Reviewer’s report

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

Version: 0 Date: 22 Dec 2016

Reviewer: Patrick Moran

Reviewer's report:

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:

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.

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.

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.

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