



Published in final edited form as:

Neurol Clin. 2015 May ; 33(2): 491–500. doi:10.1016/j.ncl.2015.01.002.

Prevention of Recurrent Stroke in Patients with Patent Foramen Ovale

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Keywords

Cryptogenic stroke; Patent foramen ovale; Ischemic stroke; Echocardiography; Secondary prevention

OVERVIEW

Although patent foramen ovale (PFO) is frequently encountered in health, the prevalence is increased for patients with cryptogenic stroke (CS). PFO provides a potential site of paradoxical embolism, although there is rarely mechanistic certainty for individuals with CS. This results in problems of attribution and therapeutic uncertainty for individuals with CS. Recent trials of device-based closure of PFO for patients with CS have not shown clear benefit. At the same time, the preferred medical therapy for patients with CS and PFO remains unclear. This article discusses the controversies that frame decisions for patients with CS and PFO, recent clinical trial data that inform the use of device-based therapies, and a recently developed predictive model that may aid in identifying individuals who might benefit from PFO closure.

PATENT FORAMEN OVALE: DEVELOPMENT AND PREVALENCE

During fetal development, the foramen ovale is the site where oxygenated blood is allowed to bypass the high-resistance pulmonary circulation. Throughout development, it is a critical component of the fetal circulation. Most commonly the septum primum and secundum fuse just after birth, thus closing this right-to-left communication. For approximately 20% to 25% of healthy individuals, however, the foramen ovale remains patent.^{1,2} For most of these patients, PFO never causes symptoms and is found only incidentally during echocardiographic investigation for other reasons. The frequency of this anatomic feature and the generally benign natural history have led some to consider PFO (in the absence of clinical significance) as a normal variant.³ Although population studies have not reliably

found that PFO is associated with ischemic stroke,⁴⁻⁶ potential effects in these studies were undoubtedly substantially diluted by the inclusion of strokes with known causes. Despite concerns of possible ascertainment bias caused by increased attention to potential right-to-left shunting when an alternative stroke mechanism has not been identified, the prevalence of PFO for patients with CS seems higher than for matched control subjects, population samples, or autopsy studies,² and is especially higher in patients with CS without conventional stroke risk factors. Thus for some, there is likely a mechanistic link between this site of right-to-left shunting and stroke.^{7,8} When PFO is found in the setting of CS, the significance (and the preferred therapy) is often unclear.

THE PROBLEM OF ATTRIBUTION

Observing a thrombus in transit through a PFO is quite rare. In the absence of this direct evidence it is not possible to know with certainty for an individual whether an observed PFO is related to stroke. Through a Bayesian transformation, however, we can estimate a PFO attributable fraction for subgroups of patients with CS. Generally, the likelihood that an observed PFO is related to an index stroke is related to the PFO prevalence in CS cases compared with control subjects. Consider the scenario described in Fig. 1.⁹ Assuming a control PFO prevalence rate of 25% in a healthy population, we would expect a 25% prevalence rate for patients with CS if PFO is completely incidental (and unrelated related to CS). As PFO prevalence for patients with CS rises above the control rate there is an increased likelihood than an observed PFO is related to their index stroke. The probability that an observed PFO is incidental is related directly to the control rate prevalence by the equation in Fig. 1.⁹

PATENT FORAMEN OVALE: ANATOMIC RISK FACTORS

Transesophageal echocardiography (TEE) remains the standard tool to evaluate PFO because it allows for direct assessment of the interatrial septum and associated anatomy.¹ There is increasing interest in using a multimodality approach and complementing TEE with contrast-transcranial Doppler to further define PFO in the setting of CS. Contrast-transcranial Doppler may have higher sensitivity for detecting PFO and may also offer prognostic information over TEE.^{10,11}

Ideally, for an individual, anatomic and physiologic features would reliably distinguish benign from pathogenic PFOs. With these goals investigators have evaluated numerous candidate echocardiographic features that seem to confer risk. One associated feature, presence of an atrial septal aneurysm, has been proposed as a marker of risk.¹² Atrial septal aneurysm describes a hypermobile interatrial septum and is seen more commonly in patients with PFO and recurrent CS. Another characteristic, severity of right-to-left microbubble movement across a PFO, a proxy for large physiologic shunt size, has been identified as a risk factor for stroke recurrence,¹³ although not consistently.¹⁴ Persistent right-to-left shunting across a PFO (throughout rest and Valsalva) has been proposed to increase risk through a similar mechanism as has persistence of a eustachian valve, an anatomic feature that preferentially shunts blood from the inferior vena cava across the PFO during fetal growth.^{15,16} Interestingly, in a recent analysis from the Risk of Paradoxical Embolism (RoPE)

database (described later) of 1294 patients with CS evaluated for PFO with TEE, three of these proposed markers of risk (atrial septal aneurysm, shunt size, and shunt at rest) were not associated with clinical features that suggested that an observed PFO is related to CS.¹⁷ Despite the use of multiple imaging tools, it seems that anatomic and physiologic features alone cannot be used to consistently distinguish incidental from pathologic PFO.

NULL INTERVENTION TRIALS?

Because right-to-left shunting provides a potential site of paradoxical embolization, there has been significant interest in device-based PFO closure. Recent clinical trials have tested the hypothesis that stroke recurrence will decrease if a mechanistically important PFO is closed. Unfortunately, the trial results raised more questions than they answered because all three missed their primary intention-to-treat outcomes.¹⁸⁻²⁰ 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 trial randomized 909 patients to closure with the STARFlex (CardioSEAL, NMT Medical, Boston, MA) device versus medical therapy and followed them for 2 years. The cumulative incidence of the composite of stroke or transient ischemic attack (TIA) was 5.5% in the device-closure group and 6.8% in the medically treated arm (adjusted hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.45–1.35; $P = .37$). A recent observation that many of the recurrent events were not caused by paradoxical embolism but instead by alternative causes further clouds the results of this trial.²¹

Two intervention trials evaluated the Amplatzer PFO Occluder (AGA Medical, Golden Valley, Minnesota/St Jude, Saint Paul, MN) device. The Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) (980 patients followed for a median of 2.1 years) and the PC Trial (414 patients for an average of 4.1 years) both evaluated device closure versus medical therapy and both missed their primary end points (various composites that include stroke, TIA, and death) (HR, 0.4; 95% CI, 0.22–1.11, $P = .08$ for RESPECT; HR, 0.63; 95% CI, 0.24–1.62; $P = .34$ for PC Trial). These trials suffered from significant loss to follow-up (relative to rates of trial end points), and because outcomes in the medical arms of these trials were rare, they were likely underpowered to detect beneficial effects if any existed. It is worthwhile to note that all of these trials (especially the Amplatzer studies) show a trend toward beneficial effect of device-based closure despite a lack of statistical significance.

Despite the consistent directionality of these trials, current guidelines from the American Heart Association/American Stroke Association further downgraded their recommendation regarding device-based closure from IIb (reasonable to consider) to III (not useful, may be harmful) (Level of Clinical Efficacy 1-0, Level of Evidence T2).²² Because the potential value of this therapeutic approach is balanced by important occasional device-related complications (eg, atrial fibrillation and thrombus formation),²³ this new recommendation concludes that the available data in summary clearly do not support closure. Recent analyses, however, suggest that this recommendation is perhaps premature and that closure may be beneficial for some.

Since the publication of these major clinical trials, there have been numerous attempts by a variety of investigators to combine these trials through meta-analysis.²⁴⁻³⁰ These efforts, taken together, demonstrate a strong but not statistically significant trend toward reduction with device-based closure in the rate of the composite outcome of recurrent stroke, TIA, or death. A statistically significant beneficial effect on the outcome of stroke alone has not been consistently seen (Fig. 2), although a beneficial effect on stroke has emerged in some studies when combining only the Amplatzer trials in fixed-effect models.^{27,31,32} More recently a network meta-analysis supplemented the three trials described previously with the results of a randomized clinical trial that compared various device-based closure techniques (Amplatzer, STARFlex, and HELEX [W.L. Gore and Associates, Flagstaff, AZ] devices) head-to-head.³³ The results of this network, which estimate comparative treatment effects by summarizing direct and indirect evidence, suggest an overall beneficial effect on recurrent stroke risk for device-based closure and, importantly, evidence that not all closure devices are similarly effective. The Amplatzer device seemed most effective in preventing recurrent stroke when compared with medical therapy (rate ratio, 0.39; 95% CI, 0.17–0.84) as compared with STARFlex (rate ratio, 1.01; 95% CI, 0.44–2.41) and HELEX devices (rate ratio, 0.71; 95% CI, 0.17–2.78) devices. As of this writing, however, the Amplatzer device remains unavailable in the United States, although PFOs may be closed using various off-label atrial septal defect devices, none of which have been designed for PFO closure.

RISK OF PARADOXIC EMBOLISM DATABASE AND SCORE

Although PFO is a congenital remnant distributed randomly in the population, and not known to be associated with other observable characteristics, among the CS population it has been repeatedly and consistently noted that patients with PFO have a very different distribution of clinical variables than patients without PFO. The relationship between PFO and other clinical variables (whereby PFO seems to “protect” patients with CS from vascular risk factors, such as diabetes, hypertension, smoking, and so forth) presumably arises because patients with PFO have a stroke mechanism that does not require the same burden of vascular risk factors as do patients with CS whose stroke is caused by some other occult mechanism. This has been formally described as index event bias, because the induced correlation between risk factors (known and unknown) can confound estimates of the causal contribution of these correlated risk factors to recurrence risk.³⁴

Nevertheless, one can use the correlation of characteristics with PFO that arise in the CS population to arrive at estimates for the PFO-attributable fraction, conditional on patient characteristics. That is, one can use the differences in characteristics in patients with CS with and without a PFO to arrive at patient-specific probabilities of finding a PFO even before a transesophageal echocardiogram, or other imaging study, is performed. In turn, through understanding the relationship between PFO prevalence and attributable fraction for patients with CS, one can estimate the likelihood an observed PFO is pathogenically related to CS. Ideally, this estimate can be used to target interventions (eg, device-based PFO closure) to those most likely to benefit.

Recently, investigators have derived and begun to apply a risk score to improve clinical decision making for patients with CS and PFO. The RoPE study was designed to examine

the ideas that only patients with a high risk of recurrent paradoxical embolism will benefit from device-based PFO closure, and that the attributable recurrence risk can be estimated based on the likelihood an observed PFO is related to CS and risk of stroke recurrence.³⁵ This research group combined 12 studies of patients with CS investigated for PFO (N = 3674) to create a multivariate regression model predicting the presence of PFO for patients with CS. This model, based on easily identifiable clinical characteristics, was converted into an easy to use point score (RoPE score, Table 1), which allows estimation of a stratum-specific PFO attributable fraction for patients with CS (Fig. 3).

In general, for patients with CS and traditional stroke risk factors (eg, older age, smoking, hypertension, diabetes) and the absence of cortical infarct location on neuroimaging, it is less likely that an identified PFO is related to their index CS. In contrast, for younger patients with CS with few of these traditional stroke risk factors and a cortical infarct location, it is more likely that an identified PFO is related to CS. One of the key observations from this large database was that stroke recurrence risk was highest for patients with the lowest PFO attributable fraction (see Fig. 3). This finding underscores the difficulty of patient selection for PFO closure. Although the clinical intuition supporting this score is compelling, whether this approach can be used to identify a more treatment-responsive population for clinical trials, or to ultimately target PFO-specific therapy, remains unclear.

OPTIMAL ANTITHROMBOTIC APPROACH

Although ischemic stroke is an arterial event, venous thromboembolism is likely the most appropriate therapeutic target in the setting of paradoxical embolism through a PFO. Theoretically, treatment aimed at venous thromboembolism (anticoagulation) might be more effective than antiplatelet therapy for minimizing the risk of recurrent stroke. Ambiguity surrounding this issue dominates the current standard of care because recent clinical trials have left decisions about medical therapy to the discretion of treating physicians.¹⁸⁻²⁰ The only relevant randomized trial of comparing antithrombotic therapies, The PFO in Cryptogenic Stroke Study, included all patients in the Warfarin-Aspirin Recurrent Stroke Study who had a TEE.³⁶ Of the subset of patients with CS and PFO (N = 98), there was no significant difference in the rate of stroke, TIA, or death at 2 years for those treated with warfarin or aspirin ($P = .48$; HR, 0.72; 95% CI, 0.29–1.81). A recent meta-analysis that included PFO in Cryptogenic Stroke Study along with observational studies of patients with CS and PFO suggests a similarly sized relative benefit for anticoagulation compared with antiplatelet therapy for patients with CS and PFO.³⁷ The component studies in this meta-analysis, however, did not control for confounding by indication, an important issue because patients treated with anticoagulation are different from those treated with antiplatelet therapy with respect to the likelihood of having purported high-risk echocardiographic or neuroradiologic features.³⁸

Currently, guidelines recommend only antiplatelet therapy for ischemic strokes unless a clear (or presumed) embolic source in the heart is identified (eg, mechanical heart valves or atrial fibrillation) (Level of Clinical Efficacy 2-1, Level of Evidence T1-T3).²² These guidelines may lead to undertreatment of an important potential therapeutic target for patients with CS that is caused by paradoxical embolism. In the absence of clear data it may

be reasonable to consider anticoagulant therapy, in essence directed toward the likely pathophysiologic cause of stroke, for patients with likely PFO-related CS with high recurrence risk and lower risk of bleeding. Those with CS in the setting of PFO most accurately represent a subgroup of patients with embolic strokes of undetermined source³⁹; an ongoing clinical trial is attempting to understand the medical treatment that is most appropriate for these patients.⁴⁰ For now there is no consensus on the preferred antiplatelet or anticoagulant medical regimes for these patients and treatment decisions are often made, in the setting of pathogenic uncertainty, with a weak evidentiary base.

SUMMARY

PFO is common in the general population and as a result it is frequently encountered in the search for cardioembolic sources of ischemic stroke. It is unclear if PFO-specific anatomic or physiologic features can identify high-risk PFOs. Recent clinical trials of device-based closure for patients with CS and PFO have not shown benefit, although they have been limited by low stroke recurrence rates. Subsequent meta-analyses have shown trends toward benefit for some, although these have generally not been statistically significant for the composite end points that emulate the primary trial analyses. Fortunately, investigators have recently developed a risk score to identify the likelihood an observed PFO is related to CS. However, more work is needed to determine whether device-based closure targeted toward a subgroup of patients might be beneficial. In the meantime optimal medical therapy for patients with CS and PFO is unknown and studies continue to better define and treat patients with likely paradoxical embolism to minimize the risk of stroke recurrence.

Treatment decisions for patients with PFO and CS should be individualized because many observed PFOs are incidental and are unrelated to an index CS. Patients with CS and PFO represent a heterogeneous group where the likelihood an observed PFO is related to CS and also the risk of stroke recurrence are highly variable, although they can be estimated. Device-based PFO closure holds promise as an effective therapy if it can be directed toward patients with a likely paradoxical embolism and a reasonably high risk of recurrence. Further research is needed to establish a firmer evidentiary basis for the optimal medical approach, and the value of device-based PFO closure.

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KEY POINTS

- Three recent clinical trials of device-based PFO closure were negative with respect to their intention-to-treat primary outcomes, although meta-analyses showed promising beneficial trends.
- Many believe that anticoagulation therapy is indicated in these patients, whose stroke may be caused by venothromboembolic disease, but reliable evidence for this is lacking.
- The RoPE score can stratify patients with CS based on easily identifiable clinical characteristics according to the likelihood a CS may be attributable to a discovered PFO.
- For patients with CS and PFO, recurrent stroke risk is lowest in those with clinical features most suggestive of a PFO-attributable stroke.
- It is unknown whether risk scores can identify patients who are likely to benefit from device-based PFO closure.

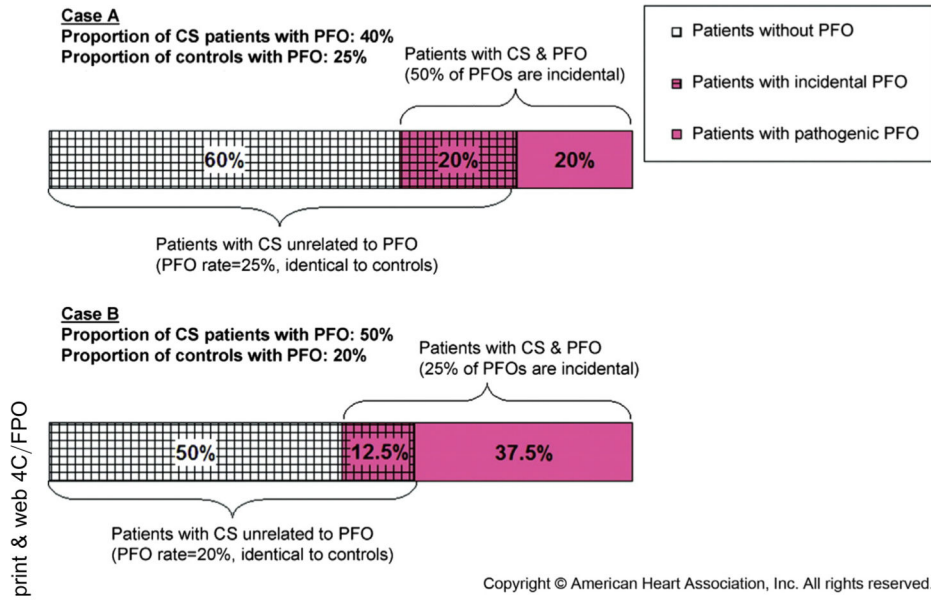


Fig. 1. Proportion of patients with CS without PFO with incidental PFO and with pathogenic PFO. This figure shows how the proportion of incidental versus pathogenic PFO in patients with CS can be calculated based on the prevalence of PFO in patients with CS and in control. (Adapted from Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? Stroke 2009;40(7):2350; with permission.)

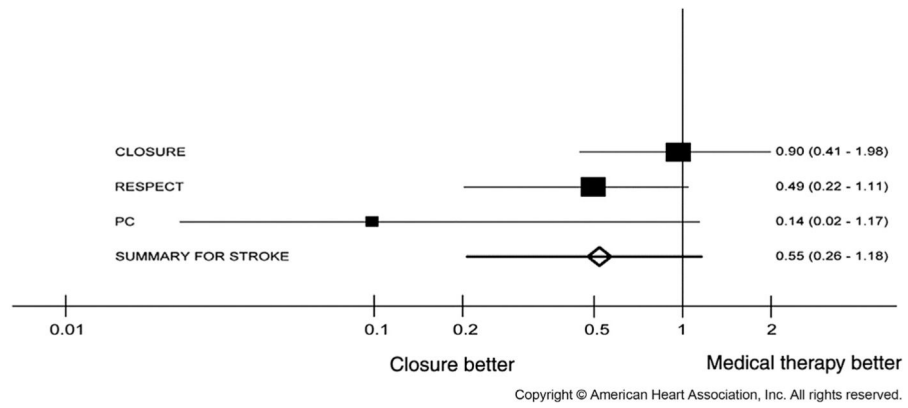


Fig. 2.

Forest plot for the meta-analysis of hazards ratios of stroke of mechanical closure vs medical treatment from 3 randomized clinical trials. (*Adapted from* Kitsios GD, Thaler DE, Kent DM. Potentially large yet uncertain benefits: a meta-analysis of patent foramen ovale closure trials. *Stroke* 2013;44(9):2641; with permission.)

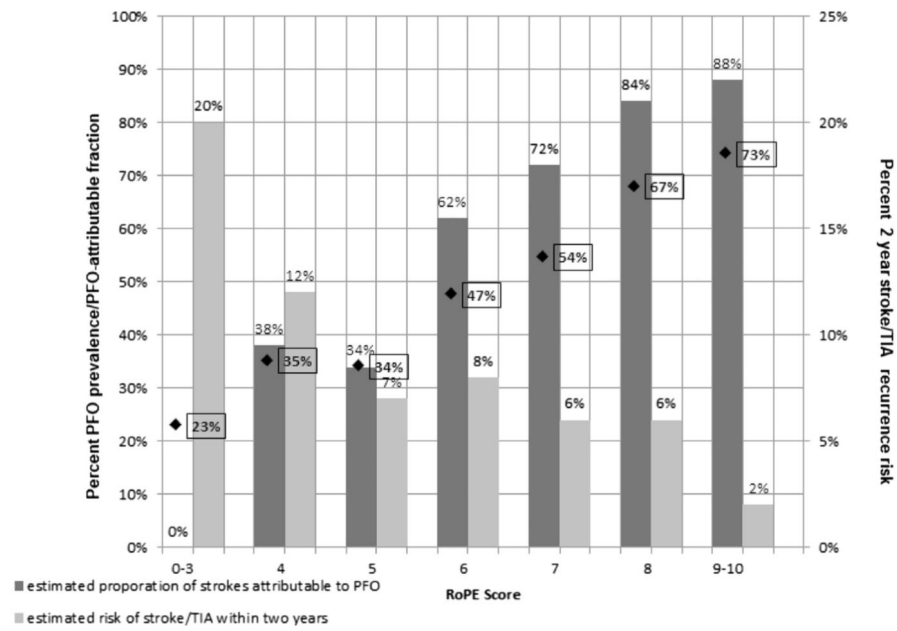


Fig. 3. Estimated proportion of strokes attributable to PFO for patients with CS and estimated risk of stroke/TIA recurrence within 2 years as a function of RoPE score (x-axis). ♦ and % in boxes represent stratum-specific PFO prevalence.

Table 1
The RoPE score

Characteristic	Points	RoPE Score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age		
18–29y	5	
30–39 y	4	
40–49 y	3	
50–59 y	2	
60–69 y	1	
70 y	0	
Total Score (sum of individual points)		
Maximum Score (A patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum Score (A patient 70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

Clinical risk score based on easily identifiable characteristics to predict the probability that an observed PFO is related to CS. Higher point score indicates an increased likelihood that a PFO is related to an index CS.

Adapted from Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related versus incidental patent foramen ovale in cryptogenic stroke. *Neurology* 2013;81(7):623; with permission.