PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Systematic Review of Percutaneous Closure versus Medical Therapy in Patients with Cryptogenic Stroke and Patent Foramen Ovale
AUTHORS	Spencer, Frederick; Lopes, Luciane; Kennedy, Sean; Guyatt, Gordon

VERSION 1 - REVIEW

REVIEWER	Bernhard Meier Bernhard Meier Professor and Chairman of Cardiology University Hospital Bern Switzerland Research grants to the institution and speaker fees of St. Jude Medical
REVIEW RETURNED	06-Nov-2013

GENERAL COMMENTS	This is one of about ten meta-analyses that are currently in the process of being published. It is an average one in terms of quality and I assume that a least five others will be published prior to this one. As it is not based on individual data, I see no additional value of this meta-analysis compared to all the others. The authors make an honorable attempt at meta-analyzing the three randomized trials published in the past two years on closure of the patent foramen ovale (PFO) for prevention of paradoxical embolism, in particular stroke. There are currently at least 10 similar meta-analysies in print or under review in a variety of cardiovascular journals and journals of internal medicine. This devaluates the originality of this particular review. The final sentence in the abstract needs to be a rephrased: “provides little support for PFO closure over medical therapy….”, could read: “provides insufficient support that PFO closure is preferable to medical therapy…”. It should then be added that it is beyond doubt that PFO closure is at least competitive and should therefore be offered as an option to all patients. The authors mention that the event rate for non-fatal ischemic stroke in the protocol subset of the PC trial were not available. However, in the published supplementum these figures are mentioned and it is also mentioned that none of the strokes was fatal. This needs to be amended. The Amplatzer device is occasionally cited as the “Amplatz device”. Please correct that.

	Under “total mortality” in the first sentence the word “par” does not make sense. Please delete. The assumption that patients lost to follow-up could have 5 times higher risks of events, appears farfetched. It is more likely that patients lost to follow-up remained clinically silent as they would have been easy to trace if they had needed medical attention during follow-up. I suggest to mention this. In the discussion it is mentioned that a paradoxical stroke may be due to a thrombus originating from the right side of an atrial septal aneurysm. Such a case has never been described to my knowledge and I suggest to drop this or reference it. Please explain why more randomized trials are asked for. It appears quite well proved by now that PFO closure it at least as efficacious as medical therapy and shows trends to be superior. You may mention at this point a study with a 10 year follow-up where a mortality reduction was documented when comparing the time after PFO closure to the time without or before the PFO closure in well matched and randomly assigned patients (Circulation 125: 803-812, 2012). Hence continuing randomized trials has a high risk to be to the detriment of the patients in the control group. This risk includes strokes, myocardial infarction, and even deaths and should not be taken lightly. Please discuss that and mention that already based on current data PFO closure has to be offered to every patient with a suspicion of a paradoxical embolic event. The last figure may be droped as the selection process is sufficiently described in the text.

REVIEWER	Laura Mauri Brigham and Women' Hospital, USA investigator on one of the trials inculded in the metaanalysis
REVIEW RETURNED	13-Nov-2013

GENERAL COMMENTS	In the weeks before this manuscript was submitted, a metaanalysis of the same 3 studies was published, JACC Cardiovasc Interv. 2013 Oct 10, by a different group. The conclusions were in direct contrast to the authors of the current manuscript. I would recommend to current authors that they reference the published manuscript, and that they change their paper to discuss how their methodolgy differs from the published metaanalysis and supports their conclusions of no benefit.

REVIEWER	John Carroll University of Colorado USA Steering Committee for RESPECT with my institution being compensated for the time spent on this trial.
REVIEW RETURNED	18-Nov-2013

GENERAL COMMENTS	This manuscript clearly involved a great deal of work and it does allow a good comparison of the three RCTs.

	It appears to lack an overall appreciation of the challenges in clinical trials and the inherent limitations. It proposes a subgroup analysis of the results based on the device used, shows statistically significant reduction of the risk of recurrent stroke with the Amplatzer device and then goes on to dismiss the results based on questionable reasoning. The paper appears biased in this regard. It fails to mention the lack of RCTs in the arena of medical therapy for secondary prevention of stroke/TIA in the presence of PFO. It proposes a trial design based on medical therapy chosen on the basis of patient preferences. This is a novel and highly odd approach to getting a scientifically credible result and adds new biases. This is one of perhaps 6 meta-analyses using the same data from the three trials and arriving at different conclusions. The critiques of the three trials (Figure 1?) needs more explanation of how these grades were derived and whether their grades were valid. Nothing new. Biased. Does nothing to move the field forward.

REVIEWER	Avinesh Pillai Department of Statistics University of Auckland Auckland New Zealand
REVIEW RETURNED	01-Jan-2014

- The reviewer completed the checklist but made no further comments.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

1. This is one of about ten meta-analyses that are currently in the process of being published. It is an average one in terms of quality and I assume that a least five others will be published prior to this one. As it is not based on individual data, I see no additional value of this meta-analysis compared to all the others.

We acknowledge that other meta-analyses may be in the process of being published. We respectfully disagree with the reviewer that our analysis provides no additional value – our review carefully assesses and pools the available data but also rigorously assesses the quality of this data using an established protocol with rigorous and explicit criteria (GRADE) (Guyatt et al, BMJ 2008; 336:924-926). Further, we have used a recently published innovative and rigorous process to address the possible impact of loss to follow-up on the results. In addition, and perhaps because of this process, our conclusions will likely differ from some of the other of these analyses. Therefore, there is substantial additional value of our meta-analysis.

2. The final sentence in the abstract needs to be a rephrased: “provides little support for PFO closure over medical therapy….”, could read: “provides insufficient support that PFO closure is preferable to medical therapy…”.

We have made the suggested change.

3. It should then be added that it is beyond doubt that PFO closure is at least competitive and should therefore be offered as an option to all patients.

We have added the following final sentence to the manuscript conclusion: "In the interval, patients should be made aware of the management options and the uncertainty underlying their effectiveness." See page 24, para 1.

4. The authors mention that the event rate for non-fatal ischemic stroke in the protocol subset of the PC trial were not available. However, in the published supplementum these figures are mentioned and it is also mentioned that none of the strokes was fatal. This needs to be amended.

We have reviewed the supplement to the PC trial manuscript again but still cannot find any mention of event rates in the “per-protocol” subset.

5. The Amplatzer device is occasionally cited as the “Amplatz device”. Please correct that.

We have made the appropriate changes.

6. Under “total mortality” in the first sentence the word “par” does not make sense. Please delete.

We have deleted the word “per” as suggested.

7. The assumption that patients lost to follow-up could have 5 times higher risks of events, appears farfetched. It is more likely that patients lost to follow-up remained clinically silent as they would have been easy to trace if they had needed medical attention during follow-up. I suggest to mention this.

In out view, it is plausible that patients lost to follow-up will have increased event rates compared to those remaining in study. For example if a patient had a subsequent stroke and is now in a rehab facility or has died, follow-up can be less likely to occur. What is the highest plausible increase in events in those lost to follow-up is a matter of judgment.

In this study an upper limit of 5-fold increase for event rates in patients lost to f/u (compared to those not lost to f/u) was used as it represents the highest ratio reported in the literature. Geng et al used a community tracker to evaluate the incidence of death among participants in scale-up programs of antiretroviral treatment in Africa who were lost to follow-up (Geng et al, JAMA 2008; 300:506-7) . They found the mortality rate to be five times higher in patients lost to follow-up compared with patients who were followed up.

Nevertheless, we have responded to the reviewer's suggestion by qualifying our conclusions regarding loss to follow-up as follows: "Although some might consider the 5 to 1 ratio we have tested beyond the range of plausibility, there is empirical support for this choice, and our results support rating down confidence in estimates for risk of bias related to missing data." (Please see page 17, para 1)

8. In the discussion it is mentioned that a paradoxical stroke may be due to a thrombus originating from the right side of an atrial septal aneurysm. Such a case has never been described to my knowledge and I suggest to drop this or reference it.

There are a number of case reports describing echocardiographic documentation of thrombus on the atrial septal aneurysm. We reference two of these in the revised manuscript. See page 22, para 3.

9. Please explain why more randomized trials are asked for. It appears quite well proved by now that PFO closure it at least as efficacious as medical therapy and shows trends to be superior. You may mention at this point a study with a 10 year follow-up where a mortality reduction was documented when comparing the time after PFO closure to the time without or before the PFO closure in well matched and randomly assigned patients (Circulation 125: 803-812, 2012). Hence continuing randomized trials has a high risk to be to the detriment of the patients in the control group. This risk includes strokes, myocardial infarction, and even deaths and should not be taken lightly. Please discuss that and mention that already based on current data PFO closure has to be offered to every patient with a suspicion of a paradoxical embolic event.

We respectfully disagree with the reviewer. As noted by the reviewer, the data "provides insufficient support that PFO closure is preferable to medical therapy". Given this and limitations of the available RCTs there is an urgent need for further RCTs. With regard to the issue of what patients should be offered, see our response to comment #3.

The aforementioned manuscript by the reviewer (Circulation 2012) is an observational study not an RCT. We have addressed the results of observational studies in the introductory section of the manuscript.

10. The last figure may be dropped as the selection process is sufficiently described in the text.

This figure is now included only as an appendix figure.

Reviewer 2

1. In the weeks before this manuscript was submitted, a metaanalysis of the same 3 studies was published, JACC Cardiovasc Interv. 2013 Oct 10, by a different group. The conclusions were in direct contrast to the authors of the current manuscript. I would recommend to current authors that they reference the published manuscript, and that they change their paper to discuss how their methodology differs from the published metaanalysis and supports their conclusions of no benefit.

As noted by the other reviewers there are several other analyses that have been published including the one mentioned here. A primary difference between the above analysis and ours is that they appear to use a composite endpoint (as defined in each RCT) for the primary outcome – this is problematic as in 2 of the studies it includes the softer endpoint of TIA (in addition to stroke and mortality). In addition it used a generic inverse variance method to analyse the data. In general, this method should only be used when it is not possible to enter data in the usual form of dichotomous, continuous or individual patient data to ensure that the reader is able to see the data by treatment group whenever possible (http://cfgd.cochrane.org/search/google-appliance/generic%20inverse). As this is not the case, their rationale for this choice is unclear. Finally, this and other reviews make no effort to perform a systematic assessment of the quality of the available evidence as we have.

We note these differences in our revised manuscript as follows: "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 endpoints18-20. 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." See page 21, para 2.

Reviewer 3

1. This manuscript clearly involved a great deal of work and it does allow a good comparison of the three RCTs. It appears to lack an overall appreciation of the challenges in clinical trials and the inherent limitations.

A fundamental issue is if a trial is done as well as the investigators can manage, but has limitations leading to risk of bias, should one increase confidence in the results because the investigators tried as hard as they could. We believe one should not.

2. It proposes a subgroup analysis of the results based on the device used, shows statistically significant reduction of the risk of recurrent stroke with the Amplatzer device and then goes on to dismiss the results based on questionable reasoning.
The paper appears biased in this regard.

The literature is replete with methodological studies demonstrating the dangers of subgroup analysis and offering criteria for judging the credibility. We have applied widely accepted criteria in judging the credibility of this analysis. We found the hypothesis did not meet the criteria as follows: “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 “ (See page 20, para 3).

3. It fails to mention the lack of RCTs in the arena of medical therapy for secondary prevention of stroke/TIA in the presence of PFO.

We note this in the revised manuscript as follows: Unfortunately there have been no RCTs adequately comparing specific antiplatelet or antithrombotic therapies for this indication. (Please see page 22, para 1).

4. It proposes a trial design based on medical therapy chosen on the basis of patient preferences. This is a novel and highly odd approach to getting a scientifically credible result and adds new biases.

We agree with the reviewer that this would be novel approach but in fact it is just a more rigorous application of the approach used in two of the three studies included in this analysis where medical therapy was left to physician discretion (which we hope but can’t be sure incorporated patient preferences). Data on rationale for specific therapies was not provided. In 2 of the 3 studies no data was provided on dosage, adherence to therapy, or whether patients remained on the same therapy throughout the study. Therefore, our suggested approach would represent an improvement over the previously utilized methodology. In addition we also suggest as an alternative a more standard approach – a 3 arm study comparing PFO closure with antiplatelet therapy or anticoagulant therapy.

5. This is one of perhaps 6 meta-analyses using the same data from the three trials and arriving at different conclusions.

Please see our response to reviewer 1 (comment 1) and reviewer 2.

6. The critiques of the three trials (Figure 1?) need more explanation of how these grades were derived and whether their grades were valid.

Figure 1 is a standard Risk of Bias tool derived from the Cochrane Group. See Risk of Bias and Confidence in Effect Assessment (see page 9, para 3). As noted in the Risk of Bias subsection in the Results (see page 15, para 3-4) and in Figure 1 the primary concern regarding bias was incomplete outcome data. We clarify this further in the revised manuscript by repeating our observation that 13.5% of patients were lost to followup with loss to f/u being 2-fold greater in the medical arm versus the intervention arm. In addition, and as noted, data on patient adherence with medical therapy was not provided.

In figure 1 we also indicate a questionable issue regarding lack of blinding. It is understandable that none of the studies were blinded (as this would have required a sham intervention). While this likely contributed to the differential follow-up rate we felt this was unlikely to impart bias with respect to outcomes given use of clinical events committees for each study. This was noted in the manuscript (see page 15, para 3). Therefore we did not rate down for bias in figure 1 for lack of blinding.

The only other issues of note in figure 1 are a) the Closure 1 study did not clearly specify that the clinical events committee was blinded to treatment allocation and b) the RESPECT study did not clearly specify that random sequence generation was utilized. Given space constraints and that we did not rate down for these issues we don't discuss them in the text.