Patent Foramen Ovale in Cryptogenic Stroke
Incidental or Pathogenic?

Alawi A. Alsheikh-Ali, MD; David E. Thaler, MD, PhD; David M. Kent, MD, MS

Background and Purpose—Patent foramen ovale (PFO) is significantly associated with cryptogenic stroke (CS). However, even in patients with CS, a PFO can be an incidental finding. We sought to estimate the probability that a PFO in a patient with CS is incidental.

Methods—A systematic search identified 23 case–control studies examining the prevalence of PFO in patients with CS versus control subjects with stroke of known cause. Using simple assumptions and Bayes’ theorem, we calculated the probability a PFO is incidental in patients with CS. Random effects meta-analyses estimated the odds ratio (OR) of a PFO in CS versus control subjects in different age populations, with or without atrial septal aneurysms, and were used to summarize across studies the probability that a PFO in CS is incidental.

Results—The summary OR (95% CIs) for PFO in CS versus control subjects was 2.9 (CI, 2.1 to 4.0). The corresponding ORs for young and old patients (< or ≥55 years) were 5.1 (3.3 to 7.8) and 2.0 (>1.0 to 3.7), respectively. The corresponding probabilities that a PFO in patients with CS is incidental were 33% (28% to 39%) in age-inclusive studies, 20% (16% to 25%) in younger patients, and 48% (34% to 66%) in older patients. These probabilities were much lower when an atrial septal aneurysm was present.

Conclusions—In patients with otherwise CS, approximately one third of discovered PFOs are likely to be incidental and hence not benefit from closure. This probability is sensitive to patient characteristics such as age and the presence of an atrial septal aneurysm, suggesting the importance of patient selection in therapeutic decision-making.

Key Words: patent foramen ovale ■ risk factors for stroke ■ secondary stroke prevention

Despite extensive workup, the cause of stroke remains unknown in approximately one third of patients. Such strokes are classified as cryptogenic stroke (CS).1 Several studies have shown a significant association between CS and the presence of a patent foramen ovale (PFO), suggesting that paradoxical emboli (ie, emboli crossing from the venous to arterial circulation through a PFO) may be an important cause of CS.2 Thus, many physicians recommend PFO closure in patients with CS for secondary stroke prevention.

Although the logic supporting PFO closure in a patient with CS seems compelling, the risk of stroke recurrence in patients with CS and PFO appears to be low with an average annualized risk across studies of approximately 2%.3,4 Furthermore, it is well appreciated that PFO is a common and generally benign finding present on autopsy in approximately 25% of the population.5,6 Thus, although CS may be associated with PFO, some may be incidental, even in the setting of CS. Presumably, closure of an incidental PFO would expose patients to procedural and device-related risks without benefit, because the cause of the CS remains undressed. Thus, for any given patient, the possibility of benefit is dependent on the risk of stroke recurrence conditional on the probability that the index stroke is attributable to the PFO.

Despite an extensive literature on the association of PFO and CS, prior studies have not addressed a critical question relevant to both clinical practice and design of PFO closure trials; namely, what is the probability that a PFO in a patient with CS is an incidental finding rather than the culprit? In the present study, we systematically review and summarize the evidence associating PFO with CS in case–control studies. Based on this evidence, we use Bayes’ theorem to estimate the probability that a PFO in a patient with CS is incidental in age-inclusive studies and in studies limited to either younger or older patients.

Methods

Probability That PFO Is Incidental in CS

As shown in Figure 1, the proportion of incidental versus pathogenic PFOs in patients with CS can be calculated based on PFO prevalence in patients with CS compared with control subjects. In Case A, PFO prevalence is 40% in the CS population and 25% in the control group. The corresponding figure indicates that, under these conditions, 50% of PFOs detected in patients with CS would be incidental.
This is based on the assumption that patients with CS who have strokes from causes unrelated to PFO will have the same PFO prevalence as the control group (in this case 25%). If the PFO prevalence in patients with CS was increased slightly to 50% and the PFO prevalence among control patients was decreased to 20% (like in Case B), then the rate of incidental PFOs among patients with CS and PFO would decrease to only 25% as shown in Figure 1.

This simple conceptual framework is a direct application of Bayes’ theorem as detailed in Supplemental Figure I, available online at http://stroke.ahajournals.org. To apply Bayes’ theorem, like in the prior examples, we made 2 assumptions: (1) if not for those strokes attributable to PFO, the prevalence of PFO would be similar in patients with CS compared with control subjects; and (2) CS in patients without a detected PFO is not caused by an undetected PFO. As shown in Supplemental Figure I, these assumptions permit the calculation of the probability that a PFO is incidental based only on the prevalence of PFO in CS cases and in control subjects according to the following equation:

\[
\text{Probability PFO is incidental in CS cases} = \frac{\text{Prevalence of PFO in controls} \times (1 - \text{Prevalence of PFO in CS cases})}{\text{Prevalence of PFO in CS cases} \times (1 - \text{Prevalence of PFO in controls})}
\]

This equation can be applied to case–control studies, because all the terms on the right side of the equation are known.

**Literature Search and Study Selection**

We sought to include all published case–control studies examining the association of PFO and CS. Our primary analysis was based on studies comparing the prevalence of PFO in cases with CS versus control subjects with ischemic stroke of determined cause, because these represent similar patient groups. A sensitivity analysis was also performed based on case–control studies comparing the prevalence of PFO in CS cases versus nonstroke control subjects. Studies were identified based on the most recently published systematic review of PFO and stroke and complemented with an updated search of MEDLINE to cover the period from 1998 (2 years before publication of the most recent systematic review) to June 2008.2 The search used the following terms: patent foramen ovale, atrial septal aneurysm, and right-to-left shunt.

**Data Extraction**

Full manuscripts of eligible studies were reviewed and data directly extracted into electronic data tables. For each study, we extracted: first author, journal, publication year, mean age, number of cases and control subjects with corresponding numbers of patients with PFO, with or without atrial septal aneurysm (ASA), and modality used to diagnose PFO (eg, transesophageal echocardiogram [TEE] versus transcranial Doppler). For studies that were included in the most recent systematic review, data were extracted by a single investigator and validated against the numbers reported in the published review.2 For more recent studies not included in the prior systematic review, independent dual data extraction was performed and differences resolved by consensus.

**Meta-Analyses of Case–Control Studies**

We performed random effects meta-analyses to estimate the summary OR and 95% CIs of having a PFO in patients with CS versus control subjects with ischemic stroke of determined cause.2 Separate meta-analyses were performed for studies that were age-inclusive (ie, set no upper or lower age limit for inclusion), those that were limited to young patients (typically defined as <55 years of age), and studies that were limited to older patients (typically ≥55 years). Heterogeneity between studies was tested using the Q statistic (considered significant at P<0.10) and its extent quantified with I². All meta-analyses were performed in Stata/SE 9.2 (StataCorp LP, College Station, Texas) using the metan procedure.

Using our Bayes’ theorem-derived equation, we calculated the probability that a discovered PFO in a patient with CS is incidental for each individual study. A summary probability for all studies combined was calculated with confidence limits based on the natural logarithm of each study’s probability that a PFO is incidental and its weight in a random effects model.9

**Sensitivity Analyses**

In separate sensitivity analyses, both the random effects meta-analyses and the corresponding Bayesian estimation of the probability a PFO is incidental were repeated using studies comparing the prevalence of PFO in cases with CS versus control subjects without stroke. We further divided these studies into ones that used referred control subjects (ie, subjects requiring evaluation for a clinical indication other than a stroke) or healthy control subjects (ie, volunteers without a clinical indication for evaluation).

**Results**

**Eligible Studies**

There were 17 age-inclusive case–control studies comparing PFO prevalence in patients with CS versus control subjects with ischemic stroke of known cause (Table 1) with a total of 1154 cases with CS (of which 427 had a PFO) and 1852 control subjects (of which 296 had a PFO).10–26 Of these studies, 5 reported separate analyses for younger and older patients.10,12,16,20,26 Six additional studies limited enrollment...
Table 1. Case–Control Studies of Patients With Cryptogenic Stroke Versus Control Subjects With Ischemic Stroke of Known Cause

<table>
<thead>
<tr>
<th>Cases (PFO/n)</th>
<th>Control Subjects (PFO/n)</th>
<th>Age Category</th>
<th>Diagnostic Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lechat, 1988</td>
<td>20/41</td>
<td>–</td>
<td>– TTE</td>
</tr>
<tr>
<td>Webster, 1988</td>
<td>19/34</td>
<td>–</td>
<td>– TTE</td>
</tr>
<tr>
<td>Jeanrenaud, 1990</td>
<td>8/11</td>
<td>–</td>
<td>– TTE</td>
</tr>
<tr>
<td>Hausmann, 1992</td>
<td>16/74</td>
<td>+ (&lt;55)</td>
<td>TTE</td>
</tr>
<tr>
<td>de Belder, 1992</td>
<td>9/35</td>
<td>+ (&lt;40)</td>
<td>TTE</td>
</tr>
<tr>
<td>Di Tullio, 1992</td>
<td>19/45</td>
<td>+ (&lt;55)</td>
<td>TTE</td>
</tr>
<tr>
<td>Di Tullio, 1993</td>
<td>9/19</td>
<td>–</td>
<td>– TEE</td>
</tr>
<tr>
<td>Cabanes, 1993</td>
<td>36/64</td>
<td>–</td>
<td>– TEE</td>
</tr>
<tr>
<td>Ranoux, 1993</td>
<td>31/54</td>
<td>–</td>
<td>– TEE</td>
</tr>
<tr>
<td>Homma, 1994</td>
<td>16/36</td>
<td>–</td>
<td>– TEE</td>
</tr>
<tr>
<td>Albers, 1994</td>
<td>3/25</td>
<td>+ (&lt;50)</td>
<td>TEE</td>
</tr>
<tr>
<td>Jones, 1994</td>
<td>14/71</td>
<td>+ (&lt;50)</td>
<td>TEE</td>
</tr>
<tr>
<td>Job, 1994</td>
<td>27/41</td>
<td>+ (&lt;45)</td>
<td>TEE</td>
</tr>
<tr>
<td>Klotzsch, 1994</td>
<td>31/40</td>
<td>–</td>
<td>– TEE</td>
</tr>
<tr>
<td>Zahn, 1995</td>
<td>50/118</td>
<td>–</td>
<td>– TEE</td>
</tr>
<tr>
<td>Schminke, 1995</td>
<td>33/60</td>
<td>–</td>
<td>– TCD</td>
</tr>
<tr>
<td>Yeung, 1996</td>
<td>43/116</td>
<td>+ (&lt;50)</td>
<td>TCD</td>
</tr>
<tr>
<td>Petty, 1997</td>
<td>22/55</td>
<td>–</td>
<td>– TEE</td>
</tr>
<tr>
<td>Roijer, 1997</td>
<td>17/67</td>
<td>+</td>
<td>– TEE</td>
</tr>
<tr>
<td>Serena, 1998</td>
<td>30/53</td>
<td>+</td>
<td>– TCD</td>
</tr>
<tr>
<td>Steiner, 1998</td>
<td>19/42</td>
<td>+</td>
<td>– TEE</td>
</tr>
<tr>
<td>Kanda, 1998</td>
<td>19/71</td>
<td>+</td>
<td>– TEE</td>
</tr>
<tr>
<td>Handke, 2007</td>
<td>77/227</td>
<td>+ (&lt;55)</td>
<td>TEE</td>
</tr>
</tbody>
</table>

TTE indicates transthoracic echocardiogram; TEE, transesophageal echocardiogram; TCD, transcranial Doppler.

Association of PFO With CS

Random effects meta-analysis of age-inclusive studies showed a significant association between PFO and CS (OR, 2.9 [2.1 to 4.0]; Supplemental Figure IIA) with significant heterogeneity among studies ($I^2 = 63\%, P<0.0001$). A stronger significant association between CS and PFO was observed in studies enrolling younger patients (OR, 5.1 [3.3 to 7.8]; Supplemental Figure IIB) without significant heterogeneity among studies ($I^2 = 0.0, P=0.47$). Conversely, the association between PFO and CS in studies enrolling older patients was weaker but did reach statistical significance (OR, 2.0 [1.0 to 3.7]; Supplemental Figure IIC) with significant between-study heterogeneity ($I^2 = 67\%, P=0.018$). Although fewer studies examined the association of PFO and concomitant ASA with CS compared with ischemic stroke of known cause, that association was quite strong; the pooled OR was 8.9 (1.2 to 64.0) for the 2 age-inclusive studies; 11.3 (2.6 to 48.9) for the 2 studies examining younger patients, and 3.9 (1.8 to 8.5) in the analysis in older patients.

Probability That PFO Is Incidental in CS

In age-inclusive studies, the proportion of patients with PFO among CS cases ranged from 12% to 78% (median 40%, interquartile range 26% to 46%), and the corresponding proportion among control subjects with ischemic stroke of known cause ranged from 6% to 33% (median 20%, interquartile range 14% to 25%). In studies of younger patients, the proportion of patients with PFO ranged from 29% to 73% (median 56%, interquartile range 45% to 59%) among cases and 0% to 33% (median 14%, interquartile range 1% to 21%) among control subjects. The corresponding proportions in studies of older patients ranged from 16% to 38% (median 28%, interquartile range 17% to 32%) in cases and 8% to 23% (median 13%, interquartile range 11% to 22%) in control subjects.

Using Bayes’ theorem as described previously, the summary probability that a PFO is incidental in patients with CS was 33% (28% to 39%) in age-inclusive studies (Figure 2A). The corresponding probability was 20% (16% to 25%) for younger patients (Figure 2B) and 48% (34% to 66%) for older patients (Figure 2C). A PFO was less likely an incidental finding when a concomitant ASA was detected with the probability of it being incidental estimated at 11% (4% to
31%) from age-inclusive studies, 9% (4% to 18%) in younger patients, and 26% (12% to 56%) in older patients (Table 2).

**Sensitivity Analyses**

These analyses were repeated using data from case–control studies examining the prevalence of PFO in cases versus control subjects with stroke of determined cause. Individual studies are represented on the left with first author and year of publication and prevalence of PFO (# PFO/total number of patients) in cases versus control subjects. Black boxes with sizes corresponding to each study’s weight in the analysis represent the point estimate of the probability that the PFO is incidental with 95% CIs represented with the gray lines (P 95% CI). The diamond in the last row represents the summary estimate of the probability. The dashed black line to the right of the panel represents a probability of 100% that the PFO was incidental (ie, not related to the CS). (A) age-inclusive studies; (B) analyses in younger patients; (C) analyses in older patients.

Figure 2. Probability that a PFO is incidental in patients with CS based on case–control studies examining the prevalence of PFO in cases with CS versus control subjects with stroke of determined cause. Individual studies are represented on the left with first author and year of publication and prevalence of PFO (# PFO/total number of patients) in cases versus control subjects. Black boxes with sizes corresponding to each study’s weight in the analysis represent the point estimate of the probability that the PFO is incidental with 95% CIs represented with the gray lines (P 95% CI). The diamond in the last row represents the summary estimate of the probability. The dashed black line to the right of the panel represents a probability of 100% that the PFO was incidental (ie, not related to the CS). (A) age-inclusive studies; (B) analyses in younger patients; (C) analyses in older patients.
Table 2. Probability a PFO With or Without an ASA Is Incidental in Patients With CS, by Age Category, Based on Case–Control Studies of Cases With CS Versus Control Subjects With Stroke of Determined Cause (Main Analysis) or Versus Control Subjects With No Stroke (Sensitivity Analysis)

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Main Analysis</th>
<th>Sensitivity Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>0.20 (0.16–0.25)</td>
<td>0.20 (0.16–0.25)</td>
</tr>
<tr>
<td>Old</td>
<td>0.48 (0.34–0.66)</td>
<td>0.84 (0.60–1.00)</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-inclusive</td>
<td>0.11 (0.04–0.31)</td>
<td>...</td>
</tr>
<tr>
<td>Young</td>
<td>0.09 (0.04–0.18)</td>
<td>0.04 (0.01–0.32)</td>
</tr>
<tr>
<td>Old</td>
<td>0.26 (0.12–0.56)</td>
<td>...</td>
</tr>
</tbody>
</table>

Discussion

We used a Bayesian approach to estimate the probability that a PFO in a patient with CS is an incidental finding rather than pathogenic in 23 case–control studies and summarized these effects using meta-analytic techniques. Our analysis estimates that approximately one third of PFOs discovered in patients with CS are likely to be incidental and unrelated to the stroke (and somewhat higher when estimates are based on studies using nonstroke control subjects). This estimate is sensitive to patient age and is higher in older patients. In addition, the probability that a PFO is incidental is much lower in any age when associated with an ASA.

Given the extensive literature associating PFO with CS, the observation that a substantial proportion of discovered PFOs in patients with CS may be incidental might seem surprising. However, the literature to date has focused on estimating the strength of the association between a PFO and CS, presenting estimates in the form of an OR, the clinical significance of which can be difficult to interpret. The Bayesian approach adopted in the present analysis goes beyond an estimate of association to address the clinically relevant question of whether the discovered PFO is likely to be etiologically related to the stroke.

The heterogeneity between the studies included in the present analysis is not surprising both because study and diagnostic methods vary and because numerous factors can potentially affect the degree of association between PFO and CS and thus the likelihood that a discovered PFO in the setting of CS is incidental. For example, PFO has been found to be more likely to be associated with CS in patients who were younger and did not have hypertension, hyperlipidemia, diabetes, or tobacco use.

In addition to age and conventional stroke risk factors, morphological features of a PFO may influence the association between PFO and CS and hence the probability that the PFO is incidental. In the present analysis, the presence of a PFO with a concomitant ASA yielded a lower probability of it being an incidental finding. Additionally, multiple studies comparing PFO characteristics of patients with CS versus strokes of known cause have found that larger PFO, greater right-to-left shunt, and higher septal wall motion mobility are more frequent in patients with CS. Thus, the likelihood that PFO is pathogenic when found in patients with CS is sensitive to multiple patient characteristics. For example, even in patients <55 years of age, incidental PFOs would be more likely if patients are near the upper margin of the age category and/or have conventional ischemic stroke risk factors (hypertension, high cholesterol, diabetes mellitus, smoking) and/or lower risk morphological/physiological PFO features on TEE. Conversely, PFOs may more likely be pathogenic even in patients in the older age range in those who do not have other stroke risk factors but do have high-risk features on TEE.

Although patient factors associated with PFOs increase the confidence that paradoxical embolism is the likely mechanism for an individual patient’s stroke, these factors may not be the same as those that predict risk of recurrent paradoxical embolism. Additionally, procedural complications of PFO closure include stroke, eg, from thrombus formation on the device, and so the risk may increase with the intervention. Given the significant number of incidental PFOs that are likely to be present and the relatively low risk of stroke recurrence while on medical therapy in patients with CS and PFO, careful assessment of the risks and benefits of treatment options is essential.

For interventions in which the risks and benefits are finely balanced, it has been demonstrated that multivariate predictive modeling can be useful to identify subgroups in clinical trials likely to benefit or not from the tested therapy. Using our Bayesian framework, baseline characteristics and PFO morphological features that predict the presence of a PFO in patients with CS can be used to predict the probability that a discovered PFO is likely to be incidental. Predictive modeling can also be performed separately to estimate the probability of stroke recurrence in patients with PFO and CS. For trials testing the efficacy of endovascular closure (RESPECT, PC-Trial), stratifying results by the joint probability that the CS was related to the PFO and the probability the stroke will recur offers the potential for a refined and novel approach to patient selection.

The present Bayesian approach used to derive the probability of an incidental PFO was informed by estimates obtained from case–control studies of PFO in CS and relied on 2 basic assumptions. Therefore, proper interpretation of these findings should take into account the inherent limitations of case–control studies, including potential selection bias, presence of unmeasured confounders, and possible differential intensity in the investigation of a PFO in CS cases versus control subjects. Furthermore, the findings are based...
on 2 assumptions, namely that the prevalence of PFO would be similar in patients with CS compared with control subjects if not for those strokes attributable to PFO and that CS in patients without a detected PFO is not caused by an undetected PFO. Although the first assumption is intuitive, the second may not necessarily be true, although presumably PFOs that go undetected are less likely to be of clinical significance. Despite these caveats, the present analysis offers a novel contribution to our intuitive interpretation of case–control studies by extending such interpretation from association to a measure of attributable risk.

In conclusion, in patients with otherwise CS, approximately one third of discovered PFOs are likely to be incidental, and hence endovascular closure is not likely to reduce their recurrent stroke risk. This probability is sensitive to patient characteristics such as age and morphological features of a PFO such as the presence of a concurrent ASA.

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References


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