Stroke prevention by percutaneous closure of patent foramen ovale: a systematic review and meta-analysis

Mathias Wolfrum,1 Georg M Froehlich,2 Guido Knapp,3 Leanne K Casaubon,4 James J DiNicolantonio,5 Alexandra J Lansky,6 Pascal Meier2,6

ABSTRACT
Context The role of percutaneous closure of patent foramen oval (PFO) in patients with cryptogenic stroke has been very controversial for years due to a lack of clear evidence.

Objective Systematic review and meta-analysis of the effect of percutaneous PFO closure for secondary prevention of cryptogenic strokes as compared to best medical therapy (BMT).

Data sources Trials were identified through a literature search until 28 May 2013.

Study selection Controlled clinical trials (randomised and non-randomised) comparing percutaneous PFO closure with BMT.

Data extraction and synthesis Main end point of interest was stroke. A random effects model was used to calculate the pooled relative risks (RR) with 95% CIs.

Results A total of 14 studies (three randomised controlled trials (RCT) and 11 non-randomised observational studies (non-RCT)), and a total of 4335 patients were included for this analysis. There was no significant treatment effect of PFO closure regarding stroke among the RCT (RR 0.66, 95% CI 0.37 to 1.19, p=0.171). However, among non-RCT stroke was reduced (RR 0.37, 95% CI 0.20 to 0.67, p<0.001) after PFO closure. A time-to-event (stroke) analysis, combining all RCT and the two non-RCT which applied strict multivariate adjustments, showed a borderline significant risk reduction after PFO closure (HR 0.58, 95% CI 0.33 to 0.99, p=0.047). Neither risk of bleeding nor mortality differed significantly between the groups. However, there was a higher incidence of new onset atrial fibrillation in the closure group (RR 3.50, 95% CI 1.47 to 8.35, p=0.005).

Conclusions Percutaneous closure of PFO in patients with cryptogenic stroke does not appear superior to medical therapy according to currently available randomised data. Furthermore, it is associated with an increased incidence of atrial fibrillation. However, there are signals pointing towards a potential benefit and more research should be strongly encouraged.

INTRODUCTION
Recent literature suggests an association between paradoxical embolic events and patent foramen ovale (PFO). However, whether this relationship is causal has been heavily disputed. There have been some documented events of paradoxical embolism through a PFO for cerebrovascular events,1 2 myocardial infarction,3 and other systemic embolic events.4 Case series and non-randomised comparative studies have indicated that surgical and percutaneous closure of a PFO can reduce the stroke risk.5 6 Very recently, three randomised controlled trials (RCT) comparing percutaneous PFO closure versus medical therapy have been published. None of them found a significant reduction in the risk of recurrent embolic events between the closure groups and medical therapy groups.7 8 However, the event rates were rather low in all trials and we therefore hypothesised that they were underpowered to detect a significant difference.

While percutaneous PFO closure appears to be a very appealing concept, potentially avoiding the need for long term anticoagulation, it comes with a periprocedural risk (eg, bleeding, device embolisation) and significant costs. It is therefore essential to assess its evidence base as best as possible.

This present study aimed to pool currently available comparative data on percutaneous closure of PFO in patients with cryptogenic stroke for secondary prevention as compared to medical therapy.

METHODS

We performed this current study according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.7 8 Two authors (MW, GMF) planned and designed the study and created an electronic database with variables of interest.

Search strategy

We searched Medline, BIOS, and ISI Web of Science databases until 28 May 2013.


Appropriate studies had to be published in full text and in the English language. In brief, we used the following search terms: ‘PFO closure’, ‘foramen ovale’, ‘septal occlude device’, ‘cryptogenic stroke’, and ‘atrial percutaneous closure’.

For a more detailed search strategy for Medline see online supplementary file 1.
controlled studies, prospective RCT and observational studies
with a control group. All studies included in the analysis were
approved by the respective ethics committees responsible and
were in compliance with the Helsinki Declaration.

Data extraction and quality assessment
All relevant information from each study was extracted, includ-
ing baseline clinical characteristics of the study population and
outcome measures utilising a pre-specified standardised data-
based. Trial quality was determined as recommended by the
Cochrane Handbook. In brief, we assessed randomisation and
allocation concealment, intention-to-treat analysis, blinded
assessment of outcome measures, premature stopping of patient
enrolment, and reporting on dropouts, but without using a
quality score given the limitations inherent to such an approach
(see online supplementary file 2).

End points and definitions
We extracted patient characteristics, types of percutaneous
closure or medical treatment used, as well as study design vari-
able, and outcome data. Outcome data included recurrent stroke
or transient ischaemic attacks (TIA), peripheral embolism, pul-
monary embolism, atrial fibrillation, and death. Definitions have
been defined in the individual studies. Our primary end point
was stroke since this treatment is intended as secondary preven-
tion therapy for patients with cryptogenic stroke, in order to
prevent recurrent events (see online supplementary file 3).

Data synthesis and analysis
Our primary analysis was based on an intention-to-treat
approach. All analyses were stratified by study type (RCT vs
observational studies).

Calculations of binary outcomes were based on a
DerSimonian and Laird random effects model. This model
assumes that the true effects vary between studies for unknown
reasons. The primary summary measure usually reported is the esti-
icated average effect across studies. Continuity correction was
used when no event occurred in one group to allow calculation
of a relative risk (RR). Heterogeneity among trials was quanti-
ified with Higgins’ and Thompson’s I². I² can be interpreted as
the percentage of variability due to heterogeneity between

RESULTS

Description of included studies
A total of 265 articles were retrieved and 14 studies (three RCT
with 2313 patients, 11 non-randomised observational studies
(non-RCT) with control groups and 2022 patients) satisfied the
predetermined inclusion criteria after reviewing (figure 1).6 28
One of these non-RCT, by Wahl et al, was a propensity score
matched analysis.

Table 1 shows the baseline characteristics of the included
studies.
Table 1  Baseline characteristics of included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Closure device</th>
<th>Inclusion criteria</th>
<th>Primary end point</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furlan et al</td>
<td>STARFlex</td>
<td>TIA, CS</td>
<td>Composite (stroke or TIA, early death from any cause*, late death from neurologic causes†)</td>
<td>24</td>
</tr>
<tr>
<td>Meier et al</td>
<td>Amplatzer PFO Occluder</td>
<td>TIA, CS, peripheral embolism</td>
<td>Composite (death, non-fatal stroke, TIA, peripheral embolism)</td>
<td>49.2/48.0 (PC/MTx)</td>
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<tr>
<td>Carroll et al</td>
<td>Amplatzer PFO Occluder</td>
<td>TIA, CS</td>
<td>Composite (stroke, early death)‡</td>
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<td>Paciaroni et al</td>
<td>Amplatzer PFO Occluder PFO STAR CardioSeal/STARflex</td>
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<td>Faggiano et al</td>
<td>na</td>
<td>TIA, CS, migraine</td>
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<td>Wahl et al</td>
<td>Amplatzer PFO Occluder PFO STAR Sideris Buttoned Angel Wing Amplatzer ASD CardioSEAL</td>
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<td>Schuchlenz et al</td>
<td>Rashkind occluder, CardioSEAL, StarFin, Amplatzer</td>
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<td>Harrer et al</td>
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<td>Cerrato et al</td>
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<td>Casaubon et al</td>
<td>Amplatzer, CardioSeal</td>
<td>CS, TIA</td>
<td>Recurrent stroke</td>
<td>32</td>
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</tbody>
</table>

*Death from any cause during first 30 days.
†Death from neurologic causes between 31 days and 2 years.
‡Closure group = death from any cause within 30 days after implantation of the device or 45 days after randomisation; medical therapy group = death from any cause within 45 days after randomisation.
CS, cryptogenic stroke; FU, follow-up; MTx, medical therapy; na, not available; PC, percutaneous closure; PFO, patent foramen oval; TIA, transient ischaemic attack.

Figure 2 Forest plot of risk ratios (RR) for stroke. Markers represent point estimates of risk ratios, marker size represents study weight in random effects meta-analysis. Horizontal bars indicate 95% CIs. BMT, best medical therapy; Closure, percutaneous patent foramen oval closure; RCT, randomised controlled trials.
Stroke
Among the three RCT, the weighted incidence of recurrent stroke was 1.7% (0.75% to 3.0%) in the closure group and 2.9% (2.0% to 4.0%) in the best medical therapy (BMT) group. For the non-RCT it was 0.7% (0.05% to 1.9%) vs 6.9% (3.8% to 10.9%).

The relative risk for stroke was lower after PFO closure: RR 0.66, 95% CI 0.37 to 1.19, p=0.171 among the RCT, and RR 0.37, 95% CI 0.20 to 0.67, p<0.001 among the non-RCT (figure 2).

A time-to-event analysis which considers the time to a recurrent stroke based on the three RCT and the two non-RCT performing strict multivariate adjustments showed a borderline significant risk reduction of HR 0.58, 95% CI 0.33 to 0.99, p=0.047 (figure 3).

Transient ischaemic attack: There was no significant difference between the groups. The RR was 0.77, 95% CI 0.42 to 1.41, p=0.405 for the RCT, and 0.55, 95% CI 0.19 to 1.60, p=0.274 for the non-RCT (figure 4).

Bleeding: Among the RCT, the weighted incidence of bleeding events was 1.8% (0.28% to 4.4%) for the closure group and 1.7% (0.1% to 4.9%) for the BMT group. Among the non-RCT, the corresponding findings were 2.1% (0.5% to 4.5%) versus 1.7% (0.1% to 4.9%). This difference was not statistically significant: RR 1.17, 95% CI 0.47 to 2.88, p=0.738 among the RCT, and RR 1.09, 95% CI 0.07 to 15.90, p=0.950 among the non-RCT (figure 5).

Mortality: The risk was not significantly different between the groups: for the RCT it was RR 0.65, 95% CI 0.23 to 1.84, p=0.458, and for the non-RCT it was RR 0.76, 95% CI 0.31 to 1.88, p=0.557 (see online supplementary file 4).

Atrial fibrillation: The weighted incidence of atrial fibrillation among the RCT was 3.7% (2.5% to 5.3%) and 1.0% (0.5% to 1.7%) among the non-RCT. The risk was significantly higher in the PFO closure group: among the RCT the RR was 3.50, 95% CI 1.47 to 8.35, p=0.005, and in the one observational study which reported on this outcome, the RR was 2.90, 95% CI 0.12 to 70.50, p=0.513 (figure 6).

Sensitivity analyses: We also performed a per-protocol analysis, which was provided by two of the RCT. This analysis only includes patients who adhered to the protocol but excludes those who were, for example, assigned to medical therapy but later underwent PFO closure. There was no significant difference in stroke risk between the treatment groups: RR 0.66, 95% CI 0.32 to 1.38, p=0.270 (see online supplementary files 5 and 6). Furthermore, we performed an analysis excluding the CLOSURE I trial which used a different closure device (StarFlex): the HR for stroke is significantly reduced at 0.44, 95% CI 0.20 to 0.94, p=0.034 in the time-to-stroke analysis, and for the traditional binary calculation the RR results in 0.48, 95% CI 0.23 to 1.02, p=0.057.

DISCUSSION
While previous meta-analyses have predominantly focused on outcomes after PFO in single arm observational studies, the focus of this meta-analysis was to assess the comparative effect of percutaneous PFO closure versus BMT in patients with cryptogenic stroke. Generally, the results confirm the findings of the individual RCT. We did not find a significant effect on stroke reduction even in the pooled analysis of RCT. However, there are signals towards a potential benefit of PFO closure if we also consider non-randomised data or if we focus on trials which used the Amplatzer closure device.

The crucial question is still not resolved. Is a PFO really a source for stroke? Data on this topic are conflicting. While some studies suggest that a PFO increased the risk for stroke, others failed to find an independent predictive association of PFO and stroke.

Unfortunately, this meta-analysis is not able to contribute to a better understanding of this issue. It failed to find a protective role of closing PFO in case of cryptogenic strokes. However, there are some signals indicating that it is too early for a definite conclusion. The point estimates tend toward a benefit of percutaneous PFO closure over medical therapy in the RCT, a finding which is supported by the finding in the non-randomised

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio</th>
<th>HR</th>
<th>95%-CI</th>
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<td>RCT</td>
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<td>PC trial</td>
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<td>CLOSURE I</td>
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<td>[0.41; 1.98]</td>
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<td>RESPECT</td>
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<tr>
<td>Random effects model</td>
<td>0.61</td>
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<td>[0.34; 1.11]</td>
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Heterogeneity: I²-squared=10.7%, tau-squared=0.0337, p=0.3262

Observational

<table>
<thead>
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<th>Study</th>
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<th>HR</th>
<th>95%-CI</th>
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<tr>
<td>Paciaroni et al</td>
<td>0.10</td>
<td></td>
<td>[0.01; 1.00]</td>
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<td>Wahl et al</td>
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<td></td>
<td>[0.05; 2.40]</td>
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Heterogeneity: I²-squared=59.1%, tau-squared=1.2, p=0.1179

<table>
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<th>95%-CI</th>
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<tbody>
<tr>
<td>Random effects model</td>
<td>0.58</td>
<td></td>
<td>[0.33; 0.99]</td>
</tr>
</tbody>
</table>

Heterogeneity: I²-squared=16.2%, tau-squared=0.0647, p=0.3114

**Figure 3** Forest plot of time-to-event analyses. Hazard ratio (HR) for end point stroke. For observational studies, adjusted HR were used. RCT, randomised controlled trials.

Systematic review
studies. While the latter are clearly prone to assignment bias, the time-to-event analysis combining the HRs of the three RCT with the carefully adjusted HR of two non-randomised studies (one of them a propensity score matched study) showed a borderline significant difference in favour of PFO closure.

On the other hand, we have to be well aware that the procedure is associated with some risks such as bleeding, vascular injury, device embolisation, thrombus formation on the device, and tamponade; it is also rather costly and, according to this analysis, it significantly increases the risk for atrial fibrillation. The latter is a major problem and defeats the purpose of the procedure in these cases. However, it is likely that some of these risks largely depend on the type of device used. The atrial fibrillation incidence was much higher in the CLOSURE I trial, which used the StarFlex device. This device is not US Food and Drug Administration (FDA) approved. So far, the FDA has approved the CardioSEAL Septal Occlusion System (NMT Medical Inc, Boston, Massachusetts, USA) and the Amplatzer PFO Occluder (AGA Medical Corp, Golden Valley, Minnesota, USA).

What current guidelines say
The 2012 American College of Chest Physicians (ACCP) guidelines recommend antiplatelet therapy for patients with cryptogenic ischaemic stroke and a PFO, and state that anticoagulation is not indicated. These guidelines recommend aspirin over no aspirin for patients with cryptogenic stroke and PFO or atrial septal aneurysm (ASA). For patients who experience recurrent events despite aspirin therapy, the ACCP guidelines suggest treatment with vitamin K antagonist therapy and consideration of device closure over aspirin. For patients with cryptogenic stroke and PFO who have evidence of deep vein thrombosis...
controlled trials.

Figure 6  Forest plot of risk ratios (RR) for atrial fibrillation. BMT, best medical therapy; RCT, randomised controlled trials.

(DVT), the ACCP guidelines recommend vitamin K antagonist therapy for 3 months and consideration of device closure over no vitamin K antagonist therapy or aspirin therapy.

The 2011 American Heart Association/American Stroke Association (AHA/ASA) guidelines state that antplatelet therapy is reasonable for patients with an ischaemic stroke or TIA and a PFO, and that oral anticoagulation is reasonable for high risk patients who have other indications such as a hypercoaguable state.12

Role of medical therapy

The post-randomisation incidence of stroke in the medical arms of the three RCT was 2.9% (2.0% to 4.0%) over their follow-up period of 2–4 years. This rather low baseline risk has to be considered when interpreting the relative risks.

Around 2/3 of patients in the BMT arm were on an antplatelet therapy. Medical therapy in all three RCT were determined by physician preference. CLOSURE recommended either warfarin adjusted to international normalised ratio (INR) 2–3 or aspirin 325 mg daily. RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) recommended either warfarin adjusted to INR 2–3, aspirin, clopidogrel or combination aspirin with dipyridamole. In the Percutaneous Closure (PC) trial, antithrombotic treatment was also left to the discretion of the treating physician and could have included antplatelet therapy or oral anticoagulation, given that patients received at least one antithrombotic drug.

As mentioned previously, the exact role of PFO in stroke is not clearly established and studies assessing associations are prone to confounding by other factors. The French PFO-ASA trial in patients with cryptogenic stroke (n=581) included 37% with a PFO. Interestingly, the study found that patients with cryptogenic stroke and PFO were younger and had fewer traditional risk factors for stroke than patients without PFO.33 In this study, all patients received aspirin 300 mg/day (with the exception of those with DVT who received warfarin). After 4 years follow-up, an isolated PFO, regardless of size, was not a significant predictor of recurrent stroke (however, the presence of a combined ASA and PFO was a significant predictor: HR 4.2, 95% CI 1.5 to 11.8). In the PICSS trial (Patent Foramen Ovale in Cryptogenic Stroke Study), involving 265 patients with cryptogenic stroke, 42 in one arm did receive aspirin 325 mg/day. In this study, no association was found between the presence of PFO alone and recurrent cerebrovascular events and, in contrast to the PFO-ASA study, the authors did not find any association in patients with a PFO and an ASA.34

Role of atrial fibrillation

The high incidence of post-procedure atrial fibrillation is of course concerning. There are probably several explanations, and the more obvious one is the PFO closure device triggering arrhythmias. Another explanation is that atrial fibrillation has been ‘under-diagnosed’ and that many of these patients had paroxysmal atrial fibrillation (PAF) to start with. These patients therefore underwent an interventional procedure despite there being another cause for their cerebrovascular event. Atrial fibrillation is notoriously challenging to diagnose.

An extensive list of other potential cardioembolic causes for stroke was outlined in the exclusion criteria of both the RESPECT and CLOSURE trials and included structural heart disease and chronic atrial fibrillation. RESPECT excluded PAF and no difference was seen in the rates of the development of atrial fibrillation in the trial. In CLOSURE, however, PAF was excluded only if it included two or more documented episodes lasting more than 30 s each and unrelated to a reversible cause, such as acute myocardial infarction, cardiac surgery, myocarditis, hyperthyroidism, or pulmonary disease.

Limitations

All three RCT suffered from slow enrolment. This is worrying in several ways: data from the initial phase (about 10 years ago) are not really comparable with the more current data due to device iterations, change in clinical practice, and medical therapy. Furthermore, it is an indicator for recruitment bias. Slow recruitment was usually not due to a lack of eligible patients, but simply due to a lack of patients enrolled into study protocols. Moreover, the control groups were relatively heterogeneous (eg, aspirin (ASS) only, while others were on warfarin). In particular, the concomitant treatment after device closure (eg, clopidogrel for several months) was also heterogeneous among the studies and might lead to significant bias (see online supplementary file 7).

It is important to note that all RCT have been industry sponsored (CLOSURE I by NMT Medical, RESPECT and PC by St Jude Medical) and several of the investigators received consulting fees from these companies. In addition, many of the investigators are ‘PFO closure enthusiasts’. Without implying...
that this has introduced a bias, it is important to consider, especially because the study designs were open label in all RCT. The limitations of the included non-randomised studies include selection bias, lack of independent event adjudication, heterogeneity in event definitions, and differences in the duration and ‘intensity’ of follow-up among the treatment arms.

Our paper focused on PFO and did not include patients with other reasons for inter-atrial shunt, such as atrial septal defect (ASD). Whether these results similarly apply to patients with ASD in unclear. Since our study has shown some signals towards a possible benefit for PFO closure, we would hypothesise that, if there is any benefit, it will be more pronounced in patients with a higher risk of and larger right-to-left shunt. The effect may therefore be even better in patients with ASD. However, we have to be aware that patients with a relevant ASD often develop atrial fibrillation and it becomes difficult to define exactly the risk of stroke due to paradoxical emboli. However, the influence of right-to-left shunt on stroke risk depends on several factors.35 36

CONCLUSION

Based on randomised data, percutaneous closure of PFO in patients with cryptogenic stroke does not appear to be superior to medical therapy. Furthermore, it appears to be associated with an increased incidence of atrial fibrillation and has a certain risk for procedural complications. Therefore, its indication needs to be carefully assessed. On the other hand, there are signals towards a potential benefit. Indeed, it is too early for a final conclusion and future studies need to focus on optimal patient and device selection.

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Contributors GFM and MW collected study data, GFM, MW and PM designed and conceptualised the study and interpreted all data, and drafted the manuscript. GK and PM performed the statistical analyses. GK, LKC, JJD and AIL interpreted the data. All authors contributed to this paper significantly and agreed to the final version.

Competing interests None.

Ethics approval This is a meta-analysis; all studies had ethical approval.

Provenance and peer review Not commissioned; externally peer reviewed.

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