Author's response to reviews

Title: Sodium Glucose Co-Transport 2 Inhibitors in the Treatment of Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Double-Blind Controlled Trials

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Version: 3
Date: 4 December 2013

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RESPONSE TO REVIEWERS’ COMMENTS

Response to Reviewer number: 1 (Flavia Prodam)

Major compulsory revisions.

Comment 1
The Authors analysed data derived by studies with SGLT2 or placebo alone or in combination with other anti-diabetic drugs. The combination therapies could have an impact on the results of the meta-analysis. A forest-plot for subgroups (mono-therapies vs combined/placebo therapies) would be important in the view of the clinical management of the patients.

Response to comment 1
First of all, the authors would like to acknowledge the reviewer for taking his/her time to review and forward valuable comments to enrich the content of the manuscript.

To address the concern on the possible clinical outcome variations when SGLT2 inhibitors used as monotherapy or in combination with other anti-diabetic drugs, we have conducted subgroup analyses (SGLT2 monotherapy vs Combination with other antidiabetic drugs) (Additional Fig 1 – Additional Fig 4). However, the therapeutic outcome of SGLT2 inhibitors when used in combination with other anti-diabetic drugs was not significantly different from SGLT2 inhibitors monotherapy (Result section: paragraph 2).

Comment 2

Response to comment 2
This is a well taken comment; for every SGLT2 inhibitors we have conducted several meta-regression analyses to determine the change in therapeutic outcomes with a change in doses of SGLT2 inhibitors (Result section: paragraph 2) (Additional Fig 5 – Additional Fig 10). In any of the meta-regression analyses increase in dose was not significantly associated with an increase in clinical response or adverse events.

Comment 3
Authors observed a reduction in weight after the treatment with SGLT-2 inhibitors. Moreover, they recorded a significant reduction in both systolic and diastolic blood pressure levels, and an increase in HDL levels. However, the last findings on blood pressure and lipids could be mediated by the weight changes, as debated for other pharmacological classes. These results should be controlled for the dependency by changes in weights. Moreover, this aspect should be discussed.
Response to comment 3
As noted by the reviewer, meta-analyses of change in blood pressure and lipids level are not controlled to the change in body weight. This is because; to the best of the authors’ knowledge, the currently available meta-analysis software are not yet designed to perform multivariate meta-analysis. To address this concern we have added statements on the possible confounding effect weight reduction on the change in blood pressure and lipids level in the revised manuscript (discussion section – paragraph 3).

Comment 4
Abstract. Inclusion and exclusion criteria for data extraction should be more described.
Response to comment 4
This is a well taken comment. In the revised manuscript we have addressed this comment.

Comment 5
Methods. Temporal brackets to be eligible for data extraction are lacking.
Response to comment 5
This is also a well taken comment. In the revised manuscript it is corrected.

Comment 6
Results. The Authors did not clearly specify how many patients received SGLT2 inhibitors alone, how many placebo alone, how many combinations etc.
Response to comment 6
A well taken comment. In the revised manuscript we have mentioned the total number of patients who received placebo, placebo with other antidiabetic drug, SGLT2 inhibitors alone and SGLT2 inhibitors with other antidiabetic drugs (Result section – paragraph 1).

Minor essential revisions.
Comment 1
Figures. Relative weights of each figure should be introduced in the forest plot.
Response to comment 1
To generate forest plots we used OpenMetaAnalyst software. This software generates forest plots with a very good resolution but without relative weights of included studies. So if the reviewer still insisted we may use other software to generate the forest plots with relative weight to each study.

Comment 2
Introduction. The Authors should better clarify the aim of the meta-analysis at the end of introduction by introducing whether they evaluated RCT only vs placebo or vs other therapies (other drugs, combinations etc).
Response to comment 2
This is a well taken comment. In the revised manuscript we have modified the aim of this meta-analysis as recommended.

Comment 3
Please, insert data about the type of the study chosen in terms of funding (sponsored or not).

Response to comment 3
This is also a well taken comment. Even if being sponsored study is not among the study inclusion criteria to this meta-analysis, all the included studies were sponsored by pharmaceutical companies. In the revised manuscript we have added a statement as a limitation in the discussion section – paragraph 5.
Response to Reviewer number: 2 (Ching-Chu Chen)

Minor Essential Revisions

Comment 1
Introduction: paragraph 2, "Intensive therapy of patients with type 2..." In fact, DCCT (ref. 6) is a study of type 1 diabetes.
Response to comment 1
First of all, the authors would like to thank the reviewer for taking his/her time to review and forward valuable comments to enrich the content of the manuscript. As the reviewer correctly identified the study listed in reference 5 is a study on type 1 diabetes. The authors admitted it was mistake. In the revised manuscript we have replaced it with other study on type 2 diabetes.

Comment 2
Results: Please indicate Fig 3 in paragraph 3; Fig 4 and Fig 5 in paragraph 4. Please report subtotal ORs (adverse events) of ipragliflozin in paragraph 4. Regarding the discontinuation of medication, the overall OR = 1.05, 95% CI, 0.81 to 1.36, instead of 1.35 (based on the report of fig 5), at the end of paragraph 4.
Response to comment 2
This is a well taken comment. Accordingly in the revised manuscript we have addressed all the comments.

Comment 3
Authors should revise the format of the references carefully. The name of the first author of reference 29 is Yale JF.
Response to comment 3
This is also a well taken comment. In accordance to the journals referencing style, we have tried to revise all the references.

Comment 4
Please report the frequency of dosing in table 1 and correct a typing error Wilding JPH et al 18().
Response to comment 4
The authors once again acknowledge the reviewer for his detailed revision. In the revised manuscript we have corrected it.