CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will consider current data on the relationship between patent foramen ovale and cryptogenic stroke when formulating a treatment plan

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Patent foramen ovale and cryptogenic stroke: Many unanswered questions

ABSTRACT

Patent foramen ovale (PFO) is associated with cryptogenic stroke, but uncertainty remains about the exact relationship and the best management. Percutaneous closure of PFO is safe and effective, but this procedure has yet to be definitely proven to be better than medical therapy. The scenario of PFO and cryptogenic stroke poses unique challenges to primary care physicians and subspecialists and requires an understanding of the relationship between cryptogenic stroke and PFO, and of current data on the safety, efficacy, and comparative effectiveness of management options.

KEY POINTS

PFO is present in up to 25% of the general population, and it is even more common in young patients with cryptogenic stroke.

PFO has not been shown to cause stroke or to significantly increase the risk of recurrent cerebrovascular events in patients treated with antiplatelet drugs.

In patients with PFO, atrial septal aneurysm and large shunt size may confer increased risk of stroke.

There is still no definitive evidence that closure of PFO is better than medical therapy in all patients with PFO and cryptogenic stroke.

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Your patient has had an ischemic stroke, and so far you have found no obvious cause such as atrial fibrillation or carotid disease. Should you look for a patent foramen ovale (PFO)? And if you find it, what should you do?

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This scenario continues to challenge primary care physicians and subspecialists and requires an understanding of the relationship between PFO and cryptogenic stroke, as well as familiarity with current data on the safety and effectiveness of the management options. PFO is known to be associated with cryptogenic stroke, but many questions remain, including:

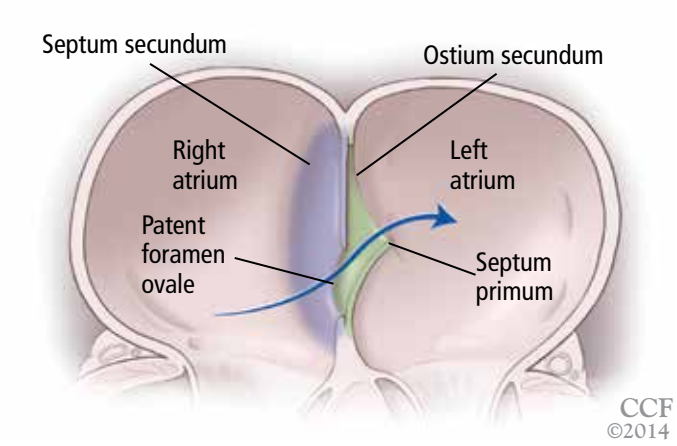
- How can we tell if PFO is a culprit ("pathologic") or an innocent bystander ("incidental") in a patient who has had a cryptogenic stroke?
- Should stroke patients receive different medical therapy if they have a PFO? In particular, should they receive warfarin in addition to aspirin? And what about the novel oral anticoagulants?
- Which patients should undergo percutaneous closure of the PFO?
- Should we even be looking for PFO in stroke patients at this point, if we cannot say with certainty what we should do if we find it?

WHY IS THIS IMPORTANT?

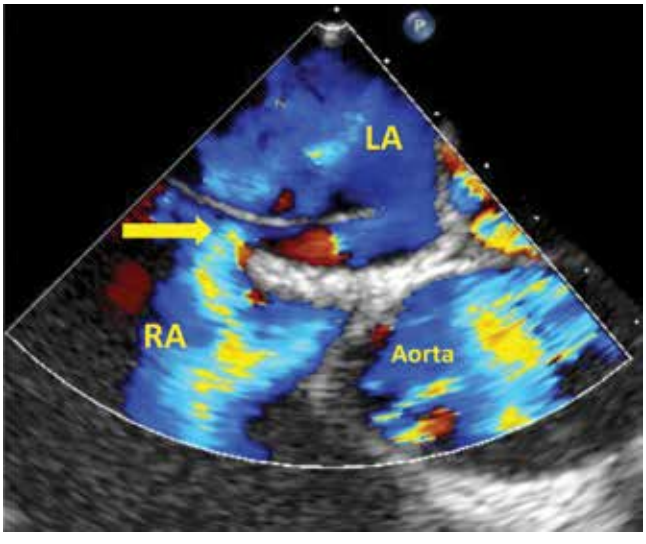
Cerebrovascular disease is common and costly. The estimated yearly incidence of stroke in the United States is 795,000 events, at a cost of nearly $30 billion.[1] The incidence of stroke

FIGURE 1

Patent foramen ovale



In utero, the foramen ovale allows blood to flow from the right atrium to the left, bypassing the lung. But in up to 25% of people, this one-way flap fails to close after birth. Patent foramen ovale (PFO) likely contributes to stroke in some patients, although identification of those at highest risk, the exact mechanism of stroke, and treatment decisions are complex.



PFO is diagnosed by either echocardiography or transcranial Doppler ultrasonography. The most sensitive technique is visualization of microbubbles passing from right-sided circulation to left after the injection of agitated saline. In the image above, color Doppler ultrasonography shows blood passing from the right atrium (RA) to the left atrium (LA) via a PFO (arrow). In cases with obvious shunting of blood on color Doppler, as in this image, agitated saline injection helps to document the size of the shunt.

in Europe is more than 1 million annually.[2]

During the diagnostic evaluation of stroke or transient ischemic attack (TIA), PFO is occasionally discovered incidentally by echocardiography. The management decisions that follow often fall to the primary care physician, who must decipher the conflicting data currently available and explain the options to the patient.

Although reviews have been published on this subject,[3] several newer key trials and data on risk stratification warrant consideration.

DEFINITIONS

PFO is the failure of the septum primum to fuse with the septum secundum, so that a communication remains between the atria (FIGURE 1). The diagnosis is commonly made by echocardiography, when agitated saline is injected into the venous system and bubbles can be seen in the left atrium within three to five cardiac cycles (see video at www.ccjm.org).

Atrial septal aneurysm is loosely defined as a septal excursion or bulging of at least 10 to 15 mm into the left and right atria during the cardiac cycle (FIGURE 2). The combination of PFO and atrial septal aneurysm may be more of a risk factor for stroke than PFO alone (see discussion below).

Cryptogenic stroke. The diagnostic workup of stroke fails to elucidate a clear cause in up to 40% of cases, which are thus called *cryptogenic*.[4] The workup varies, but typically includes a search for a cardioembolic source and for atherosclerotic disease. Embolic sources are evaluated for by electrocardiography, transthoracic echocardiography, and possibly imaging of the aortic arch. Evaluation for atherosclerotic disease of the intracranial and extracranial arteries includes magnetic resonance angiography or, if that is unavailable, computed tomographic angiography or carotid Doppler ultrasonography. If no source is found, long-term cardiac monitoring may be used to detect paroxysmal atrial fibrillation, which may be more common than previously thought.

PFO AND CRYPTOGENIC STROKE ARE COMMON

As noted, there are approximately 800,000 strokes every year in the United States. If

25% to 40% of them are cryptogenic (the true prevalence warrants more evaluation),[4,5] then 200,000 to 320,000 strokes are cryptogenic.

Autopsy studies indicate that 25% of the general population have a PFO, and if the prevalence is the same in people with cryptogenic stroke, that would equal 80,000 people with both cryptogenic stroke and PFO every year. However, the prevalence of PFO in patients with cryptogenic stroke appears to be significantly higher than in the general population.[6] Although these numbers are crude estimates, they provide some insight into the prevalence of this clinical presentation.

HOW ARE CRYPTOGENIC STROKE AND PFO RELATED?

The exact relationship between PFO and cryptogenic stroke is unknown, although cases have been reported of thrombus in transit through a PFO, supporting paradoxical embolism as the plausible cause in stroke patients with PFO.[7–9]

There is clear evidence that the two conditions are associated by more than chance. Homma and Sacco[6] reported that, in several studies, 93 (46%) of 202 patients under age 55 with cryptogenic stroke had PFOs, compared with 29 (11%) of 271 controls ($P < .05$ in all studies).[6]

In their evaluation of 23 case-control studies, Alsheikh-Ali et al[10] found that the summary odds ratio (OR) for PFO in cryptogenic stroke vs PFO in control patients was 2.9 (95% confidence interval [CI] 2.1–4), largely driven by an OR of 5.1 (3.3–7.8) in those under age 55. Through Bayesian probability theory, this correlated with only a 33% probability that PFO in a patient with cryptogenic stroke was an innocent bystander rather than the culprit.[10]

IS PFO A RISK FACTOR FOR STROKE?

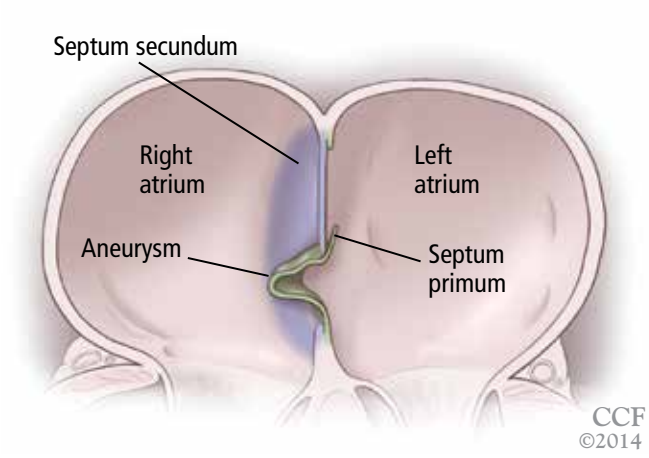
One of the more puzzling aspects of the relationship of PFO to cryptogenic stroke is that despite a clear association, there is little evidence that the relationship is causal.

Di Tullio et al[11] followed 1,100 people who had no history of stroke and found that the risk of a first stroke in those with a PFO was not significantly higher than in those without a PFO, regardless of age, sex, or ethnic or racial group. At 80 months, the hazard ratio of stroke in people who had a PFO was 1.64 (95% CI 0.87–3.09).[11] The findings were similar at 11 years, with a hazard ratio of 1.10 (95% CI 0.64–1.91).[12]

A prospective study of 585 patients found a similar risk of stroke in those with and without a PFO, with a hazard ratio of 1.46 (95% CI 0.74–2.88; $P = .28$).[13]

FIGURE 2

Atrial septal aneurysm



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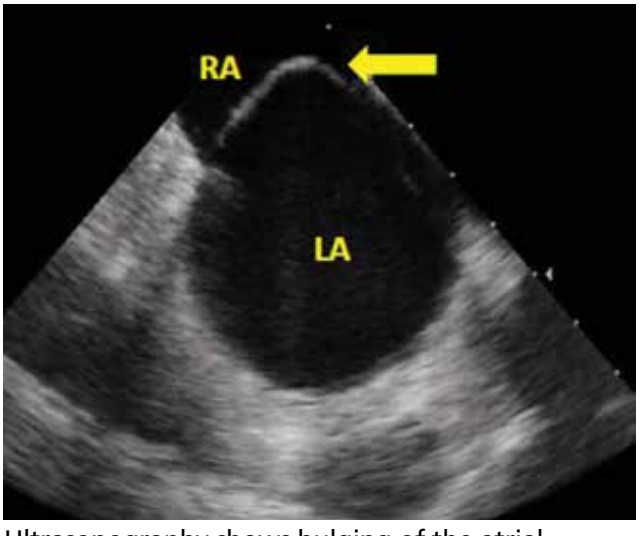

Ultrasonography shows bulging of the atrial septal aneurysm (arrow) into the right atrium (RA).

These prospective trials suggest that although previous studies have found a higher prevalence of PFOs in patients with cryptogenic stroke than in patients without stroke, there appears to be very little if any increased risk from baseline for a first stroke or TIA.

The lack of statistical significance in these trials should be interpreted with some caution, as a small increased risk is difficult to show if the event rate is low (approximately 10% of patients had events over 11 years in the study by Di Tullio et al[12]).

HOW DO WE KNOW IF A PFO IS A CULPRIT OR BYSTANDER?

Unfortunately, this is largely unanswered, though experts have suggested that echocardiographic features of the PFO, radiographic characteristics of the stroke, and clinical features of the patient may provide useful information.

'High-risk' features on echocardiography

Certain features of PFO may portend a high risk of cerebrovascular events. Both right-to-left shunting at rest and septal hypermobility were found in one study[14] to be more common in patients with a PFO who had a stroke or TIA than in patients with a PFO but no cerebrovascular events. Also, patients who had these features and had a stroke had a higher risk of recurrence than stroke patients without these features (12.5% vs 4.3%, $P = .05$).[14]

The prevalence of PFO in patients with cryptogenic stroke appears significantly higher than in the general population

Septal hypermobility and shunting at rest are easily diagnosed by echocardiography, and detecting these "high-risk" features would be useful if they could identify patients who would benefit from special therapy, such as percutaneous closure of the PFO.

Unfortunately, when investigators looked at these features in subgroup analysis of the major randomized controlled trials of percutaneous closure vs medical therapy, the results were mixed.

CLOSURE 1 (the Evaluation of the STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale)[15] found percutaneous closure to be no better than medical therapy, regardless of shunt size or the presence of atrial septal aneurysm.

Similarly, the PC trial (Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder With Medical Treatment in Patients With Cryptogenic Embolism)[16] found no statistically significant benefit of closure in those with atrial septal aneurysm.

In contrast, the RESPECT trial (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment)[17] showed percutaneous closure to be beneficial in patients with atrial septal aneurysm or large shunt.

Radiographic characteristics of the stroke

Another area of interest in trying to identify culprit PFOs is the radiographic characteristics of the stroke.

In a study comparing patients with stroke related to atrial fibrillation vs patients with cryptogenic stroke and a known PFO, those in the latter group were more likely to have a single cortical infarction (34.2% vs 3.1%; $P < .001$) or multiple small scattered lesions (23.1% vs 5.9%; $P < .01$).[18] Similarly, in a large database of patients with cryptogenic stroke and known PFO status, a superficially located stroke was associated with the presence of PFO (OR 1.54; $P < .0001$).[19]

Although these findings do not tell us with certainty that a patient's PFO was the cause of his or her stroke, they provide guidance when dealing with the uncertainty of how to manage a patient with PFO. They may be useful in clinical practice, for example, when discussing treatment options with a young patient with cryptogenic stroke who has no risk factors and a superficial single infarct and who is found to have a PFO with a right-to-left shunting at rest.

Patient characteristics

Kent et al[20] developed a 10-point index (the RoPE score) in an attempt to assign a probability to whether a stroke was PFO-related. Points were assigned for patients who were younger, who had a cortical stroke on neuroimaging, and who did not have diabetes, hypertension, smoking, or prior stroke or TIA. Patients with cryptogenic stroke with a higher RoPE score were more likely to have a PFO and thus had a higher likelihood that the index event was related to PFO. Of note, the patients with the highest likelihood of PFO-related stroke were

the least likely to have a recurrence (RoPE score of 9 to 10; PFO-attributable fraction 88%; estimated 2-year recurrence rate 2%; 95% CI 0%–4%), whereas those with a low RoPE score have more traditional risk factors for stroke and thus are more likely to have a recurrence (RoPE 0 to 3; estimated 2-year recurrence rate 20%; 95% CI 12%–28%).[20]

Again, this sheds light on a difficulty faced by randomized controlled trials: the patients who may benefit from closure of a PFO may very well be those with the lowest recurrence rates without intervention.

The RoPE index was examined in an attempt to validate previously described morphologic criteria of "high-risk" PFO,[21] though none of the previously described "high-risk" echocardiographic features (large physiologic size, hypermobile septum, shunt at rest) were more common in the group with presumed PFO-attributable stroke (RoPE score > 6). This underscores the difficulty of distinguishing pathologic PFO from incidental PFO.

KEY TREATMENT CONSIDERATIONS FOR SECONDARY PREVENTION

Given the complicated relationship between PFO and cryptogenic stroke, there has been much debate over management strategies. The three options are surgical closure, percutaneous closure with a device, and medical therapy. The goal of all three is to prevent the recurrence of stroke or TIA.

Surgical closure has largely been supplanted by percutaneous closure, but is still done in specific situations such as when a PFO is found incidentally on transesophageal echocardiography during surgery for another cardiac condition. The data on such cases[22] tend to support the argument that asymptomatic PFOs in the general population have a relatively benign natural history.

Thus, the two key questions about management that warrant discussion are: is anticoagulation superior to antiplatelet therapy? And is percutaneous closure superior to medical management?

Anticoagulant vs antiplatelet therapy

Whether to treat with aspirin or with a vitamin K antagonist has been a subject of debate, although there is no strong evidence to suggest that anticoagulation is superior to antiplatelet therapy.

The concern that aspirin alone is insufficient in some patients stems from a study by Mas et al,[23] who followed 581 patients with cryptogenic stroke who had a PFO alone, a PFO with an atrial septal aneurysm, or neither. The rate of stroke recurrence at 4 years on aspirin therapy was 2.3% in those with a PFO alone, 15.2% in those with a PFO with an atrial septal aneurysm, and 4.2% in those with neither.

Many have concluded that aspirin therapy does not sufficiently protect those with both PFO and atrial septal aneurysm, given the high recurrence rate in this group. This might lead to the suggestion that anticoagulation could be of benefit in these patients.

However, the Patent Foramen Ovale in Cryptogenic Stroke Study (PiCSS)[24] and the Spanish Multicenter Study Into Right-to-Left Shunt in Cryptogenic Stroke (CODICIA)[25] found similar recurrence rates in patients with PFO and atrial septal aneurysm compared with those with only PFO. In these two studies, recurrence rates were similar regardless of whether patients were taking aspirin or warfarin.

There is little evidence of a strong causal relationship between PFO and cryptogenic stroke

In a study that followed 140 consecutive patients with both stroke and PFO, those treated in a nonrandomized fashion with antiplatelet agents had no difference in the recurrence rate compared with those treated with anticoagulation.[26]

Although uncertainty remains because no head-to-head randomized controlled trial has been done, some patients with PFO have other indications for anticoagulation, most commonly atrial fibrillation and venous thromboembolic disease.

There are currently no data on the use of novel oral anticoagulants in this setting.

Is percutaneous closure better than medical therapy?

When cryptogenic stroke is treated with antiplatelet therapy or anticoagulation therapy, the recurrence rate is the same whether or not the patient has a PFO.[23–25] The belief that medical therapy offers adequate secondary protection is supported by a meta-analysis of 15 studies that found no increased risk of re-

current ischemic events in those with a PFO on medical therapy (antiplatelet or anticoagulant) vs those without a PFO (relative risk 1.1, 95% CI 0.8–1.5).[27]

Despite the conflicting evidence, percutaneous closure of PFO is still performed, mostly on a case-by-case basis. This has been supported by an apparent benefit in observational studies.

A systematic review of 52 single-arm studies and 7 comparative nonrandomized studies of patients with PFO and cryptogenic stroke found the rate of recurrent stroke to be 0.36 per 100 person-years with percutaneous closure vs 2.53 per 100 person-years with medical therapy.[28] However, three long-awaited randomized controlled trials (CLOSURE 1, the PC trial, and RESPECT) failed to show a significant reduction in primary end points with percutaneous closure vs standard medical therapy.[15–17]

These trials had several limitations: event rates were low, medical therapy varied by provider, and enrollment was slowed by out-of-study percutaneous closure in patients perceived to be at high risk (though, as discussed above, high risk is difficult to determine).

No strong evidence suggests that anticoagulation is superior to antiplatelet therapy

Intention-to-treat analysis in RESPECT showed no benefit from percutaneous closure, but a favorable outcome was noted with closure in as-treated analysis (HR 0.27; 95% CI 0.1–0.75; P = .007) and per-protocol analysis (HR 0.37; 95% CI 0.14–0.96; P = .03) of the 980 randomized patients.[17] This *suggests* some benefit, as does the CLOSURE 1 trial, in which 3 of the 12 recurrent strokes in the percutaneous closure group occurred before the device was implanted.[15]

The low event rates in these studies prompted several meta-analyses.[29–35] However, only two suggested a benefit of percutaneous closure over medical therapy. In one recent meta-analysis,[29] observational study data suggested benefit from percutaneous closure, whereas three randomized controlled trials failed to show a statistically significant benefit.

The conclusions of the meta-analyses must be interpreted with caution because of inherent differences in the randomized controlled trials, including the closure device used, inclusion criteria, study end points, and variations in medical therapy.

Devices differ

A meta-analysis by Khan et al[35] showed a benefit of percutaneous closure when evaluating only studies using the Amplatzer PFO occluder (AGA Medical), as in RESPECT and the PC trial.[35] As data accumulate, it is important to remember that there are differences between devices. Ongoing trials continue to investigate the Amplatzer device (NCT01550588) and the GORE HELEX Septal Occluder/GORE Septal Occluder (Gore Medical) (NCT00738894).

In another meta-analysis, Pineda et al[31] found a benefit with closure in the as-treated analysis using data from all three randomized controlled trials (OR 0.62; 95% CI 0.41–0.94; P = .02).[31] Although paradoxical embolism through the PFO as the mechanism of stroke has been questioned, this finding suggests that actual closure of a PFO may protect against further events, presumably by preventing paradoxical embolism.

Different closure devices have different side effects. The incidence of atrial fibrillation with the CardioSEAL STARFlex device (NMT Medical) is higher than with medical therapy (used in the CLOSURE trial[15]), whereas this risk was not statistically significantly increased in the PC trial[16] and RESPECT,[17] which used the Amplatzer device.

Benefit in those with atrial septal aneurysm?

Percutaneous closure has been shown to be safe and effective in patients with PFO and atrial septal aneurysm.[36] There was some benefit of closure over medical therapy in a subgroup analysis from RESPECT in these patients, with a HR of 0.19 (95% CI 0.04–0.87, P = .02),[17] although this was not seen in either CLOSURE 1 or the PC trial.

WHAT ARE THE RISKS OF PERCUTANEOUS CLOSURE?

Minor complications of percutaneous closure include bleeding, atrial arrhythmias, device embolization and fracture, and complications related to vascular access. Major complica-

tions include hemorrhage requiring transfusion, need for surgery, cardiac tamponade, pulmonary embolism, and death.

The cumulative rate of major complications in 10 observational studies was 1.5%, and the rate of minor complications was 7.9%.[37] The RESPECT investigators reported a serious adverse event in 4.2% of patients (ranging in severity from chest tightness to cardiac tamponade).[17]

Another possible consequence of percutaneous closure is the need for chronic anticoagulation because of the increased risk of postprocedural atrial fibrillation seen in meta-analyses,[29,31,32] though this may be device-specific.[32]

Percutaneous closure was considered successful—ie, to have nearly or completely eliminated shunting of blood through the defect—at 6 months of follow-up in 95.9% of patients in the PC trial, 93.5% in RESPECT, and 86.1% in CLOSURE 1.[15–17]

WHAT SHOULD WE BE DOING IN DAILY PRACTICE?

Give aspirin. Aspirin is effective in secondary stroke prevention, and data suggest that patients with PFO and cryptogenic stroke who receive aspirin therapy alone have a similar risk of recurrent events as patients without PFO.

Give warfarin if indicated. Evidence is insufficient to recommend vitamin K antagonist therapy in all patients with PFO and cryptogenic stroke. However, coexisting conditions that warrant anticoagulation must be taken into account.

Individualize. Given the lack of evidence to definitively guide management of patients with cryptogenic stroke and PFO, we need to individualize our approach, taking into account patient preferences, bleeding risk, ability to tolerate procedures, and the likelihood that the PFO is at fault.

No definitive answer on PFO closure. The most recent data suggest that closure may be beneficial, but key questions remain: Who will benefit? And what is the ideal medical therapy? Optimal management will only be established by the continued enrollment of appropriate patients into ongoing clinical trials.

Another question is whether it is possible to perform a randomized controlled trial with enough patients to definitively prove whether percutaneous closure is superior to medical therapy. Recent experience would suggest not.

In the meantime, we have some guidance from the American Heart Association and the American Stroke Association Council on Stroke[38] based on the limited evidence available.

Consider patient preference. The physician should present the options to the patient in a balanced manner to enable him or her to make an informed decision. Patients can also be encouraged to seek additional information at websites such as www.stroke.org and www.nlm.nih.gov.

Referral to an interventional cardiologist for evaluation for closure is reasonable in patients with recurrent stroke, medication failure, complicated atrial septal anatomy such as PFO with aneurysm or large shunt, concurrent thromboembolic disease, or contraindications to anticoagulation.

MORE WORK NEEDED

Areas for further study include further identifying the characteristics of patients with PFO and cryptogenic stroke that might indicate who would benefit from percutaneous closure, elucidating the mechanism of stroke in these patients, and determining whether routine stroke evaluation should include echocardiography with a bubble study if there is no change in management based on the finding of PFO.[39]

Patients who may benefit from PFO closure may also have the lowest rates of recurrence without intervention

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