Neuroimaging Findings in Cryptogenic Stroke Patients With and Without Patent Foramen Ovale

David E. Thaler, MD, PhD; Robin Ruthazer, MPH; Emanuele Di Angelantonio, MD, MSc; Marco R. Di Tullio, MD; Jennifer S. Donovan, MS; Mitchell S.V. Elkind, MD, MS; John Griffith, PhD; Shunichi Homma, MD, FACC; Cheryl Jaigobin, MD, FRCP, MSc; Jean-Louis Mas, MD; Heinrich P. Mattle, MD; Patrik Michel, MD; Marie-Luise Mono, MD; Krassen Nedeltchev, MD, FESC; Federica Papetti, MD; Joaquín Serena, MD, PhD; Christian Weimar, MD; David M. Kent, MD, CM, MSc

Background and Purpose—Patent foramen ovale (PFO) and cryptogenic stroke are commonly associated but some PFOs are incidental. Specific radiological findings associated with PFO may be more likely to indicate a PFO-related cause. We examined whether specific radiological findings are associated with PFO among subjects with cryptogenic stroke and known PFO status.

Methods—We analyzed the Risk of Paradoxical Embolism (RoPE) Study database of subjects with cryptogenic stroke and known PFO status, for associations between PFO and: (1) index stroke seen on imaging, (2) index stroke size, (3) index stroke location, (4) multiple index strokes, and (5) prior stroke on baseline imaging. We also compared imaging with purported high-risk echocardiographic features.

Results—Subjects (N=2680) were significantly more likely to have a PFO if their index stroke was large (odds ratio [OR], 1.36; \( P=0.0025 \)), seen on index imaging (OR, 1.53; \( P=0.003 \)), and superficially located (OR, 1.54; \( P<0.0001 \)). A prior stroke on baseline imaging was associated with not having a PFO (OR, 0.66; \( P<0.0001 \)). Finding multiple index strokes was unrelated to PFO status (OR, 1.21; \( P=0.161 \)). No echocardiographic variables were related to PFO status.

Conclusions—This is the largest study to report the radiological characteristics of patients with cryptogenic stroke and known PFO status. Strokes that were large, radiologically apparent, superficially located, or unassociated with prior radiological infarcts were more likely to be PFO-associated than were unapparent, smaller, or deep strokes, and those accompanied by chronic infarcts. There was no association between PFO and multiple acute strokes nor between specific echocardiographic PFO features with neuroimaging findings. (Stroke. 2013;44:675-680.)

Key Words: cryptogenic stroke  imaging  patent foramen ovale

A patent foramen ovale (PFO) is discovered in roughly half of the patients with cryptogenic stroke (CS), but the high background prevalence of PFO indicates that many are incidental. Depending on the sample, up to half of those PFOs may be unrelated to the index event. The radiological pattern of cerebral infarction might assist in the determination of stroke cause but the pattern seen in subjects with CS and PFO has not been clearly established.

Earlier studies have observed associations between the presence of PFO and radiological findings among patients with CS. Radiological findings reported to be more frequently seen among CS patients compared with those without PFO include superficial location of the infarct, infarcts in the territories of large named arteries, infarcts in the posterior circulation, lesions in the deep frontal white matter, and in the territory of the superior cerebellar artery. However, these radiological findings may be unrelated to the index event. The radiological pattern of cerebral infarction might assist in the determination of stroke cause but the pattern seen in subjects with CS and PFO has not been clearly established.
associations have not been replicated consistently.6,7 Our aim is to determine whether there are radiological variables that are associated with PFO, by using data from various studies comprising the largest database of subjects with CS and known PFO status. This permits not only increased statistical power, but the ability to examine for consistency of effects across studies. Radiological patterns associated with the presence of a PFO should be more likely to represent stroke due to paradoxical embolism. In addition, we sought to explore whether PFO-associated neuroimaging findings might be more commonly found in those patients who have PFOs with echocardiographic features purported to be high risk compared with those with PFOs lacking such features.

### Methods

This analysis uses the database created by the Risk of Paradoxical Embolism (RoPE) Study, a collaboration of investigators with published and unpublished registries of subjects with CS and transient ischemic attack (TIA).4 The RoPE Study database, described in detail in an earlier report,2 includes individual patient data for 3674 subjects with CS who were investigated for PFO with transesophageal echocardiography or transcranial Doppler. It was constructed from 12 component databases, 8 of which included CS subjects with and without PFO; the remaining 4 included only those with CS and PFO. Only the 7 databases that included subjects with and without PFO and with adequate neuroimaging data are included in this analysis. Some of these data from one of the component databases have been published previously.3

Data from MRI scans were preferred to data from computed tomography (CT) scans for the RoPE Study. If no MRI was done then CT scans were used. The majority of the radiology data were already present in the component databases, but some were missing. For those databases for which investigators had access to neuroimages, the imaging studies were reread for missing variables by the RoPE Study.9 Rereading was performed by the local RoPE contributors according to agreed-upon definitions, or the images were sent to the RoPE coordinating center in Boston for central rereading which was done by 2 vascular neurologists and a neurovascular fellow who were blinded to the clinical data.

For subjects with missing neuroimaging data, not all of the neuroimaging studies were retrievable by the local sites. In such cases, for the variable prior stroke, we permitted extraction of information from the clinical radiology report after determining reasonable agreement across studies. Radiological patterns associated with the presence of a PFO should be more likely to represent stroke due to paradoxical embolism. In addition, we sought to explore whether PFO-associated neuroimaging findings might be more commonly found in those patients who have PFOs with echocardiographic features purported to be high risk compared with those with PFOs lacking such features.

### Definitions

There were database-specific definitions for each radiological variable which we harmonized and then dichotomized in clinically meaningful ways.

#### Index Stroke Size

Measurement of infarct size was done with different units between databases. For some (Lausanne) measurements were made as a continuous variable permitting categorization for the RoPE database according to the RoPE definition. For others, however, the data were already dichotomized using lobes (PICSS, NOMASS, APRIS) as a unit of measurement. The French PFO/Atrial Septal Aneurysm Study Group used both measurements in millimeters for deep infarcts and hemisphere units for more superficial ones. We dichotomized the size variable into small and large roughly corresponding to a longest linear measurement of < or >10 to 15 mm (Table 1).

#### Index Stroke Seen on Imaging

All of the RoPE component studies included subjects with CS. The stroke definition would permit normal imaging if the neurological deficit was thought to be due to cerebral ischemia and the symptoms persisted for >24 hours. CT-negative or MRI-negative imaging is most likely to occur in stroke patients with small lesions. The stroke was seen on imaging if an acute or subacute infarct was visible on neuroimaging at the time of the index event and was consistent with the clinical presentation.

#### Index Stroke Location

Superficial is defined as involving the cerebral or cerebellar cortex. Other locations including the noncortical gray matter (thalamus, basal ganglia) and deep white matter in the cerebrum or cerebellum were considered deep. Five databases had already defined the infarct locations as superficial or deep or both, or as cortical or subcortical or both. For the RoPE Study, infarcts described as both were considered superficial (Table 2). Three studies divided the brain into 24 locations each of which was categorized as superficial or deep. The 11 cortical locations in the cerebellum and cortex were considered superficial and the 10 locations in the deep white matter and deep gray structures were considered deep. There were 3 additional borderzone locations. The deep middle cerebral artery borderzone was considered deep, whereas the middle cerebral artery/anterior cerebral artery and middle cerebral artery/posterior cerebral artery borderzones were deemed superficial.

#### Multiple Index Strokes

These are defined as discrete radiological lesions in different vascular territories or lesions which are clearly separated within one vascular territory (eg, anterior and posterior branches of the middle cerebral

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**Table 1. Definitions of Infarct Size by Study and Their RoPE Categorization as Large or Small**

<table>
<thead>
<tr>
<th>Study</th>
<th>APRIS/NOMASS</th>
<th>Lausanne</th>
<th>CODICIA</th>
<th>French PFO/ASA</th>
<th>German</th>
<th>PICSS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1 cm</td>
<td>≤15 mm</td>
<td>&lt;3 cc</td>
<td>Subcortical</td>
<td>≤15 mm</td>
<td>&lt;1 cm</td>
</tr>
<tr>
<td></td>
<td>&lt;1/2 lobe</td>
<td>&gt;15 mm</td>
<td>=small</td>
<td>&lt;15 mm</td>
<td>&gt;15 mm</td>
<td>deep only</td>
</tr>
<tr>
<td></td>
<td>&lt;1 lobe</td>
<td></td>
<td></td>
<td>&gt;1/2 hemisphere</td>
<td></td>
<td>1/2 lobe</td>
</tr>
<tr>
<td></td>
<td>&gt;1 lobe</td>
<td></td>
<td></td>
<td>&gt;15 mm</td>
<td></td>
<td>1/2 lobe</td>
</tr>
</tbody>
</table>

APRIS indicates Aortic Plaques and Risk of Ischemic Stroke Study; CODICIA, Recurrent Stroke and Massive Right-to-Left Shunt Prospective Spanish Multicenter Study; French PFO-ASA, Patent Foramen Oval and Atrial Septal Aneurysm Study Group; NOMASS, Northern Manhattan Stroke Study; PICSS, Patent Foramen Oval in Cryptogenic Stroke Study; and RoPE, Risk of Paradoxical Embolism.
artery). Most of the databases provided this variable without the need for interpretation. For the German and French PFO/Atrial Septal Aneurysm Study Group studies, we inferred multiplicity if the index stroke was in >1 named vascular territory, was bilateral, or was coded both in the anterior and in the posterior circulations. Otherwise they were coded as single lesions.

**Prior Stroke**

This is defined as a radiologically chronic infarct at the time of the index event imaging. On MRI the lesion must be >3 mm, hypointense on T1-weighted images, and hyperintense on T2-weighted images. Surrounding gliosis is seen as supportive. On CT, the lesion must also meet a minimum size of 3 mm, be infarct-like in appearance and location, and have a density similar to that of cerebrospinal fluid.

To explore whether neuroradiologic findings were different in those with high-risk versus low-risk PFOs, we divided subjects into those with and without specific echocardiographic features. The term high risk has been used to refer either to the association with CS (and by implication, with paradoxical embolism) or to the risk of recurrent stroke. The RoPE definitions of these echocardiographic features have been described previously.9 In brief, we investigated the radiological characteristics of those with physiologically large versus small shunts, hypermobile interatrial septa versus normal mobility, and shunting at rest versus shunting only with Valsalva. Shunt size was determined by bubble counts in the left atrium. Large corresponded to >10 or 15 bubbles visible in the left atrium within 3 cardiac cycles after right atrial opacification. A hypermobile, or aneurysmal, septum roughly corresponded to excursion of the septum of >10 mm from the midline. CS subjects without PFO were not included in these exploratory analyses.

**Statistical Approach**

Because definitions of the independent variables varied between sites, we used generalized linear mixed models that controlled for site as a random effect to examine the associations among these 5 variables and the presence or absence of PFO as the binary dependent variable. According to this approach, the effects of radiological markers are examined within each database, and then pooled across databases using a random effects model, that accounts for study-level heterogeneity. We also examined consistency of effects across databases, to explore differences that might arise through different study-level definitions. Our primary analysis examined the crude associations (ie, associations adjusted for site only). In a sensitivity analysis, we adjusted for clinical variables known to be associated with PFO (including diabetes mellitus, hypertension, smoking status, history of stroke, or TIA).10 This latter analysis tested whether a particular neuroradiologic feature adds incremental information (regarding PFO status) to known clinical variables.

For comparisons of neuroimaging characteristics between subgroups of patients with PFOs defined by echocardiographic features, we again used generalized linear mixed models with the neuroimaging characteristics as the independent variable of interest (continuous or binary) and the PFO status subgroup as the categorical dependent variable, controlling for site as a random effect. Again, we tested the crude (only site-adjusted) associations as our primary analysis, and subsequently examined the same associations using a fully adjusted model as above.

**Results**

A total of 2680 subjects were available from the component databases within RoPE that included CS patients with and without PFO (Table 3). We analyzed the clinical and echocardiographic variables of those subjects with missing neuroradiological data. No significant differences were found between them and the rest of the cohort except for a higher prevalence of TIA as the index event in those without imaging (81/148, 55%) when compared with those with imaging (202/2532, 8%; P<0.0001).

After controlling for site (ie, component database) as a random effect, the variables that were associated with a significantly higher prevalence of PFO were (1) a large index stroke

**Table 3. Patient Characteristics in Cases With and Without PFO (N=2680)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-PFO</th>
<th>PFO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=1539</td>
<td>n=1141</td>
</tr>
<tr>
<td>Age, y, mean</td>
<td>57.5</td>
<td>50.3</td>
</tr>
<tr>
<td>Male</td>
<td>59.2</td>
<td>59.6</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>12.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18.2</td>
<td>8.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>51.9</td>
<td>30.9</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>31.6</td>
<td>22.5</td>
</tr>
<tr>
<td>Current smoker</td>
<td>36.3</td>
<td>32.4</td>
</tr>
<tr>
<td>History of stroke</td>
<td>7.5</td>
<td>4.2</td>
</tr>
<tr>
<td>History of TIA</td>
<td>8.0</td>
<td>6.2</td>
</tr>
<tr>
<td>History of stroke or TIA</td>
<td>14.4</td>
<td>9.7</td>
</tr>
<tr>
<td>Event type, stroke*</td>
<td>89.9</td>
<td>88.8</td>
</tr>
<tr>
<td>Statins*</td>
<td>16.8</td>
<td>7.8</td>
</tr>
<tr>
<td>Antiplatelets*</td>
<td>14.4</td>
<td>8.6</td>
</tr>
<tr>
<td>Anticoagulants*</td>
<td>1.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

PFO indicates patent foramen ovale; and TIA, transient ischemic attack.
*At index event.
Table 4. PFO Prevalence by Presence or Absence of Radiological Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total, n</th>
<th>% With PFO</th>
<th>Adjusted Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index stroke large</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>681</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1290</td>
<td>43</td>
<td>1.36</td>
<td>0.0025</td>
</tr>
<tr>
<td>Index stroke seen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>265</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2040</td>
<td>43</td>
<td>1.53</td>
<td>0.003</td>
</tr>
<tr>
<td>Superficial location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>779</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1018</td>
<td>48</td>
<td>1.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multiple index strokes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1601</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>278</td>
<td>43</td>
<td>1.21</td>
<td>0.1614</td>
</tr>
<tr>
<td>Prior stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1547</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>592</td>
<td>33</td>
<td>0.66</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Odds ratios and P values are adjusted for site as a random effect. PFO indicates patent foramen ovale.

(odd ratios OR, 1.36; P<0.0025), (2) index stroke seen on imaging (OR, 1.53; P<0.0003), and (3) superficial location (OR, 1.54; P<0.0001). Prior stroke seen on the index imaging was associated with a lower prevalence of PFO (OR, 0.66; P<0.001). Multiple index strokes on imaging were not associated with the presence of a PFO (OR, 1.21; P=0.161; Table 4). When controlling for site and age alone, the relation with prior stroke was attenuated and no longer significant (OR, 0.83; P=0.099). Adjusting for imaging modality (MRI, CT, or unknown) did not affect the direction, magnitude, or significance of the findings (data not shown). Similarly, further adjusting for clinical variables (including diabetes mellitus, hypertension, smoking status, history of stroke, or TIA) did not substantially influence the findings, with the exception that prior stroke on neuroimaging ceased to be significant (Appendix in the online-only Data Supplement).

The prevalence of prior infarcts was high, being seen in 23% of those with PFO and 31% of those without, substantially more frequent than prior stroke or TIA on clinical history, 10% and 15%, respectively.

High-risk PFOs

When we restricted the analysis to only those subjects with PFO and serially divided them by PFO characteristics, no significant associations were found. None of the purported high-risk features (large shunt, shunt at rest, or associated hypermobile septum) was associated with any of the measured radiological variables, and no association was seen when those with any high-risk feature were compared with those without. This was true when the groups were adjusted only for site as a random effect and in the fully adjusted model (including diabetes mellitus, hypertension, smoking status [current], and history of stroke or TIA).

Discussion

This is the largest study to describe the neuroradiological characteristics of CS associated with PFO. We have also described the imaging features that distinguish CS associated with PFO from non–PFO-related CS. We found a significant association between PFO and large strokes and strokes that are located in the brain periphery. Prior strokes on neuroimaging are also associated with the absence of a PFO, although this finding does not provide additional information regarding the likelihood of finding a PFO when the clinical history regarding prior stroke is already known. The appearance of multiple infarcts at the time of the index event was not associated with PFO. Note that all of these comparative findings use, as a reference, patients with cryptogenic strokes without PFO, and should be appropriately interpreted (ie, CS in the setting of PFO are more frequently large compared with other cryptogenic strokes). Despite variations in the variable definitions across databases, these findings were largely consistent across the 7 studies included in this analysis.

As described previously, an excess of PFOs in populations with or without a given clinical variable can assist in identifying those PFOs which are likely to be pathogenic instead of incidental. Thus, we identified radiological variables that may help to distinguish those strokes which are PFO-related rather than related to another stroke mechanism which is also cryptogenic. The difficulty in distinguishing PFO-related CS from other non–PFO-related ones is that strokes in the latter category may also be due to cerebral embolism and may have a similar radiological signature. The pattern of PFO-related stroke may be comparable with other cryptogenic emboli. Nevertheless, several differences emerged between the CS groups with and without PFO.

Smaller studies explored the association between neuroradiological findings and PFO. Jauss et al did not discover an embolic pattern in a study of 73 subjects with CS with PFO compared with CS without PFO, and concluded that “it is not possible to discriminate between cryptogenic stroke and stroke from an assumed paradoxical embolism.” Their embolic pattern required infarcts in different vascular territories; a RoPE variable that similarly did not distinguish between those with and without PFO. Some have found that cardiogenic stroke is more likely to be associated with multiple infarcts at the time of presentation. However, even within the category of strokes that are cardiogenic there are multiple causes which may reasonably be expected to have different radiological patterns. Other variables, such as infarcts in a peripheral location, have been shown to be useful predictors of PFO even in studies of small size. We confirm those findings using our larger dataset. Steiner found that superficial infarcts are more common in subjects with medium or large PFOs (50%) than in those with small or no PFO (21%). Santamarina et al made a similar observation in those with the combination of PFO and hypermobile interatrial septa with wide confidence intervals. We did not confirm those observations; the echocardiographic variables in this study were not associated with radiological findings.

Our observation that prior radiological infarcts are less common in subjects with PFO may be interpreted in part as an age-related phenomenon because PFO subjects tend to be...
younger than patients with non–PFO-related strokes. In a prospective multicenter study by Lamy et al5 (using data from subjects that contributed to the RoPE database), prior radiological stroke was less frequent in patients with PFO but this association was lost when controlled for age. When we controlled for age, PFO subjects had a trend toward fewer old lesions but it no longer reached statistical significance. The somewhat lower burden of precurrent stroke is consistent with the observation that PFO-related recurrence is less frequent than other cryptogenic stroke mechanisms.10

The deep/superficial dichotomy that we established in this study will not distinguish perfectly between embolic or local disease. Thalamic strokes, for example, are closely associated with both small-vessel disease and with posterior cerebral artery emboli or large vessel disease. However, in spite of this caution we were able to identify significant associations with PFO status.

Our study describes the radiological findings in subjects with CS and PFO but there is an unavoidable corollary, which is to describe the stroke patterns in CS unrelated to PFO. Strokes in these subjects are more often small, deep, and recurrent, a pattern consistent with lacunar disease. Although this does not imply that all small and deep infarcts are due to the arteriolar pathology associated with lacunar disease, it does suggest that despite the effort to exclude patients with small-vessel disease in the databases that formed the RoPE Study, it may be a common alternative mechanism in populations described as cryptogenic. To emphasize the potential contribution of atherosclerotic disease in this population, it has been shown that conventional vascular risk factors contribute to stroke risk even in populations of stroke patients who are described as young. A cohort of such patients13 demonstrated an increasing incidence of atherosclerotic large- and small-vessel disease in those as young as 35 years and became significant by the age of 44 years.

The associations between PFO characteristics and neuroimaging findings have been inconsistent. Akhondi et al14 found no associations between PFO characteristics and infarct volume or stroke location except that greater septal excursion predicted infarct volume. Similarly, Bonati et al15 found no association between shunt size and any radiological variable but the presence of an atrial septal aneurysm was associated with multiple index lesions on imaging. However, Steiner found that in all patients (including noncryptogenic strokes) larger PFOs were associated with large, superficial lesions in the posterior circulation. However, we could not identify any PFO characteristics that were related to our radiological variables.

It should be kept in mind that our findings are not absolute. PFO-related strokes are statistically larger and more often superficial but many subjects without PFOs have a similar pattern. The converse is also common; small deep strokes occur in subjects with paradoxical embolism as their probable stroke mechanism. So, like many aspects of stroke diagnosis, these radiological patterns should be seen as a complement to other clinical information in support of one stroke cause or another. Our study does not support the existence of a pathognomonic signature of paradoxical embolism.

**Limitations**

Despite our efforts to reread neuroimages, this individual patient meta-analysis was limited by the collection of neuroradiologic data in the component studies. Variation in definitions across studies, the presence of missing data for some variables and the use of CT and MRI scans could have obscured associations that may have been stronger with better standardization.

However, in addition to statistical power, combining databases provides advantages. Data from multiple sources can be checked for consistency of effects, thereby improving generalizability. Also, the development of a database from many locations lessens the dependency on any particular database reducing the susceptibility to the idiosyncrasies of data sets.

**Conclusions**

This is the largest study to report the radiological characteristics of patients with CS and known PFO status. Strokes that were large, radiologically apparent, superficially located, or unassociated with prior radiological infarcts were more likely to be PFO-associated than were smaller, unapparent, or deep strokes, and those accompanied by chronic infarcts. The fact that small and deep infarcts were overrepresented in patients without PFO suggests that non–PFO-related mechanisms of CS may include lacunar disease. We did not find an association between PFO and multiple acute stroke, or any association with specific PFO features and neuroimaging findings.

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**Disclosures**

Both Drs Kent and Thaler have consulted for WL Gore Associates. Drs Thaler and Homma are consultants to St Jude Medical. The other authors have no conflicts to report.

**References**


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<table>
<thead>
<tr>
<th></th>
<th>Site-adjusted as random effect only</th>
<th>Site-and-Age adjusted only*</th>
<th>Fully-adjusted** and Site as random effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (site adj)</td>
<td>p-value</td>
<td>Adj OR</td>
</tr>
<tr>
<td>Index stroke large</td>
<td>1.36 (95% CI:1.11 to 1.66)</td>
<td>0.0025</td>
<td>1.37 (95% CI: 1.11 to 1.68)</td>
</tr>
<tr>
<td>Index stroke seen</td>
<td>1.53 (95% CI:1.16 to 2.03)</td>
<td>0.003</td>
<td>1.41 (95% CI: 1.06 to 1.87)</td>
</tr>
<tr>
<td>Superficial location</td>
<td>1.54 (95% CI:1.26 to 1.87)</td>
<td>&lt;.0001</td>
<td>1.54 (95% CI: 1.26 to 1.88)</td>
</tr>
<tr>
<td>Multiple index strokes</td>
<td>1.21 (95% CI:0.93 to 1.57)</td>
<td>0.1614</td>
<td>1.22 (95% CI: 0.93 to 1.60)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>0.66 (95% CI:0.53 to 0.81)</td>
<td>&lt;.0001</td>
<td>0.83 (95% CI: 0.67 to 1.04)</td>
</tr>
</tbody>
</table>

**Fully adjusted means adjusted for age, gender, diabetes, hypertension, smoking status, history of stroke/TIA

***All models include the SITE as a random effect

Appendix 1: PFO prevalence by presence or absence of radiological variables
Appendix 2a: List of German centers and investigators who contributed data to the RoPE project

*Indicates centers that did not provide additional imaging data.
Centre Hospitalier Universitaire (CHU) Besançon, France (T. Moulin, MD)
CHU Lariboisière and Saint-Antoine, Paris, France (F. Woimant, MD; P. Amarenco, MD)
Sainte-Anne Hospital, Paris, France (J.L. Mas, MD)
CHU Nancy, France (X. Ducrocq, MD)
CHU Tours, France (D. Saudeau, MD)
CHU Rennes, France (J.F. Pinel, MD)
Medical University of Warsaw, Poland (H. Kwiecinski, MD)
CHU Poitiers, France (J.P. Neau, MD)
CHU Vaudois, Lausanne, Switzerland (P. Arnold, MD)
CHU Rouen, France (E. Guéguen-Massardier, MD)
CHU Pitié-Salpêtrière, Paris, France (R. Manai, MD)
CHU La Timone, Marseille, France (L. Milandre, MD)
CHU Lille, France; (D. Leys, MD)
Centre Hospitalier Général, Meaux, France (F. Chedru, MD)
CHU Saint-Etienne, France (P. Garnier, MD)
Santa Maria Hospital, University of Lisbon, Portugal (T. Pinho e Melo, MD)
CHU Bordeaux, France (P. Gaïda, MD)
CHU Grenoble, France (G. Besson, MD)
CHU Purpan, Toulouse, France (J.F. Albucher, MD)
Klinikum Grosshadern, Ludwig Maximilians University, Munich, Germany (T. Pfefferkorn, MD)
Lens, France (F. Mounier-Véhier, MD)
CHU Rangueil, Toulouse, France (V. Larrue, MD)
CHU Nice, France (M.H. Mahagne, MD)
CHU Brest, France (Y. Mocquard, MD)
CHU Angers, France (H. Brugeilles, MD)
Jolimont Hospital, Haine-Saint-Paul, Belgium (G. Devuyst, MD)
Tenon Hospital, CHU Saint-Antoine, Paris (S. Alamowitch, MD)
E. Muller Hospital, Mulhouse, France (G. Rodier, MD)
Erasme Hospital, Université Libre de Bruxelles, Belgium (S. Blecic, MD)
CHU Clermont-Ferrand, France (A. Coustes-Durieux, MD)

Appendix 2b: List of centers and investigators from the French PFO-ASA study who contributed data to the RoPE project
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表4 放射線学検査の変数の有無によるPFO有率

<table>
<thead>
<tr>
<th>変数</th>
<th>全症例数</th>
<th>PFOあり%</th>
<th>調整オッズ比</th>
<th>p 値</th>
</tr>
</thead>
<tbody>
<tr>
<td>大きな脳梗塞</td>
<td>1,681</td>
<td>37</td>
<td>1.36</td>
<td>0.0025</td>
</tr>
<tr>
<td>画像で確認できる脳梗塞</td>
<td>1,290</td>
<td>43</td>
<td>1.53</td>
<td>0.003</td>
</tr>
<tr>
<td>皮質に発症</td>
<td>2,040</td>
<td>43</td>
<td>1.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>脳卒中の既往歴</td>
<td>2,040</td>
<td>43</td>
<td>1.54</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

オッズ比およびp値は、変数を含めると格安で補正を実施した。PFO: 卵円孔開存。