Recurrent Stroke and Patent Foramen Ovale
A Systematic Review and Meta-Analysis

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Background and Purpose—Recurrent cerebrovascular events are frequent in medically treated patients with patent foramen ovale (PFO), but it still remains unclear whether PFO is a causal or an incidental finding. Further uncertainty exists on whether the size of functional shunting could represent a potential risk factor. The aim of the present study was to evaluate if the presence of PFO is associated with an increased risk of recurrent stroke or transient ischemic attack and to investigate further if this relationship is related to the shunt size.

Methods—We conducted a systematic review and meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines of all available prospective studies reporting recurrent cerebrovascular events defined as cryptogenic stroke and transient ischemic attacks in medically treated patients with PFO diagnosed by echocardiography or transcranial sonography.

Results—We identified 14 eligible studies including a total of 4251 patients. Patients with stroke with PFO did not have a higher risk of the combined outcome of recurrent stroke/transient ischemic attack (risk ratio=1.18; 95% confidence interval=0.78–1.79; P=0.43) or in the incidence of recurrent strokes (risk ratio =0.85; 95% confidence interval=0.59–1.22; P=0.37) in comparison with stroke patients without PFO. In addition, PFO size was not associated with the risk of recurrent stroke or transient ischemic attack. We also documented no evidence of heterogeneity across the included studies.

Conclusions—Our findings indicate that medically treated patients with PFO do not have a higher risk for recurrent cryptogenic cerebrovascular events, compared with those without PFO. No relation between the degree of PFO and the risk of future cerebrovascular events was identified. (Stroke. 2014;45:3352-3359.)

Key Words: foramen ovale, patent ischemic attack, transient stroke transcranial Doppler ultrasonography transesophageal echocardiography

PFO size and the degree of functional shunting could represent potential risk factors for cerebral ischemia in medically treated patients with PFO. PFOs in patients with cerebral ischemia are thought to be larger and to be more frequently associated with atrial septal aneurysms, compared with the PFOs in asymptomatic patients. Moreover, in transcranial Doppler (TCD) studies, large PFOs were found to be significantly associated with more microembolic signals compared with small PFOs. However, data from other studies suggest that the shunt grade assessed with TCD is not associated with the brain infarct volume on computed tomography and that

The frequency of patent foramen ovale (PFO) in the general population has been estimated to be 15% to 35%. In patients with cryptogenic stroke, PFO is more common, but a clear causative relationship is not well established. Recurrent cerebrovascular events are frequent in medically treated patients with a history of paradoxical embolism; however, in more than one third of these patients concurrent pathogeneses (other than the sole presence of PFO) are identified. Thus, it still remains unclear whether PFO is causally related to first-ever or recurrent cerebral ischemia or constitutes an incidental finding of diagnostic work-up.

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the incidence of large shunts size is not greater in patients with probable PFO-attributable stroke. In view of the former considerations, we conducted a systematic review and meta-analysis to evaluate the potential association of PFO with an increased risk of recurrent stroke or transient ischemic attack (TIA) in medically treated patients with stroke, using data from prospective observational studies. We also investigated the relationship of shunt size with the risk of recurrent cerebrovascular events.

**Methods**

**Trial Identification and Data Abstraction**

This meta-analysis has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses. Eligible studies reporting recurrent cerebrovascular events including ischemic stroke or TIA in patients with PFO were identified by searching MEDLINE, SCOPUS, and the conference proceedings of the International Stroke Conference and the European Stroke Conference. Cochrane Database of Systematic Reviews databases was also screened for available systematic reviews on the topic. The following combination of search strings was used in the SCOPUS literature search: patent foramen ovale AND (recurrent stroke OR recurrent transient ischemic attack). No language or other restrictions was imposed. Last literature search was conducted on April 11th 2014. Reference lists of all articles that met the criteria and of relevant review articles were examined to identify studies that may have been missed by the database search. Moreover, additional data required for this meta-analysis were obtained by contacting the corresponding authors of the included studies.

All retrieved studies from the aforementioned literature search were scanned by 2 independent reviewers (A.H.K. and G.T.) to include only prospective studies (prospective cohort studies or subgroups from randomized clinical trials) that reported recurrent cryptogenic strokes or TIAs in medically treated patients with PFO. PFO was diagnosed using echocardiography or TCD in all included studies. Retrospective cohort studies, case series, case reports, or studies that reported recurrent strokes or TIAs in mixed groups of medically and invasively (eg, PFO closure procedures) treated patients were excluded from the final analysis. We excluded also those studies that reported death events mixed with cerebrovascular events (stroke or TIA). Finally, databases combining data from individual studies were excluded per se, to avoid the inclusion of overlapping patient data in the meta-analysis.

In each study that met the inclusion criteria, a predefined 10-point quality control was used to address for biases. For each quality item, the corresponding risk of bias was categorized as low, high, or unclear according to the suggestions by Higgins et al. Unavailable data were categorized by convention as unclear risk of bias. Quality control and bias identification were performed by 3 independent reviewers (A.H.K., G.T., J.P.), and all emerging conflicts were resolved with consensus.

Data on the events (recurrent cryptogenic ischemic stroke and recurrent cryptogenic TIA) and the sample sizes of medically treated patients with and without PFO were extracted independently by the 2 authors, who performed the literature search (A.H.K., G.T.). After the initial analysis of available studies on the recurrent cerebrovascular risk in medically treated patients according to the presence of PFO, we stratified shunt size according to the description that was given in each individual study protocol as small, moderate, or large. Additional details regarding shunt size stratification are provided in the Methods in the online-only Data Supplement (Shunt Size Stratification). Finally, we dichotomized in each analysis the study protocols in TCD or transesophageal echocardiography (TEE) and performed the subgroup analyses.

**Statistical Analyses**

We calculated the risk ratio (RR) in each study by dividing the number of events (recurrent strokes and TIAs) by the total number of patients.
Results

Study Selection and Study Characteristics

MEDLINE database search yielded 114 results and SCOPUS database search 232 results. Search of the International Stroke Conference and European Stroke Conference proceedings revealed an unpublished oral presentation of a research protocol on the association between the PFO size and the risk of recurrent cerebral ischemia. The required data from this study were obtained by directly contacting the corresponding author of this study. We also included preliminary data from an ongoing cohort study conducted by our group that evaluated the risk of recurrent stroke or TIA in consecutive patients with stroke/TIA and PFO.

Excluding 3 duplicate studies, the remaining 345 studies were screened for eligibility criteria. Potentially eligible studies for the meta-analysis (n=21) were retained, after screening both the titles and abstracts of all studies. After retrieving the full-text version of the aforementioned 21 studies, 5 studies were excluded because the end points of medically treated patients were mixed with the end points of surgically treated (with percutaneous or open closure) patients; 2 studies because of the absence of comparison group (patients without PFO or no shunt stratification) and 1 study because the reported end point was the combined outcome of stroke, TIA, or death. The remaining 13 studies and the available data from our study cohort were included both in the qualitative and quantitative synthesis, according to the presence of PFO (PFO present, PFO absent), the shunt size (small right-to-left shunt [RLS] versus moderate or large RLS), and the available outcome data (stroke or TIA, stroke; Figure 1). The characteristics of the included studies are summarized in Table 1. Moreover, the individual patient characteristics of included studies in the meta-analysis are shown in Table in the online-only Data Supplement.

Risk of Bias for Independent Studies

Risk of bias in the included studies is summarized in Figure 2. Consecutive patients were enrolled in 12 of the 14 studies, in 1 study patients were enrolled nonconsecutively, while

in each group. For studies with a zero cell, we used a continuity correction of 0.5, as appropriate. In cases of ≥2 zero cells, the assumption of continuity correction was not used and the corresponding point estimates were designated as not estimable. The mixed-effects model was used to calculate both the pooled point estimate in each subgroup and the overall estimates. According to the mixed-effects model, we used a random effects model (DerSimonian–Laird) to combine studies within each subgroup and a fixed effect model (Mantel–Haenszel method) to combine subgroups and estimate the overall effect. We assumed the study-to-study variance (τ-squared) to be the same for all subgroups. Tau-squared was first computed within subgroups and then pooled across subgroups. The equivalent z test was performed for each pooled RR, and P<0.05 was considered statistically significant.

Heterogeneity between studies was assessed by the Cochran Q and I² statistic. Heterogeneity was considered as statistically significant when P value derived from Cochran Q was <0.1. For the qualitative interpretation of heterogeneity, I² values of ≥50% are usually considered to represent substantial heterogeneity, whereas values of ≥75% indicate considerable heterogeneity according to the Cochrane Handbook. Publication bias (ie, assessment of bias across studies) was graphically evaluated using a funnel plot, given the rule of thumb reported in the Cochrane Handbook for Systematic Reviews of Interventions indicating that tests for funnel plot asymmetry should be used only when there are ≥10 studies included in the meta-analysis. All statistical analyses were conducted using Review Manager (RevMan) version 5.2 software (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2012).

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Population</th>
<th>N</th>
<th>Imaging Method</th>
<th>Moderate/Large Shunt</th>
<th>Mean Follow-Up (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anzola et al</td>
<td>2003</td>
<td>Italy</td>
<td>CS</td>
<td>59</td>
<td>TCD</td>
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<td>23</td>
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<td>Arauz et al</td>
<td>2011</td>
<td>Mexico</td>
<td>CS</td>
<td>186</td>
<td>TEE</td>
<td>...</td>
<td>66</td>
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<td>2012</td>
<td>United States</td>
<td>CS/TIA</td>
<td>462</td>
<td>TEE</td>
<td>&gt;10/&gt;25 μB</td>
<td>24</td>
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<tr>
<td>CODICIA</td>
<td>2008</td>
<td>Spain</td>
<td>CS</td>
<td>486</td>
<td>TCD</td>
<td>&gt;25 μB</td>
<td>24</td>
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<tr>
<td>Cujec et al</td>
<td>1999</td>
<td>Canada</td>
<td>CS/TIA</td>
<td>90</td>
<td>TEE</td>
<td>&gt;6/&gt;20 μB</td>
<td>46</td>
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<td>De Castro et al</td>
<td>2000</td>
<td>Italy</td>
<td>IS/TIA</td>
<td>350</td>
<td>TEE</td>
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<td>Di Legge et al</td>
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<td>CS</td>
<td>129</td>
<td>TEE</td>
<td>&gt;10 μB</td>
<td>24</td>
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<tr>
<td>Feurer et al</td>
<td>2010</td>
<td>Germany</td>
<td>IS</td>
<td>639</td>
<td>TCD</td>
<td>...</td>
<td>48</td>
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<td>Fukuoka et al</td>
<td>2011</td>
<td>Japan</td>
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<td>&gt;6/&gt;25 μB</td>
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<td>Homma et al</td>
<td>2004</td>
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<td>250</td>
<td>TEE</td>
<td>&gt;10 μB</td>
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<td>PFO-ASA study group</td>
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<td>CS</td>
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<td>TEE</td>
<td>&gt;10 μB</td>
<td>37.8</td>
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<tr>
<td>RESPECT</td>
<td>2013</td>
<td>United States, Canada</td>
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<td>481</td>
<td>TEE</td>
<td>&gt;20 μB</td>
<td>31.2</td>
</tr>
<tr>
<td>Tobe et al</td>
<td>2014</td>
<td>Canada</td>
<td>CS</td>
<td>340</td>
<td>TEE</td>
<td>&gt;10/&gt;30 μB</td>
<td>14</td>
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<tr>
<td>G. Tsivgoulis, et al</td>
<td>Unpublished</td>
<td>Greece, Singapore</td>
<td>IS/TIA</td>
<td>151</td>
<td>TCD</td>
<td>&gt;20 μB/curtain appearance*</td>
<td>3</td>
</tr>
</tbody>
</table>

μB indicates microbubbles; ASA, atrial septal aneurysm; CLOSURE, 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; CODICIA, Multicenter Study Into RLSH in Cryptogenic Stroke; CS, cryptogenic stroke; IS, ischemic stroke; m, multicenter; PFO, patent foramen ovale; RESPECT, Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; TCD, transcranial Doppler; TEE, transesophageal echocardiography; and TIA, transient ischemic attack.

*Bilateral TCD monitoring.
in the remaining study no information was reported about the consecutiveness of the study participants. In all studies, except for one, the inclusion criteria were clearly stated in the manuscripts. Excluding patients after initial recruitment was mentioned in 4 studies. Baseline characteristics and medications were not provided in 3 and 4 studies, respectively. TCD or TEE protocol was sufficiently presented in 12 studies while the description was unavailable in 2 studies. Loss to follow-up was reported in 8 studies and could not be evaluated in 2 studies. Only 4 studies reported no losses to follow-up after initial recruitment. Finally, a funding source (commercial or public) was acknowledged in 3 studies.

**Overall and Subgroup Analyses**

Stroke patients with PFO did not have a higher risk of the combined outcome of recurrent cryptogenic stroke/TIA (RR=1.18; 95% confidence interval [CI]=0.78–1.79; P=0.43; Figure 3A) or recurrent cryptogenic stroke (RR=0.85; 95% CI=0.59–1.22; P=0.37; Figure 3B) in comparison with stroke patients without PFO. In both analyses, no substantial heterogeneity was found (combined outcome recurrent stroke/TIA: I²=37%; P=0.17; recurrent stroke I²=26%; P=0.22). Similarly, the annual rates of recurrent stroke or recurrent stroke/TIA did not differ between cryptogenic stroke patients with and without PFO (Table 2). On the combined outcome of recurrent cryptogenic stroke/TIA, no statistical difference was evident (P=0.52) among the results of TEE (RR=0.92; 95% CI=0.54–1.55; P=0.75) and TCD subgroups (RR=0.72; 95% CI=0.44–1.20; P=0.21). From the inspection of the funnel plot in the second analysis, neither publication bias nor small study effect can be excluded (Figure I in the online-only Data Supplement). The study number in all analyses is too small (<8) to use statistical tests for detecting funnel plot asymmetry (eg, Egger linear regression test) or to make any inferences with certainty.

Patients with moderate or large RLS tended to have an overall higher, but not significant risk, for recurrent cryptogenic stroke/TIA (RR=2.08; 95% CI=0.87–4.93; P=0.10; Figure 4A), compared with patients with small RLS. However, in subgroup analysis, TCD studies suggest a higher risk of recurrent cryptogenic stroke/TIA in patients with moderate or large RLS compared with those with small RLS (RR=2.91; 95% CI=1.32–6.41; P=0.008). Moderate or large RLS was not associated with a higher risk of recurrent stroke/TIA in TEE subgroup analysis (RR=1.02; 95% CI=0.47–2.21; P=0.96). There was no association between moderate or large RLS and risk of recurrent stroke (RR=1.43; 95% CI=0.60–3.40; P=0.42; Figure 4B). No substantial heterogeneity was found in the analyses (combined outcome recurrent stroke/
TIA: $I_2=46\%; P=0.14$; recurrent stroke: $I_2=33\%; P=0.21$).

Moderate or large RLS was not associated ($P>0.4$) with risk of recurrent stroke when TCD and TEE studies were evaluated separately.

Similarly, the combined risk of recurrent cryptogenic stroke/TIA (RR=1.33; 95% CI=0.75–2.34; $P=0.33$; Figure IIA in the online-only Data Supplement) and the risk of recurrent cryptogenic stroke (RR=1.34; 95% CI=0.73–2.47; $P=0.35$; Figure IIB in the online-only Data Supplement) did not differ among patients with stroke with large shunt in comparison with patients with stroke with moderate or small shunt in both the overall and subgroup analyses (separate evaluation of TCD and TEE studies). No evidence of heterogeneity were found in the analyses (combined outcome recurrent stroke/TIA: $I_2=38\%; P=0.17$; recurrent stroke $I_2=0\%; P=0.42$).

**Discussion**

Numerous systematic reviews and meta-analyses of randomized clinical trials and observational studies have addressed to date the comparison of PFO closure versus medical therapy in patients with cryptogenic stroke or TIA. The reported results on the prevention of recurrent cerebral ischemia were conflicting, inconsistent between randomized and observational studies, and ranged from a clear benefit of PFO closure to uncertainty for the superiority of the interventional over the medical treatment and to an even higher risk incidence for PFO closure compared with medical treatment.

To the best of our knowledge, this is the first systematic attempt to summarize and evaluate meta-analytically the existing literature data on the risk of recurrent cryptogenic stroke or TIA. Our analyses indicate that the risk of recurrent cryptogenic stroke or TIA is not associated with the size of RLS and lend support to the mounting literature underscoring the lack of association between PFO and recurrent stroke risk.

**Table 2. Rates of Outcome Events in Patients With Cryptogenic Stroke Stratified by the Presence or Absence of PFO**

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>PFO (+)</th>
<th>PFO (−)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual rate* of recurrent stroke/TIA</td>
<td>5.6% (2.6%–8.5%)</td>
<td>5.0% (2.1%–7.9%)</td>
<td>0.791</td>
</tr>
<tr>
<td>Annual rate* of recurrent stroke</td>
<td>2.0% (1.1%–2.8%)</td>
<td>2.4% (1.6%–3.3%)</td>
<td>0.440</td>
</tr>
</tbody>
</table>

PFO indicates patent foramen ovale; and TIA, transient ischemic attack.

*Per 100 patient-years.
patients PFO is not related to a higher risk of recurrent cerebrovascular events in comparison with stroke/TIA patients without PFO.50,51 Interestingly, our findings are in line with 2 prospective cohort studies, showing that PFO presence was not associated with an increased risk of first-ever stroke in the general population.52,53 Finally, our analyses underscore the current recommendation issued by the American Heart Association that does not support a benefit for PFO closure for patients with a cryptogenic stroke/TIA and a PFO.54

In our meta-analysis, we included 9 TEE and 5 TCD imaging protocols that assessed the presence and the size of RLS in 4251 patients with ischemic stroke or TIA. Although TEE bubble study is currently considered as the gold standard for PFO investigation, false-negative results or misdiagnosed RLS may occur.55,56 Moreover, it is technically challenging to perform adequate Valsalva maneuver during TEE investigation.55,56 TCD is a more sensitive (sensitivity: 95%–98%) method for the diagnosis of RLS compared with TEE (sensitivity: 80%–100%)57–59 but does not provide any information about other potential cardiac and aortic embolic sources.60 Thus, the combination of TEE with TCD could be considered as the ideal method for the investigation of paradoxical embolism in patients with cryptogenic stroke.61

Figure 4. Risk of recurrent stroke or transient ischemic attack (A) and risk of recurrent stroke (B) in patients with moderate or large shunt size compared with patients with small shunt size. CI indicates confidence interval; TCD, transcranial Doppler; and TEE, transesophageal echocardiography.
Certain limitations of this report need to be acknowledged. First, associations with higher recurrence risk cannot be interpreted causally because there is no reliable way to distinguish consistently patients with paradoxical embolism from other patients with PFO and cryptogenic stroke because of other (PFO-unrelated) occult mechanisms. Second, we dichotomized shunt size, as small or moderate or large, using a cutoff point 10 microbubbles in the TCD or TEE investigation. However, neither the imaging protocol nor the stratification of shunt size was homogenous in all included studies (Table 1). Third, the mean follow-up period was not the same for all studies and in many cases for individual patients within studies. Patients were prospectively followed for 2 years in 6 studies,24,34,36,40,42,43,45 >2 years in 2 studies,24 and >2 years in the remaining 6 studies35,37,39,41,44,42 (Table 1). Fourth, the presence of atrial septal aneurysm had a variable incidence among the included echocardiographic studies (range, 8.5%–41%) and could also vary widely according to the shunt size (Table in the online-only Data Supplement). Concurrent atrial septal aneurysm in patients with PFO was shown to be associated with a higher incidence of cryptogenic strokes/TIA,60 and, therefore, could potentially increase the risk of subsequent stroke in medically treated patients with PFO.6 However, the presence of atrial septal aneurysm was not investigated in the TCD studies and consequently was not evaluated in our meta-analysis. Fifth, there is evidence of high risk for attrition bias because 8 of the study protocols reported losses to follow-up. In 6 of these studies, the percentage of patients lost to follow-up was small (0.3%–4.9%34,36,37,40,42,43,44) while in the other 2 was considerably large (16.7% and 17.2%).11,45 Sixth, selection bias cannot also be excluded in studies that enrolled patients nonconsecutively, or in those studies that excluded patients after initial recruitment. Additional causes for possible selection bias and false PFO prevalence rates in the individual studies are related to the fact that not all stroke or even cryptogenic stroke patients undergo TEE or TCD and that some patients have an insufficient transtemporal acoustic window on TCD examination.

In conclusion, the present systematic review and meta-analysis showed that medically treated stroke/TIA PFO patients do not have a higher risk for recurrent cerebrovascular ischemia, compared with those without PFO. No relation between the degree of RLS and the risk of future cerebrovascular events was found when shunt size was dichotomized as small and moderate or large. These findings endorse current American Heart Association recommendations advocating to avoid PFO closure in patients with cryptogenic stroke/TIA and a PFO.

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Disclosures
None.

References


Pristipino C, Anzola GP, Ballerini L, Bartorelli A, Cacciore M, Chessa M, et al; Italian Society of Invasive Cardiology (SICI-GISE); Italian Stroke Association (ISA-ALIS); Italian Association of Hospital Neurologists, Neuroradiologists, Neurosurgeons (SNO); Congenital Heart Disease Study Group of Italian Society Of Cardiology; Italian Association Of Hospital Cardiologists (ANMCO); Italian Society Of Pediatric Cardiology (SIPOS); Italian Society Of Cardiovascular Imaging (SICF); Italian Society Of Cardiovascular and Thoracic Surgery (SITSE). Management of patients with patent foramen ovale and cryptogenic stroke: a collaborative, multidisciplinary, position paper: executive summary. Catheter Cardiovasc Interv. 2013;82:122–129.


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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/11/3352

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/10/07/STROKEAHA.114.007109.DC1
http://stroke.ahajournals.org/content/suppl/2016/04/06/STROKEAHA.114.007109.DC2

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Shunt size stratification
According to available criteria, in transesophageal echocardiography (TEE) a PFO is present if more than one contrast microbubble (μB) appears in the left atrium. A small shunt is defined as the presence of 3-10 μB, a moderate shunt as 11-30 μB and a large shunt as more than 30 μB. In TCD examination, shunts are classified according to the presence of μB in the middle cerebral arteries (MCAs) and quantified according to the International Consensus Criteria (ICC) or the Spencer Logarithmic Scale (SLS) criteria. The ICC are commonly used for contrast TCD unilateral interpretation: negative (no μB), grade I (1-10 μB), grade II (>10 μB or “shower” appearance of μB), and grade III (“curtain” appearance of μB), while the SLS were developed to offer more grades of right-to-left shunt quantification: negative (no μB), grade I (1-10 μB), grade II (11-30 μB), grade III (31-100 μB), grade IV (101-300 μB), and grade V (>300 μB). As a cut-off point for the definition of a “small” right-to-left shunt (RLS) we used the presence of less than 10 μB in the TCD or TEE investigation. Subsequently, shunts with more than 10 μB in the TCD or TEE investigation were categorized as “moderate or large”. The risk of recurrent cerebrovascular events was then investigated among medically treated patients with “small RLS” compared to medically treated patients with “moderate or large RLS”. Similarly in a subsequent analysis shunts with less than 25-30 μB in the TCD/TEE examination were categorized as “small or moderate” and shunts with more than 25-30 μB in imaging protocols were categorized as “large”.
# Supplemental Tables

## Supplemental Table. Baseline patient characteristics in the included studies

<table>
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<tr>
<th>Study</th>
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<th>TIA</th>
<th>ASA</th>
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<th>AP</th>
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<tr>
<td>Anzola et al</td>
<td>S-shunt: 43.7 ± 12</td>
<td>S-shunt: 57.1%</td>
<td>22%</td>
<td>12%</td>
<td>S-shunt: 21%</td>
<td>S-shunt: 43%</td>
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<tr>
<td></td>
<td>M/L-shunt: 46.7 ± 13</td>
<td>M/L-shunt: 64.5%</td>
<td></td>
<td></td>
<td>M/L-shunt: 48%</td>
<td>M/L-shunt: 35%</td>
</tr>
<tr>
<td>Arauz et al</td>
<td>32.3±7.9</td>
<td>PFO(-):46.5%</td>
<td>12.9%</td>
<td>0%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>CLOSURE</td>
<td>45.7±9.1</td>
<td>48.5%</td>
<td>28.6%</td>
<td>35.7%</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>CODICIA</td>
<td>S-shunt: 56.4 ± 13.5</td>
<td>S-shunt: 40.2%</td>
<td>20.2%</td>
<td>S-shunt: 18.3%</td>
<td>21%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>M/L-shunt: 51.6 ± 15.2</td>
<td>M/L-shunt: 37%</td>
<td></td>
<td></td>
<td>M/L-shunt: 48.2%</td>
<td></td>
</tr>
<tr>
<td>Cujec et al</td>
<td>38±11</td>
<td>40%</td>
<td>50%</td>
<td>11.5%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>De Castro et al</td>
<td>47±14</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Di Legge et al</td>
<td>PFO(-):60±14</td>
<td>PFO(-):34%</td>
<td>-</td>
<td>41%</td>
<td>4.7%</td>
<td>PFO(-):26%</td>
</tr>
<tr>
<td></td>
<td>PFO(+):57±14</td>
<td>PFO(+):48%</td>
<td></td>
<td></td>
<td></td>
<td>PFO(+):25%</td>
</tr>
<tr>
<td>Feurer et al</td>
<td>PFO(-):60.6±13.5</td>
<td>PFO(-):54.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>PFO(+):53.5±15.9</td>
<td>PFO(+):30.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fukuoka et al</td>
<td>56.8 ± 14.2</td>
<td>36.17%</td>
<td>-</td>
<td>8.5%</td>
<td>48.9%</td>
<td>61.7%</td>
</tr>
<tr>
<td>Homma et al</td>
<td>PFO(-):44.5±6.6</td>
<td>PFO(-):48.1%</td>
<td>-</td>
<td>-</td>
<td>PFO(-):55.6%</td>
<td>PFO(-):44.4%</td>
</tr>
<tr>
<td></td>
<td>PFO(+):42.9±7.0</td>
<td>PFO(+):42.9%</td>
<td></td>
<td></td>
<td>PFO(+):44.9%</td>
<td>PFO(+):55.1%</td>
</tr>
<tr>
<td>PFO-ASA group</td>
<td>40.3</td>
<td>52.7</td>
<td>19.1%</td>
<td>3.1%</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>RESPECT</td>
<td>46.2±10.0</td>
<td>44.3%</td>
<td>-</td>
<td>35.1%</td>
<td>25.2%</td>
<td>74.8%</td>
</tr>
<tr>
<td>Tobe et al</td>
<td>53±14</td>
<td>61.5</td>
<td>-</td>
<td>19.3%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tsivgoulis et</td>
<td>45±10</td>
<td>39.7%</td>
<td>34.4%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

TIA: transient ischemic attack, ASA: atrial septal aneurysm, OA: oral anticoagulant AP: antiplatelet, PFO(-): PFO absent, PFO(+): PFO present, S-shunt: small shunt, M/L-shunt: moderate or large shunt
Supplemental Figures and Figure Legends

Supplemental Figure 1. Funnel plot assessing the risk of publication bias
### Supplemental Figure II. Risk of recurrent stroke or TIA (Supplemental Figure A) and risk of recurrent stroke (Supplemental Figure B) in patients with moderate or small shunt size compared to patients with large shunt size

#### A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Patients with L. shunt</th>
<th>Patients with M/S shunt</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>5.1.1 TEE studies</td>
<td>CLOSURE, 2012</td>
<td>3</td>
<td>65</td>
<td>310</td>
<td>16.5%</td>
</tr>
<tr>
<td></td>
<td>RESPECT, 2013</td>
<td>10</td>
<td>231</td>
<td>562</td>
<td>20.9%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>296</td>
<td>562</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>13</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.18; df = 1 (P = 0.67); I² = 35%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.29 (P = 0.77)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

#### B

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Patients with L. shunt</th>
<th>Patients with M/S shunt</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>5.1.2 TCD subgroup</td>
<td>CODICA, 2005</td>
<td>10</td>
<td>260</td>
<td>97</td>
<td>20.9%</td>
</tr>
<tr>
<td></td>
<td>2014</td>
<td>70</td>
<td>265</td>
<td>15</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Tengstedt et al</td>
<td>2</td>
<td>26</td>
<td>0</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>481</td>
<td>387</td>
<td>63.0%</td>
<td>1.54 [0.55, 4.44]</td>
</tr>
<tr>
<td>Total events</td>
<td>80</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.29; df = 2 (P = 0.62); I² = 52%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.09 (P = 0.92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 0.19; df = 1 (P = 0.66); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Analysis

- **A**
  - The risk of recurrent stroke or TIA was higher in patients with large shunt size compared to those with moderate or small shunt size.
  - The risk ratio was 0.67 (95% CI: 0.21, 2.16).
- **B**
  - The risk of recurrent stroke was also higher in patients with large shunt size compared to those with moderate or small shunt size.
  - The risk ratio was 1.76 (95% CI: 0.85, 3.67).
Supplemental References

Recurrent Stroke and Patent Foramen Ovale
A Systematic Review and Meta-Analysis

Aristeidis H. Katsanos, MD; J. David Spence, MDBA, MBA, MD, FRCPC; Chrysi Bogiatzi, MD; John Parissis, MD, PhD; Sotirios Giannopoulos, MD, PhD; Alexandra Frogoudaki, MD, PhD; Apostolos Safouris, MD; Konstantinos Voumvourakis, MD, PhD; Georgios Tsivgoulis, MD, PhD, FESO
(Stroke. 2014;45:3352-3359.)

Key Words: foramen ovale, patent ■ ischemic attack, transient ■ stroke ■ transcranial Doppler ultrasonography ■ transesophageal echocardiography

Background and Objectives

Anatomically patent foramen ovale (PFO) is present in the majority of the population, but does not predispose to paradoxical embolism. However, its role in the pathogenesis of recurrent stroke remains controversial. Since the only randomized clinical trial failed to show a significant difference in outcome between patients treated with PFO closure or medical therapy, several meta-analyses were performed to provide evidence-based guidelines for the management of patients with PFO. The aim of this study was to perform a systematic review and meta-analysis to study the role of PFO presence in the risk of recurrent stroke and transient ischemic attack.

Methods

This study was performed in accordance with the guidelines for systematic reviews and meta-analyses. Only prospective cohort studies with TCD or TEE were included. The primary outcome was the risk of recurrent stroke or transient ischemic attack. Data were extracted and quality of studies was assessed by 2 independent reviewers. The included studies were pooled with a random-effects model, and subgroup analysis was performed for the lesion size, type of intervention, and study design. The heterogeneity among the studies was assessed by the Cochran Q test and the I² statistic. The risk of recurrence was expressed as hazard ratio and 95% confidence interval.

Results

A total of 4,251 patients were included from 14 studies. Approaching a PFO with an interventional approach or medical therapy did not result in a significant difference in the risk of recurrence compared with those patients without a PFO. No correlation was found between the presence of PFO and the risk of recurrent stroke or transient ischemic attack. Subgroup analysis according to the size of the right-to-left shunt did not reveal any significant difference.

Conclusion

Anatomically patent foramen ovale is not a risk factor for recurrent stroke or transient ischemic attack. The role of PFO in the pathogenesis of recurrent stroke is still controversial.

Table 2. Rates of Outcome Events in Patients With Cryptogenic Stroke Stratified by the Presence or Absence of PFO

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>PFO (+)</th>
<th>PFO (−)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual rate* of recurrent stroke/TIA</td>
<td>5.6% (2.6%–8.5%)</td>
<td>5.0% (2.1%–7.9%)</td>
<td>0.791</td>
</tr>
<tr>
<td>Annual rate* of recurrent stroke</td>
<td>2.0% (1.1%–2.8%)</td>
<td>2.4% (1.6%–3.3%)</td>
<td>0.440</td>
</tr>
</tbody>
</table>

PFO indicates patent foramen ovale; and TIA, transient ischemic attack.

*Per 100 patient-years.