Format for ANSWERING REVIEWERS

August 15, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format.

Title: Antithrombotic treatment in chronic heart failure and sinus rhythm: systematic review.

Author: Daniel Caldeira, Inês Cruz, Rita Calé, Cristina Martins, Helder Pereira, Joaquim J Ferreira, Fausto J Pinto, João Costa.

Name of Journal: *World Journal of Meta-analysis*

ESPS Manuscript NO: 11405

The manuscript has been improved according to the suggestions of editors and reviewers:

1. Format has been updated

2 Revision has been made according to the suggestions of the reviewers:

Comment 1: The manuscript "Lack of benefit of antithrombotic treatment in patients with CHF and SR" is a systemic review and metanalysis of two studies adressing antitheombotic drugs in patients with CHF and sinus rhythm. The manuscript is well written and adds new points to the discussion of anticoagulation

Answer 1*: No answer.*

Comment 2: Comments to "Lack of benefit of antithrombotic treatment in patients with chronic heart failure ans sinus rhythm....." The study has several serious limitations: - from a total of 196 references only 2 studies met the inclusion criteria. Therefore the additional information of a meta-analysis is limited. This especially is true for the ASS arm evaluated only by one study.

Answer 2: *We intended to evaluate the best available evidence about the topic. And there are only 2 trials. Meta-analysis in this case reinforces the recommendation for not to prescribe any antithrombotic drugs for patients without any other established conditions that require antithrombotic treatment. The meta-analysis does not add new information but strengthens the lack of efficacy of any antithrombotic drugs with the actual evidence.*

Comment 3: The included databases may not be sufficient, at least EMBASE should also be included. - the most important points of the search strategy including keywords, MeSH-terms and study filters have to be provided within the manuscript

Answer 3: *According to CRD guidance for Systematic Reviews "Due to the diversity of questions addressed by systematic reviews, there can be no agreed standard for what constitutes an acceptable search in terms of the number of databases searched". EMBASE would increase the number of record obtained but we are pretty confident that the sensibility would not change. Strategy of search is outlined in the Supplementary File.*

Comment 4: The baseline characteristics of the included studies and their patients have to be listed in a table including the PICOS of the included studies, furthermore in detail age, gender, ejection fraction and other echo characteristics, underlying heart diseases, the most important concomitant risk diseases (e.g. diabetes, hypertension, renal failure, COPD etc.) other medications, interventions like ICD, CRT. All these conditions potentially have influence on the prognostic outcome. Potential bias arising from this should be evaluated and discussed.

Answer 4: *We agree that it is easier to retrieve information from a table, however we would be duplicating the text's information. There for we added information about comorbidities in the text. The use of devices was not reported.*

Comment 5: A major limitation of the analysis are the selected endpoints. As stroke is the primary endpoint, this may seriously be influenced by death, which clinically has priority. Moreover, in time to first event analysis it also statistically has priority. The presented analysis therefore may seriously be biased by competing risks. The problem of competing risks also has to be faced with respect to all other secondary endpoints, especially the composite.

Answer 5: *The biological rationale for antithrombotic drugs in heart failure relies mainly on the prevention of embolic events (fatal and non-fatal) as in atrial fibrillation (AF). We agree that death has clinical priority but we believe that our approach is acceptable focusing on the AF example (and is shared by others: PLoS One. 2013 Oct 25;8(10):e77694.). Now we have stated that stroke was fatal or non-fatal.*

Concerning the competing risk of mortality in time to first event analysis: the trials reported the raw data for each outcome and for the composite outcome, therefore such bias risk is not high.

Comment 6: - it also is unclear how sinus rhythm has been proved in the included studies. Many of these patients may have had unrecognized paroxysmal atrial fibrillation periods - it is unclear how "worsening of heart failure" has been defined - the trend of an increased risk by aspirin treatment with respect to the composite may be a random phenomenon under these conditions, and all potential explanations are highly speculative.

Answer 6: *Yes. We agree that unrecognized paroxysmal atrial fibrillation periods can bias our results. However it would bias in favour of antithrombotics drugs. However we acknowledged in our revision.*

Our discussion included a paragraph about ACE inhibitors and Aspirin role in the potential heart failure worsening, and the role of WARCEF study in the clarification of this topic.

Comment 7: This also should be discussed from the background of patients with ischemic cardiomyopathy, who normally are advised to take ASS in low doses.

Answer 7: This topic was discussed in Discussion "ESC Working Group on Thrombosis corroborates our conclusions.[29] This consensus document stated that warfarin and acetylsalicylic acid should not be routinely used for thromboprophylaxis in patients with systolic heart failure and sinus rhythm, in the absence of concomitant comorbidities with clear indications for anticoagulation (e.g. atrial fibrillation) or acetylsalicylic acid (e.g. documented coronary artery disease)." And Limitations "Furthermore the dosage of acetylsalicylic acid used in this trial was considerably higher than recommended.[33]"

3 References and typesetting were corrected

Thank you for considering our manuscript in the *World Journal of Meta-analysis*.

Sincerely yours,

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