Peer Review File

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Responses to Reviewer A's Comments:

Comment 1:

The authors report the effects of SGLT2i in specific subgroups of patients in this meta-analysis of the main RCT of SGLT2i. The authors report that SGLT2i are beneficial 1) independently of NYHA class, but are more effective in NYHA 2 vs NYHA 3-4; 2) independently of race, but are more effective in Asians and Blacks than in Caucasians; 3) independently of baseline LVEF, geographical location or baseline disease ((T2DM vs HF vs CKD) but without any subgroup differences; and 4) as a group, although three of them (empa, cana, dapa, sota) are more effective than ertugliflozin.

The authors are to be praised for investigating in depth the effect of SGLT2i on different subgroups. Particularly relevant is the investigation of race differences: although EMPEROR-Reduced already hinted at more efficacy of SGLT2i in Asian-Blacks than Caucasians, this has been confirmed and expanded in this manuscript. The methods are solid (meta-analysis are the highest degree of evidence), the results are consistent and novel, the discussion is balanced, the conclusion is supported by the data, and the manuscript is short and reads well.

Reply 1:

Thank you very much for these positive comments. Please see our itemized responses.

Changes in the text:

None.

Comment 2:

- References 13-15 were selected for the meta-analysis according to the first sentence of the Results section, but those data are not used anymore. The data for those 3 studies should be included in this meta-analysis.

Reply 2:

In fact, the relevant data from those 3 articles [1-3] were included in quantitative synthesis. Because the original publication [4] of the CANVAS Program trial provided the data of heart failure composite outcome [i.e., a composite of cardiovascular death (CVD) or hospitalization for heart failure (HHF)] in overall participants (i.e., patients with type 2 diabetes) but did not provide those in the subgroup of patients with heart failure (HF) whereas the Reference 13 [1] provided those subgroup data, the relevant data from the Reference 13 were included in the meta-analysis for the subgroup of HF patients. Similarly, the relevant data from the References 14 [2] and 15[3] were included in the meta-analysis for the subgroup of HF patients and for the subgroup of CKD patients, respectively. All the original data extracted from included articles, including the data from overall participants and the data from various subgroups, are presented in **Appendix 2**.

Changes in the text:

As for this Comment, we have not made required revisions.

Comment 3:

- One additional subgroups should be included: diabetic vs non-diabetic patients in HF and CKD

Reply 3:

A meta-analysis [5] based on the two trials of the DAPA-HF trial [6] and the EMPEROR-Reduced trial [7]) conducted in HF patients has demonstrated that SGLT2 inhibitors provide the similar benefits on heart failure composite outcome for HF patients regardless of with/without T2D. Moreover, the only cardiorenal outcome trial conducted in CKD patients (i.e., the DAPA- CKD trial [8]) has demonstrated that dapagliflozin provides the similar benefits on renal and cardiovascular composite endpoint for CKD patients regardless of with/without T2D. Thus, we conclude that patients with/without T2D do not have significant effects on the efficacy of SGLT2 inhibitors on heart failure composite outcome in HF patients and in CKD patients. Accordingly, in this present meta-analysis we did not conduct subgroup analysis stratified by the status of T2D in HF patients or CKD patients any more.

However, more specific subgroup analyses, such as the analysis in the subgroup of patients with HF and CKD without T2D and the analysis in the subgroup of patients with HF, CKD and T2D, are needed to assess the more specific subgroup effects of SGLT2 inhibitors. We failed to do those analyses due to the lack of patient-level data. This limitation has been added into the first point of the Limitations section in the second-to-last paragraph of the revised manuscript.

Changes in the text:

The relevant sentences have been added into the first point of the Limitations section in the second-to-last paragraph of the revised manuscript.

Comment 4:

- The authors should mention that the benefit in outcomes with SGLT2i is paralleled by reverse cardiac remodeling (please quote PMID: 33197559 and PMID: 33186500), improvement in quality of life (please quote PMID: 33197559, PMID 33420498 and DAPA-HF) and prevention in diabetes (please quote)

Reply 4:

Thank you very much for giving such good suggestion. We have quoted these articles in the third-to-last paragraph of the revised manuscript.

Changes in the text:

The relevant sentences have been added into the third-to-last paragraph of the revised manuscript.

Comment 5:

- The authors should hypothesize why Asians and Blacks derive more benefit than Caucasians. Is it because they are minorities and thus not treated with optimal medical therapy, so they benefit the most of this new therapy?

Reply 5:

Thank you very much for this good hypothesis. We have added this hypothesis into the third-to-last paragraph of the revised manuscript.

Changes in the text:

The relevant sentences have been added into the third-to-last paragraph of the revised manuscript.

Responses to Reviewer B's Comments:

Comment 1:

Sodium-glucose transporter 2 inhibitors (SGLT-2i) is a novel class of anti-hyperglycaemic drugs.

Emerging data now are demonstrating its impressive effects on cardiorenal protection. This study aimed to evaluate the effects of six clinically important factors on the efficacy of SGLT-2i on heart failure-associated endpoints. Generally, this is an interesting topic and needs to be concerned.

Reply 1:

Thank you very much for these positive comments. Please see our itemized responses.

Changes in the text:

None.

Comment 2:

Overall, studies enrolled in this meta-analysis are of high quality. However, being very limited studies in several pooled subgroup analysis, some confounders related to "patients-depending" may be inevitable. For example, when stratifying by underlying disease of CKD, it is noted that not all the patients had T2DM, and the status of T2DM or heart failure may significantly change benefit scales of heart failure outcomes. Thus, it is more perfect to perform analysis in more specific subgroup, like T2MD-CKD (or T2DM-HF, CKD-HF et al) patients with SGLT-2i or not.

Reply 2:

Thank you very much for your kind concern about the subgroup analysis in our manuscript. I understand your concern very well.

Two meta-analyses [9, 10] based on the trials conducted in T2D patients have demonstrated that SGLT2 inhibitors provide the similar benefits on various cardiorenal endpoints for T2D patients regardless of with/without HF, and regardless of with/without CKD. A meta-analysis [5] based on the two trials of the DAPA-HF trial [6] and the EMPEROR-Reduced trial [7]) conducted in HF patients has demonstrated that SGLT2 inhibitors provide the similar benefits on heart failure composite outcome for HF patients regardless of with/without T2D, and regardless of with/without CKD. Furthermore, the only cardiorenal outcome trial conducted in CKD patients (i.e., the DAPA-CKD trial [8]) has demonstrated that dapagliflozin provides the similar benefits on renal and cardiovascular composite endpoint for CKD patients regardless of with/without T2D, and regardless of with/without HF. Thus, in this present meta-analysis we accomplished the subgroup analysis stratified by type of underlying diseases, simply by means of doing the analysis in the subgroup of T2D patients (regardless of with/without HF, and regardless of with/without CKD), in the subgroup of HF patients (regardless of with/without T2D, and regardless of with/without CKD), and in the subgroup of CKD patients (regardless of with/without T2D, and regardless of with/without HF).

However, more specific subgroup analyses, such as the analysis in the subgroup of patients with HF and CKD without T2D and the analysis in the subgroup of patients with HF, CKD and T2D, are needed to assess the more specific subgroup effects of SGLT2 inhibitors. We failed to do those analyses due to the lack of patient-level data. This limitation has been added into the first point of the Limitations section in the second-to-last paragraph of the revised manuscript.

Changes in the text:

The relevant sentences have been added into the first point of the Limitations section in the second-to-last paragraph of the revised manuscript.

Comment 3:

The discussion part is really poor: it mainly presents a repetition of the results and have no explanations of findings. Basically, I am very curious about and interested in the potential

mechanisms about racial and regional disparities in the efficacy of SGLT-2i. And why better NYHA heart functional class had greater benefits?

Reply 3:

In fact, the subgroup effect according to geographic region was not statistically significant.

The possible mechanisms for the significant subgroup effects according to NYHA class and race have been added into the third-to-last paragraph of the revised manuscript.

Changes in the text:

The relevant sentences have been added into the third-to-last paragraph of the revised manuscript.

Comment 4:

Subgroup analysis with only 1~2 study is not suitable for pooling up. Sometimes the results may be misleading. I would like to suggest to cancel the subgroups stratified by different SGLT-2i.

Reply 4:

I do agree that test for subgroup effect is with lack of statistic power when some subgroups only include 1~2 study. However, test for subgroup effect might, more or less, suggest possible results although they are not completely certain.

On the other hand, any of the subgroup analyses was conducted completely according to a prior study protocol for this meta-analysis. Thus, we have kept all the subgroup analysis results and meanwhile have added the statement of the limitation relevant with the lack of statistic power in some tests for subgroup effect into the second-to-last paragraph of the revised manuscript.

Changes in the text:

The relevant sentences have been added into the second point of the Limitations section in the second-to-last paragraph of the revised manuscript.

Comment 5:

Limitation part is lack, and it really important to point out.

Reply 5:

Three main limitations of this study have been added into the second-to-last paragraph of the revised manuscript.

Changes in the text:

The relevant sentences have been added into the second-to-last paragraph of the revised manuscript.

Comment 6:

Language revision is greatly needed. The structure of some sentences are same.

Reply 6:

We have carefully revised the full-text manuscript in terms of written English.

Changes in the text:

Some of the words and sentences marked as blue have been revised due to this point.

Comment 7:

Method part: it may be better if database of Cochrane Central Registry of Controlled Trials was included in searching strategy, as this is a meta-analysis of clinical trials.

Reply 7:

This is a good suggestion. We have additionally searched the database of Cochrane Central Register

of Controlled Trials (CENTRAL), and we have not identified new randomized trials eligible for inclusion.

Changes in the text:

We have added the retrieval of Cochrane Central Register of Controlled Trials (CENTRAL) into the second paragraph of the Methods section.

Comment 8:

Method part: Whether conference or grey articles were allowed in this study should be stated clearly.

Reply 8:

We have stated, in the Methods section of the revised manuscript, that "This meta-analysis did not consider any of the conference articles and grey articles".

Changes in the text:

In the second paragraph of the Methods section, we have added the following sentence: "This meta-analysis did not consider any of the conference articles and grey articles".

Comment 9:

Method part: It should have more detailed information about data extraction and quality assessment part. For example, what variables do you extract from original articles, what items were included in Cochrane quality assessment tool? Moreover, assessment of publication bias should be noted and conducted.

Reply 9:

We have clarified, in detail, what variables were extracted from original articles and what items were considered according to the Cochrane quality assessment tool, by means of greatly extending the third paragraph of the Methods section.

Test of publication bias, using either funnel plot method, Egger's test, or Begg's test, has the limited value when the number of included studies is less than 10. Because in most of the subgroup analyses conducted in this meta-analysis the corresponding subgroups included a limited number of original studies, we did not perform test of publication bias. On the contrary, we have added this limitation of failing to perform test of publication bias into the third point of the Limitations section in the second-to-last paragraph.

Changes in the text:

Relevant sentences have been added into the third paragraph of the Methods section as for data extraction and quality assessment. Relevant sentences have been added into the third point of the Limitations section in the second-to-last paragraph as for publication bias.

Comment 10:

Result part: The layout of Result part is really messy. Strongly recommend to add some subheads and essential descriptions of results, eg, demographic data, total numbers of studies or participants enrolled for each subgroup and so on.

Reply 10:

We have added several subheads in the Results section. The demographic data, the numbers of events, and the numbers of patients in original studies and the numbers of included studies in various subgroup analyses are detailed in the forest plots (i.e., **Figures 1-3** in the main text and **Figures S3-S5** in **Appendix 1**) of the manuscript. However, we failed to calculate the total numbers of events

and patients in various subgroups since the numbers of events or patients were not available in some original articles. Because we performed this meta-analysis based on the trial-level survival data, namely hazard ratios (HRs) and 95% confidence intervals (CIs) as reported in original articles, the lack of the numbers of events and/or patients in original articles did not bias the results of meta-analysis at all.

Changes in the text:

Several subheads have been added into the Results section.

References

[1] Radholm K, Figtree G, Perkovic V, et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus. Circulation 2018;138:458-68.

[2] Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. Eur Heart J 2016;37:1526-34.

[3] Wanner C, Lachin J M, Inzucchi S E, et al. Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease. Circulation 2018;137:119-29.

[4] Neal B, Perkovic V, Mahaffey K W, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017;377:644-57.

[5] Zannad F, Ferreira J P, Pocock S J, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet 2020.

[6] Mcmurray J, Solomon S D, Inzucchi S E, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019;381:1995-2008.

[7] Packer M, Anker S D, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 2020.

[8] Heerspink H, Stefánsson B V, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020.

[9] Qiu M, Liu S Y, Gu J S, et al. Do reductions in risk of cardiorenal events with SGLT2 inhibitors in type 2 diabetes vary with baseline characteristics? A meta-analysis. Endocrine 2020.

[10] Arnott C, Li Q, Kang A, et al. Sodium-Glucose Cotransporter 2 Inhibition for the Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. J Am Heart Assoc 2020;9:e14908.