Author’s response to reviews

Title: Effect of liraglutide on blood pressure: a meta-analysis of liraglutide randomized controlled trials

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Author’s response to reviews:

Dear editor and reviewers,

Thank you for your letter dated 02 Sep 2018, and for the reviewers’ comments concerning our manuscript "Effect of liraglutide on blood pressure: a meta-analysis of liraglutide randomized controlled trials" (BEND-D-18-00260). Those comments are all valuable and very helpful for revising and improving our paper, and have important guiding significance to our further research. Based on your comment and request, we have made modification on the original manuscript. A revised manuscript with the corrections red-marked was attached for easy check/editing purpose and for your approval.

The main corrections in the paper and the response to the reviewer’s comments are as follows. Should you have any questions, please contact us without hesitation.

Editor Comments: All the reviewers and this Editor agrees that the major limit of this meta-analysis is the large heterogeneity of the studies, which may significantly affect the relatively small effect of liraglutide on systolic blood pressure. While there are no accepted guidelines to decide when a meta-analysis should or should not be completed, some actions to explore and to minimize the heterogeneity should be used (subgroup analysis, limitation of study eligibility, etc.). This is particularly relevant in this case as the clinical effect of liraglutide found here is very small.

Response: It is really true as editor suggested that some actions to explore and to minimize the heterogeneity should be used. We have restricted the limitation of study eligibility (Methods section, line 15, page 4 and line 18, page 4). We exclude the LEADER trial as a result of its unstable pharmacological therapy throughout the trial. Also, Tonneijck 2016 trial demanded subjects to drink 10 mL/kg tap water for stimulating diuresis, which may impact on volume load.
We conducted subgroup analysis defined by the dose of liraglutide and duration of intervention (Results section, line 23, page 17).

Stefano Taddei (Reviewer 1):

1. Comment: The authors do not report how blood pressure was measured in the selected trials and whether the different methods were comparable.

Response: As Reviewer suggested, we have added a column of measurement of BP in Table 1 (Results section, page 7-12).

2. Comment: Baseline blood pressure values are not reported. This is another crucial bias since the degree of blood pressure reduction is usually dependent on basal values.

Response: It is awfully reasonable as Reviewer suggested that the baseline blood pressure is a crucial influencing factor of the degree of blood pressure reduction. We have added a column of baseline SBP and DBP in Table 2 (Results section, page 12-16). However, we are not able to accurately assess the comparability of studies as we cannot obtain the original data.

3. Comment: Concomitant treatment is not reported. How many diabetic patients were on antihypertensive pharmacological treatment?

Response: We are very sorry for our negligence of not reporting concomitant treatment. We have added a column of antihypertensive pharmacological therapy in Table 1 to report concomitant treatment of hypertension (Results section, page 7-12). However, most of trials do not report the specific number of subjects who were on antihypertensive pharmacological therapy. We contacted the authors to ask for original data but without any reply.

4. Comment: What is the clinical significant of such results?

Response: The UK prospective diabetes study found that tight blood pressure control in patients with hypertension and type 2 diabetes substantially reduce the risk of death and complications due to diabetes. The ADVANCE study found that tight blood pressure control reduced the risk of macrovascular complications. Our meta-analysis showed that SBP was reduce, by approximately 5 mmHg, which may be a cardioprotective benefit. We have made correction according to the Reviewer’s comments (Discussion section, line 9, page 20).

Alon Eisen (Reviewer 2):
1. Comment: Overall the Heterogeneity of all studies is moderate (I2=55%). As the authors mention this might be due to several reasons. The main reason might be the duration of treatment. Since blood pressure is a continuous variable which changes with time it is very important to stratify the patients by time of treatment. As the authors reported they stratified the patients to <=1 year of treatment. This exploration should be shown also in a forest plot and specify the heterogeneity. With this regards, It is quite surprising that the effect of liraglutide on SBP is diminished when including only studies > 1 year of treatment (the majority of patients are from the LEADER trial which demonstrated a reduction in SBP).

Response: To minimize the heterogeneity, we have restricted the limitation of study eligibility (Methods section, line 15, page 4 and line 18, page 4) and conducted subgroup analysis. The purpose of LEADER trial is to explore the cardiovascular safety of liraglutide, requiring investigators to adjust antihypertensive pharmacological treatment based on individual patient need to a target blood pressure (130/80 mmHg). Tonneijck 2016 trial demanded subjects to drink 10 mL/kg tap water for stimulating diuresis, which may impact on volume load. Consequently, the LEADER trial and Tonneijck 2016 trial are excluded. We conducted subgroup analysis defined by the dose of liraglutide and duration of intervention (Results section, line 23, page 17).

2. Comments: The discussion should be significantly improved. The authors must discuss mechanisms of action, and clinical implications for their findings. The discussion should include other insights such as the effect of liraglutide on renal outcomes and whether this might be explained by the effect on SBP? the effect of liraglutide on weight loss and the relationship to blood pressure? Also discuss the results of BP in the LEADERS trial which is the main contributor to this meta analysis.

Response: We have improved the discussion according to the Reviewer’s suggestion (Discussion section, line 9, page 20). Whereas, to minimize the heterogeneity, we restrict the limitation of study eligibility. We have to exclude the LEADERS trial, because the trial require investigators to adjust antihypertensive pharmacological treatment based on individual patient need to a target blood pressure (130/80 mmHg), which may contribute to the heterogeneity.

3. Comment: Can the authors extract the data and examine the effect of liraglutide on BP in patients with/without hypertension at baseline?

Response: Special thanks to you for your good comments. However, almost all of trials do not report the specific number of patients with/without hypertension at baseline. We contacted the authors to ask for original data but without any reply. We are very sorry for our inability.

4. Comment: All abbreviations should be defined when first mentioned in the text (eg. SBP, DBP)

Response: We are very sorry for our incorrect writing. We have checked our manuscript earnestly for any abbreviation.
5. Comments: An English grammar editing may be helpful.
Response: We have requested the American Journal Experts to edit our English grammar.

6. Comments: To table 1, please add a column of the phase of the study (phase 1-phase 4). This will help the reader to understand how many clinical trials were included.
Response: We have added a column in Table 1 according to the Reviewer’s comments (Results section, page 7-12).

Thanks again for your good comments.