

## PEER-REVIEW REPORT

**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:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Italy

**Author's Country/Territory:** India

**Manuscript submission date:** 2021-12-26

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-12-30 10:36

**Reviewer performed review:** 2021-12-30 13:01

**Review time:** 2 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

**Peer-reviewer  
statements**

Peer-Review: [☒] Anonymous [☐] Onymous

Conflicts-of-Interest: [☐] Yes [☒] No

## **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.

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**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 00227375

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Japan

**Author's Country/Territory:** India

**Manuscript submission date:** 2021-12-26

**Reviewer chosen by:** Xin Liu (Online Science Editor)

**Reviewer accepted review:** 2022-02-25 09:52

**Reviewer performed review:** 2022-02-25 11:07

**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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**Peer-reviewer  
statements**

Peer-Review: ☒ Anonymous ☐ Onymous

Conflicts-of-Interest: ☐ Yes ☒ No

#### **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.

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**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 02446043

**Position:** Editorial Board

**Academic degree:** FACC

**Professional title:** Lecturer

**Reviewer's Country/Territory:** Malaysia

**Author's Country/Territory:** India

**Manuscript submission date:** 2021-12-26

**Reviewer chosen by:** Xin Liu (Online Science Editor)

**Reviewer accepted review:** 2022-02-26 03:30

**Reviewer performed review:** 2022-02-26 04:15

**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

**Peer-reviewer  
statements**Peer-Review: [☒] Anonymous [☐] OnymousConflicts-of-Interest: [☐] Yes [☒] No**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 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.

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**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:** Xin Liu (Online Science Editor)

**Reviewer accepted review:** 2022-02-24 12:22

**Reviewer performed review:** 2022-02-27 09:19

**Review time:** 2 Days and 20 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

**Peer-reviewer  
statements**

Peer-Review: [ ☐ ] Anonymous [ ☒ ] Onymous

Conflicts-of-Interest: [ ☐ ] Yes [ ☒ ] No

## 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 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.



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**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:** Xin Liu (Online Science Editor)

**Reviewer accepted review:** 2022-02-24 13:51

**Reviewer performed review:** 2022-03-05 10:56

**Review time:** 8 Days and 21 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

**Peer-reviewer  
statements**

Peer-Review: [☒] Anonymous [☐] Onymous

Conflicts-of-Interest: [☐] Yes [☒] No

## **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 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.

## PEER-REVIEW REPORT

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**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 00174138

**Position:** Editorial Board

**Academic degree:** FACC, FACP, FRACP, FRCP (Hon), MD, MRCP

**Professional title:** Professor

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** India

**Manuscript submission date:** 2021-12-26

**Reviewer chosen by:** Xin Liu (Online Science Editor)

**Reviewer accepted review:** 2022-02-24 15:01

**Reviewer performed review:** 2022-03-05 23:17

**Review time:** 9 Days and 8 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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<b>Peer-reviewer statements</b>	Peer-Review: [ <input checked="" type="radio"/> ] Anonymous [ <input type="radio"/> ] Onymous Conflicts-of-Interest: [ <input type="radio"/> ] Yes [ <input checked="" type="radio"/> ] No
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#### **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 abbreviations appears only as a footnote of the figures and could be listed initially. The heterogeneity of the drugs and their clinical effects also principally appears only in the figures and could be more prominently noted in the body of the paper

## 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

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer</b>	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [ ☐ ] Yes [ ☒ ] 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.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**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

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

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

## **SPECIFIC COMMENTS TO AUTHORS**

all reviews carried out. Thanks



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**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

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [ ☐ ] Yes [ ☒ ] 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.