Reviewer’s report

Title: Targeting the DPP-4-GLP-1 pathway improves exercise tolerance in heart failure patients: A systematic review and meta-analysis

Version: 0 Date: 09 May 2019

Reviewer: David Webb

Reviewer's report:

The authors present a systematic review and mixed methods meta analysis of exploratory data from four RCTS. The research question; whether drugs targeting the incretin system may have an effect on a) exercise capacity and b) oxygen consumption in patients with heart failure is both interesting and potentially important, as we do not fully understand the actions of these drugs beyond glucose lowering.

In reviewing this manuscript I refer the authors to the correct reference for the PRISMA checklist referring to systematic reviews: Moher D. Ann Int Med 2009; 151;264-269.

I have a number of comments / suggestions in respect to this work:

1) Introduction

Whilst I agree with the authors sentiment that progress with treating HF and its outcomes (especially in DM) is not as good as other CVDs and better treatments are urgently needed, I did not think this point was particularly well articulated in the introductory paragraph nor the link between physical activity, and increased oxygen capacity/reserve as a potential treatment for HF. Supportive evidence for the proposed research question was relatively limited (there is GLP-1 data on exercise capacity etc.. in non HF patients for example) and the statement that the pharmacological effects of GLP-1 receptor analogues and DPP-IV inhibitors are identical is not necessarily correct. Indeed there is some speculation that certain drugs from these classes these may actually impair cardiac function eg. saxagliptin in the Savor-TIMI 53 trial NEJM 2013; 369:1317-1326.

2) Methods

Is the study protocol available and / or registered on PROSPERO ? - this would enable a robust assessment of potential reporting bias.

Whilst I accept including an exhaustive list of MESH search terms is tedious I would recommend including some reference to how the search was conducted in the main manuscript. Good to see the date of search was included.

I am slightly confused by the authors eligibility criteria - why were comparator studies agents other than insulin glargine excluded, was this done a priori?

Presumably the primary outcome of these studies was not necessarily 6MWT or peak O2 consumption - consideration of this as a limitation of adopted approach needs to be considered

There is some interchange of important measures in the text - eg. are exercise capacity and tolerance the same?
It would be useful to give the reader some context of the activity measures - what are 6MWT and peak O2 consumption measures of exactly and why where they chosen? Are there other measures which are commonly utilised?

3) Results
PRISMA flow chart is included and numerically correct. Statistical analyses performed appear sound given the studies obtained from the search
Tests of heterogeneity were highly statistically significant yet not really mentioned in either the results of discussion sections
The data extraction table pertaining to Arturi et al doesnt mention the DPP-IV inhibitor Sitagliptin - but the forest plots do.
I am not so sure that this is quite the way to determine the safety of these drugs in patients with heart failure and not too much can be inferred from this particular search - for me this is overstated

4) Discussion
This section needs some work around spelling and is grammatically challenged at times. It really reiterates the introduction and results section without really engaging in detail either the possible mechanisms for the findings, their implications, or future directions for research. The limitations section could be expanded upon.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.
Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
I am able to assess the statistics
Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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