19; 95% CI, 0.62-2.27) in preventing recurrent events.<sup>51</sup> However, the PICSS investigators found no significant ( $P = .49$ ) difference between warfarin and aspirin in 2-year recurrent stroke or death rates in the patients with PFO, although there was a trend toward superiority of warfarin to aspirin in the cryptogenic stroke cohort.<sup>19</sup> Limitations of this study were that it was underpowered and the cryptogenic stroke cohort was composed of older individuals. The PICSS investigators did not compare medical treatment with device or surgical closure therapy.

In a large, prospective study of 581 younger patients (age  $\leq 55$  years)

with cryptogenic stroke treated with 300 mg of aspirin over 4 years, Mas et al<sup>46</sup> found no difference in the incidence of recurrent neurologic events between patients with either PFO or ASA and patients with neither atrial septal abnormality. However, the combination of PFO and ASA constituted a subgroup at substantially increased risk for recurrent stroke or transient ischemic attack (TIA). The study was limited by small numbers of patients within each subgroup.

Although direct surgical closure of the PFO is the definitive treatment, stroke recurrence rates after surgical closure have ranged from 0%<sup>32,52</sup> to 19.5%.<sup>53</sup> This variability in recurrence rates reflects differences between patient populations studied, levels of associated risk factors (and thus other possible embolic sources), and duration of follow-up. Dearani et al<sup>36</sup> reported on outcomes after direct surgical closure of PFO at Mayo Clinic, Rochester, Minn. In 91 patients with 1 or more strokes or TIAs who had surgical closure between 1982 and 1998, the mean PFO diameter was 5.4 mm (measured by TEE in all but 1 patient). At 4 years of follow-up, 83% of the patients were free of recurrent TIA, the only recurrent event type in this cohort. Ten patients (11%) had an associated hypercoagulable state. None received anti-



**Figure 4.** Algorithm for managing patent foramen ovale (PFO) in patients with cryptogenic stroke. TIA indicates transient ischemic attack.

coagulation after surgical closure of the PFO, and their risk of recurrent stroke was not higher than that of the other patients. A limited incision was used in approximately 20% of patients and is currently preferred in our practice. Homma et al<sup>53</sup> reported on 28 patients who underwent direct surgical closure of PFO. The mean PFO diameter was approximately 4 mm on TEE, and none of the patients received anticoagulation after surgery. At a mean follow-up of 13 months, the recurrence rate of TIA or stroke was 19.5%. The greatest risk factor for event recurrence was age. Using contrast TEE, Devuyst et al<sup>32</sup> studied 30 patients with cryptogenic stroke and PFO who underwent direct surgical closure. They found that PFO diameter was less than 1 cm in 24 patients and more than 1 cm in 6 patients. None of the patients received warfarin after surgery. At a mean follow-up of 23 months, there were no recurrent neurologic events.

Other investigators have used analytic models to derive optimal management strategies, including recommendations for combining surgical PFO closure with long-term anticoagulation in select patients at increased risk for recurrent stroke.<sup>54</sup> Mas et al<sup>46</sup> advised alternative preventive strategies to aspirin therapy in patients with a

combination of ASA and PFO. In a Markov-based analytic model in which decision algorithms using published data were developed, Nendaz et al<sup>54</sup> showed that if the estimated risk of recurrent stroke exceeded 0.8% per year, therapeutic intervention with anticoagulation or surgery was superior to no treatment. The superiority of surgery or anticoagulation, or both, in these patients was dependent on age, bleeding rates, and surgery-related case fatality rates.

Newer percutaneous device techniques to close a PFO have been introduced in the past decade. These include use of the following devices: Amplatzer PFO Occluder (AGA Medical Corp, Golden Valley, Minn), CardioSEAL Septal Occluder and STARFlex Occluder (NMT Medical Inc, Boston, Mass), the Buttoned device (Pediatric Cardiology and Custom Medical Devices, Amarillo, Tex), the ClamShell (C. R. Bard, Billerica, Mass), the Helix Septal Occluder (W. L. Gore and Associates, Flagstaff, Ariz), and the PFO Star (Cardia, Inc, Burnsville, Minn). The effective PFO occlusion rates, defined as no or trivial residual shunt after device deployment, have ranged from 63% to 100%.<sup>20,55,56</sup> Moreover, a progressive decrease in the incidence of residual shunt during the first 2 years

after device deployment and a low need for surgical or catheter-based intervention for a marked residual shunt have been reported.<sup>20</sup> Recurrent neurologic or peripheral embolic events have ranged from 0% to 3.8% per year.<sup>20,56-59</sup> Because most recurrences occur within the first year after device implantation, a more intensive antiplatelet regimen or warfarin anticoagulation or both may be necessary during this vulnerable period.<sup>20</sup> As with any new procedure, operator experience greatly influences outcome. At present, both the CardioSEAL Septal Occluder and the Amplatzer PFO Occluder have been granted a humanitarian device exemption by the US Food and Drug Administration for PFO closure in patients who have had multiple strokes and in whom conventional drug therapy with warfarin has failed.

Complications may occur during device implantation. These include venous access complications, air embolism through the transseptal sheath, device embolization, and atrial wall perforation with pericardial effusion and resultant cardiac tamponade.<sup>56-58</sup> After implantation, other complications may occur, including device embolization, bacterial endocarditis, frame fracture and deformity, and thrombus formation around the device. The most commonly reported complication during percutaneous device implantation is embolization of the device.<sup>20,55,56,60</sup> The risk of device dislodgment, embolization, or misplacement ranges from 1.4% to 20%.<sup>20,55</sup>

## CONCLUSIONS

The optimal management of patients with PFO and cryptogenic stroke remains unclear because of the difficulties in establishing a cause-effect relationship and the lack of randomized trials comparing the different treatment options. Until more data become available, we propose the management algorithm shown in **Figure 4**, which incorporates the management principles and caveats listed below.

1. In younger individuals presenting with stroke, initial evaluation should include an evaluation of secondary causes (Table 1), includ-

**Table 4. Factors Suggesting a Need for Closure of a Patent Foramen Ovale (PFO)**

Younger patient (age <50 y)
No other cause of stroke identified
Large PFO
Coexisting atrial septal aneurysm
Recurrent neurologic events
Valsalva maneuver associated with previous events
Failure of anticoagulation therapy to prevent events
Intolerance of anticoagulation
High risk of recurrent deep venous thrombosis or pulmonary embolus

ing a survey for a hypercoagulable state, evaluation for collagen vascular disease (vasculitis), TEE, computed tomography or magnetic resonance imaging of the brain, imaging of the cervicocephalic vessels (magnetic resonance angiography, computed tomographic angiography, or conventional angiography), neurologic evaluation, and ophthalmologic consultation if visual symptoms are present.

2. Several diseases and conditions (eg, glaucoma, seizure disorder, multiple sclerosis, migraine, and brain tumor) can masquerade as TIA or stroke symptoms. Recurrent identical events are less likely to have a cardioembolic cause.

3. In patients with hypercoagulable states, the benefits of PFO closure should be weighed against the short- and long-term risks of anticoagulation, particularly the risks associated with subtherapeutic anticoagulation and the risk of recurrent embolic events.<sup>61,62</sup>

4. Patent foramen ovale closure (by surgical procedure or percutaneous device) does not ensure freedom from recurrent neurologic events unless detailed postprocedural echocardiographic studies using agitated saline contrast injections with and without Valsalva maneuver exclude residual right-to-left shunting at the atrial, ventricular, and pulmonary artery levels. Moreover, given the current limitations of diagnosing hypercoagulable states,<sup>61,62</sup> patients may require continued anticoagulation with close therapeutic monitoring even after surgical or percutaneous device closure of the PFO.

5. Patent foramen ovale closure is advisable in patients with high-risk PFO characteristics (**Table 4**), patients with documented recurrent cerebral infarction without evidence of vascular disease, and younger patients (age <50 years) with cryptogenic stroke. Other associations reported in the literature that might prompt closure of a PFO include platypnea orthodeoxia, refractory hypoxemia, and decompression illness.<sup>63,64</sup>

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