Author’s response to reviews

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

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Author’s response to reviews:

Dear professor Michael Schwarzer

Thank you for your attention to this manuscript. I wirted an e-mail to you to ask for your opinions whether I should remove the safety outcomes (professor David Webb’s comment) 2 weeks ago but do not receive responses. Since I had completed the revision of this manuscript for 1 week, I think I should hand back now. I apologize that I do not wait for the responses, but I have written down all my views why I don’t want to remove this part in this cover letter to respond to professor David Webb’s comments. I think the nice reviewers will like to see the revised manuscript as soon as possible.

The improvement of English language was revised with the help of Springer Nature Author Services and all the track changes were preserved. Since there were many track changes that will make the manuscript difficult to understand, we upload a manuscript (PDF) with all track changes as supplement 4 to show the revised areas.

I ensure all changes to the manuscript are indicated in the text by highlighting or using track changes and do not add, remove, or change the order of authors. I also revised manuscript conforms to the journal style

Dear professor Tien Dung Nguyen

Thanks for your comments. We have carefully revised the manuscript with the help of Springer Nature Author Services and all the track changes were preserved. Since there were many track changes that will make the manuscript difficult to understand, we upload a manuscript (PDF)
Dear professor David Webb

Thank you for your attention to our manuscript. For the language problem, we have carefully revised the manuscript with the help of Springer Nature Author Services and all the track changes were preserved. Since there were many track changes that will make the manuscript difficult to understand, we upload a manuscript (PDF) with all track changes as supplement 4 to show the revised areas. Now I answer the comments point by point.

1. The permeating message that DPP-IV/ GLP-1 activation could somehow be used as a HF remedy through improved exercise tolerance is still not really justified. This is important since all of the studies included in this meta analysis didn't demonstrate much effect on cardiac function anyway. Why cant it just be stated that DPP-IV / GLP-1 possible pleiotropic actions may be to improve exercise tolerance in HF and possibly other populations - justification for this is...and the significance of which is unknown.

2. Whilst now acknowledging that all of the studies reported 6MWT or peak O2 as exploratory outcomes - the primary outcome of these studies being cardiac function measures - this could be more explicit and the limitations of using this type of secondary data discussed.

Answer: I think these 2 comments can be answered together. Actually, we are not going to recommend DPP-4 inhibitor/GLP-1 Ra to HF. I think need to talk about why we designed this project.

At the beginning, we notice HF is one of the leading causes of death. Patients may have impairment of heart function and most of the studies about HF have focused on heart function or mortality. According to the guideline, dyspnœa and fatigue are the most significant features of HF and can cause exercise intolerance. However, very few trials focused on this, which contributes to the decrease of quality of life. Thus, this project was originally designed to investigate the effect of DPP-4 inhibitor/GLP-1 Ra on patients’ daily life. Since there had no data about the improvement of dyspnœa and fatigue, thus, our primary outcome was exercise tolerance (it has specific data and standard measurement). We highlighted some sentence as purple and we think it can help reader to better understand our aim.

The reason why we choose DPP-4 inhibitor/GLP-1 Ra is these studies were all published within 5 years. The new thing is more interesting than the old. Moreover, some evidences have demonstrated DPP-4/GLP-1 activation benefit to exercise tolerance and heart function. We have highlighted the evidences as orange. We did not investigate heart function because HF can be divided into 3 categories (preserved, reduced and mid LVEF), patients with preserved LVEF have normal ejection function. And this project was designed to study the effect of patients’ daily life. Additionally, previous meta-analyses have done it(they measured LVEF). Thus, heart function is not a necessary outcome in this work.
The primary outcomes of the eligible trials were not exercise tolerance. As I have mentioned above, heart function in this project was not a necessary outcome. 6MWT and peak O2 consumption are the standard methods to measure exercise tolerance, we think these data can be used and the aim of this project needed them.

In the conclusion section, we said “it may be a good choice for T2DM patients with HF” without other diseases. Here are our considerations. This project was designed in HF patients with or without diabetes. DPP-4 inhibitor/GLP-1 Ra was the anti-diabetes drug and have no indication in HF. Furtherly, we did not know whether the cause of exercise intolerance was the same among the diseases. But we also encourage further investigation to other diseases (highlighted as purple in the abstract and discussion section).

I acknowledge this meta-analysis do not have a perfect result. But we processed and got the result all according to the Cochrane Hand Book and PRISMA statement. More importantly, we reminded people should pay more attention to patients’ quality of life and have demonstrated DPP-4-GLP-1 pathway may be a potential target. We also reminded investigators that HF with prior myocardial infarction may benefit more from the treatment and serum DPP-4/GLP-1 may be a predictor of treatment efficacy. These may worth further investigations. I think some readers may interested in them.

3. Unfortunately there is still no indication of which studies measured 6MWT or peak O2 consumption or the importance if any of that. No peak o2 consumption data was presented anyway - although at least one study reported it.

Answer: In the result section, we have reported which studies measured the outcomes by using references. I highlighted it as red. Also, the data of peak O2 consumption was added. I think the details of how to apply 6MWT or peak O2 consumption was not necessary because this is a meta-analysis but not a clinical trial.

4. As mentioned previously the inclusion of a table pertaining to mortality and SAEs is not relevant to the research question. Whether DPP-IV /GLP-1 RA are safe for use in HF is a pertinent but different point. Consideration should be given to removing this highly selective data.

Answer: Mortality and SAEs contributes to QoL a lot. Thus, I think I should not remove this part. I totally agree with your point that this outcome is a highly selective data. But I think if someone wanted to further investigate the use of DPP-4 inhibitor/GLP-1 Ra in exercise intolerance patients, he/she may want to find the safety outcomes. I have revised the sentences (highlighted as blue) to tell the readers I could not draw a conclusion that the treatment was totally safe, they should consider by themselves. Since the readers may be the doctors/experts/students in this field, I think it does not a problem.

The following is my own opinions about this paper.
There are many clinical trials and meta-analyses that focused on traditional outcomes like mortality, heart function or other organ functions but take less care about patients’ quality of life.
Sometimes I think about the question that whether longer life means better enjoy their lives, especially for patients. Thus, in this paper, I set the outcomes all related to daily life. I am very grateful I meet the nice reviewers like you that help me a lot. Thank you for your attention to this work again.