Author’s response to reviews

Title: The effects of rhythm control strategies versus rate control strategies for atrial fibrillation and atrial flutter. A protocol for a systematic review with meta-analysis and Trial Sequential Analysis

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Author’s response to reviews:

Dear Editor,

Thank you for your very positive response, and for your attention to the reviews of our manuscript.

After careful consideration, we want to change the title to “The effects of rhythm control strategies versus rate control strategies for atrial fibrillation and atrial flutter. A protocol for a systematic review with meta-analysis and Trial Sequential Analysis.” We believe that rhythm control in most identified trials should be considered as the experimental intervention and we, therefore, suggest to change the order of the interventions in the title and in the manuscript.

Additionally, after careful discussions, the author group have decided to merge the two originally planned assessment time points into one (“We will for all outcomes use the trial results reported at maximal follow-up. However, if the trialists report results at multiple time points, we will primarily use the results reported at the time-point closest to 24 months.” See page 19 in the revised protocol with track changes). The reason is that the two originally planned assessment time points will often be very similar and the largest previous trials have used a mean assessment time-point of approximately two years as their primary time-point.
We have carefully gone through the peer review comments and revised the manuscript accordingly.

We have attached the point-to-point responses to the editorial comments down below.

We have also attached the revised manuscript both with and without track-changes.

We hope that we have modified the manuscript to your satisfaction. If you continue to see issues we have overlooked or we still need to engage, please let us know.

Thanks again for your close attention to this manuscript.

On behalf of the authors,


Comments from peer reviewer

Reviewer #1: The review protocol presents a thorough and well thought out plan for conducting a systematic review of the evidence comparing rate and rhythm control strategies in the treatment of atrial fibrillation. A high degree of methodological rigour is evident from the plan for the statistical analysis, and reasonable subgroups have been identified. I have the following comments that the authors may want to consider:

Our response: We thank the reviewer for these very positive comments!

1- The authors have already identified one of the main difficulties with this review, which is that the outcomes of AF related mortality and stroke are strongly affected by the choice of antithrombotic therapy, so any differences in the antiplatelet or anticoagulant treatment used between the arms of trials may confound the effect of rate or rhythm control interventions, and any between-study differences may increase the heterogeneity of the pooled analysis. Careful extraction and consideration of co-interventions is therefore warranted.

Our response: We strongly agree that differences in the antiplatelet or anticoagulant treatment between the groups should be taken into consideration when interpreting the review results. We have, therefore, added a subgroup analysis assessing "duration of anticoagulation therapy: anticoagulation therapy until sinus rhythm for at least 4 weeks, anticoagulation therapy for at
least 12 weeks, or anticoagulation therapy until end of follow-up’ (see page 32 in the revised protocol with track-changes). Further, we have planned a thorough assessment of the statistical heterogeneity and we will ultimately decide if meta-analysis should be avoided if the statistical heterogeneity is substantial (see page 28-29 in the revised protocol with track changes). Hence, we will investigate if different recommendations for anticoagulation therapy affect the results of the outcomes.

2. The analysis is also complicated by the fact there are multiple different types of rhythm and rate control interventions, rather than each of these being one single drug, and so the decision of the authors to carry out subgroup analysis by type of rate or rhythm control treatment is sensible. The wording of the subgroup analysis implies that this will compare different types of each intervention to each other (i.e. one type of rate control intervention to another type, e.g. beta blockers vs calcium channel blockers), could the authors clarify whether this is the plan, or whether this subgroup analysis will involve comparing a single type of rate control intervention to single type of rhythm control intervention (e.g. beta blockers vs amiodarone). If it was the former than the search would have to identify studies comparing treatments within each group as well as those comparing these treatment groups to each other. As an aside, depending on the number and heterogeneity of the studies identified, the former approach may also present a good opportunity to carry out a network meta-analysis.

Our response: We thank the reviewer for this important comment, and we agree that this had to be clarified. We have now in our revised protocol changed the name of the subgroups: 1) comparison of individual rate control interventions with any rhythm control intervention; 2) comparison of individual rhythm control interventions with any rate control intervention (see page 32 in the revised protocol with track-changes). The formal test for subgroup differences (Review Manager 5.3) compare the effects between trials belonging to one subgroup to the effects of trials belonging to other subgroups. Hence, subgroup analyses are, by definition, not strict head-to-head comparisons (as the ‘rhythm control versus rate control comparison’) and we should therefore not include/search for trials comparing different rate control interventions. We agree that it might be warranted to conduct a network meta-analysis and we will consider this in the future. We have now added these considerations. Thank you.

3. The statistical analysis plan is quite conservative, with an apriori decision being made that conclusions will only be based on studies with a low risk of bias, the meta-analysis model will be chosen based on which gives the lowest effect size, etc. While the authors are no doubt familiar with the literature in this area, there is a risk that this could lead to valuable evidence being omitted from the primary analysis that would change the conclusion if it was included. It might be more advisable to consider reporting the meta-analysis of all trials as
the primary result, and carry out subgroup analysis by risk of bias. Equally it might be advisable to await an analysis of the level and likely causes of heterogeneity within the pooled analysis of studies before deciding on the most appropriate model to use for the meta-analysis. However, these choices are ultimately a matter for the authors, and the approach they describe in the protocol has the advantage of decreasing the risk of type I errors.

Our response: We agree that our statistical analyses are conservative. However, as also stated by the peer reviewer, we find this approach to be the most correct, as it decreases the risks of type I and type 2 errors. Furthermore, large meta-epidemiological studies have shown that trials at high risks of bias tend to overestimate benefits and underestimate harms of experimental interventions [1-7]. We will, therefore, suggest not changing our approach. Moreover, in our forest plots, people can still see the naïve confidence intervals and the naïve P values of the comparisons, so readers wanting to apply a less conservative approach can do so freely.

We thank the reviewer for noticing that we have not clarified how we will investigate possible heterogeneity. We have now clarified that: “We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly assess the presence of statistical heterogeneity by Chi2 test (threshold P < 0.10) and measure the quantities of heterogeneity by the I2 statistic [8, 9].

We will follow the recommendations for threshold by the Cochrane Handbook for Systematic Reviews of Interventions [10]:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: may represent considerable heterogeneity.

We will investigate possible heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided [10] (see page 28-29 in the revised protocol with track-changes).


