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25th November 2019

Dear Editor,

Please receive our revised manuscript of the invited review entitled: 'Do Age-associated Changes of Voltage-Gated Sodium Channel Isoforms Expressed in the Mammalian Heart Predispose the Elderly to Atrial Fibrillation?' for further consideration for publication in the journal World Journal of Cardiology by the authors Isaac, Cooper, Jones and Loubani.

Thank you for the summarised comments from the 3 peer-reviewers. We have given comprehensive answers to the questions in a point-by-point manner in our response and edited the manuscript as appropriate with tracked changes for resubmission.

Hopefully with the changes made you will be happy to continue with the full publication of this work.

Best wishes and our thank you for your continued handling of our manuscript,

Yours Sincerely



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RESPONSE TO REVIEWERS FROM THE AUTHORS OF MANUSCRIPT NO: 52295

Title: Do Age-associated Changes of Voltage-Gated Sodium Channel Isoforms Expressed in the Mammalian Heart Predispose the Elderly to Atrial Fibrillation?

Authors: Emmanuel Isaac, Stephanie M Cooper, Mahmoud Loubani and Sandra A Jones

We have given comprehensive answers to the questions in a point-by-point manner in our responses below, and edited the manuscript as appropriate with tracked changes for resubmission. We sincerely hope that these amendments are to your satisfaction.

Reviewer #1: RESPONSE TO COMMENTS:

Dear reviewer #1, thank you for your comment. We have now included more text demonstrating an appreciation of the current pharmacological approach to the treatment of AF in everyday clinical practice.

Reviewer #2: RESPONSE TO COMMENTS:

Dear Reviewer #2, thank you for your comments. We trust our responses clarify your questions raised regarding the work presented in this review for publication.

Firstly, regarding the grammatical errors, We would like to thank you for recommending the application '*Grammarly*': We have now corrected the grammatical mistakes and typos it identified.

Secondly, your point that too much focus was on the two drugs, Ranolazine and Irbesartan, has been taken into consideration and amendments made. We have included text demonstrating an appreciation of the current pharmacological approach to the treatment of AF in everyday clinical practice, with reference to agents within the NICE guidelines for the management of AF for example Amiodarone and Digoxin, then proceeded to build upon this story within our review.

This section of the paper is specifically focused on sodium channel blockade as a novel therapeutic strategy. As your comment suggests, we have compiled a detailed table of all available sodium channel blockers, summarised their mode of action and clinical use. This section continues to expand specifically with Ranolazine, as this is reflective of current literature as the most studied agent as well as the most effective, noteworthy and novel approach in treating AF through sodium channel blockade. Many of the papers cited compares Ranolazine with traditional agents such as Flecainide and Amiodarone, building upon traditional knowledge regarding therapeutic approaches to AF.

With regards to the focus on Irbesartan in the prevention of AF: We appreciate that other drugs have anti-fibrotic effects however evaluation of all available agents which have anti-fibrotic effects may be beyond the scope of this review and might be slightly tangential. Irbesartan is discussed uniquely and in detail due its relevance with regards to sodium channel remodelling and efficacy in the elderly both of which are central focus points of the paper. The discussion of Irbesartan falls under the section of 'Prevention of Atrial Fibrillation' where non-pharmacological lifestyle approaches have also been discussed in depth, offering a holistic perspective on the issue.

Reviewer #3: RESPONSE TO COMMENTS:

Dear reviewer #3, thank you for your comments. We have investigated use of the PRISMA and found that this protocol is recommend when conducting a full-scale systematic review, which was not the aim of this current manuscript. As such, PRISMA was not employed and we have not included a checklist. In response to your comment regarding the expansion of figure legends, this has been acted upon and a more detailed description of the figures given. Also, sentence structure has been revised where we thought necessary as recommended.

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02/01/2020

Dear Ze-Mao Gong

Science Editor, Editorial Office

Baishideng Publishing Group Inc

Re: World Journal of Cardiology Manuscript Revision-Manuscript NO: 52295

Dear Ze Mao Gong

Thank you for your continued handling of our manuscript.

Regarding the missing references for the figures included these have now been included-apologies for this oversight.

Regarding permission certificates for the tables and figures, we were under the impression that permission certificates were only required if figures were directly reproduced from a journal. All the figures within this manuscript have been adapted and edited.

Table 1: This table collating the information on voltage-gated-sodium channels is not a reproduction rather a collection of information from a published review.

Figure 1: This has been adapted from the paper titled, "Emerging clinical role of ranolazine in the management of Angina" published in an online open-source journal Dovepress. I've had a look at the permissions section from this publisher which states the following:

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Figures 2 & 3: These illustrations adapted from a review published in JACC clinical electrophysiology. Under their permissions section (<https://www.elsevier.com/about/policies/copyright/permissions>)

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Table 2: Similar to table 1, this is a collection of information from a larger body of information published in an open source online publication by Circulation that has been adapted.

Given this, could you please clarify if all of these materials require a formal request for permission certificates from the publishers?

Many thanks for your time.

Yours Sincerely



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