Dear Dr Weber,
Thank you again for your consideration of our manuscript entitled "Risk of hypoglycaemia related to the addition of DPP-4 inhibitors to sulphonylureas: systematic review and meta-analysis" (Manuscript ID: BMJ.2015.026084).
You will find below a point-by-point reply to the Reviewers' comments.

Also for this second review, we have submitted two versions of the manuscript, one in which the changes are made apparent using Word track changes, and one in which these modifications are not apparent.
We hope that the manuscript will now be acceptable for publication in the BMJ.

Yours sincerely,
Francesco Salvo

Response to reviewers

Manuscript "Risk of hypoglycaemia related to the addition of DPP-4 inhibitors to sulphonylureas: systematic review and meta-analysis"
Manuscript ID: BMJ.2015.026084.R1

Reviewer: 1

Recommendation:

Comments:
Statistical Review

Risk of hypoglycaemia related to the addition of DPP-4 inhibitors to sulphonylureas: systematic review and meta-analysis

The authors have taken on board comments about the computations of numbers needed to treat in their revised manuscript. I still have the following issues.

Reviewer (R) 1, Comment 1: I previously pointed out that computation of an NNT requires stating an expected event rate, and as more events accumulate the longer a group is followed, any computation of the NNT needs to be conditioned on a stated period of follow-up. In their response, the authors agree with this, and identified estimates of expected event rates for different durations. However, most of their NNT computations, including those in the abstract are for studies with mixed and unstated follow-up, which continues their original error. Whilst it is always possible to put together a set of studies with mixed follow-up to compute an expected event rate, the answer you obtain cannot be applied. I would request that any NNT that is stated in the paper is specific to a stated follow-up period.

Authors' Reply: As suggested by the Reviewer, we now provide specific durations of study follow-up for each NNT reported in the new version of the manuscript.

R1, Comment 2: The authors have chosen to compute an expected event rate used for computation of NNTs using data from a different meta-analysis, and not the data in their meta-analysis. I am not convinced of why they needed to do this – and it is notable that the expected event rates in the chosen MA are around twice as high as in their data, leading to the NNTs being twice as strong (e.g. the NNT is 10 rather than an NNT of 20). Given that this computation is now post hoc, a very strong justification needs to be made as to why the studies in their meta-analysis are not suitable for making this computations, whereas the ones included in someone else's meta-analysis are preferable.

Authors' Reply: We agree with the Reviewer on the fact that the choice of an external reference for NNT can be considered as a post-hoc analysis, thus requiring justification. In the current version of the manuscript, this choice is now clearly explained. For the sake of completeness, please find below the reasons that led us to consider an external source for our computations:
a) The possibility of using an external reference was raised by the Reviewer in his previous assessment of the manuscript when he suggested computing NNT(H)s based on Assumed Control Risk (ACR) for different treatment durations.
b) Starting from the Reviewer's comment, we firstly evaluated the duration of follow-up of studies included in our meta-analysis: nine of ten studies followed patients for no more than 6 months. Therefore, the use of our internal assumed control risk would only allow NNT(H) to be computed for treatment durations ≤6 months. This was computed at 19 (95%CI 13-35).
c) We thus made an extensive review of the literature concerning SU to search for additional ACR data and found a Cochrane meta-analysis from 2013 that included 27 RCTs with different study lengths. Using these data, we computed the NNT(H) for different treatment durations as recommended: "The NNT(H) was 17 (95%CI 11 to 30) for a treatment duration <6 months, 15 (9 to 26) for 6.1 to 12 months, and 8 (5 to 15) for a treatment duration longer than one year." The NNT(H) for treatment durations ≤6 months obtained from this external source appeared consistent with those obtained from our internal ACR.
d) To provide NNT(H) estimates obtained on a homogeneous basis, we thus decided to present only those obtained using this external source.
We agree with the Reviewer that this aspect is crucial regarding the validity of the NNT(H)s estimates that can be drawn from our meta-analysis. We believe that the most important aspect was to provide estimations for different study durations. In the approach we finally chose, we decided to favour the data source that would make it possible to obtain estimates computed on a homogeneous basis. However, an alternative would be to use internal sources whenever available (in the present situation, for ACR and estimates regarding treatment durations ≤6 months) and to complement them with external sources for other treatment durations (the Cochrane meta-analysis would thus be used to compute NNT(H) estimates for treatment durations longer than 6 months). If the Editor considers this approach as more reliable, we would be happy to modify our presentation as both appear equally consistent and comparable in terms of results.
Whatever the approach chosen, the limitation will be the same and has been highlighted in the revised version of the manuscript: "In the present study, the pooled RR was retrieved mainly from studies with a follow-up of less than 6 months. Thus, the NNT(H) calculation for other study durations is based on the assumption of a constant risk over time. In the absence of data in this regard, the most reliable estimation of NNT(H) is that reported for the first six months of treatment."

R1, Comment 3: The statistical reporting in the abstract needs improvement, particularly the methods and results.
Authors' Reply: The "design" paragraph of the abstract has been modified to state that we used fixed models with the M-H method and that we performed subgroup analyses. We have also modified the Results section of the abstract to report NNT(H)s related to specific study durations.

R1, Comment 4: Page 9 (all page numbers refer to track changed word file) states "The study was performed in accordance with PRISMA". PRISMA is a reporting standard not a performance standard, so it could be reported in accordance with PRISMA.
Authors' Reply: Thank you for highlighting this. The manuscript has been revised accordingly.

R1, Comment 5: Page 9 – please check whether the abbreviation PBO is defined – I do not think it is now defined in the text.
Authors' Reply: The Reviewer was correct, the abbreviation PBO is now defined in the main text (Methods section, end of Eligibility criteria paragraph).

R1, Comment 6: Statistical methods – page 10 states that the subgroups were compared with Cochrane Q test and I2 index. First it is Cochran, not Cochrane. Second the Cochran Q test measures the heterogeneity in a group, not a difference between groups. Please refer to the Cochrane Handbook for the correct way to describe this test.

Authors' Reply: We thank the Reviewer for his careful reading and suggestions. We have corrected the typo (Cochran) and the Methods section has been updated in order to refer to the statements in the Cochrane Handbook for this type of analysis. In particular we now refer to Cochrane suggestions for using the standard test for heterogeneity across subgroup results rather than across individual study results. Moreover, a statement concerning the use of the I2 statistic in subgroup analyses has been added in order to clarify that it was used to evaluate the proportion of variability in effect estimates from the different subgroups (rather than from different study estimates).

R1, Comment 7: How did you judge that patient characteristics were imbalanced across groups?
Authors' Reply: The point is indeed pertinent. Following the suggestion of a reviewer regarding the original submission, we checked for imbalances among groups on patients' key characteristics. We noted that in the studies reported by Barnett et al. and Lewin et al., the gender distribution appeared different across DPP4-i and PBO groups (e.g. in Barnett et al., 10% difference in the proportion of male subjects between the compared groups). We did not test the imbalance across groups, as it seemed notable enough in the context of randomised trials. Consequently, we have reworded this section more judiciously ("apparent imbalance").

R1, Comment 8: This is not included in the quality assessment, and is usually a very subjective judgement.

Authors' Reply: We agree with the Reviewer on this aspect. In accordance also with Reviewer 1, comment 9, we have added the explanation for the assessment of each item in the quality assessment in the Supplement. The apparent imbalance in sex distribution across the compared groups was one of the main reasons for the prudence with which we assessed the efficiency of the randomisation procedure in the studies reported by Barnett et al. and Lewin et al., and for which we scored this item as "unclear" in both.

R1, Comment 9: In reporting the quality assessment, the only detail that is given is that three studies were judged to have a high risk of reporting bias and one a high risk of detection bias. Could you please explain why you came to these judgements? What was it about these studies which supports these judgements?

Authors' Reply: We fully agree with the Reviewer that this aspect could have been more clearly detailed. The Supplement now contains full details on the risk of bias assessment performed for each study.

R1, Comment 10: IN the discussion page 15 that the risk of bias assessment indicated that study quality was high which was confirmed by the GRADE assessment. As GRADE is based (in part) on the quality assessment, it is rather a nonsense to imply that GRADE confirms the quality assessment was correct? Clearer expression is needed.
Authors' Reply: We agree with the Reviewer about the potentially misleading expression. We have thus reworded this section and moved the sentence concerning GRADE assessment to the end of the paragraph detailing the strength of the present work. We feel that this is its place as GRADE provides an overall assessment of the value of the meta-analysis that goes beyond study quality per se (i.e. not only study quality but also consistency, directness, effect size, etc.).

R1, Comment 11: There are other points in the discussion which need more careful wording – for example where the results of sensitivity analyses are interpreted as saying there was no significant change – no assessment of the significance of differences is undertaken in a sensitivity analysis.

Authors' Reply: We fully agree and apologise for the inappropriate wording. We have modified the manuscript accordingly.

Additional Questions:
Please enter your name: Jon Deeks

Reviewer: 2

Recommendation:

Comments:
R2, Comment 1: Thank you for the revised manuscript. My only remaining comment is that I believe the key paragraph on Eligibility Criteria in Methods could be made even more clear. You now state that a criteria was that the studies were placebo controlled, but I think it should say explicitly that studies were eligible if the control arm was treated with placebo + SU. This is made clear otherwise throughout the manuscript, and it should be clearly stated here as well. Thank you.

Authors' Reply: We thank the Reviewer for this suggestion. The Methods section has been modified accordingly.

Adina L. Feldman

Reviewer: 3

Recommendation:

Comments:
Comment to the editor
R3, Comment to the Editor 1: The authors fail to use proper background information on hypoglycaemia.

Authors' Reply: We agree with the reviewer that using proper background information on hypoglycaemia is crucial in a manuscript like ours. This is why we used the latest Cochrane review available on the subject (Hemmingsen B, et al. Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. Cochrane Database Syst Rev 2013; 4: CD009008). The reviewer may have been under the impression that we used a reference from 2015 instead (Hemmingsen B, et al. WITHDRAWN: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. Cochrane Database Syst Rev 2015; 7: CD009008). That reference was irrelevant as it has been withdrawn.

R3, Comment to the Editor 2: They use meaningless references and in general have a lack of knowledge of hypoglycaemia from a clinical point of view.
Authors' Reply: For obvious reasons we did not and could not cite all meaningful references on hypoglycaemia. However, the references we selected were published by known authors and in top-level journals. We believe they cannot be considered meaningless, either regarding only severe hypoglycaemia (Goto A, et al. BMJ 2013;347:f4533; Bonds DE, et al. BMJ 2010;340:b4909) or any hypoglycaemia (Currie CJ, et al. Lancet 2010;375:481-9; Accord Study Group. NEJM 2011;364:818-28; Huang ES, et al. JAMA Intern Med 2014;174:251-8; Johnston SS, et al. Diabetes Obes Metab 2012;14:634-43; Budnitz DS, et al. NEJM 2011;365:2002-12; etc). Consequently, we take the comment from the reviewer to mean that some important meaningful references were missing. We have thus complemented the bibliography by including additional references concerning incidence of mild and severe hypoglycaemia (Schopman J, et al. Diabetes Metab Res Rev 2014; 30(1): 11–22) and the clinical relevance of hypoglycaemia, which certainly cannot be considered only on a short-term basis (Gilbert RE & Krum H. Lancet 2015;385(9982):2107-17).

R3, Comment to the Editor 3: For instance, impaired awareness of hypoglycaemia is not a problem for patients with type 2 diabetes that are treated with oral medication.

Authors' Reply: The mechanisms underling hypoglycaemia unawareness are manifold and, up to now, not completely understood (NEJM 2013; 369: 362-72). While hypoglycaemia unawareness is classically illustrated with regard to Type I and advanced Type II diabetic patients, it has also been recognised in non-diabetic subjects (Heller SR, Cryer PE. Diabetes 1991;40:223-6; Segel SA, et al. Diabetes 2001;50:1911-7; Arbeláez AM, et al. Diabetes 2008;57: 470-5). The condition of its occurrence is that subjects experience hypoglycaemia not followed by an adequate decrease in insulin secretion.

R3, Comment to the Editor 4: They also mix up prevalence and incidence of hypoglycaemia

Authors' Reply: Clearly our study only deals with incident events. The term "prevalence" was used once by mistake in the previously submitted version. This has now been corrected together with the two inappropriate uses of the word "frequency".

R3, Comment to the Editor 5: and they are not differentiating mild from severe hypoglycaemia which is clinically relevant information.

Authors' Reply: We believe that the Reviewer focused on the short-term consequences of hypoglycaemia, while this differentiation is of lesser importance when long-term consequences are considered (among others: Gilbert RE & Krum H. Lancet 2015;385(9982):2107-17; Accord Study Group. NEJM 2011;364:818-28).

Although they might have provided a technically well performed meta-analysis they fail to translate this properly to diabetes care. I do feel that this paper is not suitable for publication in BMJ.

Comment to the authors

Major comments:
R3, Comment 1: Please provide a more balanced introduction about hypoglycaemia. There should be a clear difference between severe hypoglycaemia and mild hypoglycaemia throughout the article. Severe hypoglycaemia is potentially life-threatening and might be a cause for hospitalisation. Mild hypoglycaemia is an unwanted event for a number of reasons, but this is not directly life-threatening.

Authors' Reply: We agree with Reviewer 3 and have made this point clearer in the revised version of the manuscript. We underline that severe hypoglycaemia is of primary importance as it is potentially immediately life-threatening, which is not the case with moderate/mild hypoglycaemia. For the latter, we point out that, while the short-term risk is less clear, the event appears to be a clinical concern, as it has been associated, among others, with an increased risk of cardiovascular events and death over time (Gilbert RE & Krum H. Lancet 2015;385(9982):2107-17; Accord Study Group. NEJM 2011;364:818-28).

R3, Comment 2: Remove the part about hypoglycaemic associated autonomic failure and impaired awareness of hypoglycaemia from introduction and discussion section. This is not a problem for diabetes patients with residual beta-cell function (all patients that are treated with oral medication have residual beta cell function, otherwise they would need insulin). This can also be read in Harrison, the textbook you refer to.

Authors' Reply: We agree that hypoglycemia-associated autonomic failure (HAAF) is mainly a problem for patients with Type I diabetes or advanced Type II diabetes (as made clear in the Harrison). However, as Reviewer 3 is aware, the pathophysiological mechanisms underlying hypoglycaemia-associated autonomic failure (HAAF) leading to hypoglycaemia unawareness are manifold and not fully elucidated to date (NEJM 2013; 369: 362-72). On the other hand, it is known that HAAF can be induced by recent hypoglycaemia also in non-diabetic subjects (Heller SR, Cryer PE. Diabetes 1991;40:223-6; Segel SA, et al. Diabetes 2001;50:1911-7.; Arbeláez AM, et al. Diabetes 2008;57: 470-5). This is the result of an absence of decrease in insulin secretion in hypoglycaemic situations, which could typically occur in Type II diabetic patients with enhanced insulin secretion, as in patients treated with DPP4-i and SU.

R3, Comment 3: Reference number 13 and 14 are meaningless and should be removed.
Authors' Reply: We agree with the Reviewer: the scope of references 13 and 14 is different from the others. However, in our opinion, these references provide a certain added value since, unlike the other works cited, they analysed hypoglycaemia unawareness from a clinical perspective and its potential impact on the day-to-day life of patients concerned.

R3, Comment 4: Prevalence and incidence of hypoglycaemia are both relevant. Please, provide more details about the

prevalence and incidence of mild and severe hypoglycaemia in sulfonylurea or DPP4-treated patients. What are the estimates?

Authors' Reply: According to the suggestions of Reviewer 3, we have added references about the incidence of mild and severe hypoglycaemia in SU-treated patients, while these data for DPP4-i are still unavailable to our knowledge.

R3, Comment 5: Reference 26 is withdrawn by the Cochrane Collaboration. Please provide other references.
Hemmingsen B, Schroll JB, Lund SS, Wetterslev J, Gluud C, Vaag A, Sonne DP,
Lundstrøm LH, Almdal TP. WITHDRAWN: Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2015 Jul 29;7

Authors' Reply: Reviewer 3 cited a reference from 2015. Even if it was performed by the same authors and has the same title, reference 26 included in the first revision of our manuscript concerns a systematic review performed in 2013 and has never been withdrawn. Thus we used the latest Cochrane review available to estimate the ACR in SU-treated patients. We therefore feel that this reference is the most appropriate in this regard.

R3, comment 6: Study characteristics
Studies that permitted the use of insulin should be omitted from your analysis. Patients that are insulin treated have different characteristics (less or no beta cell function and therefore have an increased risk of hypoglycaemia)

Authors' Reply: We agree with the reviewer that insulin-treated patients differ from non-insulin-treated ones. However, this not would mean that they would not be concerned by an added risk of hypoglycaemia when using DPP4-i. For this reason, and to take into account their potential differences, we considered eligible studies that allowed the use of insulin and performed a sensitivity analysis in which they were excluded. This sensitivity analysis, planned a priori, answers the Reviewer's comment since it provides comparable results as mentioned in the Discussion section of the manuscript.

R3, comment 7: Meta-analysis
Please provide information on severe hypoglycaemia. Did patients in your selected studies have any episodes?

Authors' Reply: Unfortunately, not all studies provided information on severe hypoglycaemia. However, as previously mentioned, the scope of our manuscript was not to analyse severe hypoglycaemia but hypoglycaemia; this did not hamper the completion of our work.

R3, comment 8: Minor comments:
Page 26, line 4-5
This meta-analysis found about a 50% increase in the risk of hypoglycaemia when DPP4-i and SU were associated in type II diabetes. Please find another word for associated.

Authors' Reply: According to the suggestion of Reviewer 3, the first sentence of the discussion section has been reworded to avoid using the term "associated". The sentence is now: "This meta-analysis found about a 50% increase in the risk of hypoglycaemia when a DPP4-i was added to SU"

Additional Questions:
Please enter your name: Josefine Schopman

Job Title: Resident internal medicine

1. R2_Response to reviewers.doc PDF HTML