

Response to the reviewers

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We greatly appreciate the opportunity to revise of our manuscript and we greatly thank the reviewers for very important and constructive suggestions. Now, we have revised the manuscript based on the reviewer's suggestions.

To reviewer 1:

Reviewer 1's comments:

Thank you for the very nice review of literature pertaining to the effects of PPIs on glycemic control. The article is very well referenced and written. The one recommendation I would make would be to discuss the clinical significance of A1C reductions observed in studies to date versus A1C reductions that may be expected with currently available pharmacotherapeutic options for T2DM.

Response to the reviewer 1:

Thank you for your very important and constructive comments.

“The one recommendation I would make would be to discuss the clinical significance of A1C reductions observed in studies to date versus A1C reductions that may be expected with currently available pharmacotherapeutic options for T2DM”.

This is very important suggestion. Based on the published data to date, the degrees of the reduction of HbA1c by PPIs therapy in the studies with positive results appears to be approximately 0.6-0.9%. I think that this is somewhat milder or similar compared with those by recent available anti-diabetic drugs such as DPP4 inhibitors or SGLT 2 inhibitors. I believe that the effect of PPIs for glycemic control is probably moderate and that therefore PPIs may have the potential for clinical benefit on glycemic control in patients with T2DM. I described this content in “The effect of PPIs on glycemic control in patients with type 2 diabetes: results of clinical studies” section as follows:

P13, L5 in revised manuscript: **“Based on the published data to date, the degrees of the reduction of HbA1c by PPIs therapy in the studies with positive results appears to be approximately 0.6-0.9%. This is somewhat milder or similar compared with those by recent available anti-diabetic drugs such as dipeptidyl peptidase-4 (DPP4) inhibitors [51] or sodium-glucose co-transporter 2(SGLT2)**

inhibitors [52]. This suggests that the effect of PPI for glycemic control is probably moderate and that therefore PPI may have the potential for clinical benefit on glycemic control in patients with T2DM.” is added.

In addition, I added ref. 51 and 52 as new reference. Therefore reference number 51-72 in original manuscript is changed to 53-74, respectively as showed in boldface in revised manuscript.

To reviewer 2:

Reviewer 2's comments:

This is a nice review of the use of PPIs in the treatment of T2DM. There was a good explanation of the patho and good flow of the article. I love the figure. I would recommend just putting one author in the trial table, be specific about treatment, add outcome measures and then key findings (which is your A1c) and safety. I would add p values too. In the trial section, consider expanding a bit on a few of the trials, vs a line or two about many trials. I would use the abbreviation T2DM throughout the article. Good job overall.

Response to the reviewer 2:

Thank you for your very important and constructive comments.

“I would recommend just putting one author in the trial table, be specific about treatment, add outcome measures and then key findings (which is your A1c) and safety. I would add p values too”.

Thank you very much for your valuable suggestion. According to your suggestion, I entirely revised (changed) the Table 1. I put just one author (left side) in the Table. And I added “Outcome measures”, “Key finding”, and “Safety information”. I also added P values in the respective needed portions.

“In the trial section, consider expanding a bit on a few of the trials, vs a line or two about many trials. I would use the abbreviation T2DM throughout the article”.

Again, thank you for your very important suggestion. According to your suggestion, in trial section, I described in more detail in some studies as follows.

P9, L16 in revised manuscript: **“When these patients were assigned to two groups by the treatment of diabetes, those taking insulin and concurrent PPIs had better**

glycemic control, compared with those taking insulin but not PPI (-0.8% reduction, **P =0.022**).” is added.

P10, L6 in revised manuscript “**The increase of the differences was observed in patients treated with insulin and in those treated with combination of PPIs and GLP-1 based therapy [28].**” is added.

P10, L16 in revised manuscript: is revised to “No change in HbA1c was **found** in the entire control group and in a subgroup with HbA1c >9.0% in control group (9.2 to 9.0%, **P =0.455**; 10.3 to 10.0%, **P =0.287**, respectively).”

P11, L3 in revised manuscript “**Although there was no significant difference in mean HbA1c in a metformin monotherapy (6.81 treated with PPIs vs. 7.10% treated without PPIs, P =0.25), mean HbA1c was significantly lower in a concomitant therapy including metformin and/or sulfonylurea and/or glitazone (7.26 treated with PPIs vs. 7.80 treated without PPIs, n =27, P =0.002).**” is added.

P11, L10: “**Metformin monotherapy did not change HbA1c compared with a combination therapy including metformin and a therapy in antidiabetic agents not including metformin [24].**” is added.

Furthermore, because you suggested that p values should be added in Table, also in text, we added p values in respective suitable portions as showed in boldface in text.

In addition, we used the word “T2DM” as you suggested. In the revised manuscript, “type 2 diabetes” is changed to “T2DM” as abbreviation after first description of “type 2 diabetes”.