41697-Answering Reviewers

Manuscript Type: OBSERVATIONAL STUDY

**Using real world data to assess cardiovascular outcomes of two antidiabetic treatment classes**

**Manfred P Stapff, TriNetX Inc., Cambridge, MA, USA**

Thank you for your careful review and the comments/suggestions to my manuscript. The following are the responses to the Administrator's comments in the Word document "41697-Edicted.docx ". (note: I did not see any questions from the reviewers):

**Author contributions:**
TriNetX is a federated network with real time access to analyses of electronic medical records. Large retrospective observational studies can be done directly in a user-friendly browser based real time system by a researcher without the need of biostatisticians or programmers. Insofar there are no direct other contributions to the manuscript than the ones by the author. I am not sure if the section "author contributions" is even necessary for a one-author manuscript. If you still think it should be there, then it could read like :
Stapff M developed the scientific concept, literature search, study design, applied the data querying, result interpretation, scientific discussion, and prepared the manuscript.

**Institutional review board statement:** As a federated network TriNetX received a general waiver from Western IRB for its scientific work since only aggregated counts, statistical summaries of de-identified information, but no protected health information is received, and no study specific activities are performed in retrospective observational analyses. Therefore, no IRB review was necessary for this particular study.

**Informed consent statement:** This was an observational study based on analyses of anonymized electronic medical records describing real world treatment. No intervention or any study specific activity was done on patients. Therefore, no informed consent was necessary and would even have been not feasible considering the anonymized and retrospective character of the analysis.

**Conflict-of-interest statement:** The author is employee of TriNetX Inc., the data network and analytics platform used for this publication. TriNetX as a company was not involved in the design of the study; the collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication. The author

does not declare conflicting interests (including but not limited to commercial, personal, political, intellectual, or religious interests).

**ARTICLE HIGHLIGHTS**

Research background

Therapy of diabetes mellitus intends to control blood glucose values, to prevent or delay diabetic complications such as chronic kidney disease or retinopathy, and to reduce the likelihood of cardiovascular events like myocardial infarction or stroke. Several randomized clinical trials and sophisticated European registries have suggested that SGLT2 inhibitors may have an advantage in preventing cardiovascular events.

Research motivation

Randomized clinical trials are conducted on highly selected patient populations and follow very artificial treatment protocols. This makes it sometimes questionable whether the results are representative and can be applied to routine medical practice.

Research objectives

To evaluate if the positive results of randomized clinical trials with SGLT2 inhibitors can be confirmed by real world data coming from actual medical routine practice in the US.

Research methods

A federated research network was used allowing analyses of electronic medical records from 38 Million patients in 35 large Health Care Organizations predominately in the USA. Cardiovascular events have been counted occurring during a three-year observation period after start of a therapy with an SGLT2 inhibitor and compared to a control group starting DPP4 inhibitors. Comorbidity strata have been created to address potential confounders.

Research results

In the overall cohort and in all comorbidity strata the risk of experiencing a cardiovascular event was similarly in favor of SGLT2, with risk ratios ranging from 0.62 to 0.81.

Research conclusions

The analysis of data from patients with a much broader cardiovascular risk profile than the very selected population in randomized clinical trials could replicate the results of such trials. This validates the methods, the quality of data in the network, and allows extrapolation of the trial results to the general patient population.

Research perspectives

Sophisticated analyses of high quality electronic medical records can complement costly, complex and lengthy randomized clinical trials, can assess their representativity for

actual medical practice in real world, and may, in certain instances, even be able to replace them.