PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Glycaemic durability with DDP-4 inhibitors in type 2 diabetes: a systematic review and meta-analysis of long-term randomised controlled trials
AUTHORS	Esposito, Katherine; Chiodini, Paolo; Maiorino, Maria Ida; Bellastella, Giuseppe; Capuano, Annalisa; Giugliano, Dario

VERSION 1 - REVIEW

REVIEWER	Jake Olivier Associate Professor School of Mathematics and Statistics University of New South Wales Sydney, Australia
REVIEW RETURNED	01-May-2014

GENERAL COMMENTS	This manuscript is an overall well written systematic review of studies assessing the association between DPP-4 inhibitors on HbA1c in type 2 diabetes patients. I only have a few comments to make. 1. A1c is sometimes written as subscript and others times not, please be consistent in the manuscript 2. I^2 is stated as being significant without any p-values, I would agree that it's quite large but please reserve the term "significant" for hypothesis testing (alternatively, insert the p-value into the abstract) 3. The intermediate observation happens over a long period of time, can the authors discuss the effect this has on the analysis, it seems like a limitation here 4. Why was p=0.1 used as a cut-point for statistical significance for the Q statistic?

REVIEWER	Matteo Monami Careggi Teachin Hospital, Firenze, Italy. Matteo Monami has received speaking fees from Bristol Myers Squibb. Astra Zeneca. Boehringer- Ingelheim. Eli-Lilly. Merck. Novonordisk. Merck. and Takeda. and research grants from Bristol Myers Squibb.
REVIEW RETURNED	12-May-2014

GENERAL COMMENTS	The authors made an attempt to assess the glycemic durability of DPP-4 inhibitors. They hypothesized that durability of glycaemic control may be a surrogate marker to test the hypothesis that DPP-4

	inhibitors influence beta-cell loss. To test this hypothesis, they included in the present metanalysis 12 randomized trials evaluating the long-term effect (up to 108 weeks) of DPP-4 inhibitors on haemoglobin A1c (HbA1c) level. Major criticisms 1) The most important problem of this very well-conducted meta-analysis (i.e. appropriate methods) is the fact that 2 years is a very short time for assessing the glycemic durability of a glucose lowering agent. The same ADOPT (5-yr RCT comparing rosiglitazone, metformin and glyburide) should be paradoxically considered a relatively short-term trial! 2) The second major problem is the heterogeneity of the trials included. In fact, in some studies, patients allocated to the DPP-4i arm were allowed to use other GLA, such as SU, and in others, DPP-4i was administered as monotherapy. This latter point is not negligible at all, and can theoretically affecting the results obtained by the authors. In fact, it is well-known that SUs can affect the beta-cell function in a time-dependent manner. 3) last but not the least, the number of trials and patients included in the present analysis is relatively scarce, making difficult any reliable conclusion on this very important and interesting issue.

REVIEWER	Karen Rascati University of Texas USA
REVIEW RETURNED	15-May-2014

GENERAL COMMENTS	Great paper and important insight

VERSION 1 – AUTHOR RESPONSE

Reviewer 1.

Thank you for the appreciation.
1. We tried to avoid writing the same word in different ways. Thanks.
2. We have deleted the term significant from the abstract, inserted the p value, and used the term significant in a more appropriate way.
3. This aspect, i.e. the long period of time of the intermediate observation, has been discussed in Discussion, under limitations of the study.
4. The Q test has a low statistical power to assess heterogeneity between studies; therefore, it is usually set at a higher level ($p < 0.1$, as reported in page 6, last two lines). On the other hand, the p values of the Q test are all $p < 0.0001$.

Reviewer 2.
1. It may be true that a 2-years period is short to assess glycaemic durability. As argued in Discussion, our aim was to see whether there was a difference of effect (on HbA1c) between year 1 and year 2; we still think that this may indicate a trend, at least.
2. Heterogeneity between trials may be a problem; however, sensitivity analyses and subgroup analyses went in the same direction, independent of which drug the DPP-4 inhibitor was added on. Only one trial tested sulfonylurea.
3. The number of trials and patients may be seen as scarce; on the other hand, 12 studies may be enough to see a trend, and other meta-analyses base their findings on lesser studies and people.

Reviewer 3. Thanks for the nice words.