Dear Reviewers and Editors,

Thank you so much for all your constructive comments and suggestions. We realized that some confusion has creeped up regarding methodology of meta-analysis. We would like to clarify that in the first section on metabolic effect of SGLT-2Is and GLP-1RAs dual therapy, we have descriptively analyzed the data from all available studies and previous meta-analysis, and we put a perspective. However, for the second section on cardiovascular outcomes with dual therapy, we have conducted a systematic review (as mentioned in the text) followed by a proper meta-analysis. A flow diagram according to PRISMA statement has been added in figure 2 as suggested. While we did not apply the Cochrane's tool for the risk of bias for those RCTs finally chosen for the meta-analysis considering the robustness of these double-blind RCTs, we did conduct a publication bias (funnel plot using the "trim and fill" adjustment, rank correlation test and the Egger's test) and an additional sensitivity exclusion analysis of met-analysis to find whether any individual study may have skewed the outcomes, as mentioned in the text. We have thoroughly checked the manuscript for grammatical errors and typos.

Yours faithfully

Awadhesh Kumar Singh

Ritu Singh

Reviewer's & Editors comment	Authors reply	Action taken
Reviewer #1: **Scientific Quality:** Grade B (Very good) **Language Quality:** Grade A (Priority publishing) **Conclusion:** Accept (General priority) **Specific Comments to Authors:** The content of the manuscript is of interest but it is difficult to read with the plethora of abbreviations. A listing of abbreviatons appears only as a footnote of the figures and could be liisted initially. The hetrogenicity of the drugs and their clinical effects also principally appears omly in the figures and could be more prominently noted in the body of the paper	Thank you! Full form of all abbreviations has been mentioned before its first use across the manuscript except the eponyms of cardiovascular and renal outcome trials. Clinical effect of drugs also appears in the body of the text but we did not intend to repeat all values in the body of text to avoid text cluttering.	-
Reviewer #2: **Scientific Quality:** Grade B (Very good) **Language Quality:** Grade B (Minor language polishing) **Conclusion:** Minor revision **Specific Comments to Authors:** The meta-analysis suggest a similar reduction in major adverse cardiovascular event with dual therapy compared to GLP-1RA or SGLT-2I alone, but an additional benefit in heart failure hospitalization is likely. Currently, GLP-1RA and SGLT-2i are "hard edged" in the treatment of diabetes, especially for patients with type 2 diabetes mellitus (T2DM) with high risk of cardiovascular risk. However, the pathophysiology mechanism of diabetes is	Thank you for your comments. As you know these RCTs have been conducted in matched group of participants receiving a similar background (traditional therapy) in both active vs. placebo arm, hence any differential outcome observed is likely related to drug studied against placebo. Risk of bias is minimal and these double-blind randomized controlled trials.	-

complex, and multiple pathways can increase blood sugar together. Monotherapy can not comprehensively address the complex pathological mechanism of T2DM, so it is necessary to combine multiple mechanisms. The author does not have a clear idea on the hypothesis and elaboration of the new mechanism, and needs to further comb and interpret the latest research content. In the discussion part, there is no corresponding background elaboration on the content of multi-drug combination, such as the combination of traditional drugs and new drugs, which may lead to possible bias in the results.

Reviewer #3:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: Dear authors, The paper represents the opinion review aiming to answer the research question about what additional metabolic and cardiovascular benefit is achievable with SGLT-2 inhibitors and GLP-1 receptor agonists combination therapy in type 2 diabetes? The article is written with the acceptable English-speaking adduction of the arguments. The article is sufficiently novel and very interesting to warrant publication. All the key elements are presented and described clearly. The most discussable options in the article are: 1) Please correct all your multiple grammar errors and typos. 2) This is a sort of the systematic review and it means that there must be more numbers with details of any statistical

Thank you for your constructive comments. We humbly read both initial positive and later negative comments.

With regard to queries – 1. We have corrected all grammatical errors and typos across the manuscript, 2. As mentioned in the text this is a systematic review followed by a proper meta-analysis to find out the CV

-

patterns revealed in the quoted studies. For example, in case of «Thus, SGLT-2I administration can lead to a marked increase in plasma glucagon-to-insulin ratio (GIR) by a tune of 50-100% [7, 8]», this is not a scientific way to represent data. Please harmonize it! 3) What your table 2 exactly means? Is that your meta-analysis? If it is yours, there must be methods and proper presentation of your data with all the required elements. If it is not yours, there must be any critical evaluation. Your vision and a style how you present your data is simply confusing. 4) The statistical power and any bias in the referenced studies must be characterized. The flaws in the studies must be underlined. It must be clear can we trust any data at all! Please improve your table with the necessary information. Here is also another point of the clinical outcomes. Please, underline the primary outcome in all the studies. You have to emphasize on the concerns regarding to the clinical outcomes in these studies exposing obvious limitations of that research.	outcome with dual therapy from the RCTs that exclusively reported CV outcomes with either SGLT-2Is or GLP-1RAs or combination therapy. We have now added figure 2 of PRISMA flow diagram, 3. Table 2 depicts the results of metabolic outcomes with dual therapy in previous meta-analysis done by various authors earlier. We did not conduct any meta-analysis for metabolic outcomes since as it was already conducted by several authors previously, 4. Our meta-analysis conducted for the CV outcomes assessed the publication bias as shown in supplementary figure 1. We did not conduct Cochrane risk of bias assuming high qualities of these double-blind RCTs as mentioned in text.	New figure 2 added
Reviewer #4: **Scientific Quality:** Grade B (Very good) **Language Quality:** Grade B (Minor language polishing) **Conclusion:** Accept (General priority) **Specific Comments to Authors:** This is a good comprehensive review of SGLT-2 inhibitors and GLP-1 agonists trials on cardiovascular outcomes in diabetic therapy. The article is a useful descriptive opinion piece that can be published. However it is not a formal meta-analysis, which requires formal search methodology and a	Thank you for your constructive comments. We have added figure 2 PRISMA flow diagram of this systematic review and met-analysis we conducted. We apologize for any inconvenience caused.	New figure 2 added

completely different write up. Figures 1 to 3 are merely statistical analyses of studies selected by the authors to support their conclusions in the opinion piece. They should avoid the use of "meta-analysis" in the abstract and text.

Reviewer #5:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is an excellent review including meta-analysis of CV outcomes about GLP-1RA and SGLT-2I combination therapy. This manuscript is nicely structured and well written. I have no question about this manuscript.

Thank you so much!

-

Reviewer #6:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: In the Manuscript, titled "What additional metabolic and cardiovascular benefit is achievable with SGLT-2 inhibitors and GLP-1 receptor agonists combination therapy in type 2 diabetes?", Awadhesh Kumar Singh and Ritu Singh, describe the effects of combination therapy with GLP-1RA plus SGLT-2I on HbA1c, body weight and SBP compared to either agent alone. The

topic is very interesting for the scientific community, and it has been clearly and extensively developed. I only advice the authors some minor remarks: 1) In the paragraph "What is the rational of this combination in type 2 diabetes?" authors describe how GLP-1RA and SGLT-2I work through different mechanisms of actions in different organs. Combination therapy with these agents is expected to have a complementary or perhaps a synergistic effect on metabolic outcomes. These theories are very fascinating. Please add an image summarizing the pathophysiological mechanisms. 2) The synergistic effect of the two drugs could be used to reduce intolerance to sglt2i about urinary infections: the strong hypoglycaemic action of glp1ra could in fact be sufficient to maintain blood glucose levels below the renal threshold, resulting in a reduction/absence of glycosuria. In this way, sglt2i can be used as drug to treat heart failure or kidney failure with minimal risk of urinary infections in diabetic patients. Authors should suggest this further rationale for the use of the two drugs.	1. We have added the complementary mechanism of action of individual agents and dual therapy as suggested in figure 1 now. 2. With regard to risk of UTI with SGLT-2Is alone vs. dual therapy (SGLT-2Is plus GLP-1RAs), there is no published evidence available that suggest dual therapy reduce UTI compared to SGLT-2I alone. While data did suggest that at least GTI was less with DPP-4 inhibitors plus SGLT-2I vs. SGLT-2I alone, no such data yet available with GLP-RA combination to SGLT-2I.	Figure 1 added
(1) Science editor: Respected authors, this is a well written paper and covers an interesting topic. Nevertheless, there are a number points that may deserve some revisions. The format of the table should be a three line table. The manuscript is not a simple meta-analysis, and the author's work is not very standardized, but it is necessary to give the retrieval method and flow chart. Language Quality: Grade B (Minor language polishing)	Thank you for your generous comments. We have changed all table to three-line format now as suggested. We have also added retrieval (search) methodology of this systematic review and a PRISMA flow diagram in figure 2 as asked.	All tables are having three-line now. Figure 2 added.

Scientific Quality: Grade B (Very good) **(2) Company editor-in-chief:** I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Cardiology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words). Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.	Thank you so much! We have shortened the title of topic to less than 18 words as suggested. We have also changed all tables to three-line format now as asked.	Blue colored title.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Cardiology*

Manuscript NO: 74514

Title: Metabolic and cardiovascular benefits with SGLT-2 inhibitors and GLP-1 receptor agonists combination therapy in type 2 diabetes

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03846820

Position: Editorial Board

Academic degree: FACC, FESC, MD

Professional title: Academic Research, Assistant Professor, Doctor

Reviewer's Country/Territory: Netherlands

Author's Country/Territory: India

Manuscript submission date: 2021-12-26

Reviewer chosen by: Han Zhang (Online Science Editor)

Reviewer accepted review: 2022-04-01 07:07

Reviewer performed review: 2022-04-01 07:51

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Peer-reviewer	Peer-Review: [ ] Anonymous [Y] Onymous

statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Dear authors, Thank you very much for your efforts to improve the article. I have a few suggestions though: 1) The structure of the article seems not clear generally. There is no straight logic. It looks very unbalanced when you start from general description without proper argumentation and then going to some focused ideas without clear logical relation between. 2) Would you please kindly underline the main points of any effects on cardiovascular outcomes, and particularly when you are mentioning heart failure, it must be clear what kind of heart failure with or without diabetes. Some points must be emphasized.

Reply from authors:

1.   We have rephrased the sentences in the last section on CV outcomes for better clarity – as asked (blue colored text).

2.   Since categorization on type of heart failure were not made in these RCTs included here in meta-analysis, we have mentioned about this in under limitation section (purple colored text).

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Cardiology*

Manuscript NO: 74514

Title: Metabolic and cardiovascular benefits with SGLT-2 inhibitors and GLP-1 receptor agonists combination therapy in type 2 diabetes

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02991432

Position: Peer Reviewer

Academic degree:

Professional title:

Reviewer's Country/Territory: Italy

Author's Country/Territory: India

Manuscript submission date: 2021-12-26

Reviewer chosen by: Han Zhang (Online Science Editor)

Reviewer accepted review: 2022-04-01 19:31

Reviewer performed review: 2022-04-01 19:39

Review time: 1 Hour

Scientific quality	[　] Grade A: Excellent　 [Y] Grade B: Very good　 [　] Grade C: Good [　] Grade D: Fair　 [　] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing　 [　] Grade B: Minor language polishing [　] Grade C: A great deal of language polishing　 [　] Grade D: Rejection
Conclusion	[　] Accept (High priority)　 [Y] Accept (General priority) [　] Minor revision　 [　] Major revision　 [　] Rejection
Peer-reviewer	Peer-Review: [Y] Anonymous　 [　] Onymous

| statements | Conflicts-of-Interest: [   ] Yes   [Y] No |

SPECIFIC COMMENTS TO AUTHORS

all reviews carried out. Thanks

Reply from authors:

Thank you!

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Cardiology*

Manuscript NO: 74514

Title: Metabolic and cardiovascular benefits with SGLT-2 inhibitors and GLP-1 receptor agonists combination therapy in type 2 diabetes

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05847926

Position: Peer Reviewer

Academic degree: MD

Professional title: Associate Professor

Reviewer's Country/Territory: China

Author's Country/Territory: India

Manuscript submission date: 2021-12-26

Reviewer chosen by: Han Zhang (Online Science Editor)

Reviewer accepted review: 2022-04-03 14:49

Reviewer performed review: 2022-04-03 15:17

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is an good review including meta-analysis of CV outcomes about GLP-1RA and SGLT-2I combination therapy. This manuscript is nicely structured and well written. I have no question about the revised manuscript.

Reply from authors:

Thank you!