22-Jan-2016

Dear Dr. Salvo

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

Thank you for sending us your paper. We sent it for external peer review again (including statistical review). We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the reviewer's comments, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

Tiago Villanueva
Assistant Editor
tvillanueva@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=e4c4cd92368d4408b110d0cf97d9abd6

** Comments from the external peer reviewers**

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.

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.

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.

3) The statistical reporting in the abstract needs improvement, particularly the methods and results.

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.

5) Page 9 – please check whether the abbreviation PBO is defined – I do not think it is now defined in the text.

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.

7) How did you judge that patient characteristics were imbalanced across groups? This is not included in the quality assessment, and is usually a very subjective judgement.

8) 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?

9) 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. 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.

Additional Questions:
Please enter your name: Jon Deeks

Job Title: PRofessor of Biostatistics

Institution: University of Birmingham

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
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.

Adina L. Feldman

Additional Questions:
Please enter your name: Adina L. Feldman

Job Title: Career Development Fellow

Institution: University of Cambridge

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 3

Recommendation:

Comments:
Comment to the editor

The authors fail to use proper background information on hypoglycaemia. They use meaningless references and in general have a lack of knowledge of hypoglycaemia from a clinical point of view. For instance, impaired awareness of hypoglycaemia is not a problem for patients with type 2 diabetes that are treated with oral medication. They also mix up prevalence and incidence of hypoglycaemia and they are not differentiating mild from severe hypoglycaemia which is clinically relevant information. 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:
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.

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. Reference number 13 and 14 are meaningless and should be removed.

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? 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

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)

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

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.

Additional Questions:
Please enter your name: Josefine Schopman

Job Title: Resident internal medicine

Institution: Academic Medical Center

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

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c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)

ii. For a cohort study: Absolute event rates over time (eg 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)
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v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

g. Footnotes and statements

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Date Sent: 22-Jan-2016