Author’s response to reviews

Title: SGLT2 inhibitors in T2D and associated comorbidities — differentiating within the class

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Author’s response to reviews:

Point-by-point rebuttal

Schernthaner et al. SGLT2 inhibitors in T2D and associated comorbidities — differentiating within the class
Reviewer 1 (Gabriel Chodick)

1. This is a very timely summary of a group of medical experts from the Central and Eastern European Region on the class effects of SGLT2 inhibitors. I applaud the authors for their review and conclusion that despite the encouraging CV and renal data from the EMPA-REG OUTCOME® and CANVAS Program, the class effect in all-cause mortality, CV death and safety, require further investigation.

> We thank the reviewer for these kind comments. We agree that this is a timely summary and discussion that will be of interest to journal readers.<

2. Their conclusion is fully supported by the recently published results of DECLARE-TIMI RCT. While Dapagliflozin was found to reduce the risk of cardiovascular death or HHF (HR= 0.83; 95% CI, 0.73 to 0.95), most of this effect was due to a lower rate of HHF (HR= 0.73; 95% CI, 0.61 to 0.88). Dapagliflozin had no or little effect in reducing the risk of cardiovascular death (HR= 0.98; 95% CI, 0.82 to 1.17) or MACE (HR= 0.93; 95% CI, 0.84 to 1.03; P=0.17), irrespective to CVD status at baseline. In addition, it had no effect in reducing all-cause mortality. The results of this important study should be incorporated into the summary.

> We agree that these new results are highly relevant, and thank the reviewer for the suggestion. The DECLARE-TIMI results had not yet been disclosed when we previously submitted the manuscript. However, we have now added a brief section summarising the key findings (on page 14–15), and made several updates to the discussion on considering the CVOTs together (page 15–19) to also take into account this new study.

Please note that, to prevent the manuscript from becoming overly long in light of these additions, we have slightly shortened the summaries of the other two CVOT studies discussed.<

3. The authors have rightfully addressed real-world evidence in their summary. These studies add to the confusion regarding the class effect of SGLT2-I in reducing CVD and all-cause mortality. Some important studies should be mentioned including the EASEL cohort study. With less than two years of median follow-up, the authors concluded that SGLT2i was associated with 43% reduction in all-cause mortality and HHF and 33% reduction in major adverse cardiovascular events. Importantly, SGLT2i initiation was also associated with a 2-fold higher risk of below-knee lower extremity amputation. Similar results have been shown in an additional observational study- CVD REAL2- an international study of patients with T2D from the Asia Pacific, the Middle East, and North America. These observational studies should be discussed in the summary.
A brief summary of the EASEL study was in fact already included in the paper, including the 2-fold higher risk of below-knee lower extremity amputation. However, we thank the reviewer for the suggestion to provide more specific details on efficacy. The specific values have now been added on page 21.

We also thank the reviewer for the suggestion to include a summary of CVD-REAL 2, which we have now added on page 20–21, immediately following the discussion of the first CVD-REAL study. Similarly, we have added a brief summary of initial results from the EMPRISE study (page 21–22), which were not available when we initially submitted the manuscript, but we believe are highly relevant alongside CVD-REAL, CVD-REAL 2 and EASEL.

Please note that, to prevent the manuscript from becoming overly long by these additions, we have removed the brief discussion of CVD-REAL Nordics, as this was not a new study but instead a partial analysis of CVD-REAL, and we believe the results from CVD-REAL 2, as a new and large study covering new geographical areas, and from the ongoing EMPRISE study, as a new study with an active comparator, will be of more interest to journal readers.

Reviewer 2 (anonymous)

"PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

N/A - no methodology

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

N/A - no experiments or analyses
Statistics - Is the use of statistics in the manuscript appropriate?

N/A - there are no statistics in this study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: As an expert opinion paper it is well-written, gives a good walkthrough and over-view of the current evidence. If possible it would be nice to have some of the updates from ADA'18 and EASD’18 included e.g. the results from the HARMONY Trial with regards to GLP1-treatment and results from CVD-REAL 2.

We thank the reviewer for these kind comments, and for appreciating our objective in providing a useful overview of, and expert discussion around, the current evidence on SGLT2 inhibitors from CVOTs.

As mentioned in our rebuttal to Reviewer 1, we agree with the helpful suggestion to include a summary of CVD-REAL 2, and this can now be found on page 20–21.

We also agree that the HARMONY disclosures on albiglutide have helped to add to the picture of GLP-1 RA agent CVOTs. Although these were not originally the subject of our discussions, and thus not included in the initial version of the manuscript, it is clear that there are some interesting parallels to be drawn with our discussion of SGLT2 inhibitors, and that this context will likely be of interest to journal readers. Therefore, we have now briefly mentioned this parallel in the section on class effect (page 23).<
REQUESTED REVISIONS:

Consider giving the readers the absolute numbers and/or numbers need to treat (NNT) instead of only the relative risk reductions reported.

>Thank you for this excellent suggestion, which we agree will help readers understand the fuller context of the reported reductions in CV and renal risk. We have added absolute numbers for rates per 1,000 patient-years and absolute risk reductions for all three CVOTs to Table 2 (page 32). The reason for using events per patient-year and not events per se is that the CANVAS Program paper only reports result in the patient-year format.

NNT numbers have generally not been reported for these CVOTs, except for the NNT for death by any cause in EMPA-REG OUTCOME®, which we have now added on page 7 in the summary of EMPA-REG OUTCOME® CV and mortality outcomes. Although NNT can be crudely calculated from ARR, this is complicated by the different durations of the trials and declining numbers of patients at risk, and so to avoid confusion we have not calculated any additional NNT values.<

It also would be nice if the abbreviations were written out first time they were used (unless required otherwise by the journal)

> We apologise for not ensuring that all abbreviations were clearly defined. We have tried to make sure they are all written out in full on first use in the revised manuscript.<

ADDITIONAL REQUESTS/SUGGESTIONS:

The potential immortal time bias in CVD REAL has been discussed by Suissa and Thuresson in Diabetes Care and could maybe be commented upon.

> We agree that this is an interesting point and for this reason had in fact briefly discussed the concern raised by Suissa regarding immortal time bias in the initial version of the manuscript. In accordance with the reviewer suggestion, we have now added some brief additional discussion, including a reference to Thuresson et al’s rebuttal, on page 22.<

The importance of urinary tract infections as potential complication and the impact on patient compliance could be discussed in more detail.
We thank the reviewer for this suggestion, and agree that the picture of adverse events is an important aspect of the studies that should be discussed. A paragraph discussing urogenital infections has now been added on page 17–18. Another paragraph discussing bone fracture and DKA was also added on page 17, to ensure that readers are fully aware of these adverse events. We have also added DKA events to Table 3 (page 33).

The references no. 49, 50 and 51 look odd.

Thank you to the reviewer for pointing this out. The formatting of all references has now been checked and, where necessary, corrected.

Editor comments

1. The individual contributions of ALL authors to the manuscript should be specified in the Authors’ Contributions section. Guidance and criteria for authorship can be found here:

http://www.biomedcentral.com/submissions/editorial-policies#authorship

Thank you for bringing this to our attention. This section has now been updated.