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PEER-REVIEW REPORT

Reviewer's code: 02459759

SPECIFIC COMMENTS TO AUTHORS

This article is the usual, nothing new

Author reply: We express sincere gratitude to the esteemed reviewer for the review!! We have made modifications to the manuscript to improve its quality. Thanks

Reviewer's code: 02602042

SPECIFIC COMMENTS TO AUTHORS

This article has an interesting topic. Authors compared the CV safety of linagliptin and gliclazide in patients with T2DM. Although authors could not find any comparative study for the risk of hypoglycemia between Gliclazide and Linagliptin, the analysis showed gliclazide had shown similar glycemic efficacy and 50% lesser risk of hypoglycemic compared to Glimpiride, and gliclazide can be considered as glucose lowering drugs that can be given safely in T2DM patients with CVD or at high risk of CVD. The topic has delivered promising clinical message and should be of great interest to the readers. It can cause us to concern the effects of SUs on the treatment of diabetes with CV. The submission is worthy of publication.

Author reply: We express sincere gratitude to the esteemed reviewer for the encouraging words!!



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Reviewer's code: 05445949

SPECIFIC COMMENTS TO AUTHORS

The authors narratively reviewed glicla vs lina regarding beneficial cardiovascular effects. The study is of importance in clinical practice. But, the study benefit is questionable as dSU are significantly less used in CV patients.

Author reply: Thanks for your valuable comment. We agree that Sus are significantly less used in CV patients and therefore we have included trials where adults with T2D did not have CVD nor were at high risk of it. The use of Sus in T2D is very common in resource limited country like India because it is less costly than other glucose lowering drugs.



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Reviewer's code: 05463920

SPECIFIC COMMENTS TO AUTHORS

The authors systematically analyzed the incidence of hypoglycemia and 3-point mace in T2DM patients treated with linagliptin and gliclazide. This is a very interesting topic and the results also have good clinical application. If the authors can modify some improper expressions or use in the paper, I believe the quality of the manuscript will increase a lot. I suggest the following modifications:

Abbreviations should not be used in the title.

Author reply: Thanks for your suggestion! Abbreviations have been removed from the title and sub-headings.

What are MACE and 3P-MACE (in the text)? It should be explained clearly.

Author reply: Thanks for your suggestion! We have standardized this to MACE and explained what MACE includes (cardiovascular death, nonfatal myocardial infarction/ischemia/acute coronary syndrome, or nonfatal stroke) at first mention.

ADVANCE, CARMELINA and CAROLINA trial have the same application value. Therefore, the Abstract should be written in parallel, not only focusing on the CAROLINA trial, but also the other two. Moreover, it should not be mentioned completely in "Introduction" and should also be briefly described. Otherwise, overwrite the summary Abstract.

Author reply: Thanks for your guidance. We have re-written a major portion of the abstract. Please see if it is fine now. Also, we agree that ADVANCE, CARMELINA and CAROLINA trials are important landmark trials and have dedicated a section to them in the main body of the systematic review.



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In the Abstract, it is stated that “A systematic review was conducted to identify all the clinical studies published from by 2008 which compared the two drugs in patients with T2DM” (Page2), while in “Study selection”, it is stated that... Records published before 2008 were removed” (Page6). Please check clearly.

Author reply: Thanks for pointing this out. We have corrected the mistake. Please see if it is fine now

Although most readers understand some abbreviations, when they first appear in the text, they should be explained in full name, and the abbreviations of the same term in the same article should be consistent. Such as T2DM/T2D, HbA1c, DPP-4/DPP4, HR, 95%CI/95% CI, MACE/3P-MACE/3-P MACE, BG/SMBG, P=/ P =, GLD,..... Please check the whole manuscript to standardize these abbreviations.

Author reply: Many thanks for pointing this out. We have now standardized the abbreviations and re-checked for expansion at first mention.

What is the point of “Key Summary Points”? Need to be improved? Unclear.

Author reply: Many thanks for pointing this out. This was left behind by mistake. We have deleted this section. Instead, we have added a brief summary of 100 words highlighting the importance of this systematic review.

In Page 2, “23 Hypoglycemia was a secondary endpoint of the ADVANCE trial”, “23” in this sentence means?



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Author reply: Thanks for pointing this out. 23 was the citation number. We have corrected it now to match the style without track changes.

Like CARMELINA (need further improvement), what is the abbreviation of ADVANCE and CAROLINA? It should be clarified according to the literature.

Author reply: Thanks.

“Cardiovascular and Renal Microvascular Outcome Study With Linagliptin” (CARMELINA) expansion has been taken from Rosenstock et al (2019) Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial
“CARDiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes” (CAROLINA) has been expanded under the section ‘Linagliptin versus gliclazide or sulfonylureas’

“Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation” (ADVANCE) has been expanded under ‘excluded gliclazide trials’

All abbreviations appearing in the manuscript should be listed in Abbreviations.

Author reply: Thanks a lot for the suggestion. Since there was no section for this as per the author guidelines, and based on your suggestion, we took care to see that all abbreviations were expanded at the first mention. Hope this is fine.

The stratification of articles is not clear enough. Is there a difference between “Introduction” and “Background”? “Study selection” and “narrative synthesis of data”



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are inappropriate as introductions.

Author reply: Thanks for pointing this out. We have removed the sub-headings from the introduction. 'Study Selection' was another header and this has been renamed as 'Methodology' and "narrative synthesis of data" was another heading which has now been named as 'Data analysis'. Hope it is fine now.

It can't just be "synthesis" without "narration". For each section of the Result, use 1-2 sentences to clarify the purpose and the result.

Author reply: Thanks for your suggestion. We have added a couple of lines before each section to explain the purpose.

Does "±" in "Gliclazide/linagliptin ± metformin (no comparator)" indicate whether or not to combine (the same question is asked in other places)? Please state clearly.

Author reply: Thanks for pointing this out. We have now clarified that this section includes trials assessing either drug alone or with metformin without comparing it with placebo or any other comparator.

Don't just be loyal to the literature. The units of the same marker should be consistent. For example, BG has four units, namely mmol / liter, mg / deciliter, mg / dl and mmol / L. It should be unified in international units to facilitate readers to read by comparison. In addition, if both international units and customary units are given, then each blood sugar value should be the same, so that the whole manuscript can be unified. Check the whole manuscript and revise the inconsistent results.

Author reply: Many thanks for pointing this out. We have now standardized by including both international and customary units at all places.



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In "(P <0.0001for treatment difference) [42]" (Page12), check the significant digits and spaces of this P value?

Author reply: Thanks, we checked it again. The P-value is P<0.0001.

Round 2

Specific Comments To Authors: After the revision, the quality of the manuscript has been significantly improved, and there is still a suggestion for revision, which is worth considering. 1) It is not necessary to extract the statistical value when quoting others' results and/or conclusions as evidence. Moreover, most original articles have statistical differences set as "P<0.05 (very few are also set at P<0.01)". Therefore, as a review manuscript, it is best to delete the P value without uniform text. 2) Please note that in the manuscript I saw (78886_Auto_Edited), only 10 references were attached, while 60 references were cited.

Reply:

Dear Editor, We express sincere gratitude to the esteemed reviewer for the review!! We have made minor changes needed in the manuscript. Thanks. We have addressed the minor comments, where removal of 'p' value needed. Please also see the detailed reply to your comments. SPECIFIC COMMENTS TO AUTHORS We have received the Specific Comments To Authors: After the revision, the quality of the manuscript has been significantly improved, and there is still a suggestion for revision, which is worth considering. 1) It is not necessary to extract the statistical value when quoting others' results and/or conclusions as evidence. Moreover, most original articles have statistical differences set as "P<0.05 (very few are also set at P<0.01)". Therefore, as a review manuscript, it is best to delete the P value without uniform text. Author Reply: As



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suggested, we removed the p values from manuscript. 2) Please note that in the manuscript I saw (78886_Auto_Edited), only 10 references were attached, while 60 references were cited. -----Please reply within seven days, thank you! Author Reply: We have mentioned this issue in our last email, that due to some technical reasons at the website, its not taking more than 10 references as copy-paste. To overcome the issue, we had submitted a separate file of references as supplementary file. Revised clean file with full references being uploaded now. I look forward to see the manuscript accepted now. Thank you for all support. Best Regards, Dr. Rajnish Dhediya