Author's response to reviews

Title: The consequences of delaying insulin initiation in UK type 2 diabetes patients failing oral hyperglycaemic agents: a modelling study

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Version: 3 Date: 28 August 2009

Author's response to reviews: see over
Dear Sir,

We would like to express our thanks to the editorial team at BioMed Central and the reviewers for their valuable review and comments on the manuscript.

We have addressed the reviewer’s comments below and have made the required changes to the manuscript (highlighted in red text). We hope that our responses to the comments are satisfactory and look forward to hearing from BMC Endocrine Disorders.

Response to reviewer’s comments – manuscript 1155502152214134 – The consequences of delaying insulin initiation in UK type 2 diabetes patients failing oral hyperglycaemic agents: a modeling study

We would like to extend our thanks to the reviewers of this manuscript for their time and their valuable input with regards to this manuscript.

We have addressed the reviewer’s comments in the text below and amended the manuscript. We have also amended the manuscript in line with the reviewer’s comments (additions to the manuscript are shown in red in the accompanying version of the manuscript).

Reviewer’s report
Title: The consequences of delaying insulin initiation in UK type 2 diabetes patients failing oral hyperglycaemic agents: a modelling study
Version: 2 Date: 15 April 2009
Reviewer: Edoardo Mannucci

Reviewer’s report:
The new version of the paper is much more balanced than the original manuscript. A few more corrections should be made.

Minor essential revisions
1) I agree with the authors that the UKPDS results on MI are the best possible choice for modeling the effects of intensified diabetes treatment on cardiovascular events. However, those results were not statistically significant; this should be clearly and explicitly recognized in the Methods section, and included as a limitation in the Discussion section.

We believe the reviewer is referring to the results from the UKPDS 33 publication (Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33): The Lancet 1998 352, 837-53) which did show that there was a non-significant difference between the intensive and conventional arms of the trial in terms of MI events. However, UKPDS 35 (Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study: BMJ 2000 321, 405-12) clearly demonstrates a relationship between improved glycaemia and both microvascular and macrovascular
outcomes (including MI) across both arms. The evidence from this analysis of the UKPDS data demonstrated that a 1% decrease in HbA1c levels was responsible for a highly significant 14% reduction in the risk of MI. Whilst we acknowledge the reviewer’s point with regards to UKPDS 33, in light of the evidence mentioned above in this instance we respectfully disagree with the reviewer and have not further edited this section of the manuscript.

2) Although the existing (epidemiological) evidence suggesting that insulin treatment is associated with higher cancer-related mortality cannot be considered fully convincing, I think that it deserves a proper citation in the Discussion, to highlight a further possible limitation of the study. The reference is Bowker et al., Diabetes Care 2006; 29: 254.

We have added a paragraph to the discussion section that refers to the results reported by Bowker et al. (Diabetes Care 2006;29:254–8). We have also referred to the recent findings of Hemkens et al. (Diabetologia, June 2009), who reported a positive association between insulin use (in particular the use of insulin glargine) and the diagnosis of malignant neoplasm. However, as noted by Smith and Dale (Diabetologia, June 2009), the timeframe over which the study by Hemkens et al. was performed was relatively short (5 years), and the same authors also state that the differences in risk observed by Hemkens et al. over this timeframe is almost unprecedented in oncology studies. Both EMEA and the FDA have further questioned these findings and the FDA has stated that “variations in patient characteristics across the treatment groups could have played a role in the finding of increased cancer risk”.

We hope that the paragraph that has been added provides a succinct and objective discussion of the issue of the proposed link between insulin and cancer.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I have received speaking fees, consultancy fees, and/or research grants from manufacturers of insulin (Eli Lilly, Novo Nordisk, Sanofi Aventis) and from manufacturers of hypoglycemic drugs potentially alternative to insulin (the same as above, plus Novartis, Merck Sharp & Dohme, Glaxo SmithKline, Takeda, Merck KgA, Guidotti, Abiogen).
Reviewer's report

Title: The consequences of delaying insulin initiation in UK type 2 diabetes patients failing oral hyperglycaemic agents: a modelling study

Version: 2 Date: 13 May 2009

Reviewer: Andreas Pfützner

Reviewer's report:
I have reviewed the changes made by the authors, which in my consideration have appropriately addressed the raised criticisms. I would therefore consider the manuscript to be now suitable for publication in BMC Endocrine disorders.