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

We have submitted two versions of the manuscript, one in which the modifications are indicated using Word track changes function, and one in which these modifications are not apparent.

We hope that the manuscript is now 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

Editorial committee (EC), Comment 1: Our statistician felt this appeared to be a reasonably well executed and reported systematic review. He added it appeared to add over the results of the individual studies as few of these individually showed statistically significant findings, but it is dominated by results from 3 studies.

Authors' Reply: We agree with this comment. It is common in meta-analyses that a small number of large studies dominate the final results. In the present case, the studies reported by White et al., Owens et al., and Chacra et al. contribute for more than 80% of the final result but without preventing small studies from contributing usefully. In an analysis excluding the three main trials (i.e. considering all studies but those reported by White, Owens, and Chacra et al.), the risk estimate (1.99 [1.37; 2.88]; Q=10.02; p=0.22; I2=40%) was consistent, and even higher than that found in the principal analysis (1.52 [1.29; 1.80]), without strong evidence of heterogeneity. Therefore, the principal analysis is likely to be conservative. We have added this point about the impact of large trials on the final results to the Discussion section of the revised Manuscript (paragraph regarding study limitations). The results of the sensitivity analysis described above have been treated as "data not shown". However, we would be happy to detail these in the manuscript Supplement if the Committee felt this added significant value for the reader.

EC, Comment 2: There is a problem in the way that you have computed the numbers needed to treat that you report which is detailed in the statistical report below.

Authors' Reply: The method of NNT(H) computation has been modified according to the suggestions of Reviewer 4 (comments 6 and 7). We now use the method recommended by the Cochrane Collaboration. For this, we used external data selected to provide a reference for Assumed Control Risk calculation; these were obtained from a meta-analysis that evaluated the use of sulphonylureas (SU) in more than 6,300 type II diabetic patients (meta-analysis published in 2013 that included 27 clinical trials; ref: Cochrane Database Syst Rev 2013; 4: CD009008).
Furthermore, and as suggested by Reviewer 4, we extracted data from this meta-analysis in order to obtain Assumed Control Risk estimates for different durations of treatment: <6 months (7 studies); 6-12 months (9 studies); >12 months (11 studies). Consequently, we were able to calculate the NNT(H) for different assumptions for treatment durations. These have been added to the Results section.

EC, Comment 3: The editors had mixed opinions, with one editor not being supportive and another not being convinced enough of the relevance of the research question.

Authors' Reply: The Introduction section has been reinforced to highlight the clinical relevance of the research question. In particular, we have developed the serious nature of hypoglycaemia (citing some recent studies), irrespective of its severity. For instance:
i) Hypoglycaemia has emerged as a dominant complication of treated diabetes in older adults with a longer history of disease; it is the second cause of hospitalisation in treated type II diabetic patients;
ii) These hospitalisations for hypoglycaemia in type II diabetic patients mostly result from severe iatrogenic hyperglycaemia, which accounts for 20%-25% of all emergency room hospitalisations for adverse drug events;
iii) Hypoglycaemia can cause falls and fractures in the elderly;
iv) Mild to moderate hypoglycaemia decreases the normal adrenergic response to hypoglycaemia; it thus may lead to unawareness of hypoglycaemia and thus increase the risk of recurrent, and severe hypoglycaemia.

We have also underlined the importance of hypoglycaemia and the relevance of the research question in the Discussion section.

For all these reasons, which may also explain the negative effect of excessive glucose control, the risk of hypoglycaemia is a major concern in treated diabetics. Any intervention that increases the awareness in prescribers and patients of the importance of avoiding or preventing hypoglycaemia is of major importance.

EC, Comment 4: Another editor felt that the results are not surprising and the findings may thus not change practice.

Authors' Reply: We agree with the fact that hypoglycaemia, per se, is not a surprising outcome when glucose-lowering drugs are used, as this is their pharmacological effect. The fact remains that the risk of such a frequent event needs to be quantified, as its public health impact could be very large. Prescribers need to be informed about the actual impact of "well known" adverse effects. For example, some adverse effects perceived as particularly frequent by prescribers may differ greatly across products and be much less frequent in practice than assumed, as is nowadays the case for GI bleeding with NSAIDs.
The risk of hypoglycaemia is known and quantified for sulphonylureas used alone and for DPP4-i also when taken alone; to our knowledge, it has never been quantified when DPP4-i are taken with sulphonylureas. The present meta-analysis found a surprisingly high risk of hypoglycaemia with a very meaningful impact (a NNT(H) of about 10 in the revised analyses) which could be the cause of a significant if not large number of cases of hypoglycaemia, which in part are preventable.
We therefore believe that quantification of this risk is crucial for prescribers, as:
- They could review their practice when considering whether they should strengthen diabetes control but at the expense of the risk of severe hypoglycaemia
- This change in practice may be reinforced as the efficacy of the recommended minimisation strategy for that risk (i.e. lowering the dose of SU at DPP4-i initiation) has not yet been evaluated, neither on the reduction of the hypoglycaemia risk nor on the maintenance of the health benefit of adding DPP4-i to the treatment of diabetic patients.

EC, Comment 5: Other editors said that the study was useful to researchers and that it had a clear clinical message.

Thank you.

REFEREES COMMENTS

Reviewer: 1

The authors performed a systematic review and meta-analysis about the risk of hypoglycaemia related to the addition of a DPP4-inhibitor to sulphonylurea derivatives. The authors address a very interesting issue and have an important message. The risk of overall hypoglycaemia would increase with 50% when a DPP4-i is added to SU therapy.
The systematic review and meta-analysis is well conducted, but I have some issues I would like to address. Please find my comments below.

Reviewer (R) 1, Comment 1: General: the article is not so well written and flow could be improved. Please note that hypoglycaemia is an uncountable noun. Please solicit help from a native English speaker to improve English and flow.

Authors' Reply: A native-speaking copyeditor has now gone through the paper.

R1, Comment 2: Title: the current title is: "Risk of hypoglycaemia related to DPP-4 inhibitors plus sulphonylureas: systematic review and meta-analysis". I would suggest to change this into "Risk of hypoglycaemia related to the addition of DPP-4 inhibitors to sulphonylureas: systematic review and meta-analysis". The studies that were included in the review investigated the effect of adding DPP4-I to SU therapy.

Authors' Reply: The title of the article has been modified accordingly.

R1, Comment 3: Introduction: I would suggest that you add information about hypoglycaemia incidence in patients with type 2 diabetes on sulfonylurea monotherapy and DPP4-i monotherapy. This will help the reader to interpret the increased risk of hypoglycaemia that was found in the current review.

Authors' Reply: We agree with the Reviewer; the risk of mono-therapies has been added to the Introduction section.

Please enter your name: J.E. Schopman

Reviewer: 2

R2, Comment 1: The inclusion and exclusion criteria were not described in the text. Did the authors limit the study design only to completely randomized design? Or they also included other study designs, e.g. factorial design, partial factorial design, etc.

Authors' Reply: As suggested by Reviewer 2, we have revised the manuscript to make the inclusion and exclusion criteria clearer, and to specify that we included only the randomised study designs.

R2, Comment 2: The event rates varied a lot across studies in this meta-analysis. For example, the even rate in the treatment group was as low as about 1% (Seino, 2012). In such situation, RR from this study may be unstable. Did the author consider any specific method to treat rare event (e.g. 1%), e.g. Poisson random effects model?

Authors' Reply: We agree with the Reviewer. We obviously thought about using Poisson models as most studies included concerned a large number of patients (e.g. more than 100) and few cases of hypoglycaemia were reported (e.g. fewer than five), and (putatively) the number of outcomes could follow a Poisson distribution. Nevertheless, we decided to comply as strictly as we could with the Cochrane recommendations for conducting meta-analyses. The Cochrane recommends using the Mantel-Haenszel method when studies with a low number of cases (such as those reported by Seino et al. or Kikuchi et al.) are included in a meta-analysis. For that reason, the Mantel-Haenszel method was used in the original analyses. The Methods section has been revised to clarify this aspect.

R2, Comment 3: The statistical heterogeneity test showed there was no variation across 10 included studies (I-square=20%,

P=0.26). However, this heterogeneity test only reflected the difference in the effect estimates (RRs) from each study. It could not reflect the event rate levels themselves. There are a huge variation between even rates themselves, e.g. the even rate in the treatment group was as low as about 1% (Seino, 2012), and as high as about 30% (Barnett, 2013), which deserved a discussion.

Authors' Reply: A difference in the event incidence is usual when meta-analysing clinical trials. However, we agree that in this particular case, it is of a certain importance given the incidence of hypoglycaemia related to the follow-up duration of the study.
The Discussion section of the manuscript has been revised to take into account this point. In particular, we now underline that incidence of hypoglycaemia differs across studies, mainly because of different durations of follow-up. However, this difference did not have any impact on the estimated pooled risk as no heterogeneity in the results was found, nor on the NNT(H) calculation, which in the revised version is based on an external Assumed Control Risk of hypoglycaemia retrieved from 27 clinical studies included in a meta-analysis of the Cochrane library.

R2, Comment 4: The extracted information should be listed for each arm, not for overall. Though randomization can improve the balance of these characteristics between groups, it cannot guarantee the balance. It would be better to show important variables, e.g, HbA1c and age, by study arm. And compare whether there is a significant difference in these key factors. It there is unbalance, the related variables should still be adjusted in a meta-regression framework.

Authors' Reply: Thanks to the suggestion of Reviewer 2, we have reported the key characteristics per group in the revised version of the manuscript.
No meaningful difference in mean HbA1c, mean age, or sex distribution was found, except for the latter in the studies reported by Barnett et al. and Lewin et al. In the study reported by Barnett et al. the proportion of male patients was 72% in the DPP4-i group and 62% in the PBO group; in the study reported by Lewin et al. the proportion of male patients was 48% in the DPP4-i group, and 62% in the PBO group. Thus, this was not sufficient to allow a valid meta-regression to be performed. Excluding these studies from the analysis did not change the results (RR 1.52; [1.27; 1.81]; Q = 10.70, p = 0.15; I2 = 35%).
The per-group patient characteristics of included studies have now been added to Table 1, the imbalance of sex ratio has been noted in the Results section, the sensitivity analysis reported (Meta-analysis subsection of Results), and a figure has been added to the Supplement.

R2, Comment 5: The authors missed some important information such as statistical design (here I mean completely randomized design, factorial design, etc, since all of them are RCTs), and gender (e.g. male proportion) in table 1.

Authors' Reply: As stated in the reply to Reviewer 2 Comment 1, only randomised studies are included in the present meta-analysis (the Methods section has been revised to clarify this). We have thus only added the proportion of male subjects to Table 1, and according to our reply to Reviewer 2 Comment 4, we have reported this per arm.

R2, Comment 6: Since hypoglycaemia is a serious adverse event, the relation between such adverse event and medication should be commonly evaluated in a RCT. Therefore, this meta-analysis should also pool the risk ratio for adverse effect if possible, though most of the adverse events may be adverse effects.

Authors' Reply: The Reviewer's remark regarding the serious nature of hypoglycaemia irrespective of biological severity is of importance and the paper has been revised to reinforce this concept.
Concerning the causal role of the drugs, none of the included RCTs reported the effect (event with an established or at least strongly suspected causal role of a given drug, or a given drug association) rates but only event rates. This has no consequence on association estimates, as, by definition, events include effects, and as differences in event rates in randomised studies are supposed to come only from differences in effect rates. It is in fact even better to rely on event rates, as reporting of effects depends on the validity of event adjudication, which may vary across studies.

Minor concerns:
R2, Comment 7: Page 2, line 34 to 41, what is the P for interaction between the dose (full vs. low) and DPP4-I use?

Authors' Reply: The full vs. low dose analysis was decided a priori as this has a clinical meaning; we considered that a sub-group analysis had to be presented irrespective of the results. In the version of the paper submitted initially, we forgot to detail the results of the test for subgroup differences that was performed according to the Cochrane recommendations. This has been added to the revised version (Figure 4, and page 12 of the manuscript). The Q test did not reach significance (p=0.32). This could result from a lack of power: the low dose analysis is based on a population that is half the size of that on which the full dose analysis is based. This is now discussed together with the potential lack of power regarding the estimate of the risk found for low-dose DPP4-i associated with SU.

R2, Comment 8: Page 2, line 46, 50% should be 52%, or about 50%, also please correct throughout the text.

Authors' Reply: The manuscript has been revised to "about 50%".

R2, Comment 9: Page 4, line 6 to 8, the full name should be given for ACCORD.

Authors' Reply: The manuscript has been revised accordingly.

R2, Comment 10: Page 6, line 13 to 19, based on the description here, the authors of this meta-analysis should have gotten some requested data from the principal authors. But this reviewer did not find any sign to indicate there is such data throughout the text.

Authors' Reply: This is has now been clarified in the Supplement (page 2), and in the Acknowledgments section we thanked the EXAMINE study group for the availability of the data, which were not available in the full text of their work.

R2, Comment 11: Page 7 to 8, statistical analysis part, since the significance level was set as 0.10 for heterogeneity test, the authors should also report the level for publication bias test, and for main analysis.

Authors' Reply: The level of significance of the Egger test has been added to the Methods section.

R2, Comment 12: Page 24, Figure 1, the last sentence in the legend does not match the numbers in the box. Out of 13 studies that could be eligible, data from three studies, not four studies, were not available.

Authors' Reply: Point taken. The sentence has been revised to "data from three studies were not available".

R2, Comment 13: Page 30, Figure 7, the x-axis should be ln(RR), not RR.

Authors' Reply: We thank Reviewer 2 for this comment. This was indeed a typographical error that has now been rectified accordingly.

R2, Comment 14: Page 31 and 32, Table 1 and 2 could be combined, not necessary to separate them.

Authors' Reply: The tables have been merged in the revised version of the manuscript.

R2, Comment 15: Page 37, it is debatable to combine low risk of bias and unknown risk of bias.

Authors' Reply: Yes it is debatable; however, there is no clear cut off for the sensitivity analyses based on the quality of the studies, and none of the included studies was judged to be free of bias. Thus, the only option was to perform sensitivity analyses including studies with low and unclear risk of bias.

Please enter your name: Pengcheng Xun

Reviewer: 3

The authors have undertaken a systematic review and meta-analysis to quantify the relative risk of hypoglycemia as an adverse effect of diabetes treatment with DPP-4i + SU in clinical trials that compared this treatment vs. placebo + SU. 10 studies published between 2007 and 2013 were included. Their finding show that the both the relative and absolute risk of hypoglycemia associated with DPP-4i treatment in combination with SU is high and they conclude that this risk should be taken seriously.
The study is relevant, interesting, rigorously performed and clearly described. I have only minor comments.

R3, Comment 1: Methods/Eligibility criteria. Make it clear that only studies that included placebo + SU in the control arm were eligible.

Authors' Reply: The eligibility criteria have been revised for clarity.

R3, Comment 2: Please already list in methods the brand names of DPP4i treatments that were eligible.

Authors' Reply: We have added the brand name of DPP4-i treatments in the Methods section as suggested.

R3, Comment 3: Page 11, line 27. You write that the results for low doses of DPP-4i were not significant. That's true, but the estimate was still elevated and further down in the same paragraph you mention that no heterogeneity was found between low and high doses. Thus, this statement, although correct, is slightly misleading as the results are in line with there still being an elevated risk even with low doses of DPP-4i.

Authors' Reply: We have reformulated the Results section on this aspect in the revised version of the Manuscript. In particular, we have underlined that the subgroup analysis showed no difference between low and usual dose, and that the increased risk seen for low doses was not significant, probably because of a lack of power in the analysis (see also Reviewer 4 Comment 5 and Reviewer 2 Comment 7).

R3, Comment 4: Figure 2 is redundant, the same results are made clear in the forest plot (fig 3).

Authors' Reply: This figure provides the overall estimation of quality of the included studies, while the forest plots provide the risk of bias for each study. Thus we believe that it is somewhat useful for the readers, who would otherwise only have an overall vision of the quality of the RCTs included in this meta-analysis. For this reason we would prefer to leave this figure in the main manuscript. However, we would be happy to remove it if the Committee also believed it had no added value for the reader.

R3, Comment 5: Consider ordering the studies in fig 3 by chronological calendar year instead of strength of association. It is telling that the first study is the strongest as well.

Authors' Reply: We fully agree with the Reviewer. In the revised version of the figures, studies now appear in chronological

order in all forest plots.

R3, Comment 6: - Can table 1 and 2 not be combined?

Authors' Reply: These tables have been merged in the revised version of the manuscript.

Adina L. Feldman

Reviewer: 4

Risk of hypoglycaemia related to DPP-4 inhibitors plus sulphonylureas: systematic review and meta-analysis
I apologise for the delay in completing this report.
The authors have conducted a meta-analysis of RCTs looking at the risk of hypoglycaemia. They undertake two analyses, a meta-analysis of relative risks (RR) and a meta-analysis of numbers needed to treat (NNT) to observe a harmful event.

R4, Comment 1: The RR meta-analysis method is described on page 7, and is based on either a fixed effect or random effects model dependent on the statistical significance of the test of heterogeneity (using a $P<0.1$ criteria). No method is described for comparing subgroups.

Authors' Reply: We apologise for this omission. The tests used to make subgroup comparisons were the Cochrane Q test and the I2 index, as suggested by chapter 9 of the Cochrane handbook for comparing subgroup results (citation added). The Methods section has been revised accordingly.

R4, Comment 2: The NNT meta-analysis method is described on page 8, and the methodological description simply described as "pooled in a forest plot". This is an inadequate description and it is unclear what has been done.

Authors' Reply: We have added a paragraph to the Methods section explaining the method used, which is now the approach recommended by Reviewer 4 in Comments 6 and 7.

R4, Comment 3: For the RR analysis, the authors report results of comparisons of subgroups (according to definition of hypoglycaemia, according to dose) but do not explain what test for the required tests for differences between subgroups have been undertaken.

Authors' Reply: Again, we apologise for this omission. See above (R4 Comment 1) how we performed this comparison (Q test and I2 index) and how we have revised the Methods section of the manuscript.

R4, Comment 4: For the comparison of hypoglycaemia a P-value is reported for "evidence of heterogeneity between the groups" on line 7 of page 10, but we do not have a method.

Authors' Reply: As stated in the reply to the previous comment (R4, Comment 3), the Methods section has been revised in order to clearly state that the subgroups were compared using the Cochrane Q test and I2 index.

R4, Comment 5: For comparison of doses the focus is on whether each group is statistically significant rather than assessing for differences between the groups (lines 9-10), which is regarded as a misleading way of undertaking subgroup analyses.

Authors' Reply: As stated in our reply to Reviewer 3 Comment 3, we have reformulated the Results section on this aspect in the revised version of the Manuscript. In particular, we underline that the subgroup analysis showed no differences between low and full DPP4-i dose and that the increased risk found for low doses was not significant.

R4, Comment 6: It is not recommended that an average NNT is computed by pooling, as appears to have been done in this manuscript (although the method used is not clear). This is because NNTs mathematically depend on the underlying event rates, which typically vary across studies, introducing heterogeneity. For example, one determinant of event rates is length of follow-up, which always increases event rates. Thus pooling studies with mixed length of follow-up (here studies vary between White with 76 weeks follow-up and baseline event rate of 6.3% and Kikucho and Seino with 12 weeks follow-up both with baseline event rates of 1.0%) is likely to introduce heterogeneity for NNTs, whereas the relative effects are more likely to be consistent at different follow-up points.

Authors' Reply: The Methods section has been updated to clarify how the NNT(H) was calculated (please see our reply to next comment for more details).

R4, Comment 7: The recommended approach (as stated in the Cochrane Handbook) to estimate an average NNT is to obtain the pooled RR estimate from the meta-analysis and to estimate NNTs from it across a range of prevalences which reflect different settings. These prevalences may be obtained from the data in the trials, or from other sources. Clearly here it is important to standardise for the length of follow-up time, and the NNT needs to be stated conditional on that duration of treatment (the longer you treat for the more events will happen).

Authors' Reply: In the revised version of the manuscript, we used an external data source to calculate the NNT(H); the meta-analysis reported by Hemmingsen et al. (Cochrane Database Syst Rev 2013; 4: CD009008) was used as a reference to calculate the Assumed Control Risk in sulphonylurea-treated patients. Moreover, according to the suggestion of Reviewer 4 and the assumption that the prevalence of hypoglycaemia could vary according to the duration of follow-up, four scenarios were considered according to the duration of RCTs included in this meta-analysis: any duration (27 studies); <6 months (7 studies);

6-12 months (9 studies); >12 months (11 studies). Numbers of cases and treated patients for each group, as well as the references of the corresponding studies, are detailed in the revised version of the Supplement.

R4, Comment 8: I would also encourage the authors to stick with the notation and terminology introduced by Altman for NNTs, which is the NNT for one person to be harmed NNT(H) or benefit NNT(B). The authors introduce this at the beginning, but then slip into the rather inappropriate NNH – number needed to harm. Although widely used, this abbreviation is erroneous.

Authors' Reply: NNH has been revised to NNT(H) throughout the manuscript.

Please enter your name: Jon Deeks