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Systematic Review of Percutaneous Closure versus Medical Therapy in Patients with Cryptogenic Stroke and Patent Foramen Ovale

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Abstract

Background: Three randomized control trials (RCTs) comparing patient foramen ovale (PFO) closure to medical therapy have been published – none showed PFO closure to be statistically superior to medical therapy but each reported trends favoring PFO closure.

Objectives: To provide a comprehensive comparison of PFO closure versus medical therapy in patients with cryptogenic stroke or transient ischemic attack (TIA) and demonstrated PFO.

Design: Systematic review with complete case meta-analysis and sensitivity analyses

Data sources: Medline, Embase 1980 up to May 2013

Eligibility criteria: All randomized controlled trials (RCTs) comparing treatment with percutaneous catheter-based closure of PFO to medical therapy (anticoagulant or antiplatelet therapy) in patients with cryptogenic stroke or TIA and echocardiographically confirmed PFO or atrial septal defect (ASD) were eligible.

Methods: The primary outcome of interest was recurrence of ischemic stroke. We utilized data from complete cases only for the primary endpoint and combined data

from trials to estimate the pooled risk ratio (RR) and associated 95% confidence intervals (CI) calculated using random effects models.

Results: We identified 284 potentially eligible articles of which 3 RCTs including 2303 patients proved eligible and 1967 patients had complete data. Of the 1026 patients randomized to PFO closure and followed to study conclusion 22 experienced non-fatal ischemic strokes, as did 34 of 941 patients randomized to medical therapy (Risk Ratio 0.61, 95% CI 0.34, 1.07; Heterogeneity: p =0.34, I2 = 8%, confidence in estimates low due to risk of bias and imprecision). Analyses for ischemic stroke restricted to "per-protocol" patients or patients with concomitant atrial septal aneurysm did not substantially change the observed risk ratios. Complication rates associated with either PFO closure or medical therapy were low.

Conclusions: Pooled data from 3 RCTs provides little support for PFO closure over medical therapy for secondary prevention of cryptogenic stroke in patients with PFO.

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Study strengths

- Estimation of absolute benefits and risks of treatment strategies
- Careful assessment of risk of bias of individual studies using Cochrane criteria
- Evaluation of overall confidence in pooled outcome(s) estimates using GRADE

Limitations

- Primary analysis was restricted to patients with available data (complete case analysis). If event rates differed in those with missing data in intervention and control groups - of particular concern would be higher rates of events in those lost to follow-up in the PFO closure arm that the medical therapy arm - the complete case results may be misleading
- Individual patient-level data not available

Introduction

Observational studies suggest that younger patients with cryptogenic stroke are more likely to have a patent foramen ovale (PFO) than the general population. [1,2] A proposed mechanism for stroke in these patients is passage of thrombi from the venous circulation to the arterial circulation through the PFO. Although what proportion of cryptogenic strokes are due to paradoxical embolism remains unknown, percutaneous closure of PFO using devices approved for hemodynamically significant secundum atrial septal defect (ASD) has increased greatly in the last 2 decades. A systematic review of observational studies suggests PFO closure may be superior to medical therapy (antiplatelet or anticoagulant agents) for secondary prevention of stroke in patients with patent foramen ovale and cryptogenic stroke. [3]

In the last two years 3 three randomized control trials (RCTs) comparing PFO closure to medical therapy have been published – none showed PFO closure to be statistically superior to medical therapy for the primary composite outcome but each reported trends favoring PFO closure.[4-6] In one study, PFO closure was superior to medical therapy for the prevention of recurrent neurologic events in prespecified per-protocol and as-treated analyses.[5]

One systematic review and meta-analysis that included the 3 RCTs, and a second meta-analysis, have addressed this issue. Both were limited, however, by failure to

fully consider risk of bias issues, failure to use the GRADE approach to determine overall confidence in estimates of intervention effect, and failure to consider the limitations of composite endpoints.

We therefore undertook a systematic review of all RCTs comparing percutaneous PFO closure to medical therapy in patients with cryptogenic stroke or TIA and PFO or ASD. As composite endpoints varied between trials, we focused on individual endpoints of recurrent non-fatal stroke, recurrent TIA, death, major bleeding, and atrial fibrillation. We also examined per protocol rates of recurrent stroke in patients undergoing PFO closure compared to the medical therapy arm. Outcomes were defined as in each study.

Methods

Eligibility criteria

We included all RCTs comparing treatment with percutaneous catheter-based closure of PFO to medical therapy (anticoagulant or antiplatelet therapy) in patients with cryptogenic stroke or TIA and echocardiographically confirmed PFO or ASD. We excluded trials including participants with other indications for PFO/ASD closure (e.g. hemodynamic significance) or other indications for anticoagulant therapy (e.g. atrial fibrillation).

Included articles met two prespecified criteria: 1) RCTs that compared PFO closure to medical therapy (antiplatelet or anticoagulant agents); 2) Greater than 90% of

patients had prior unexplained stroke, TIA, or other arterial embolism, or this subset was reported separately. When more than one study reported data from a population, we used the most complete and updated results.

Data sources and search strategy

We searched Medline and Embase from 1980 to May 2013. We restricted the search to human subjects. Keywords included patent foramen ovale *or* atrial septal defect. Results were then limited to randomize controlled trial *or* controlled clinical trial *or* phase 3 clinical trial *or* phase 4 clinical trial. For every eligible study we identified, and for studies such as review articles that included citations to potentially eligible studies, one reviewer examined the reference list.

Study selection

Teams of two investigators independently screened each title and abstract from this search. If either of the two screeners identified a citation as potentially relevant, we obtained the full text article for detailed review. Teams of two reviewers independently determined the eligibility of all studies that underwent full text evaluation. Disagreements were resolved through discussion between the two reviewers.

Data abstraction

Using a custom made data collection form two of three reviewers (FAS, LCL, SAK) abstracted the following information from each identified study: mean follow-up

time, total patient years follow-up (overall and per cohort), number of patients withdrawn or lost to follow-up, number of patients crossing over from medical therapy to PFO closure, number of patients undergoing PFO closure attempt, number of patients in whom PFO closure was technically successful, procedural complications (other than major bleeding) from PFO closure, and outcome event rates.

Disagreements regarding data abstraction results were resolved through discussion between the two reviewers. The primary author abstracted additional information on study funding, eligibility criteria, patient demographics, and treatment characteristics.

Risk of Bias and Confidence in Effect Assessment

Two reviewers (FAS, LL) independently assessed, using the Cochrane risk for bias tool, seven domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding for outcome assessment, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the other 6 domains.[7]

We used GRADE methodology to rate confidence in estimates of effect for each outcome as high, moderate, low or very low.[8] We used detailed GRADE guidance to

assess overall risk of bias[9], imprecision[10], inconsistency[11], indirectness[12] and publication bias[13], and summarized results in an evidence profile.

For decisions regarding eligibility, risk of bias assessment, and data abstraction, reviewers resolved disagreement through discussion.

Data Synthesis and Statistical Analysis

We report descriptive statistics as proportions for categorical variables, and mean/median for continuous variables. Our primary analyses for non-fatal ischemic stroke, TIAs, and mortality included only patients with complete follow-up. We excluded patients for whom complete data was unavailable: those lost to follow-up, those who withdrew consent, or those who were found to not have PFO/ASD or history of TIA/stroke after randomization. For outcomes of bleeding and atrial fibrillation we used data as reported by the investigators from the intention to treat analyses.

Rates of non-fatal ischemic stroke in patients treated as "per-protocol" from two of the three studies were also abstracted and pooled. The definition of per-protocol varied from study to study (CLOSURE 1: all randomized patients who received the treatment to which they were randomized, who had no major inclusion/exclusion criteria violations, and who had a follow-up of at least 22 months; RESPECT: patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment, and did not have a major inclusion or exclusion

violation). Event rates for non-fatal ischemic stroke in the "per protocol" subset were not reported in PC Trial manuscript. The primary author of the manuscript did not respond to email requests for further information.

As previous observational studies suggest that patients with cryptogenic stroke and PFO may be at higher risk for recurrent stroke if they have a concomitant atrial septal aneurysm, we performed an additional complete case analysis for a primary composite outcome in the subset of patients with atrial septal aneurysm (data on non-fatal ischemic stroke alone not reported in any of the studies for this subset). Composite outcomes in the 3 studies included some combination of non-fatal ischemic stroke, TIA, peripheral embolism, and death.

As two of the three studies used the Amplatz device and one used the STARFlex device (CLOSURE 1) we conducted a sensitivity analysis for non-fatal ischemic stroke excluding the CLOSURE study. We evaluated for subgroup difference (2 Amplatz studies vs. STARFlex study) using a chi-square test.

Given high rate of patients excluded from complete case analyses (most due to loss to follow-up) we also conducted 2 additional analyses: 1) Worst case scenario in which we assumed that all patients with missing data in the PFO closure arms suffered non-fatal ischemic strokes and all patients lost to follow-up in the medical arms did not; 2) Plausible worst case scenario in which all patients with missing data from the PFO closure arm were assumed to have 5 times the rate of stroke as

the complete cases and b) those excluded from the medical therapy arm were assumed to have 1/5 times the rate of stroke as the complete cases.[14]

We calculated pooled risk ratios (RR) and associated 95% confidence intervals (CI) for non-fatal ischemic stroke and TIAs using random effects models applying Mantel Haenszel method. Absolute effects (and 95% CI) were calculated by multiplying pooled RRs and 95% CI by pooled control rate of outcomes. As event rates were very low for death, atrial fibrillation, and major bleeding (leading to skewed 95% CI), pooled risk difference (RD) and 95% CI was used to calculate absolute effects for these outcomes.[15] Statistical heterogeneity was assessed by the I^2 statistic. Analyses were performed using RevMan version 5.2 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration).

Results

Trial Identification

Our search yielded 284 abstracts - all were identified from the electronic database search- of which 47 were duplicates and excluded. We excluded an additional 229 articles based on a review of the title and abstract, leaving 8 articles for full review. Of these studies, 5 were excluded – 2 were descriptions of methodology for subsequently reported RCTs, 1 was a comparison of different devices for closure but did not include a medical therapy arm, and 2 were prospective cohort studies of PFO

closure. (See Appendix Figure) We included 3 randomized trials enrolling 2303 patients. [4-7]

Trial and Patient Characteristics

Table 1 presents the characteristics of the 3 eligible studies. Two of the three studies (RESPECT, PC Trial) used the Amplatz occluder device whereas the other used the STARFlex device (CLOSURE I). Crossover from medical therapy to PFO closure occurred in only one study (13.3%) (PC Trial). The percentage of patients in the PFO closure arm undergoing a PFO closure attempt ranged from 90.6 to 96.1% with success rates ranging from 89.4% to 99.1%.

In the CLOSURE I study all patients undergoing PFO closure were assigned to clopidogrel 75 mg per day times 6 months and aspirin 81 or 325 mg per day for 2 years. In the RESPECT study all patients undergoing closure received aspirin 81-325 mg plus clopidogrel for one month followed by aspirin monotherapy for 5 months. Antiplatelet treatment thereafter was left to the discretion of the site investigator. In the PC Trial, managing clinicians were counseled to recommend aspirin 100 to 325 mg per day for 5 to 6 months and ticlopidine (250 to 500 mg per day) or clopidogrel (75 mg to 150 mg per day) for 1 to 6 months. However at discharge from PFO closure in the PC trial, 182 patients (89.2%) were using aspirin, 104 (51%) thienopyridines, 6 (2.9%) oral anticoagulation, and 8 (3.9%) were not using antithrombotic prophylaxis.

Treatment in the medical therapy arms also varied across studies. In Closure I, patients assigned to medical therapy were treated with warfarin (with a target international normalized ratio of 2.0 to 3.0), aspirin (325 mg daily), or both, at the discretion of the principal investigator at each site (further details not provided). In RESPECT five medical therapies were initially allowed (after randomization aspirin alone was used in 223 patients (46.5%), warfarin alone in 121 (46.5%), clopidogrel alone in 67 patients (14%), aspirin with dipyridamole in 39 patients (8.1%), and aspirin with clopidogrel in 30 (6.2%). In the PC Trial antithrombotic treatment was also left to the discretion of the treating physician and could have included antiplatelet therapy or oral anticoagulation (after randomization, 120 (57.1%) of subjects were using aspirin, 35 (16.7%) thienopyridines, 64 (30.5%) oral anticoagulation, and 5 (2.4%) were not using antithrombotic prophylaxis.

Adherence with medical therapy/changes in medical therapy was not clearly documented in 2 of the 3 studies. In the PC trial, the percentage of patients using no antithrombotic prophylaxis increased from 2.4% following randomization to 7.7% at 2 years, 11.3% at 3 years, 11.1% at 4 years, and 12.8% at 5 years. The distribution of other therapies changed little over 5 years.

A total of 311 (13.5%) subjects were lost to follow-up or withdrew consent (range within studies 12% to 18%). Loss to follow-up/withdrawal of consent was higher in the medical therapy arm (n = 204, 18%) than in the PFO closure arm (n = 107, 9%). In addition, 14 patients (CLOSURE I = 12, PC Trial = 1, RESPECT = 1) were

demonstrated to have no PFO after randomization and 11 patients were determined to have no prior history of stroke or TIA (CLOSURE I). Therefore 336 subjects were excluded from our complete case analyses.

The three studies enrolled similar patients (e.g. age range from 44.5 to 46 years) with some differences in medical history (Table 2). In two of the studies approximately 70-80% of patients were enrolled with an index diagnosis of cryptogenic stroke with most of the rest having an index diagnosis of TIA. In one study (RESPECT), all patients enrolled had a diagnosis characterized as stroke but patients with less than 24 hours of symptoms and radiologic evidence for infarct were included in this category.

Assessment of Risk of Bias

Overall risk of bias was deemed high for all 3 studies due to missing data (see Figure 1). There is also lack of clear description regarding how compliance with medical therapy was assessed – in only 1 study was medical therapy usage at different time points described.

Participants and study personnel were not blinded in any of the three studies, which likely contributed to differential rates of loss to follow-up. It is unclear if this would have led to additional bias with respect to the observed outcome rates as a clinical events committee adjudicated events in all three studies.

Outcomes Assessment

Non-fatal ischemic Stroke

There were a total of 22 non-fatal ischemic strokes among 1026 patients randomized to PFO closure vs. 34 strokes among 941 patients randomized to medical therapy (Risk Ratio 0.61, 95% CI 0.34, 1.07; Heterogeneity: p =0.34, I^2 = 8%) (Figure 2). Using our best estimate of baseline from the available randomized trials of 52 non-fatal ischemic strokes over 5 years in 1000 patients treated medically, PFO closure may be associated with 20 fewer strokes per 1000 treated over a period of 5 years (confidence interval 34 fewer to 4 more strokes, low confidence in estimates because of risk of bias and imprecision) (Table 3).

In a sensitivity analysis including the 2 studies using the Amplatz device, PFO closure was associated with a decreased risk of non-fatal ischemic stroke (RR 0.44, 95% 0.21, 0.93; Heterogeneity: p = 0.42, I^2 = 0%). In the CLOSURE I Study (Starflex device), there was no difference between PFO closure and medical therapy with respect to non-fatal ischemic stroke (RR 0.87, 95% CI 0.40, 1.87). The test for interaction between these two subset analyses revealed differences consistent with chance (Chi^2 = 1.52, p = 0.22).

We conducted analyses imputing non-fatal strokes for patients excluded from the complete case analysis. In our worst-case analysis (all PFO intervention arm patients excluded from complete case analysis having non-fatal ischemic stroke, none of subjects excluded from the medical therapy arm having non-fatal ischemic stroke), RR = 4.22, 95% CI 2.93, 6.08 (Heterogeneity: p = 0.39, I^2 = 0%). In our

plausible worst case analysis in which excluded PFO closure patients had 5-fold increased rate of stroke (relative to included subjects) and excluded medical therapy patients had a 1/5 rate of stroke (relative to included subjects), PFO closure was associated with a RR = 0.96, 95% CI 0.56, 1.66 (Heterogeneity: p = 0.28, I^2 = 21%). These results support rating down confidence in estimates for risk of bias related to missing data.

In the 2 studies providing per-protocol event rates for non-fatal ischemic stroke there were 18 vs. 27 non-fatal ischemic strokes yielding a RR of 0.66, 95% CI 0.32, 1.38 (Heterogeneity: p = 0.23, I^2 = 32%)

As previous observational studies suggest that patients with cryptogenic stroke and PFO may be at higher risk for recurrent stroke if they have a concomitant atrial septal aneurysm, we also examined pooled rates of the primary composite endpoint of the studies in this subset. There were 13 events among 378 patients with atrial septal aneurysm undergoing closure compared to 20 events among 380 patients undergoing medical therapy (RR 0.71, 95% CI 0.22, 2.27; Heterogeneity: p = 0.11, I^2 = 55%).

TIAs

Pooling complete case data from the 3 studies, there were 23 vs. 28 TIAs in the PFO closure and medical treatment groups respectively (RR 0.76, 95% CI 0.44, 1.32; Heterogeneity: p = 0.64, I^2 = 0%). PFO closure may be associated with 6 fewer TIAs

over a period of 5 years (confidence interval 15 fewer to 9 more) (moderate confidence because of risk of bias (Figure 3, Table 3).

Total mortality

There were 7 deaths per in the PFO closure arm vs. 10 deaths in the medical treatment arm of the 3 studies (RD -0.00, 95% CI -0.01, 0.01; Heterogeneity: p = 0.23, I^2 = 31%). None of the deaths were deemed secondary to treatment (PFO closure or antithrombotic therapy) or stroke. PFO closure may have no effect on mortality over a period of 5 years (confidence interval 10 fewer to 10 more) (low confidence because of risk of bias and imprecision) (Table 3).

Adverse events

Pooling data from all 3 studies, bleeding occurred in 13 vs. 7 patients in the PFO closure vs. medical treatment arms (all were major bleeds except 2 bleeds from RESPECT study not classified) (RD 0.00, 95% CI -0.01, 0.02; Heterogeneity p = 0.12, I^2 = 53%) (see Figure 4). PFO closure may have no effect on major bleeding over a period of 5 years (CI 10 fewer to 20 more) (moderate confidence because of risk of bias) (Table 3).

Atrial fibrillation occurred in 32 patients undergoing PFO closure vs. 8 patients treated with medical therapy (RD 0.02, 95% -0.02, 0.06; Heterogeneity: p <0.00001, I^2 = 93%). PFO closure may be associated with 20 more cases of atrial fibrillation per 1000 treated compared to medical therapy over a period of 5 years (CI 20 fewer

to 60 more) (very low confidence because of risk of bias, inconsistency, and imprecision) (Table 3). Of 23 cases of atrial fibrillation reported after PFO closure in the CLOSURE I study 6 were deemed "sustained" – atrial fibrillation in the medical group was not characterized. Of 8 cases of atrial fibrillation in the PC Trial occurring after PFO closure 2 were transient (in PFO closure arm) and 6 required cardioversion or were sustained. Atrial fibrillation was not characterized as transient or sustained in the RESPECT study.

We were unable to pool data regarding procedural or device related complications given differences between studies in reporting styles. Serious procedural or device related adverse events (in addition to bleeding, ischemic stroke, atrial fibrillation which have already been captured in previous analyses) were reported in 15 patients in the RESPECT trial (3%). This included 8 procedural related events. Major vascular events related to the procedure occurred in 13 of the 402 patients (3.2%) in whom PFO closure was attempted in CLOSURE I – these included 6 major bleeding episodes already captured above. The total number of serious procedural related adverse events was not specifically reported in the PC Trial although it was noted that no device related thrombi occurred.

Discussion

A decade ago a meta-analysis of observational studies suggested transcatheter closure of PFO in patients with cryptogenic stroke may prevent more

strokes than medical therapy.[3] The authors noted important limitations in available data and highlighted the need for RCTs to resolve the issue. Since that time, thousands of patients have undergone this procedure in a non-RCT setting.

We now have data from 3 RCTs comparing transcatheter PFO closure to medical therapy in patients with cryptogenic stroke or TIA and PFOs. Our analysis suggests a possible benefit of closure on the major outcome of stroke (RR 0.61, 95% CI 0.34, 1.07). Confidence in the estimate of 20 fewer strokes per 1,000 is, however, low, both because of problems with risk of bias and imprecision (confidence intervals include an increase in stroke of 4 per 1,000). Analyses for ischemic stroke restricted to "per-protocol" patients or patients with concomitant atrial septal aneurysm did not substantially change the observed risk ratios.

We conducted subgroup analyses evaluating the impact of PFO closure on non-fatal stroke separately in the 2 studies using the Amplatz closure device vs. the one study using the STARFlex device. Pooled data from the Amplatz studies suggests PFO closure may be associated a decrease in non-fatal ischemic stroke (RR 0.44, 95% CI 0.21, 0.93) whereas no benefit was observed in the study using the STARFlex device. Although the subgroup hypothesis was made a priori and differences are in the anticipated direction, the analysis is based on between group differences, has not been replicated, and differences between results with the two devices is easily explained by chance (p = 0.22). Thus the subgroup hypothesis has low credibility.[16]

As suggested in two other recently published analyses, our data could be interpreted to suggest a potential substantial benefit may exist for PFO closure.[17,18]

It is possible that a larger sample size and more rigorously done studies would definitively identify an important benefit in the total patient population, or in a subgroup. Our review demonstrates, however, that such additional studies may also fail to demonstrate benefit or, in comparison to effective antithrombotic prophylaxis, an increase in strokes.

Although some concern arises from possible lack of concealment of randomization in one study and the apparent failure to blind outcome adjudication in another study, the major problem in terms of risk of bias is the high loss to follow-up in these studies and the two fold greater loss to follow-up in patients in the medical therapy arms than the PFO closure arms (overall 9% in PFO and 18% in the medical therapy arms).

Our primary analysis was restricted to patients with available data (complete case analysis). If event rates differed in those with missing data in intervention and control groups - of particular concern would be higher rates of events in those lost to follow-up in the PFO closure arm that the medical therapy arm - the complete case results may be misleading. In an additional analysis in which patients lost to follow-up in the PFO arm were assumed to have 5 fold increased risk of stroke and those lost to follow-up in the medical therapy arm had a 5-fold decreased risk of stroke, there was no longer a trend favoring PFO closure (RR 0.96). This finding supports our rating down confidence in estimates of effect for risk of bias.

Another issue is the rigor with which control arm clinicians encouraged compliance with antithrombotic prophylaxis in medical patients. In two of the studies dose and type of antithrombotic therapy in the medical therapy arm were

left to the treating physician's discretion. Only one of the studies reported adherence and/or changes over time in medical therapy in both arms. Leaving therapy in the medical arm to the physician's discretion could be considered to represent "usual care" for those randomized to medical therapy. Usual care may, however, change over time, and differ in the jurisdictions in which the trial is conducted in comparison to other jurisdictions. Patients and clinicians may, therefore, be more interested in the effect of PFO closure versus a particular antithrombotic regimen with a high level of adherence.

Stroke occurring due to paradoxical emboli through a PFO results from thrombi originating in the venous circulation or perhaps the right atrial side of an associated atrial septal aneurysm. Warfarin has been shown to be more effective than antiplatelet therapy for the treatment and secondary prevention of venous thromboembolic events. Observational studies suggest oral anticoagulation is superior to aspirin for the prevention of stroke in patients with PFO albeit with increased bleeding.[19,20] In the Patent Foramen Ovale in Cryptogenic Stroke study (substudy of the randomized Warfarin-Aspirin Recurrent Stroke study) there were 98 patients with cryptogenic stroke and PFO - 42 were randomized to warfarin and 56 received aspirin.[21] Two-year rates of recurrent stroke were lower in patients receiving warfarin (9.5% vs. 17.9%,) but chance easily explains this ($p = 0.28$).

Given the uncertainty of the optimal antithrombotic regimen, subsequent trials must give this issue careful thought. One option for the medical arm would be careful exploration of individual patient values and preferences. Patients highly averse to bleeding risk and the burdens of anticoagulant therapy could receive only

an antiplatelet agent, while those less bleeding and burden averse could receive an anticoagulant. Use of an oral anticoagulant rather than warfarin in those choosing anticoagulation would be a possibility. Such an approach might represent optimal medical care, perhaps the appropriate comparator to PFO closure. Another option would be three-arm study with both antiplatelet and anticoagulant arms

We conclude that the available data warrants only low confidence in the impact of PFO versus medical therapy. Thus, additional RCTs are still required – two such studies are listed as actively recruiting on the NIH website ClinicalTrials.gov. Ideally, when pooled across studies, sample sizes will be large enough to definitively establish the impact of PFO closure versus medical therapy on the most important outcome, ischemic stroke. As important, results will be more compelling if the ongoing studies have implemented successful strategies to ensure complete or near-complete follow-up and have paid careful attention to decisions regarding medical prophylaxis and optimizing adherence in both arms of the study.

Figure legends:

Figure 1 Risk of bias in individual studies

Figure 2 Pooled risk of non-fatal ischemic stroke with PFO closure versus medical therapy

Figure 3 Pooled risk of transient ischemic attack with PFO closure versus medical therapy

Figure 4 Pooled risk of major bleeding with PFO closure versus medical therapy

References

1. Webster MW, Chancellor AM, Smith HJ, et al. Patent foramen ovale in young stroke patients. *Lancet.* Jul 2 1988;2(8601):11-12.
2. Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med.* May 5 1988;318(18):1148-1152.
3. Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med.* Nov 4 2003;139(9):753-760.
4. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med.* Mar 15 2012;366(11):991-999.
5. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med.* Mar 21 2013;368(12):1092-1100.
6. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med.* Mar 21 2013;368(12):1083-1091.
7. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
8. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* Apr 26 2008;336(7650):924-926.
9. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol.* Apr 2011;64(4):407-415.
10. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol.* Dec 2011;64(12):1283-1293.
11. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *J Clin Epidemiol.* Dec 2011;64(12):1294-1302.
12. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *J Clin Epidemiol.* Dec 2011;64(12):1303-1310.
13. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *J Clin Epidemiol.* Dec 2011;64(12):1277-1282.
14. Neumann I, Rada G, Claro JC, et al. Oral direct Factor Xa inhibitors versus low-molecular-weight heparin to prevent venous thromboembolism in patients undergoing total hip or knee replacement: a systematic review and meta-analysis. *Ann Intern Med.* May 15 2012;156(10):710-719.
15. Murad MH, Montori VM, Walter SD, Guyatt GH. Estimating risk difference from relative association measures in meta-analysis can infrequently pose interpretational challenges. *J Clin Epidemiol.* Aug 2009;62(8):865-867.
16. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ.* 2010;340:c117.

17. Pineda AM, Nascimento FO, Yang SC, Kirtane AJ, Sommer RJ, Beohar N. A meta-analysis of transcatheter closure of patent foramen ovale versus medical therapy for prevention of recurrent thromboembolic events in patients with cryptogenic cerebrovascular events. *Catheter Cardiovasc Interv.* Jul 5 2013.

18. Kitsios GD, Thaler DE, Kent DM. Potentially Large yet Uncertain Benefits: A Meta-analysis of Patent Foramen Ovale Closure Trials. *Stroke.* Sep 2013;44(9):2640-2643.

19. Cujec B, Mainra R, Johnson DH. Prevention of recurrent cerebral ischemic events in patients with patent foramen ovale and cryptogenic strokes or transient ischemic attacks. *Can J Cardiol.* Jan 1999;15(1):57-64.

20. Orgera MA, O'Malley PG, Taylor AJ. Secondary prevention of cerebral ischemia in patent foramen ovale: systematic review and meta-analysis. *South Med J.* Jul 2001;94(7):699-703.

21. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation.* Jun 4 2002;105(22):2625-2631.

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Dr. Frederick Spencer contributed to the conception and design of the study, the acquisition, analysis and interpretation of the data, drafting the work, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Luciane Lopes contributed to the design of the study, the acquisition, analysis and interpretation of the data, critical revision of the work for important intellectual content, and gave final approval of the version to be published. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Mr. Sean Kennedy contributed to the design of the study, the acquisition, analysis and interpretation of the data, critical revision of the work for important intellectual content, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Gordon Guyatt contributed to the design of the study, the acquisition, analysis and interpretation of the data, drafting and critical revision of the work for important intellectual content, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Table 1

Trial (patients)	Trial Type	Intervention	Medical therapy	Withdrew or Loss to Followup PFO closure (%)	Withdrew/Loss to Followup Medical Therapy (%)	Crossover from Medical Therapy to PFO Closure (%)	% PFO closure attempts/patients enrolled in PFO cohort (%)	% technical success /PFO closure attempts (%)
CLOSURE I (909)	Multicentre Randomized Open label	STARFLEX Device Clopidogrel x 6 mo ASA x 2 years	Warfarin (INR 2-3), ASA 325 per day, or both (clinician's discretion)	1.8	0.7	0	90.6	89.4
PC Trial (414)	Multicentre Randomized Open Label	Amplatz Occluder ASA 5-6 mo. Clopidogrel or ticlopidine 1-6 mo.	Antiplatelet or anticoagulation (clinician's discretion)	15.2	20	13.3	96.1	97.4
RESPECT (980)	Multicentre Randomized Open Label	Amplatz Occluder ASA 6 mo Clopidogrel 1 mo.	Antiplatelet or anticoagulation (clinician's discretion)	9.2	17.2	0	93	99.1

Table 2 Characteristics of Patients in Eligible Studies

	CLOSURE 1	RESPECT	PC Trial
N	909	980	414
Mean Age +/- SD	46.0	45.9	44.5
Male (%)	51.8	54.7	49.8
Smoker (%)	22.1	13.3	23.9
Medical History (%)			
Diabetes	NR	7.4	2.7
Hypertension	31.0	31.4	25.8
Hyperlipidemia	44.1	39.5	27.1
Ischemic heart disease	1.1	2.9	1.9
Myocardial infarction	1.3	0.7	1
Valvular dysfunction	10.3	NR	3.1
Peripheral vascular disease	1.3	0.6	1.2
Index event (%)			
Stroke	72	100*	79.2
TIA	28	0	18.1
Peripheral arterial embolism	0	0	2.7
PFO characteristics (%)			
Moderate or higher shunt	52.9	75.2	65.6**
Atrial septal aneurysm >10 mm	37.8***	35.6	23.7

*Included patients with symptoms for less than 24 hours if new neuroradiologically relevant cerebral infarct on imaging
** 369 of 414 patients with TEE
***151/400 patients with TEE

Table 3 – GRADE assessment of quality of evidence

Bibliography:									
Quality assessment						**Summary of findings**			
No of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Relative effect or risk difference (95% CI)**	**Anticipated absolute effects Time frame: 5 years**		**Quality of evidence**
							Risk with medical therapy	**Risk difference with PFO closure (95% CI)**	
Non-fatal ischemic stroke (critical outcome)									
1968 (3 RCTs)	**Serious limitations**[1]	No serious limitations	No serious limitations	**Imprecise** CI includes benefit and no effect	Undetected	**RR 0.61** (0.34 to 1.07)	**52 per 1000**[2]	**20 fewer per 1000** (from 34 fewer to 4 more)	⊕⊕OO **LOW** due to risk of bias and imprecision
TIA (important outcome)									
1968 (3 RCTs)	**Serious limitations**[1]	No serious limitations	No serious limitations	No serious limitations[3]	Undetected	**RR 0.76** (0.44 to 1.32)	**27per 1000**[4]	**6 fewer per 1000** (from 15 fewer to 9 more)	⊕⊕⊕O **MODERATE** due to risk of bias
Total mortality (critical outcome)[5]									
1968 (3 RCTs)	**Serious limitations**[1]	No serious limitations	No serious limitations	**Imprecise** CI includes benefit and harm	Undetected	**RD 0.00** (-0.01, 0.01)	**15 per 1000**[6]	**0 fewer per 1000** (from 10 fewer to 10 more)	⊕⊕OO **LOW** due to risk of bias and imprecision
Major bleeding (important outcome)									
2254 (3 RCTs)	**Serious limitations**[1]	No serious inconsistency	No serious limitations[3]	No serious limitations	Undetected	**RD 0.00** (-0.01, 0.02)	**7 per 1000**[7]	**0 more per 1000** (10 fewer to 20 more)	⊕⊕⊕O **MODERATE** due to risk of bias
Atrial fibrillation (important outcome)[8]									
2254 (3 RCTs)	**Serious limitations**[1]	**Serious inconsistency**[9]	No serious limitations	**Imprecise** CI includes benefit and harm	Undetected	**RD 0.02** (-0.02, 0.06)	**12 per 1000**[10]	**20 more per 1000** (20 fewer to 60 more)	⊕OOO **VERY LOW** due to risk of bias and imprecision

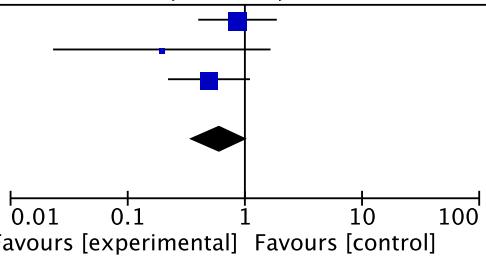
[1]Serious risk of bias due to substantial loss to followup in each of 3 studies; loss to followup greater in medical therapy arms. See text for other potential sources of bias in individual studies.
[2]Baseline rate derived from pooled Respect and PC trial data - 21 non-fatal ischemic strokes detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years
[3]Although CI includes benefit and harm, but magnitude of extremes for this type of outcome deemed too low to appreciably impact patient decision making.
[4]Baseline rate derived from pooled Respect and PC trial data - 11 TIAs detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years
[5]None of deaths due to stroke, treatment related bleeding, or device implantation
[6]Baseline rate derived from pooled Respect and PC trial data - 6 cases of total mortality detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years
[7]Baseline rate derived from pooled Respect and PC trial data – 3 cases of major bleeding detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years
[8]Type of atrial fibrillation (transient vs. sustained) not reported in medical therapy arms or in PFO closure arm of RESPECT study. Of 31 cases of atrial fibrillation in the remaining 2 studies 19 were characterized as transient.
[9]I^2 = 93%, p = <0.00001
[10]Baseline rate derived from pooled Respect and PC Trial data – 5 cases of atrial fibrillation detected in the medical therapy arm over a total of 2019 pt-yrs x 1000 x 5 years.

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
CLOSURE I
PC Trial
RESPECT

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
CLOSURE I	12	401	13	376	48.2%	0.87 [0.40, 1.87]
PC Trial	1	172	5	168	7.0%	0.20 [0.02, 1.65]
RESPECT	9	453	16	398	44.7%	0.49 [0.22, 1.11]
Total (95% CI)		**1026**		**942**	**100.0%**	**0.61 [0.34, 1.07]**
Total events	22		34			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 2.16$, df = 2 (P = 0.34); $I^2 = 7\%$

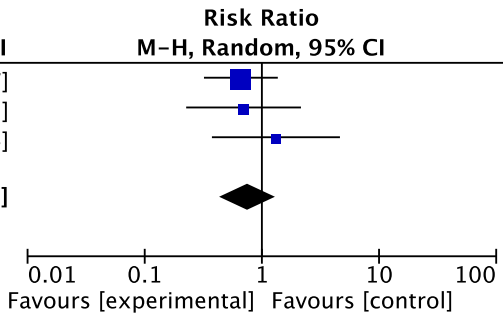
Test for overall effect: Z = 1.71 (P = 0.09)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
CLOSURE I	12	401	17	376	57.3%	0.66 [0.32, 1.37]
PC Trial	5	172	7	168	23.7%	0.70 [0.23, 2.15]
RESPECT	6	453	4	398	19.0%	1.32 [0.37, 4.64]
Total (95% CI)		**1026**		**942**	**100.0%**	**0.76 [0.44, 1.32]**
Total events	23		28			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.90$, df = 2 (P = 0.64); $I^2 = 0\%$

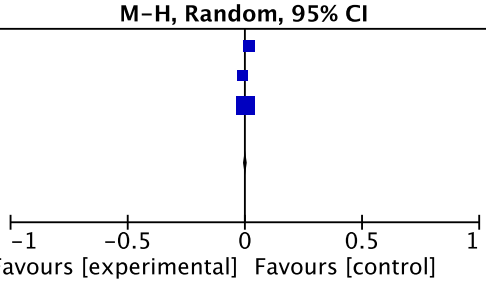
Test for overall effect: Z = 0.96 (P = 0.34)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
CLOSURE I	10	402	4	458	25.8%	0.02 [-0.00, 0.03]
PC Trial	1	204	3	210	23.8%	-0.01 [-0.03, 0.01]
RESPECT	2	499	0	481	50.4%	0.00 [-0.00, 0.01]
Total (95% CI)		**1105**		**1149**	**100.0%**	**0.00 [-0.01, 0.02]**
Total events	13		7			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.30$, df = 2 (P = 0.12); $I^2 = 53\%$

Test for overall effect: Z = 0.66 (P = 0.51)



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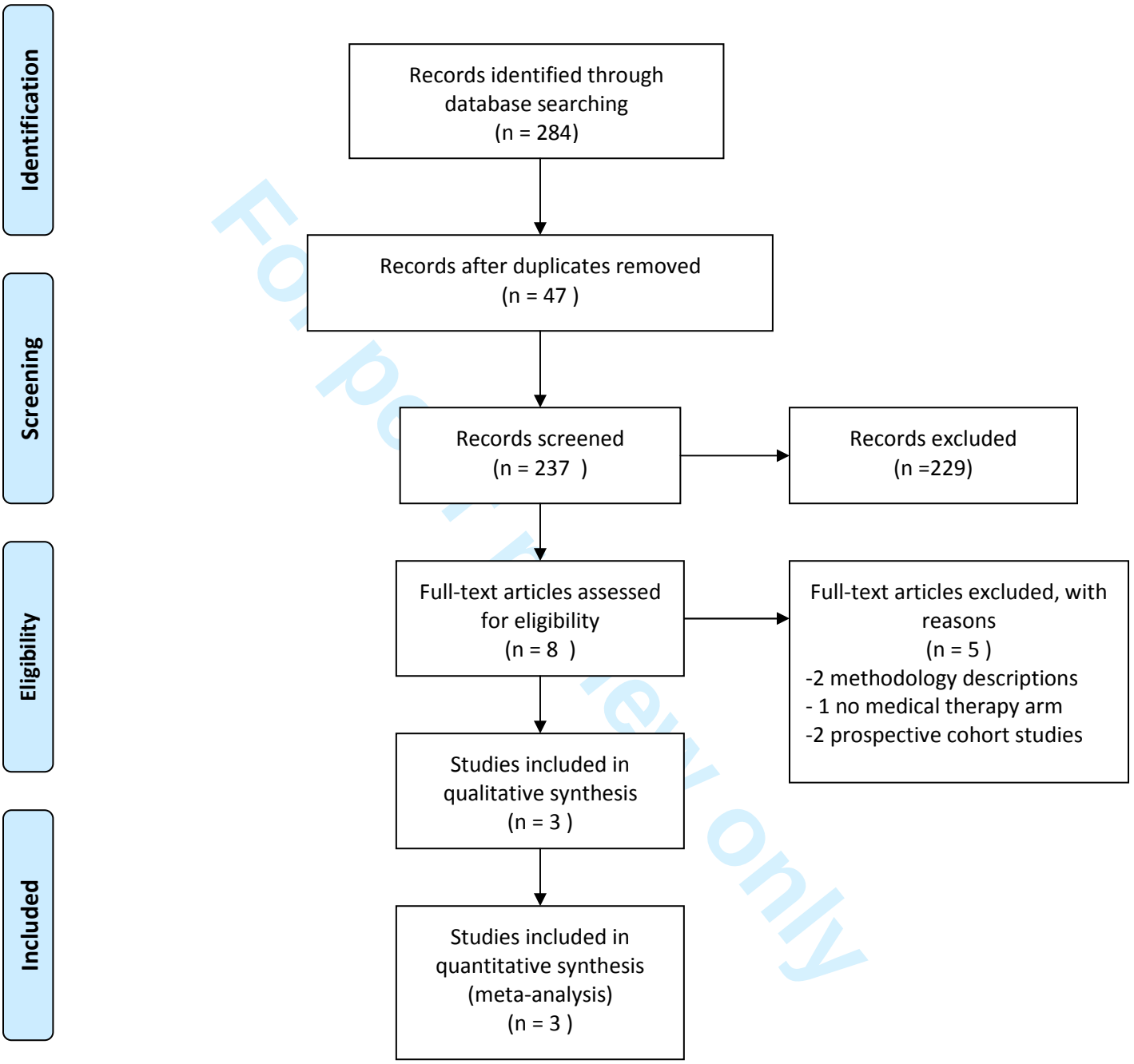

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-11

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11-12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-14 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14 Figure 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-18 Figures 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15-18 Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	15-16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Systematic Review of Percutaneous Closure versus Medical Therapy in Patients with Cryptogenic Stroke and Patent Foramen Ovale

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Secondary Subject Heading:	Cardiovascular medicine, Neurology
Keywords:	Thromboembolism < CARDIOLOGY, Stroke < NEUROLOGY, Stroke medicine < INTERNAL MEDICINE

Systematic Review of Percutaneous Closure versus Medical Therapy in Patients with Cryptogenic Stroke and Patent Foramen Ovale

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Word count: 4271

Abstract

Objectives: To provide a comprehensive comparison of PFO closure versus medical therapy in patients with cryptogenic stroke or transient ischemic attack (TIA) and demonstrated PFO.

Design: Systematic review with complete case meta-analysis and sensitivity analyses. Data sources included Medline and Embase from 1980 up to May 2013. All randomized controlled trials (RCTs) comparing treatment with percutaneous catheter-based closure of PFO to anticoagulant or antiplatelet therapy in patients with cryptogenic stroke or TIA and echocardiographically confirmed PFO or atrial septal defect (ASD) were eligible.

Participants: 1967 subjects with prior stroke or TIA and echocardiographically confirmed PFO or ASD.

Primary outcome measures: The primary outcome of interest was recurrence of ischemic stroke. We utilized data from complete cases only for the primary endpoint and combined data from trials to estimate the pooled risk ratio (RR) and associated 95% confidence intervals (CI) calculated using random effects models.

Results: We identified 284 potentially eligible articles of which 3 RCTs including 2303 patients proved eligible and 1967 patients had complete data. Of the 1026 patients randomized to PFO closure and followed to study conclusion 22

experienced non-fatal ischemic strokes, as did 34 of 941 patients randomized to medical therapy (Risk Ratio 0.61, 95% CI 0.34, 1.07; Heterogeneity: p =0.34, I2 = 8%, confidence in estimates low due to risk of bias and imprecision). Analyses for ischemic stroke restricted to "per-protocol" patients or patients with concomitant atrial septal aneurysm did not substantially change the observed risk ratios. Complication rates associated with either PFO closure or medical therapy were low.

Conclusions: Pooled data from 3 RCTs provides insufficient support that PFO closure is preferable to medical therapy for secondary prevention of cryptogenic stroke in patients with PFO.

Abstract word count: 279

Study strengths

- Estimation of absolute benefits and risks of treatment strategies
- Careful assessment of risk of bias of individual studies using Cochrane criteria
- Evaluation of overall confidence in pooled outcome(s) estimates using GRADE

Limitations

- Primary analysis was restricted to patients with available data (complete case analysis). If event rates differed in those with missing data in intervention and control groups - of particular concern would be higher rates of events in those lost to follow-up in the PFO closure arm that the medical therapy arm - the complete case results may be misleading
- Individual patient-level data not available

Introduction

Observational studies suggest that younger patients with cryptogenic stroke are more likely to have a patent foramen ovale (PFO) than the general population. [1,2] A proposed mechanism for stroke in these patients is passage of thrombi from the venous circulation to the arterial circulation through the PFO. Although what proportion of cryptogenic strokes are due to paradoxical embolism remains unknown, percutaneous closure of PFO using devices approved for hemodynamically significant secundum atrial septal defect (ASD) has increased greatly in the last 2 decades. A systematic review of observational studies suggests PFO closure may be superior to medical therapy (antiplatelet or anticoagulant agents) for secondary prevention of stroke in patients with patent foramen ovale and cryptogenic stroke. [3]

In the last two years 3 three randomized control trials (RCTs) comparing PFO closure to medical therapy have been published – none showed PFO closure to be statistically superior to medical therapy for the primary composite outcome but each reported trends favoring PFO closure.[4-6] In one study, PFO closure was superior to medical therapy for the prevention of recurrent neurologic events in prespecified per-protocol and as-treated analyses.[5]

One systematic review and meta-analysis that included the 3 RCTs, and a second meta-analysis, have addressed this issue. Both were limited, however, by failure to fully consider risk of bias issues, failure to use the GRADE approach to determine

overall confidence in estimates of intervention effect, and failure to consider the limitations of composite endpoints.

We therefore undertook a systematic review of all RCTs comparing percutaneous PFO closure to medical therapy in patients with cryptogenic stroke or TIA and PFO or ASD. As composite endpoints varied between trials, we focused on individual endpoints of recurrent non-fatal stroke, recurrent TIA, death, major bleeding, and atrial fibrillation. We also examined per protocol rates of recurrent stroke in patients undergoing PFO closure compared to the medical therapy arm. Outcomes were defined as in each study.

Methods

Eligibility criteria

We included all RCTs comparing treatment with percutaneous catheter-based closure of PFO to medical therapy (anticoagulant or antiplatelet therapy) in patients with cryptogenic stroke or TIA and echocardiographically confirmed PFO or ASD. We excluded trials including participants with other indications for PFO/ASD closure (e.g. hemodynamic significance) or other indications for anticoagulant therapy (e.g. atrial fibrillation).

Included articles met two prespecified criteria: 1) RCTs that compared PFO closure to medical therapy (antiplatelet or anticoagulant agents); 2) Greater than 90% of patients had prior unexplained stroke, TIA, or other arterial embolism, or this

subset was reported separately. When more than one study reported data from a population, we used the most complete and updated results.

Data sources and search strategy

We searched Medline and Embase from 1980 to May 2013. We restricted the search to human subjects. Keywords included patent foramen ovale *or* atrial septal defect. Results were then limited to randomize controlled trial *or* controlled clinical trial *or* phase 3 clinical trial *or* phase 4 clinical trial. For every eligible study we identified, and for studies such as review articles that included citations to potentially eligible studies, one reviewer examined the reference list.

Study selection

Teams of two investigators independently screened each title and abstract from this search. If either of the two screeners identified a citation as potentially relevant, we obtained the full text article for detailed review. Teams of two reviewers independently determined the eligibility of all studies that underwent full text evaluation. Disagreements were resolved through discussion between the two reviewers.

Data abstraction

Using a custom made data collection form two of three reviewers (FAS, LCL, SAK) abstracted the following information from each identified study: mean follow-up time, total patient years follow-up (overall and per cohort), number of patients

withdrawn or lost to follow-up, number of patients crossing over from medical therapy to PFO closure, number of patients undergoing PFO closure attempt, number of patients in whom PFO closure was technically successful, procedural complications (other than major bleeding) from PFO closure, and outcome event rates.

Disagreements regarding data abstraction results were resolved through discussion between the two reviewers. The primary author abstracted additional information on study funding, eligibility criteria, patient demographics, and treatment characteristics.

Risk of Bias and Confidence in Effect Assessment

Two reviewers (FAS, LL) independently assessed, using the Cochrane risk for bias tool, seven domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding for outcome assessment, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the other 6 domains.[7]

We used GRADE methodology to rate confidence in estimates of effect for each outcome as high, moderate, low or very low.[8] We used detailed GRADE guidance to assess overall risk of bias[9], imprecision[10], inconsistency[11], indirectness[12] and publication bias[13], and summarized results in an evidence profile.

For decisions regarding eligibility, risk of bias assessment, and data abstraction, reviewers resolved disagreement through discussion.

Data Synthesis and Statistical Analysis

We report descriptive statistics as proportions for categorical variables, and mean/median for continuous variables. Our primary analyses for non-fatal ischemic stroke, TIAs, and mortality included only patients with complete follow-up. We excluded patients for whom complete data was unavailable: those lost to follow-up, those who withdrew consent, or those who were found to not have PFO/ASD or history of TIA/stroke after randomization. For outcomes of bleeding and atrial fibrillation we used data as reported by the investigators from the intention to treat analyses.

Rates of non-fatal ischemic stroke in patients treated as "per-protocol" from two of the three studies were also abstracted and pooled. The definition of per-protocol varied from study to study (CLOSURE 1: all randomized patients who received the treatment to which they were randomized, who had no major inclusion/exclusion criteria violations, and who had a follow-up of at least 22 months; RESPECT: patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment, and did not have a major inclusion or exclusion violation). Event rates for non-fatal ischemic stroke in the "per protocol" subset

were not reported in PC Trial manuscript. The primary author of the manuscript did not respond to email requests for further information.

As previous observational studies suggest that patients with cryptogenic stroke and PFO may be at higher risk for recurrent stroke if they have a concomitant atrial septal aneurysm, we performed an additional complete case analysis for a primary composite outcome in the subset of patients with atrial septal aneurysm (data on non-fatal ischemic stroke alone not reported in any of the studies for this subset). Composite outcomes in the 3 studies included some combination of non-fatal ischemic stroke, TIA, peripheral embolism, and death.

As two of the three studies used the Amplatzer device and one used the STARFlex device (CLOSURE 1) we conducted a sensitivity analysis for non-fatal ischemic stroke excluding the CLOSURE study. We evaluated for subgroup difference (2 Amplatzer studies vs. STARFlex study) using a chi-square test.

Given high rate of patients excluded from complete case analyses (most due to loss to follow-up) we also conducted 2 additional analyses: 1) Worst case scenario in which we assumed that all patients with missing data in the PFO closure arms suffered non-fatal ischemic strokes and all patients lost to follow-up in the medical arms did not; 2) Plausible worst case scenario in which all patients with missing data from the PFO closure arm were assumed to have 5 times the rate of stroke as

the complete cases and b) those excluded from the medical therapy arm were assumed to have 1/5 times the rate of stroke as the complete cases.[14]

We calculated pooled risk ratios (RR) and associated 95% confidence intervals (CI) for non-fatal ischemic stroke and TIAs using random effects models applying Mantel Haenszel method. Absolute effects (and 95% CI) were calculated by multiplying pooled RRs and 95% CI by pooled control rate of outcomes. As event rates were very low for death, atrial fibrillation, and major bleeding (leading to skewed 95% CI), pooled risk difference (RD) and 95% CI was used to calculate absolute effects for these outcomes.[15] Statistical heterogeneity was assessed by the I^2 statistic. Analyses were performed using RevMan version 5.2 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration).

Results

Trial Identification

Our search yielded 284 abstracts - all were identified from the electronic database search- of which 47 were duplicates and excluded. We excluded an additional 229 articles based on a review of the title and abstract, leaving 8 articles for full review. Of these studies, 5 were excluded – 2 were descriptions of methodology for subsequently reported RCTs, 1 was a comparison of different devices for closure but did not include a medical therapy arm, and 2 were prospective cohort studies of PFO

closure. (See Appendix Figure) We included 3 randomized trials enrolling 2303 patients. [4-7]

Trial and Patient Characteristics

Table 1 presents the characteristics of the 3 eligible studies. Two of the three studies (RESPECT, PC Trial) used the Amplatzer occluder device whereas the other used the STARFlex device (CLOSURE I). Crossover from medical therapy to PFO closure occurred in only one study (13.3%) (PC Trial). The percentage of patients in the PFO closure arm undergoing a PFO closure attempt ranged from 90.6 to 96.1% with success rates ranging from 89.4% to 99.1%.

In the CLOSURE I study all patients undergoing PFO closure were assigned to clopidogrel 75 mg per day times 6 months and aspirin 81 or 325 mg per day for 2 years. In the RESPECT study all patients undergoing closure received aspirin 81-325 mg plus clopidogrel for one month followed by aspirin monotherapy for 5 months. Antiplatelet treatment thereafter was left to the discretion of the site investigator. In the PC Trial, managing clinicians were counseled to recommend aspirin 100 to 325 mg per day for 5 to 6 months and ticlopidine (250 to 500 mg per day) or clopidogrel (75 mg to 150 mg per day) for 1 to 6 months. However at discharge from PFO closure in the PC trial, 182 patients (89.2%) were using aspirin, 104 (51%) thienopyridines, 6 (2.9%) oral anticoagulation, and 8 (3.9%) were not using antithrombotic prophylaxis.

Treatment in the medical therapy arms also varied across studies. In Closure I, patients assigned to medical therapy were treated with warfarin (with a target international normalized ratio of 2.0 to 3.0), aspirin (325 mg daily), or both, at the discretion of the principal investigator at each site (further details not provided). In RESPECT five medical therapies were initially allowed (after randomization aspirin alone was used in 223 patients (46.5%), warfarin alone in 121 (46.5%), clopidogrel alone in 67 patients (14%), aspirin with dipyridamole in 39 patients (8.1%), and aspirin with clopidogrel in 30 (6.2%). In the PC Trial antithrombotic treatment was also left to the discretion of the treating physician and could have included antiplatelet therapy or oral anticoagulation (after randomization, 120 (57.1%) of subjects were using aspirin, 35 (16.7%) thienopyridines, 64 (30.5%) oral anticoagulation, and 5 (2.4%) were not using antithrombotic prophylaxis.

Adherence with medical therapy/changes in medical therapy was not clearly documented in 2 of the 3 studies. In the PC trial, the percentage of patients using no antithrombotic prophylaxis increased from 2.4% following randomization to 7.7% at 2 years, 11.3% at 3 years, 11.1% at 4 years, and 12.8% at 5 years. The distribution of other therapies changed little over 5 years.

A total of 311 (13.5%) subjects were lost to follow-up or withdrew consent (range within studies 12% to 18%). Loss to follow-up/withdrawal of consent was higher in the medical therapy arm (n = 204, 18%) than in the PFO closure arm (n = 107, 9%). In addition, 14 patients (CLOSURE I = 12, PC Trial = 1, RESPECT = 1) were

demonstrated to have no PFO after randomization and 11 patients were determined to have no prior history of stroke or TIA (CLOSURE I). Therefore 336 subjects were excluded from our complete case analyses.

The three studies enrolled similar patients (e.g. age range from 44.5 to 46 years) with some differences in medical history (Table 2). In two of the studies approximately 70-80% of patients were enrolled with an index diagnosis of cryptogenic stroke with most of the rest having an index diagnosis of TIA. In one study (RESPECT), all patients enrolled had a diagnosis characterized as stroke but patients with less than 24 hours of symptoms and radiologic evidence for infarct were included in this category.

Assessment of Risk of Bias

Overall risk of bias was deemed high for all 3 studies due to missing data (see Figure 1) – as noted 13.5% of subjects were lost to follow-up with twice as many lost to follow-up in the medical arm compared to the PFO closure arm. There is also lack of clear description regarding how compliance with medical therapy was assessed – in only 1 study was medical therapy usage at different time points described.

Participants and study personnel were not blinded in any of the three studies, which likely contributed to differential rates of loss to follow-up. It is unclear if this would have led to additional bias with respect to the observed outcome rates as a clinical events committee adjudicated events in all three studies.

Outcomes Assessment

Non-fatal ischemic Stroke

There were a total of 22 non-fatal ischemic strokes among 1026 patients randomized to PFO closure vs. 34 strokes among 941 patients randomized to medical therapy (Risk Ratio 0.61, 95% CI 0.34, 1.07; Heterogeneity: p =0.34, I^2 = 8%) (Figure 2). Using our best estimate of baseline from the available randomized trials of 52 non-fatal ischemic strokes over 5 years in 1000 patients treated medically, PFO closure may be associated with 20 fewer strokes per 1000 treated over a period of 5 years (confidence interval 34 fewer to 4 more strokes, low confidence in estimates because of risk of bias and imprecision) (Table 3).

In a sensitivity analysis including the 2 studies using the Amplatzer device, PFO closure was associated with a decreased risk of non-fatal ischemic stroke (RR 0.44, 95% 0.21, 0.93; Heterogeneity: p = 0.42, I^2 = 0%). In the CLOSURE I Study (Starflex device), there was no difference between PFO closure and medical therapy with respect to non-fatal ischemic stroke (RR 0.87, 95% CI 0.40, 1.87). The test for interaction between these two subset analyses revealed differences consistent with chance (Chi^2 = 1.52, p = 0.22).

We conducted analyses imputing non-fatal strokes for patients excluded from the complete case analysis. In our worst-case analysis (all PFO intervention arm patients excluded from complete case analysis having non-fatal ischemic stroke, none of subjects excluded from the medical therapy arm having non-fatal ischemic

stroke), RR = 4.22, 95% CI 2.93, 6.08 (Heterogeneity: p = 0.39, I^2 = 0%). In our plausible worst case analysis in which excluded PFO closure patients had 5-fold increased rate of stroke (relative to included subjects) and excluded medical therapy patients had a 1/5 rate of stroke (relative to included subjects), PFO closure was associated with a RR = 0.96, 95% CI 0.56, 1.66 (Heterogeneity: p = 0.28, I^2 = 21%). Although some might consider the 5 to 1 ratio we have tested beyond the range of plausibility, there is empirical support for this choice[16], and our results support rating down confidence in estimates for risk of bias related to missing data.

In the 2 studies providing per-protocol event rates for non-fatal ischemic stroke there were 18 vs. 27 non-fatal ischemic strokes yielding a RR of 0.66, 95% CI 0.32, 1.38 (Heterogeneity: p = 0.23, I^2 = 32%)

As previous observational studies suggest that patients with cryptogenic stroke and PFO may be at higher risk for recurrent stroke if they have a concomitant atrial septal aneurysm, we also examined pooled rates of the primary composite endpoint of the studies in this subset. There were 13 events among 378 patients with atrial septal aneurysm undergoing closure compared to 20 events among 380 patients undergoing medical therapy (RR 0.71, 95% CI 0.22, 2.27; Heterogeneity: p = 0.11, I^2 = 55%).

TIAs

Pooling complete case data from the 3 studies, there were 23 vs. 28 TIAs in the PFO closure and medical treatment groups respectively (RR 0.76, 95% CI 0.44, 1.32; Heterogeneity: p = 0.64, I^2 = 0%). PFO closure may be associated with 6 fewer TIAs over a period of 5 years (confidence interval 15 fewer to 9 more) (moderate confidence because of risk of bias (Figure 3, Table 3).

Total mortality

There were 7 deaths in the PFO closure arm vs. 10 deaths in the medical treatment arm of the 3 studies (RD -0.00, 95% CI -0.01, 0.01; Heterogeneity: p = 0.23, I^2 = 31%). None of the deaths were deemed secondary to treatment (PFO closure or antithrombotic therapy) or stroke. PFO closure may have no effect on mortality over a period of 5 years (confidence interval 10 fewer to 10 more) (low confidence because of risk of bias and imprecision) (Table 3).

Adverse events

Pooling data from all 3 studies, bleeding occurred in 13 vs. 7 patients in the PFO closure vs. medical treatment arms (all were major bleeds except 2 bleeds from RESPECT study not classified) (RD 0.00, 95% CI -0.01, 0.02; Heterogeneity p = 0.12, I^2 = 53%) (see Figure 4). PFO closure may have no effect on major bleeding over a period of 5 years (CI 10 fewer to 20 more) (moderate confidence because of risk of bias) (Table 3).

Atrial fibrillation occurred in 32 patients undergoing PFO closure vs. 8 patients treated with medical therapy (RD 0.02, 95% -0.02, 0.06; Heterogeneity: p <0.00001, I^2 = 93%). PFO closure may be associated with 20 more cases of atrial fibrillation per 1000 treated compared to medical therapy over a period of 5 years (CI 20 fewer to 60 more) (very low confidence because of risk of bias, inconsistency, and imprecision) (Table 3). Of 23 cases of atrial fibrillation reported after PFO closure in the CLOSURE I study 6 were deemed "sustained" – atrial fibrillation in the medical group was not characterized. Of 8 cases of atrial fibrillation in the PC Trial occurring after PFO closure 2 were transient (in PFO closure arm) and 6 required cardioversion or were sustained. Atrial fibrillation was not characterized as transient or sustained in the RESPECT study.

We were unable to pool data regarding procedural or device related complications given differences between studies in reporting styles. Serious procedural or device related adverse events (in addition to bleeding, ischemic stroke, atrial fibrillation which have already been captured in previous analyses) were reported in 15 patients in the RESPECT trial (3%). This included 8 procedural related events. Major vascular events related to the procedure occurred in 13 of the 402 patients (3.2%) in whom PFO closure was attempted in CLOSURE I – these included 6 major bleeding episodes already captured above. The total number of serious procedural related adverse events was not specifically reported in the PC Trial although it was noted that no device related thrombi occurred.

Discussion

A decade ago a meta-analysis of observational studies suggested transcatheter closure of PFO in patients with cryptogenic stroke may prevent more strokes than medical therapy.[3] The authors noted important limitations in available data and highlighted the need for RCTs to resolve the issue. Since that time, thousands of patients have undergone this procedure in a non-RCT setting.

We now have data from 3 RCTs comparing transcatheter PFO closure to medical therapy in patients with cryptogenic stroke or TIA and PFOs. Our analysis suggests a possible benefit of closure on the major outcome of stroke (RR 0.61, 95% CI 0.34, 1.07). Confidence in the estimate of 20 fewer strokes per 1,000 is, however, low, both because of problems with risk of bias and imprecision (confidence intervals include an increase in stroke of 4 per 1,000). Analyses for ischemic stroke restricted to "per-protocol" patients or patients with concomitant atrial septal aneurysm did not substantially change the observed risk ratios.

We conducted subgroup analyses evaluating the impact of PFO closure on non-fatal stroke separately in the 2 studies using the Amplatzer closure device vs. the one study using the STARFlex device. Pooled data from the Amplatzer studies suggests PFO closure may be associated a decrease in non-fatal ischemic stroke (RR 0.44, 95% CI 0.21, 0.93) whereas no benefit was observed in the study using the STARFlex device. Although the subgroup hypothesis was made a priori and differences are in the anticipated direction, the analysis is based on between group differences, has not been replicated, and differences between results with the two

devices is easily explained by chance (p = 0.22). Thus the subgroup hypothesis has low credibility.[17]

There have been 3 other meta-analyses. They are limited, however, by failure to fully consider risk of bias issues, failure to use the GRADE approach to determine overall confidence in estimates of intervention effect, and failure to consider the limitations of composite endpoints. .[18-20]. In the most recent of these analyses, PFO closure was associated with an effect-estimate hazard ratio of 0.67 (95% confidence interval [CI]: 0.44 to 1.00) for the prevention of "neurologic events". However it appears that this composite endpoint included the softer endpoint of TIA in addition to stroke and mortality.

It is possible that a larger sample size and more rigorously done studies would definitively identify an important benefit in the total patient population, or in a subgroup. Our review demonstrates, however, that such additional studies may also fail to demonstrate benefit or, in comparison to effective antithrombotic prophylaxis, an increase in strokes.

Although some concern arises from possible lack of concealment of randomization in one study and the apparent failure to blind outcome adjudication in another study, the major problem in terms of risk of bias is the high loss to follow-up in these studies and the two fold greater loss to follow-up in patients in the medical therapy arms than the PFO closure arms (overall 9% in PFO and 18% in the medical therapy arms).

Our primary analysis was restricted to patients with available data (complete case analysis). If event rates differed in those with missing data in intervention and

control groups - of particular concern would be higher rates of events in those lost to follow-up in the PFO closure arm that the medical therapy arm - the complete case results may be misleading. In an additional analysis in which patients lost to follow-up in the PFO arm were assumed to have 5 fold increased risk of stroke and those lost to follow-up in the medical therapy arm had a 5-fold decreased risk of stroke, there was no longer a trend favoring PFO closure (RR 0.96). This finding supports our rating down confidence in estimates of effect for risk of bias.

Another issue is the rigor with which control arm clinicians encouraged compliance with antithrombotic prophylaxis in medical patients. In two of the studies dose and type of antithrombotic therapy in the medical therapy arm were left to the treating physician's discretion. Only one of the studies reported adherence and/or changes over time in medical therapy in both arms. Leaving therapy in the medical arm to the physician's discretion could be considered to represent "usual care" for those randomized to medical therapy. Usual care may, however, change over time, and differ in the jurisdictions in which the trial is conducted in comparison to other jurisdictions. Patients and clinicians may, therefore, be more interested in the effect of PFO closure versus a particular antithrombotic regimen with a high level of adherence. Unfortunately there have been no RCTs adequately comparing specific antiplatelet or antithrombotic therapies for this indication.

Stroke occurring due to paradoxical emboli through a PFO results from thrombi originating in the venous circulation or perhaps from the associated atrial septal aneurysm itself.[21,22] Warfarin has been shown to be more effective than

antiplatelet therapy for the treatment and secondary prevention of venous thromboembolic events. Observational studies suggest oral anticoagulation is superior to aspirin for the prevention of stroke in patients with PFO albeit with increased bleeding.[23,24] In the Patent Foramen Ovale in Cryptogenic Stroke study (substudy of the randomized Warfarin-Aspirin Recurrent Stroke study) there were 98 patients with cryptogenic stroke and PFO - 42 were randomized to warfarin and 56 received aspirin.[25] Two-year rates of recurrent stroke were lower in patients receiving warfarin (9.5% vs. 17.9%,) but chance easily explains this (p = 0.28).

Given the uncertainty of the optimal antithrombotic regimen, subsequent trials must give this issue careful thought. One option for the medical arm would be careful exploration of individual patient values and preferences. Patients highly averse to bleeding risk and the burdens of anticoagulant therapy could receive only an antiplatelet agent, while those less bleeding and burden averse could receive an anticoagulant. Use of an oral anticoagulant rather than warfarin in those choosing anticoagulation would be a possibility. Such an approach might represent optimal medical care, perhaps the appropriate comparator to PFO closure. Another option would be three-arm study with both antiplatelet and anticoagulant arms

We conclude that the available data warrants only low confidence in the impact of PFO versus medical therapy. Thus, additional RCTs are still required – two such studies are listed as actively recruiting on the NIH website ClinicalTrials.gov. Ideally, when pooled across studies, sample sizes will be large enough to definitively establish the impact of PFO closure versus medical therapy on the most important outcome, ischemic stroke. As important, results will be more

compelling if the ongoing studies have implemented successful strategies to ensure complete or near-complete follow-up and have paid careful attention to decisions regarding medical prophylaxis and optimizing adherence in both arms of the study. In the interval, patients should be made aware of the management options and the uncertainty underlying their effectiveness.

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Data sharing: There are no additional data available.

Contributorship: Dr. Frederick Spencer contributed to the conception and design of the study, the acquisition, analysis and interpretation of the data, drafting the work, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Luciane Lopes contributed to the design of the study, the acquisition, analysis and interpretation of the data, critical revision of the work for important intellectual content, and gave final approval of the version to be published. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Mr. Sean Kennedy contributed to the design of the study, the acquisition, analysis and interpretation of the data, critical revision of the work for important intellectual content, and gave final approval of the version to be published. He agrees to be

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Figure legends:

Figure 1 Risk of bias in individual studies

Figure 2 Pooled risk of non-fatal ischemic stroke with PFO closure versus medical therapy

Figure 3 Pooled risk of transient ischemic attack with PFO closure versus medical therapy

Figure 4 Pooled risk of major bleeding with PFO closure versus medical therapy

References

1. Webster MW, Chancellor AM, Smith HJ, et al. Patent foramen ovale in young stroke patients. Lancet 1988;2:11-2.
2. Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988;318:1148-52.
3. Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. Ann Intern Med 2003;139:753-60.
4. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med 2012;366:991-9.
5. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med 2013;368:1092-100.
6. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med 2013;368:1083-91.
7. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
8. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
9. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol 2011;64:407-15.
10. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol 2011;64:1283-93.
11. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol 2011;64:1294-302.
12. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol 2011;64:1303-10.
13. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol 2011;64:1277-82.
14. Akl EA, Briel M, You JJ, et al. Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): systematic review. Bmj 2012;344:e2809.
15. Murad MH, Montori VM, Walter SD, et al. Estimating risk difference from relative association measures in meta-analysis can infrequently pose interpretational challenges. J Clin Epidemiol 2009;62:865-7.
16. Geng EH, Emenyonu N, Bwana MB, et al. Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa. JAMA : the journal of the American Medical Association 2008;300:506-7.
17. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010;340:c117.
18. Pineda AM, Nascimento FO, Yang SC, et al. A meta-analysis of transcatheter closure of patent foramen ovale versus medical therapy for prevention of recurrent thromboembolic events in patients with cryptogenic cerebrovascular events. Catheter Cardiovasc Interv 2013.

19. Kitsios GD, Thaler DE, Kent DM. Potentially Large yet Uncertain Benefits: A Meta-analysis of Patent Foramen Ovale Closure Trials. Stroke 2013;44:2640-3.
20. Khan AR, Bin Abdulhak AA, Sheikh MA, et al. Device closure of patent foramen ovale versus medical therapy in cryptogenic stroke: a systematic review and meta-analysis. JACC Cardiovascular interventions 2013;6:1316-23.
21. Aryal MR, Pradhan R, Pandit AA, et al. A "teapot" atrial septal aneurysm with spontaneous thrombus in an asymptomatic patient. Circulation 2013;128:e409-10.
22. Schneider B, Hanrath P, Vogel P, Meinertz T. Improved morphologic characterization of atrial septal aneurysm by transesophageal echocardiography: relation to cerebrovascular events. Journal of the American College of Cardiology 1990;16:1000-9.
23. Cujec B, Mainra R, Johnson DH. Prevention of recurrent cerebral ischemic events in patients with patent foramen ovale and cryptogenic strokes or transient ischemic attacks. Can J Cardiol 1999;15:57-64.
24. Orgera MA, O'Malley PG, Taylor AJ. Secondary prevention of cerebral ischemia in patent foramen ovale: systematic review and meta-analysis. South Med J 2001;94:699-703.
25. Homma S, Sacco RL, Di Tullio MR, et al. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. Circulation 2002;105:2625-31.

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Table 1

Trial (patients)	Trial Type	Intervention	Medical therapy	Withdrew or Loss to Followup PFO closure (%)	Withdrew/Loss to Followup Medical Therapy (%)	Crossover from Medical Therapy to PFO Closure (%)	% PFO closure attempts/patients enrolled in PFO cohort (%)	% technical success /PFO closure attempts (%)
CLOSURE I (909)	Multicentre Randomized Open label	STARFLEX Device Clopidogrel x 6 mo ASA x 2 years	Warfarin (INR 2-3), ASA 325 per day, or both (clinician's discretion)	1.8	0.7	0	90.6	89.4
PC Trial (414)	Multicentre Randomized Open Label	Amplatzer Occluder ASA 5-6 mo. Clopidogrel or ticlopidine 1-6 mo.	Antiplatelet or anticoagulation (clinician's discretion)	15.2	20	13.3	96.1	97.4
RESPECT (980)	Multicentre Randomized Open Label	Amplatzer Occluder ASA 6 mo Clopidogrel 1 mo.	Antiplatelet or anticoagulation (clinician's discretion)	9.2	17.2	0	93	99.1

Table 2 Characteristics of Patients in Eligible Studies

	CLOSURE 1	RESPECT	PC Trial
N	909	980	414
Mean Age +/- SD	46.0	45.9	44.5
Male (%)	51.8	54.7	49.8
Smoker (%)	22.1	13.3	23.9
Medical History (%)			
Diabetes	NR	7.4	2.7
Hypertension	31.0	31.4	25.8
Hyperlipidemia	44.1	39.5	27.1
Ischemic heart disease	1.1	2.9	1.9
Myocardial infarction	1.3	0.7	1
Valvular dysfunction	10.3	NR	3.1
Peripheral vascular disease	1.3	0.6	1.2
Index event (%)			
Stroke	72	100*	79.2
TIA	28	0	18.1
Peripheral arterial embolism	0	0	2.7
PFO characteristics (%)			
Moderate or higher shunt	52.9	75.2	65.6**
Atrial septal aneurysm >10 mm	37.8***	35.6	23.7

*Included patients with symptoms for less than 24 hours if new neuroradiologically relevant cerebral infarct on imaging
** 369 of 414 patients with TEE
***151/400 patients with TEE

Table 3 – GRADE assessment of quality of evidence

Bibliography:									
Quality assessment						**Summary of findings**			
No of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Relative effect or risk difference (95% CI)**	**Anticipated absolute effects Time frame: 5 years**		**Quality of evidence**
							Risk with medical therapy	**Risk difference with PFO closure (95% CI)**	
Non-fatal ischemic stroke (critical outcome)									
1968 (3 RCTs)	**Serious limitations**[1]	No serious limitations	No serious limitations	**Imprecise** CI includes benefit and no effect	Undetected	**RR 0.61** (0.34 to 1.07)	**52 per 1000**[2]	**20 fewer per 1000** (from 34 fewer to 4 more)	⊕⊕OO **LOW** due to risk of bias and imprecision
TIA (important outcome)									
1968 (3 RCTs)	**Serious limitations**[1]	No serious limitations	No serious limitations	No serious limitations[3]	Undetected	**RR 0.76** (0.44 to 1.32)	**27per 1000**[4]	**6 fewer per 1000** (from 15 fewer to 9 more)	⊕⊕⊕O **MODERATE** due to risk of bias
Total mortality (critical outcome)[5]									
1968 (3 RCTs)	**Serious limitations**[1]	No serious limitations	No serious limitations	**Imprecise** CI includes benefit and harm	Undetected	**RD 0.00** (-0.01, 0.01)	**15 per 1000**[6]	**0 fewer per 1000** (from 10 fewer to 10 more)	⊕⊕OO **LOW** due to risk of bias and imprecision
Major bleeding (important outcome)									
2254 (3 RCTs)	**Serious limitations**[1]	No serious inconsistency	No serious limitations[3]	No serious limitations	Undetected	**RD 0.00** (-0.01, 0.02)	**7 per 1000**[7]	**0 more per 1000** (10 fewer to 20 more)	⊕⊕⊕O **MODERATE** due to risk of bias
Atrial fibrillation (important outcome)[8]									
2254 (3 RCTs)	**Serious limitations**[1]	**Serious inconsistency**[9]	No serious limitations	**Imprecise** CI includes benefit and harm	Undetected	**RD 0.02** (-0.02, 0.06)	**12 per 1000**[10]	**20 more per 1000** (20 fewer to 60 more)	⊕OOO **VERY LOW** due to risk of bias and imprecision

[1]Serious risk of bias due to substantial loss to followup in each of 3 studies; loss to followup greater in medical therapy arms. See text for other potential sources of bias in individual studies.
[2]Baseline rate derived from pooled Respect and PC trial data - 21 non-fatal ischemic strokes detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years
[3]Although CI includes benefit and harm, but magnitude of extremes for this type of outcome deemed too low to appreciably impact patient decision making.
[4]Baseline rate derived from pooled Respect and PC trial data - 11 TIAs detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years
[5]None of deaths due to stroke, treatment related bleeding, or device implantation
[6]Baseline rate derived from pooled Respect and PC trial data - 6 cases of total mortality detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years
[7]Baseline rate derived from pooled Respect and PC trial data – 3 cases of major bleeding detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years
[8]Type of atrial fibrillation (transient vs. sustained) not reported in medical therapy arms or in PFO closure arm of RESPECT study. Of 31 cases of atrial fibrillation in the remaining 2 studies 19 were characterized as transient.
[9]I^2 = 93%, p = <0.00001
[10]Baseline rate derived from pooled Respect and PC Trial data – 5 cases of atrial fibrillation detected in the medical therapy arm over a total of 2019 pt-yrs x 1000 x 5 years.

Systematic Review of Percutaneous Closure versus Medical Therapy in Patients with Cryptogenic Stroke and Patent Foramen Ovale

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Abstract

~~Background: Three randomized control trials (RCTs) comparing patient foramen ovale (PFO) closure to medical therapy have been published – none showed PFO closure to be statistically superior to medical therapy but each reported trends favoring PFO closure.~~

Objectives: To provide a comprehensive comparison of PFO closure versus medical therapy in patients with cryptogenic stroke or transient ischemic attack (TIA) and demonstrated PFO.

Design: Systematic review with complete case meta-analysis and sensitivity analyses. Data sources included

~~Data sources:~~ Medline and ~~,~~Embase from 1980 up to May 2013.

~~Eligibility criteria:~~ All randomized controlled trials (RCTs) comparing treatment with percutaneous catheter-based closure of PFO to ~~medical therapy {~~anticoagulant or antiplatelet therapy~~}~~ in patients with cryptogenic stroke or TIA and echocardiographically confirmed PFO or atrial septal defect (ASD) were eligible.

Participants: 1967 subjects with prior stroke or TIA and echocardiographically confirmed PFO or ASD.

~~Methods~~Primary outcome measures: The primary outcome of interest was recurrence of ischemic stroke. We utilized data from complete cases only for the primary endpoint and combined data from trials to estimate the pooled risk ratio (RR) and associated 95% confidence intervals (CI) calculated using random effects models.

Results: We identified 284 potentially eligible articles of which 3 RCTs including 2303 patients proved eligible and 1967 patients had complete data. Of the 1026 patients randomized to PFO closure and followed to study conclusion 22 experienced non-fatal ischemic strokes, as did 34 of 941 patients randomized to medical therapy (Risk Ratio 0.61, 95% CI 0.34, 1.07; Heterogeneity: p =0.34, I2 = 8%, confidence in estimates low due to risk of bias and imprecision). Analyses for ischemic stroke restricted to "per-protocol" patients or patients with concomitant atrial septal aneurysm did not substantially change the observed risk ratios. Complication rates associated with either PFO closure or medical therapy were low.

Conclusions: Pooled data from 3 RCTs provides insufficient~~little~~ support ~~for~~ that PFO closure is preferable to~~over~~ medical therapy for secondary prevention of cryptogenic stroke in patients with PFO.

Abstract word count: ~~299~~279

Data sharing: No additional data are available.

Study strengths

- Estimation of absolute benefits and risks of treatment strategies
- Careful assessment of risk of bias of individual studies using Cochrane criteria
- Evaluation of overall confidence in pooled outcome(s) estimates using GRADE

Limitations

- Primary analysis was restricted to patients with available data (complete case analysis). If event rates differed in those with missing data in intervention and control groups - of particular concern would be higher rates of events in those lost to follow-up in the PFO closure arm that the medical therapy arm - the complete case results may be misleading
- Individual patient-level data not available

Introduction

Observational studies suggest that younger patients with cryptogenic stroke are more likely to have a patent foramen ovale (PFO) than the general population. [1,2] A proposed mechanism for stroke in these patients is passage of thrombi from the venous circulation to the arterial circulation through the PFO. Although what proportion of cryptogenic strokes are due to paradoxical embolism remains unknown, percutaneous closure of PFO using devices approved for hemodynamically significant secundum atrial septal defect (ASD) has increased greatly in the last 2 decades. A systematic review of observational studies suggests PFO closure may be superior to medical therapy (antiplatelet or anticoagulant agents) for secondary prevention of stroke in patients with patent foramen ovale and cryptogenic stroke. [3]

In the last two years 3 three randomized control trials (RCTs) comparing PFO closure to medical therapy have been published – none showed PFO closure to be statistically superior to medical therapy for the primary composite outcome but each reported trends favoring PFO closure.[4-6] In one study, PFO closure was superior to medical therapy for the prevention of recurrent neurologic events in prespecified per-protocol and as-treated analyses.[5]

One systematic review and meta-analysis that included the 3 RCTs, and a second meta-analysis, have addressed this issue. Both were limited, however, by failure to fully consider risk of bias issues, failure to use the GRADE approach to determine overall confidence in estimates of intervention effect, and failure to consider the limitations of composite endpoints.

We therefore undertook a systematic review of all RCTs comparing percutaneous PFO closure to medical therapy in patients with cryptogenic stroke or TIA and PFO or ASD. As composite endpoints varied between trials, we focused on individual endpoints of recurrent non-fatal stroke, recurrent TIA, death, major bleeding, and atrial fibrillation. We also examined per protocol rates of recurrent stroke in patients undergoing PFO closure compared to the medical therapy arm. Outcomes were defined as in each study.

Methods

Eligibility criteria

We included all RCTs comparing treatment with percutaneous catheter-based closure of PFO to medical therapy (anticoagulant or antiplatelet therapy) in patients with cryptogenic stroke or TIA and echocardiographically confirmed PFO or ASD. We excluded trials including participants with other indications for PFO/ASD closure (e.g. hemodynamic significance) or other indications for anticoagulant therapy (e.g. atrial fibrillation).

Included articles met two prespecified criteria: 1) RCTs that compared PFO closure to medical therapy (antiplatelet or anticoagulant agents); 2) Greater than 90% of patients had prior unexplained stroke, TIA, or other arterial embolism, or this subset was reported separately. When more than one study reported data from a population, we used the most complete and updated results.

Data sources and search strategy

We searched Medline and Embase from 1980 to May 2013. We restricted the search to human subjects. Keywords included patent foramen ovale *or* atrial septal defect. Results were then limited to randomize controlled trial *or* controlled clinical trial *or* phase 3 clinical trial *or* phase 4 clinical trial. For every eligible study we identified, and for studies such as review articles that included citations to potentially eligible studies, one reviewer examined the reference list.

Study selection

Teams of two investigators independently screened each title and abstract from this search. If either of the two screeners identified a citation as potentially relevant, we obtained the full text article for detailed review. Teams of two reviewers independently determined the eligibility of all studies that underwent full text evaluation. Disagreements were resolved through discussion between the two reviewers.

Data abstraction

Using a custom made data collection form two of three reviewers (FAS, LCL, SAK) abstracted the following information from each identified study: mean follow-up time, total patient years follow-up (overall and per cohort), number of patients withdrawn or lost to follow-up, number of patients crossing over from medical therapy to PFO closure, number of patients undergoing PFO closure attempt, number of patients in whom PFO closure was technically successful, procedural complications (other than major bleeding) from PFO closure, and outcome event rates.

Disagreements regarding data abstraction results were resolved through discussion between the two reviewers. The primary author abstracted additional information on study funding, eligibility criteria, patient demographics, and treatment characteristics.

Risk of Bias and Confidence in Effect Assessment

Two reviewers (FAS, LL) independently assessed, using the Cochrane risk for bias tool, seven domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding for outcome assessment, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the other 6 domains.[7]

We used GRADE methodology to rate confidence in estimates of effect for each outcome as high, moderate, low or very low.[8] We used detailed GRADE guidance to assess overall risk of bias[9], imprecision[10], inconsistency[11], indirectness[12] and publication bias[13], and summarized results in an evidence profile.

For decisions regarding eligibility, risk of bias assessment, and data abstraction, reviewers resolved disagreement through discussion.

Data Synthesis and Statistical Analysis

We report descriptive statistics as proportions for categorical variables, and mean/median for continuous variables. Our primary analyses for non-fatal ischemic stroke, TIAs, and mortality included only patients with complete follow-up. We excluded patients for whom complete data was unavailable: those lost to follow-up, those who withdrew consent, or those who were found to not have PFO/ASD or history of TIA/stroke after randomization. For outcomes of bleeding and atrial

fibrillation we used data as reported by the investigators from the intention to treat analyses.

Rates of non-fatal ischemic stroke in patients treated as "per-protocol" from two of the three studies were also abstracted and pooled. The definition of per-protocol varied from study to study (CLOSURE 1: all randomized patients who received the treatment to which they were randomized, who had no major inclusion/exclusion criteria violations, and who had a follow-up of at least 22 months; RESPECT: patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment, and did not have a major inclusion or exclusion violation). Event rates for non-fatal ischemic stroke in the "per protocol" subset were not reported in PC Trial manuscript. The primary author of the manuscript did not respond to email requests for further information.

As previous observational studies suggest that patients with cryptogenic stroke and PFO may be at higher risk for recurrent stroke if they have a concomitant atrial septal aneurysm, we performed an additional complete case analysis for a primary composite outcome in the subset of patients with atrial septal aneurysm (data on non-fatal ischemic stroke alone not reported in any of the studies for this subset). Composite outcomes in the 3 studies included some combination of non-fatal ischemic stroke, TIA, peripheral embolism, and death.

As two of the three studies used the ~~Amplatz~~Amplatzer device and one used the STARFlex device (CLOSURE 1) we conducted a sensitivity analysis for non-fatal ischemic stroke excluding the CLOSURE study. We evaluated for subgroup difference (2 ~~Amplatz~~Amplatzer studies vs. STARFlex study) using a chi-square test.

Given high rate of patients excluded from complete case analyses (most due to loss to follow-up) we also conducted 2 additional analyses: 1) Worst case scenario in which we assumed that all patients with missing data in the PFO closure arms suffered non-fatal ischemic strokes and all patients lost to follow-up in the medical arms did not; 2) Plausible worst case scenario in which all patients with missing data from the PFO closure arm were assumed to have 5 times the rate of stroke as the complete cases and b) those excluded from the medical therapy arm were assumed to have 1/5 times the rate of stroke as the complete cases.[14]

We calculated pooled risk ratios (RR) and associated 95% confidence intervals (CI) for non-fatal ischemic stroke and TIAs using random effects models applying Mantel Haenszel method. Absolute effects (and 95% CI) were calculated by multiplying pooled RRs and 95% CI by pooled control rate of outcomes. As event rates were very low for death, atrial fibrillation, and major bleeding (leading to skewed 95% CI), pooled risk difference (RD) and 95% CI was used to calculate absolute effects for these outcomes.[15] Statistical heterogeneity was assessed by the I^2 statistic. Analyses were performed using RevMan version 5.2 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration).

Results

Trial Identification

Our search yielded 284 abstracts - all were identified from the electronic database search- of which 47 were duplicates and excluded. We excluded an additional 229 articles based on a review of the title and abstract, leaving 8 articles for full review. Of these studies, 5 were excluded – 2 were descriptions of methodology for subsequently reported RCTs, 1 was a comparison of different devices for closure but did not include a medical therapy arm, and 2 were prospective cohort studies of PFO closure. (See Appendix Figure) We included 3 randomized trials enrolling 2303 patients. [4-7]

Trial and Patient Characteristics

Table 1 presents the characteristics of the 3 eligible studies. Two of the three studies (RESPECT, PC Trial) used the ~~Amplatz~~Amplatzer occluder device whereas the other used the STARFlex device (CLOSURE I). Crossover from medical therapy to PFO closure occurred in only one study (13.3%) (PC Trial). The percentage of patients in the PFO closure arm undergoing a PFO closure attempt ranged from 90.6 to 96.1% with success rates ranging from 89.4% to 99.1%.

In the CLOSURE I study all patients undergoing PFO closure were assigned to clopidogrel 75 mg per day times 6 months and aspirin 81 or 325 mg per day for 2

years. In the RESPECT study all patients undergoing closure received aspirin 81-325 mg plus clopidogrel for one month followed by aspirin monotherapy for 5 months. Antiplatelet treatment thereafter was left to the discretion of the site investigator. In the PC Trial, managing clinicians were counseled to recommend aspirin 100 to 325 mg per day for 5 to 6 months and ticlopidine (250 to 500 mg per day) or clopidogrel (75 mg to 150 mg per day) for 1 to 6 months. However at discharge from PFO closure in the PC trial, 182 patients (89.2%) were using aspirin, 104 (51%) thienopyridines, 6 (2.9%) oral anticoagulation, and 8 (3.9%) were not using antithrombotic prophylaxis.

Treatment in the medical therapy arms also varied across studies. In Closure I, patients assigned to medical therapy were treated with warfarin (with a target international normalized ratio of 2.0 to 3.0), aspirin (325 mg daily), or both, at the discretion of the principal investigator at each site (further details not provided). In RESPECT five medical therapies were initially allowed (after randomization aspirin alone was used in 223 patients (46.5%), warfarin alone in 121 (46.5%), clopidogrel alone in 67 patients (14%), aspirin with dipyridamole in 39 patients (8.1%), and aspirin with clopidogrel in 30 (6.2%). In the PC Trial antithrombotic treatment was also left to the discretion of the treating physician and could have included antiplatelet therapy or oral anticoagulation (after randomization, 120 (57.1%) of subjects were using aspirin, 35 (16.7%) thienopyridines, 64 (30.5%) oral anticoagulation, and 5 (2.4%) were not using antithrombotic prophylaxis.

Adherence with medical therapy/changes in medical therapy was not clearly documented in 2 of the 3 studies. In the PC trial, the percentage of patients using no antithrombotic prophylaxis increased from 2.4% following randomization to 7.7% at 2 years, 11.3% at 3 years, 11.1% at 4 years, and 12.8% at 5 years. The distribution of other therapies changed little over 5 years.

A total of 311 (13.5%) subjects were lost to follow-up or withdrew consent (range within studies 12% to 18%). Loss to follow-up/withdrawal of consent was higher in the medical therapy arm (n = 204, 18%) than in the PFO closure arm (n = 107, 9%). In addition, 14 patients (CLOSURE I = 12, PC Trial = 1, RESPECT = 1) were demonstrated to have no PFO after randomization and 11 patients were determined to have no prior history of stroke or TIA (CLOSURE I). Therefore 336 subjects were excluded from our complete case analyses.

The three studies enrolled similar patients (e.g. age range from 44.5 to 46 years) with some differences in medical history (Table 2). In two of the studies approximately 70-80% of patients were enrolled with an index diagnosis of cryptogenic stroke with most of the rest having an index diagnosis of TIA. In one study (RESPECT), all patients enrolled had a diagnosis characterized as stroke but patients with less than 24 hours of symptoms and radiologic evidence for infarct were included in this category.

Assessment of Risk of Bias

Overall risk of bias was deemed high for all 3 studies due to missing data (see Figure 1) – as noted 13.5% of subjects were lost to follow-up with twice as many lost to follow-up in the medical arm compared to the PFO closure arm. There is also lack of clear description regarding how compliance with medical therapy was assessed – in only 1 study was medical therapy usage at different time points described.

Participants and study personnel were not blinded in any of the three studies, which likely contributed to differential rates of loss to follow-up. It is unclear if this would have led to additional bias with respect to the observed outcome rates as a clinical events committee adjudicated events in all three studies.

Outcomes Assessment

Non-fatal ischemic Stroke

There were a total of 22 non-fatal ischemic strokes among 1026 patients randomized to PFO closure vs. 34 strokes among 941 patients randomized to medical therapy (Risk Ratio 0.61, 95% CI 0.34, 1.07; Heterogeneity: p =0.34, I^2 = 8%) (Figure 2). Using our best estimate of baseline from the available randomized trials of 52 non-fatal ischemic strokes over 5 years in 1000 patients treated medically, PFO closure may be associated with 20 fewer strokes per 1000 treated over a period of 5 years (confidence interval 34 fewer to 4 more strokes, low confidence in estimates because of risk of bias and imprecision) (Table 3).

In a sensitivity analysis including the 2 studies using the ~~Amplatz~~Amplatzer device, PFO closure was associated with a decreased risk of non-fatal ischemic stroke (RR

0.44, 95% 0.21, 0.93; Heterogeneity: p = 0.42, I^2 = 0%). In the CLOSURE I Study (Starflex device), there was no difference between PFO closure and medical therapy with respect to non-fatal ischemic stroke (RR 0.87, 95% CI 0.40, 1.87). The test for interaction between these two subset analyses revealed differences consistent with chance (Chi^2 = 1.52, p = 0.22).

We conducted analyses imputing non-fatal strokes for patients excluded from the complete case analysis. In our worst-case analysis (all PFO intervention arm patients excluded from complete case analysis having non-fatal ischemic stroke, none of subjects excluded from the medical therapy arm having non-fatal ischemic stroke), RR = 4.22, 95% CI 2.93, 6.08 (Heterogeneity: p = 0.39, I^2 = 0%). In our plausible worst case analysis in which excluded PFO closure patients had 5-fold increased rate of stroke (relative to included subjects) and excluded medical therapy patients had a 1/5 rate of stroke (relative to included subjects), PFO closure was associated with a RR = 0.96, 95% CI 0.56, 1.66 (Heterogeneity: p = 0.28, I^2 = 21%). Although some might consider the 5 to 1 ratio we have tested beyond the range of plausibility, there is empirical support for this choice[16], and our ~~These~~ results support rating down confidence in estimates for risk of bias related to missing data.

In the 2 studies providing per-protocol event rates for non-fatal ischemic stroke there were 18 vs. 27 non-fatal ischemic strokes yielding a RR of 0.66, 95% CI 0.32, 1.38 (Heterogeneity: p = 0.23, I^2 = 32%)

As previous observational studies suggest that patients with cryptogenic stroke and PFO may be at higher risk for recurrent stroke if they have a concomitant atrial septal aneurysm, we also examined pooled rates of the primary composite endpoint of the studies in this subset. There were 13 events among 378 patients with atrial septal aneurysm undergoing closure compared to 20 events among 380 patients undergoing medical therapy (RR 0.71, 95% CI 0.22, 2.27; Heterogeneity: p = 0.11, I^2 = 55%).

TIAs

Pooling complete case data from the 3 studies, there were 23 vs. 28 TIAs in the PFO closure and medical treatment groups respectively (RR 0.76, 95% CI 0.44, 1.32; Heterogeneity: p = 0.64, I^2 = 0%). PFO closure may be associated with 6 fewer TIAs over a period of 5 years (confidence interval 15 fewer to 9 more) (moderate confidence because of risk of bias (Figure 3, Table 3).

Total mortality

There were 7 deaths ~~per~~ in the PFO closure arm vs. 10 deaths in the medical treatment arm of the 3 studies (RD -0.00, 95% CI -0.01, 0.01; Heterogeneity: p = 0.23, I^2 = 31%). None of the deaths were deemed secondary to treatment (PFO closure or antithrombotic therapy) or stroke. PFO closure may have no effect on mortality over a period of 5 years (confidence interval 10 fewer to 10 more) (low confidence because of risk of bias and imprecision) (Table 3).

Adverse events

Pooling data from all 3 studies, bleeding occurred in 13 vs. 7 patients in the PFO closure vs. medical treatment arms (all were major bleeds except 2 bleeds from RESPECT study not classified) (RD 0.00, 95% CI -0.01, 0.02; Heterogeneity p = 0.12, I^2 = 53%) (see Figure 4). PFO closure may have no effect on major bleeding over a period of 5 years (CI 10 fewer to 20 more) (moderate confidence because of risk of bias) (Table 3).

Atrial fibrillation occurred in 32 patients undergoing PFO closure vs. 8 patients treated with medical therapy (RD 0.02, 95% -0.02, 0.06; Heterogeneity: p <0.00001, I^2 = 93%). PFO closure may be associated with 20 more cases of atrial fibrillation per 1000 treated compared to medical therapy over a period of 5 years (CI 20 fewer to 60 more) (very low confidence because of risk of bias, inconsistency, and imprecision) (Table 3). Of 23 cases of atrial fibrillation reported after PFO closure in the CLOSURE I study 6 were deemed "sustained" – atrial fibrillation in the medical group was not characterized. Of 8 cases of atrial fibrillation in the PC Trial occurring after PFO closure 2 were transient (in PFO closure arm) and 6 required cardioversion or were sustained. Atrial fibrillation was not characterized as transient or sustained in the RESPECT study.

We were unable to pool data regarding procedural or device related complications given differences between studies in reporting styles. Serious procedural or device

related adverse events (in addition to bleeding, ischemic stroke, atrial fibrillation which have already been captured in previous analyses) were reported in 15 patients in the RESPECT trial (3%). This included 8 procedural related events. Major vascular events related to the procedure occurred in 13 of the 402 patients (3.2%) in whom PFO closure was attempted in CLOSURE I – these included 6 major bleeding episodes already captured above. The total number of serious procedural related adverse events was not specifically reported in the PC Trial although it was noted that no device related thrombi occurred.

Discussion

A decade ago a meta-analysis of observational studies suggested transcatheter closure of PFO in patients with cryptogenic stroke may prevent more strokes than medical therapy.[3] The authors noted important limitations in available data and highlighted the need for RCTs to resolve the issue. Since that time, thousands of patients have undergone this procedure in a non-RCT setting.

We now have data from 3 RCTs comparing transcatheter PFO closure to medical therapy in patients with cryptogenic stroke or TIA and PFOs. Our analysis suggests a possible benefit of closure on the major outcome of stroke (RR 0.61, 95% CI 0.34, 1.07). Confidence in the estimate of 20 fewer strokes per 1,000 is, however, low, both because of problems with risk of bias and imprecision (confidence intervals include an increase in stroke of 4 per 1,000). Analyses for ischemic stroke

restricted to "per-protocol" patients or patients with concomitant atrial septal aneurysm did not substantially change the observed risk ratios.

We conducted subgroup analyses evaluating the impact of PFO closure on non-fatal stroke separately in the 2 studies using the ~~Amplatz~~Amplatzer closure device vs. the one study using the STARFlex device. Pooled data from the ~~Amplatz~~Amplatzer studies suggests PFO closure may be associated a decrease in non-fatal ischemic stroke (RR 0.44, 95% CI 0.21, 0.93) whereas no benefit was observed in the study using the STARFlex device. Although the subgroup hypothesis was made a priori and differences are in the anticipated direction, the analysis is based on between group differences, has not been replicated, and differences between results with the two devices is easily explained by chance (p = 0.22). Thus the subgroup hypothesis has low credibility.[17]

~~As suggested in~~ There have been 3 other meta-analyses. They are limited, however, by failure to fully consider risk of bias issues, failure to use the GRADE approach to determine overall confidence in estimates of intervention effect, and failure to consider the limitations of composite endpoints. ~~two other recently published analyses, our data could be interpreted to suggest a potential substantial benefit may exist for PFO closure~~.[18-20]. In the most recent of these analyses, PFO closure was associated with an effect-estimate hazard ratio of 0.67 (95% confidence interval [CI]: 0.44 to 1.00) for the prevention of "neurologic events". However it appears that this composite endpoint included the softer endpoint of TIA in addition to stroke and mortality.

It is possible that a larger sample size and more rigorously done studies

would definitively identify an important benefit in the total patient population, or in a subgroup. Our review demonstrates, however, that such additional studies may also fail to demonstrate benefit or, in comparison to effective antithrombotic prophylaxis, an increase in strokes.

Although some concern arises from possible lack of concealment of randomization in one study and the apparent failure to blind outcome adjudication in another study, the major problem in terms of risk of bias is the high loss to follow-up in these studies and the two fold greater loss to follow-up in patients in the medical therapy arms than the PFO closure arms (overall 9% in PFO and 18% in the medical therapy arms).

Our primary analysis was restricted to patients with available data (complete case analysis). If event rates differed in those with missing data in intervention and control groups - of particular concern would be higher rates of events in those lost to follow-up in the PFO closure arm that the medical therapy arm - the complete case results may be misleading. In an additional analysis in which patients lost to follow-up in the PFO arm were assumed to have 5 fold increased risk of stroke and those lost to follow-up in the medical therapy arm had a 5-fold decreased risk of stroke, there was no longer a trend favoring PFO closure (RR 0.96). This finding supports our rating down confidence in estimates of effect for risk of bias.

Another issue is the rigor with which control arm clinicians encouraged compliance with antithrombotic prophylaxis in medical patients. In two of the studies dose and type of antithrombotic therapy in the medical therapy arm were left to the treating physician's discretion. Only one of the studies reported

adherence and/or changes over time in medical therapy in both arms. Leaving therapy in the medical arm to the physician's discretion could be considered to represent "usual care" for those randomized to medical therapy. Usual care may, however, change over time, and differ in the jurisdictions in which the trial is conducted in comparison to other jurisdictions. Patients and clinicians may, therefore, be more interested in the effect of PFO closure versus a particular antithrombotic regimen with a high level of adherence. Unfortunately there have been no RCTs adequately comparing specific antiplatelet or antithrombotic therapies for this indication.

Stroke occurring due to paradoxical emboli through a PFO results from thrombi originating in the venous circulation or perhaps from the ~~right atrial side of an~~ associated atrial septal aneurysm itself.[21,22] Warfarin has been shown to be more effective than antiplatelet therapy for the treatment and secondary prevention of venous thromboembolic events. Observational studies suggest oral anticoagulation is superior to aspirin for the prevention of stroke in patients with PFO albeit with increased bleeding.[23,24] In the Patent Foramen Ovale in Cryptogenic Stroke study (substudy of the randomized Warfarin-Aspirin Recurrent Stroke study) there were 98 patients with cryptogenic stroke and PFO - 42 were randomized to warfarin and 56 received aspirin.[25] Two-year rates of recurrent stroke were lower in patients receiving warfarin (9.5% vs. 17.9%,) but chance easily explains this (p = 0.28).

Given the uncertainty of the optimal antithrombotic regimen, subsequent trials must give this issue careful thought. One option for the medical arm would be careful exploration of individual patient values and preferences. Patients highly

averse to bleeding risk and the burdens of anticoagulant therapy could receive only an antiplatelet agent, while those less bleeding and burden averse could receive an anticoagulant. Use of an oral anticoagulant rather than warfarin in those choosing anticoagulation would be a possibility. Such an approach might represent optimal medical care, perhaps the appropriate comparator to PFO closure. Another option would be three-arm study with both antiplatelet and anticoagulant arms

We conclude that the available data warrants only low confidence in the impact of PFO versus medical therapy. Thus, additional RCTs are still required – two such studies are listed as actively recruiting on the NIH website ClinicalTrials.gov. Ideally, when pooled across studies, sample sizes will be large enough to definitively establish the impact of PFO closure versus medical therapy on the most important outcome, ischemic stroke. As important, results will be more compelling if the ongoing studies have implemented successful strategies to ensure complete or near-complete follow-up and have paid careful attention to decisions regarding medical prophylaxis and optimizing adherence in both arms of the study. In the interval, patients should be made aware of the management options and the uncertainty underlying their effectiveness.

Figure legends:

Figure 1 Risk of bias in individual studies

Figure 2 Pooled risk of non-fatal ischemic stroke with PFO closure versus medical therapy

Figure 3 Pooled risk of transient ischemic attack with PFO closure versus medical therapy

Figure 4 Pooled risk of major bleeding with PFO closure versus medical therapy

References

1. Webster MW, Chancellor AM, Smith HJ, et al. Patent foramen ovale in young stroke patients. Lancet 1988;2:11-2.
2. Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988;318:1148-52.
3. Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. Ann Intern Med 2003;139:753-60.
4. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med 2012;366:991-9.
5. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med 2013;368:1092-100.
6. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med 2013;368:1083-91.
7. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
8. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
9. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol 2011;64:407-15.
10. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol 2011;64:1283-93.
11. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol 2011;64:1294-302.
12. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol 2011;64:1303-10.
13. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol 2011;64:1277-82.
14. Akl EA, Briel M, You JJ, et al. Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): systematic review. Bmj 2012;344:e2809.
15. Murad MH, Montori VM, Walter SD, Guyatt GH. Estimating risk difference from relative association measures in meta-analysis can infrequently pose interpretational challenges. J Clin Epidemiol 2009;62:865-7.
16. Geng EH, Emenyonu N, Bwana MB, Glidden DV, Martin JN. Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa. JAMA : the journal of the American Medical Association 2008;300:506-7.
17. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010;340:c117.
18. Pineda AM, Nascimento FO, Yang SC, Kirtane AJ, Sommer RJ, Beohar N. A meta-analysis of transcatheter closure of patent foramen ovale versus medical therapy for prevention of recurrent thromboembolic events in patients with cryptogenic cerebrovascular events. Catheter Cardiovasc Interv 2013.

19. Kitsios GD, Thaler DE, Kent DM. Potentially Large yet Uncertain Benefits: A Meta-analysis of Patent Foramen Ovale Closure Trials. Stroke 2013;44:2640-3.
20. Khan AR, Bin Abdulhak AA, Sheikh MA, et al. Device closure of patent foramen ovale versus medical therapy in cryptogenic stroke: a systematic review and meta-analysis. JACC Cardiovascular interventions 2013;6:1316-23.
21. Aryal MR, Pradhan R, Pandit AA, Polinsky R. A "teapot" atrial septal aneurysm with spontaneous thrombus in an asymptomatic patient. Circulation 2013;128:e409-10.
22. Schneider B, Hanrath P, Vogel P, Meinertz T. Improved morphologic characterization of atrial septal aneurysm by transesophageal echocardiography: relation to cerebrovascular events. Journal of the American College of Cardiology 1990;16:1000-9.
23. Cujec B, Mainra R, Johnson DH. Prevention of recurrent cerebral ischemic events in patients with patent foramen ovale and cryptogenic strokes or transient ischemic attacks. Can J Cardiol 1999;15:57-64.
24. Orgera MA, O'Malley PG, Taylor AJ. Secondary prevention of cerebral ischemia in patent foramen ovale: systematic review and meta-analysis. South Med J 2001;94:699-703.
25. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. Circulation 2002;105:2625-31.

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All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Contributorship statement:

Dr. Frederick Spencer contributed to the conception and design of the study, the acquisition, analysis and interpretation of the data, drafting the work, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Luciane Lopes contributed to the design of the study, the acquisition, analysis and interpretation of the data, critical revision of the work for important intellectual content, and gave final approval of the version to be published. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Mr. Sean Kennedy contributed to the design of the study, the acquisition, analysis and interpretation of the data, critical revision of the work for important intellectual content, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Gordon Guyatt contributed to the design of the study, the acquisition, analysis and interpretation of the data, drafting and critical revision of the work for important intellectual content, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Table 1

Trial (patients)	Trial Type	Intervention	Medical therapy	Withdrew or Loss to Followup PFO closure (%)	Withdrew/Loss to Followup Medical Therapy (%)	Crossover from Medical Therapy to PFO Closure (%)	% PFO closure attempts/patients enrolled in PFO cohort (%)	% technical success /PFO closure attempts (%)
CLOSURE I (909)	Multicentre Randomized Open label	STARFLEX Device Clopidogrel x 6 mo ASA x 2 years	Warfarin (INR 2-3), ASA 325 per day, or both (clinician's discretion)	1.8	0.7	0	90.6	89.4
PC Trial (414)	Multicentre Randomized Open Label	~~Amplatz~~Amplatzer Occluder ASA 5-6 mo. Clopidogrel or ticlopidine 1-6 mo.	Antiplatelet or anticoagulation (clinician's discretion)	15.2	20	13.3	96.1	97.4
RESPECT (980)	Multicentre Randomized Open Label	~~Amplatz~~Amplatzer Occluder ASA 6 mo Clopidogrel 1 mo.	Antiplatelet or anticoagulation (clinician's discretion)	9.2	17.2	0	93	99.1

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Table 2 Characteristics of Patients in Eligible Studies

	CLOSURE 1	RESPECT	PC Trial
N	909	980	414
Mean Age +/- SD	46.0	45.9	44.5
Male (%)	51.8	54.7	49.8
Smoker (%)	22.1	13.3	23.9
Medical History (%)			
Diabetes	NR	7.4	2.7
Hypertension	31.0	31.4	25.8
Hyperlipidemia	44.1	39.5	27.1
Ischemic heart disease	1.1	2.9	1.9
Myocardial infarction	1.3	0.7	1
Valvular dysfunction	10.3	NR	3.1
Peripheral vascular disease	1.3	0.6	1.2
Index event (%)			
Stroke	72	100*	79.2
TIA	28	0	18.1
Peripheral arterial embolism	0	0	2.7
PFO characteristics (%)			
Moderate or higher shunt	52.9	75.2	65.6**
Atrial septal aneurysm >10 mm	37.8***	35.6	23.7

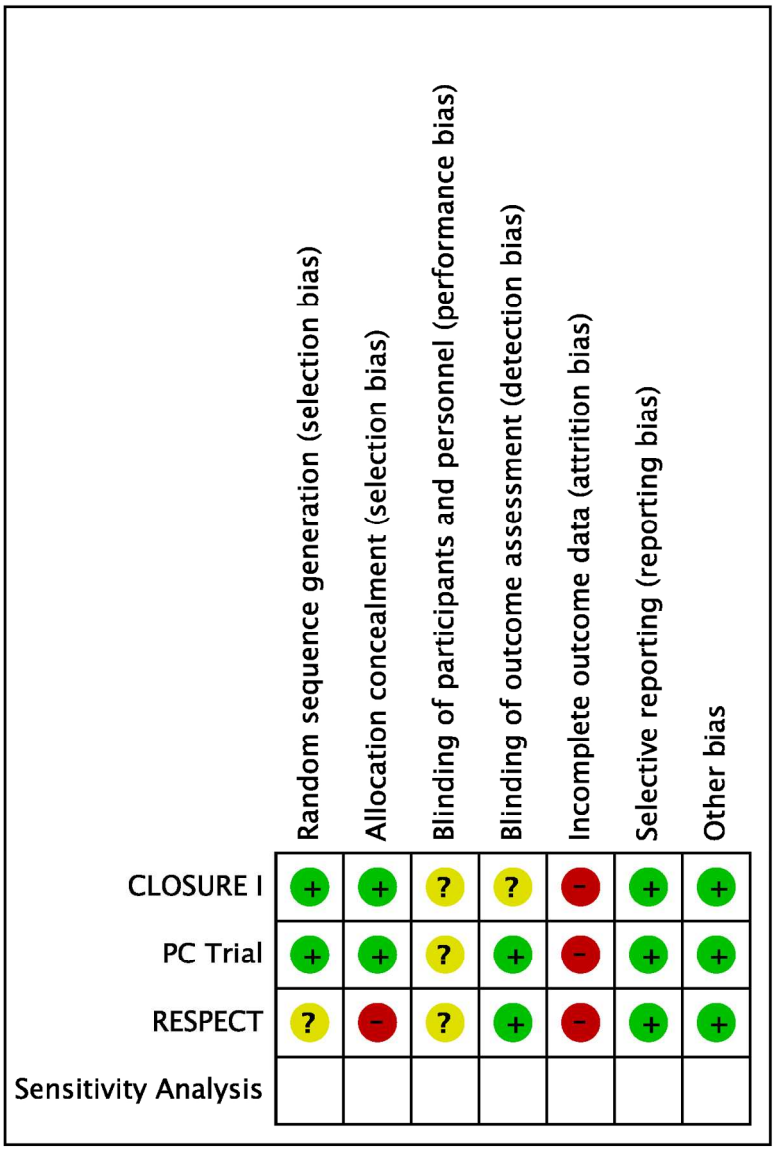
*Included patients with symptoms for less than 24 hours if new neuroradiologically relevant cerebral infarct on imaging
** 369 of 414 patients with TEE

***151/400 patients with TEE

Table 3 – GRADE assessment of quality of evidence

Bibliography:									
Quality assessment						**Summary of findings**			
No of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Relative effect or risk difference (95% CI)**	**Anticipated absolute effects Time frame: 5 years**		**Quality of evidence**
							Risk with medical therapy	**Risk difference with PFO closure (95% CI)**	
Non-fatal ischemic stroke (critical outcome)									
1968 (3 RCTs)	**Serious limitations**[1]	No serious limitations	No serious limitations	**Imprecise** CI includes benefit and no effect	Undetected	**RR 0.61** (0.34 to 1.07)	**52 per 1000**[2]	**20 fewer per 1000** (from 34 fewer to 4 more)	⊕⊕OO **LOW** due to risk of bias and imprecision
TIA (important outcome)									
1968 (3 RCTs)	**Serious limitations**[1]	No serious limitations	No serious limitations	No serious limitations[3]	Undetected	**RR 0.76** (0.44 to 1.32)	**27per 1000**[4]	**6 fewer per 1000** (from 15 fewer to 9 more)	⊕⊕⊕O **MODERATE** due to risk of bias
Total mortality (critical outcome)[5]									
1968 (3 RCTs)	**Serious limitations**[1]	No serious limitations	No serious limitations	**Imprecise** CI includes benefit and harm	Undetected	**RD 0.00** (-0.01, 0.01)	**15 per 1000**[6]	**0 fewer per 1000** (from 10 fewer to 10 more)	⊕⊕OO **LOW** due to risk of bias and imprecision
Major bleeding (important outcome)									
2254 (3 RCTs)	**Serious limitations**[1]	No serious inconsistency	No serious limitations[3]	No serious limitations	Undetected	**RD 0.00** (-0.01, 0.02)	**7 per 1000**[7]	**0 more per 1000** (10 fewer to 20 more)	⊕⊕⊕O **MODERATE** due to risk of bias
Atrial fibrillation (important outcome)[8]									
2254 (3 RCTs)	**Serious limitations**[1]	**Serious inconsistency**[9]	No serious limitations	**Imprecise** CI includes benefit and harm	Undetected	**RD 0.02** (-0.02, 0.06)	**12 per 1000**[10]	**20 more per 1000** (20 fewer to 60 more)	⊕OOO **VERY LOW** due to risk of bias and imprecision

[1]Serious risk of bias due to substantial loss to followup in each of 3 studies; loss to followup greater in medical therapy arms. See text for other potential sources of bias in individual studies.
[2]Baseline rate derived from pooled Respect and PC trial data - 21 non-fatal ischemic strokes detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years
[3]Although CI includes benefit and harm, but magnitude of extremes for this type of outcome deemed too low to appreciably impact patient decision making.
[4]Baseline rate derived from pooled Respect and PC trial data - 11 TIAs detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years
[5]None of deaths due to stroke, treatment related bleeding, or device implantation
[6]Baseline rate derived from pooled Respect and PC trial data - 6 cases of total mortality detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years
[7]Baseline rate derived from pooled Respect and PC trial data – 3 cases of major bleeding detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years
[8]Type of atrial fibrillation (transient vs. sustained) not reported in medical therapy arms or in PFO closure arm of RESPECT study. Of 31 cases of atrial fibrillation in the remaining 2 studies 19 were characterized as transient.
[9]I^2 = 93%, p = <0.00001
[10]Baseline rate derived from pooled Respect and PC Trial data – 5 cases of atrial fibrillation detected in the medical therapy arm over a total of 2019 pt-yrs x 1000 x 5 years.



Risk of bias in individual studies
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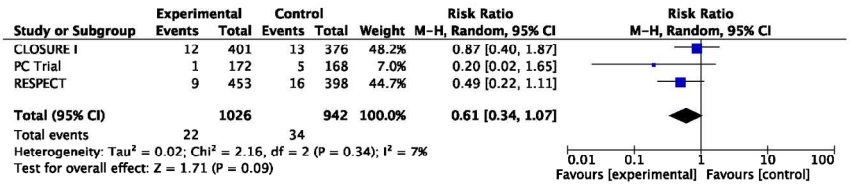

Pooled risk of non-fatal ischemic stroke with PFO closure versus medical therapy
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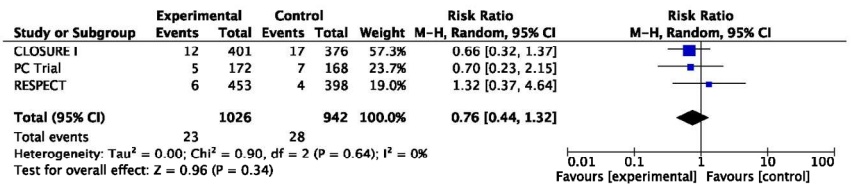

Pooled risk of transient ischemic attack with PFO closure versus medical therapy
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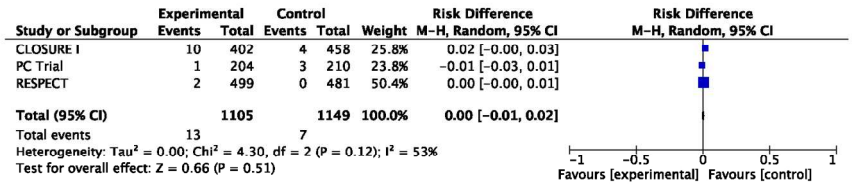

Pooled risk of major bleeding with PFO closure versus medical therapy
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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-11

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11-12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-14 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14 Figure 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-18 Figures 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15-18 Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	15-16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

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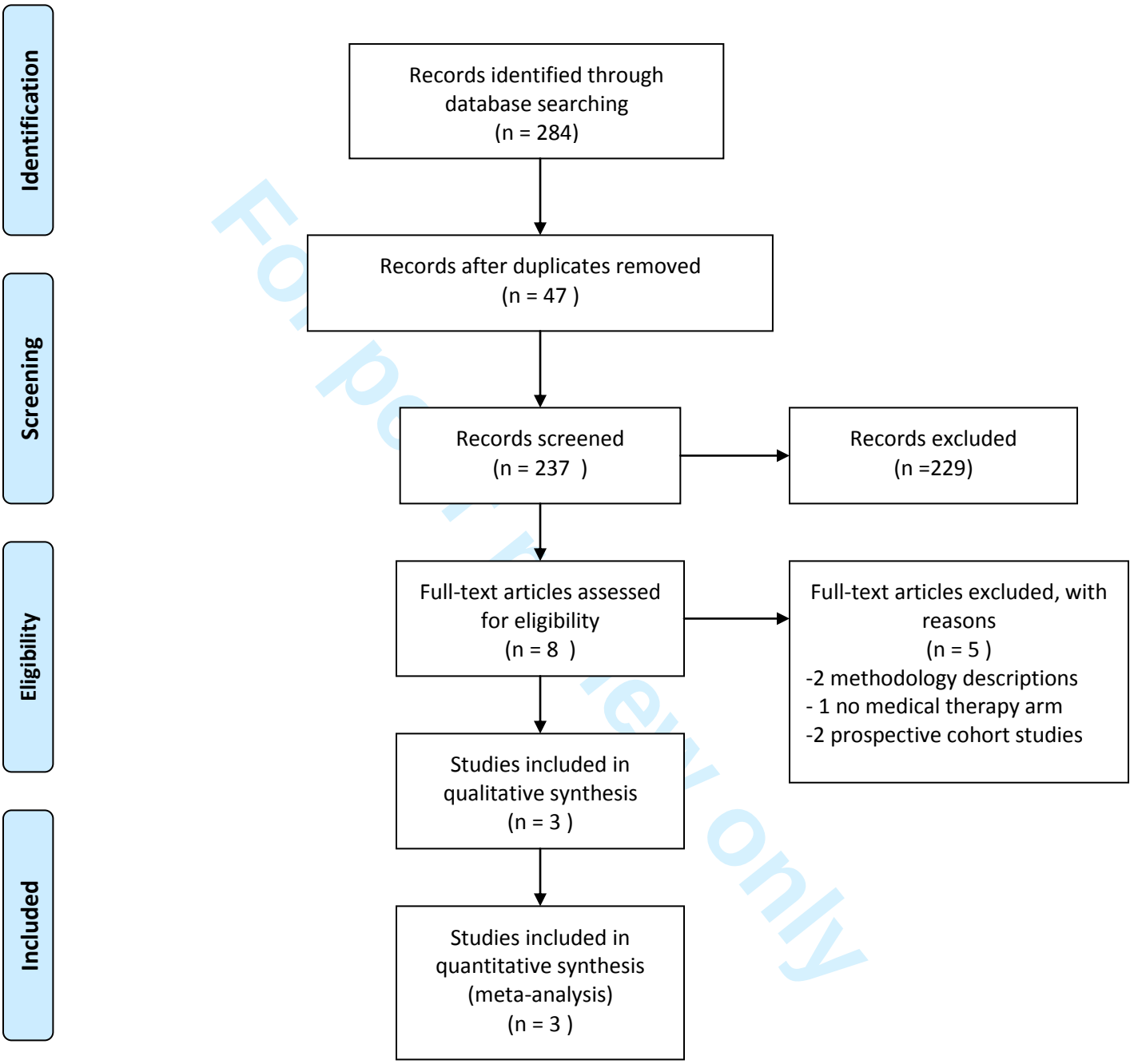

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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