PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Safety and effectiveness of dipeptidyl peptidase-4 inhibitors versus intermediate-acting insulin or placebo for patients with type 2 diabetes failing two oral antihyperglycemic agents: A systematic review and network meta-analysis
AUTHORS	Tricco, Andrea; Antony, Jesmin; Khan, Paul; Ghassemi, Marco; Hamid, Jemila; Ashoor, Huda; Blondal, Erik; Soobiah, Charlene; Yu, Catherine; Hutton, Brian; Hemmelgarn, Brenda; Moher, David; Majumdar, Sumit; Straus, Sharon

VERSION 1 - REVIEW

REVIEWER	Arne Ring PhD, AFHEA Professor of Statistics CTU Principal Statistician Leicester Clinical Trials Unit University of Leicester Leicester Diabetes Centre Leicester Previously employed by Boehringer Ingelheim Pharma (Germany) and the Diabetes Trials Unit Oxford (UK). Received consultation fees from Roche, Boehringer Ingelheim and Novartis.
REVIEW RETURNED	08-Jul-2014

GENERAL COMMENTS	* While the title mentions "insulin" as one of the main subjects of this review, the abstract conclusion does not. Also the "negative" outcomes of insulin should be mentioned in the abstract conclusion. * Protocol registration (Jan 2013) and publication of protocol (submission Feb 2013) were in time, hence raising the credibility of the review. * When references are given as internet links, the full date of last access should be given, not just the year. In particular the authors should confirm during the revision whether the links are still accessible. * P.8, line 148 states: "Sub-group analysis was conducted when significant heterogeneity was observed (e.g., I2 statistic >75%). " Question 1: I could not find any outcome on the heterogenity assessments. This should be presented and discussed, in particular as the protocol stated: "We will subsequently determine whether a random effects meta-analysis [21] is feasible and appropriate." Question 2: The authors have performed a subgroup analysis by

	individual drugs (p12, line 221 onwards). Was this analysis maybe triggered by the hetergogenity assessment? If not, it should be stated clearly that this analysis was not pre-planned in their protocol (ref.6). The authors should comment why they would like to include the statement in line 222-225, because absence of evidence is not evidence of absence. In contrast, lines 226-229 appear to have a clear basis (using SUCRA) and hence allow for a meaningful interpretation of potential HbA1c lowering; but I would recommend that the probability of all drugs should be reported - maybe best with a figure in the appendix illustrating the posterior distributions of HbA1c lowering of each drug.

REVIEWER	Dr Victoria Allgar University of York, England
REVIEW RETURNED	04-Aug-2014

GENERAL COMMENTS	The methodology is clearly stated and appropriate for data. However it was not clear whether fixed or random effects analysis was used, based on the test for heterogeneity. The testing of assumptions is not clear in the analysis.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1: Dr. Arne Ring
1. While the title mentions "insulin" as one of the main subjects of this review, the abstract conclusion does not. Also the "negative" outcomes of insulin should be mentioned in the abstract conclusion.

On page 4, we modified the conclusions as follows:
'DPP-4 inhibitors were superior to placebo in reducing A1C levels in adults with T2DM taking at least two oral agents. Compared with placebo, no safety signals were detected with DPP-4 inhibitors and there was a reduced risk of infection. There was no significant difference in A1C observed between NPH and placebo or NPH and DPP-4 inhibitors.'

2. Protocol registration (Jan 2013) and publication of protocol (submission Feb 2013) were in time, hence raising the credibility of the review.

Thanks for noting this.

3. When references are given as internet links, the full date of last access should be given, not just the year. In particular the authors should confirm during the revision whether the links are still accessible.

We have checked all of the URLs, revised any that were incorrect and modified the date of access.

4. P.8, line 148 states: "Sub-group analysis was conducted when significant heterogeneity was observed (e.g., I2 statistic >75%)".

a. I could not find any outcome on the heterogenity assessments. This should be presented and discussed, in particular as the protocol stated: "We will subsequently determine whether a random effects meta-analysis [21] is feasible and appropriate."

We have added the heterogeneity assessment to the NMA results. The statistical heterogeneity is available in the meta-analyses results.
Line 212-214:
'Patients receiving a DPP-4 inhibitor (plus metformin and a sulfonylurea/exenatide/ pioglitazone) had an average reduction in A1C (MD: 0.62%, 95% credible interval: 0.33 to 0.93, I2=87%) versus placebo plus metformin and a sulfonylurea/exenatide/ pioglitazone in network meta-analysis including 8 RCTs (Figure 2).'

b. The authors have performed a subgroup analysis by individual drugs (p12, line 221 onwards). Was this analysis maybe triggered by the hetergogenity assessment? If not, it should be stated clearly that this analysis was not pre-planned in their protocol (ref.6).

We have clarified that these sensitivity analyses were not preplanned and were triggered by the heterogeneity that was identified.
Line 225:
'Because of the statistically significant heterogeneity identified in the NMA, we conducted several unplanned sensitivity analyses. A sensitivity analysis was conducted with each of the drugs were included separately in the model (i.e., without grouping the DPP-4 inhibitors together). Only sitagliptin plus metformin and a sulfonylurea, and vildagliptin plus metformin and a sulfonylurea significantly reduced A1C versus placebo plus metformin and a sulfonylurea (MD: -0.83%, 95% credible interval: -1.55 to -0.14 and MD: -0.97%, 95% credible interval: -1.89 to -0.19, respectively). According to SUCRA values (Table 5), vildagliptin plus metformin and a sulfonylurea had the greatest probability (85%) of being the most effective in reducing A1C compared with all agents included in the model, while sitagliptin plus metformin and a sulfonylurea had the second greatest probability (76%) of being the most effective in reducing A1C. Furthermore, sensitivity analyses were conducted to control for baseline A1C values and account for imputations on missing data; no changes in the results were observed.'

5. The authors should comment why they would like to include the statement in line 222-225, because absence of evidence is not evidence of absence.

We included this statement because we limited reporting to statistically significant results; we have outlined in the discussion that the NMA is limited by the lack of available trials that can contribute data and thus the results may change if larger trials are conducted in the future.

6. In contrast, lines 226-229 appear to have a clear basis (using SUCRA) and hence allow for a meaningful interpretation of potential HbA1c lowering; but I would recommend that the probability of all drugs should be reported - maybe best with a figure in the appendix illustrating the posterior distributions of HbA1c lowering of each drug.

We have added Table 5 that provides the SUCRA for all of these agents.

Reviewer #2: Dr. Victoria Allgar

1. The methodology is clearly stated and appropriate for data. However it was not clear whether fixed or random effects analysis was used based on the test for heterogeneity.

On page 8, we state that,
'When sufficient data were available, random effects meta-analysis was conducted to calculate the pooled mean difference (MD) for continuous outcomes and relative risk (RR) for dichotomous outcomes.'
And we also state:

‘In addition, we conducted a Bayesian random effects network meta-analysis using R and WinBUGS19 for A1C, the primary outcome of interest.’

2. The testing of assumptions is not clear in the analysis.

We have added details in the methods and results as follows:
Lines 165-167:
‘Important network inconsistency was explored using sensitivity analysis. We assessed the transitivity assumption by examining the comparability of the distribution of the treatment effect modifiers across comparisons, including A1C levels (<8% versus ≥8%).’