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: 2 Date: 27 March 2009

Author's response to reviews: see over
Dear Editor BMC Endocrine Disorders

Firstly we would like to thank the staff and reviewers for their time and effort in the reviewing and preparation of comments regarding our manuscript.

We have responded to each of the reviewers written comments in turn and attempted to fully address all of their questions and concerns. Our responses are highlighted in red text in this letter and in blue text in the updated manuscript which accompanies this response.

We hope that we have understood all of the issues and responded accordingly and that our manuscript will be accepted for publication in BMC Endocrine Disorders.

Yours sincerely

Gordon Goodall
Reviewer's report
Title: The consequences of delaying insulin initiation in UK type 2 diabetes patients failing oral hyperglycaemic agents: a modelling study
Version: 1 Date: 12 January 2009
Reviewer: Edoardo Mannucci

Reviewer's report:
Major Compulsory Revisions
1) The analysis is based on the assumption that improvement of metabolic control can substantially reduce cardiovascular morbidity and mortality. Although epidemiological data show that a higher HbA1c is associated with higher incidence of fatal and nonfatal cardiovascular disease, results of RCTs are not unequivocal. To date, the only trial showing an improvement of macrovascular outcome as a result of stricter metabolic control in type 2 diabetes is the UKPDS Legacy (UKPDS 80) - with an effect much smaller than that assumed in the paper, while the other available trials (UKPDS 33, ACCORD, ADVANCE, and most recently VADT) failed to detect a similar benefit. Based on current evidence, the effect of reduction of HbA1c on CVD morbidity seems to be smaller than that predicted on the basis of observational studies, whereas the benefit in terms of mortality could be null. On this basis, the effects of early insulin therapy should be recalculated, assuming a beneficial effect on microvascular complications, without any effect on macrovascular complications or all-cause mortality.

We agree with the reviewer that by and large there is little evidence from RCTs demonstrating a reduction in the incidence of macrovascular complications with improved glycaemic control. However, given that the UKPDS remains the largest and most comprehensive trial in type 2 diabetes we feel that omitting a pivotal finding such as the reduction in incidence of MI with improved glycaemic control would not be appropriate. Also, as this is the only example of a direct effect of HbA1c on macrovascular outcomes in the diabetes model used in this analysis and as we are unable to simply switch this off we propose that rerunning the analysis is not necessary. It should be noted that the UKPDS Outcomes Model which was constructed directly from the UKPDS data incorporates HbA1c as a risk factor for MI. This emphasizes that prior to the publication of UKPDS 80 there was an observed effect on MI of HbA1c levels. Furthermore, those responsible for the ADVANCE trial have stated that in their view a difference in macrovascular outcomes would have been observed between arms if the follow up period had been extended.

The effect on long-term macrovascular outcomes that the reviewer observes and refers to is also due to the reduced incidence of other health states that contribute to cardiovascular risk. We hope the reviewer would agree that there is considerable evidence that incidence of nephropathy is a key factor for the increased risk of cardiovascular disease (for example, Valmadrid et al. Arch Intern Med 2000;160(8):1093-100). This effect is captured within the model and as improved HbA1c control reduces the risk of nephropathy over time, this in turn impacts on the risk of cardiovascular complications. We believe this is one of the strengths of the model in that it accounts the interdependence and association between states in the model to better reflect a highly complex disease. Ultimately removing these and other interactions between health states within the model would lead to a substantial underestimation of clinical outcomes and unrealistic conclusions.

2) Another assumption is that the reduction of HbA1c leads to the same long-term outcomes, irrespective of the therapeutical tools used. This point is controversial. The authors should acknowledge that, in the only long-term comparative trial available to date, insulin was associated with a higher mortality in comparison with an oral drug (metformin); furthermore, the epidemiological analysis of the DIGAMI-2 trial showed a significant association of insulin therapy with a poorer outcome in comparison with oral treatments. The observational data associating insulin with a higher cancer-related mortality should also be recollected. Although available data are not sufficient to establish a difference in outcomes between different pharmacological treatments, this possibility should be more clearly and extensively recognized in the Discussion. The authors should also mention the fact that many clinicians believe that reaching the therapeutic targets by non-pharmacological means (diet and exercise), whenever possible, could grant a more favorable outcome than any drug therapy.
We acknowledge that in the epidemiological analysis of the DIGAMI-2 trial there was an increase in the cumulative endpoints of death, reinfarction and stroke. However, there are a number of limitations with this data (acknowledged by the authors of the report) that highlight the difficulties in interpreting the findings. In this context we are happy to include a reference to this study and uncertainties regarding the interpretation of findings from our analysis. It should be noted though that on average the time to a first MI event in the analysis presented here is longer than the delay to initiation of insulin (10.04 and 9.28 years). Therefore, the differences between the two alternatives being compared in the base case here would be minimal. Finally, as we have conducted a comparative analysis of insulin based regimens the issue of differences in outcomes when utilizing metformin, sulfonylureas or other non-insulin intervention is largely outside the scope of this study.

We are unaware of any reliable evidence that insulin use is an independent risk factor or significant cause of cancer (as the reviewer states). We believe this would be an inappropriate forum for discussion of such a contentious issue and we have not included any comment of this in the manuscript.

The modelling of a chronic and complex disease such as type 2 diabetes is extremely difficult to carry out and because of the limitations of data availability it remains the best option for estimating long-term outcomes. We have attempted to incorporate the most robust data available in the model to project these outcomes and where possible this would include differences due to treatment modalities. The safeguard to erroneous assumptions in this regard is the external validation of the model against published trial data. Although we are happy to include discussion of the possible variation in outcomes by intervention, independent of the effect on parameters used within the model to calculate risk, we believe that this is unlikely to distort the findings to a substantial degree.

Although the reviewer may be correct and anecdotal evidence may indicate that some physicians believe that lifestyle modification may “grant a more favorable outcome than any drug therapy” it is our understanding that this possible effect is largely due to poor patient compliance with lifestyle modification when a pharmaceutic intervention is also prescribed. The evidence almost unequivocally indicates that improving glycaemic control leads to improved clinical outcomes. The current ADA guidelines on treating type 2 diabetes specifically recommend metformin in conjunction with lifestyle modification as first line therapy now due to the benefits seen with improved glycaemic control. We are happy to include a comment highlighting the general point that not all treatments are equivalent but we feel that further discussion of this point is outside the scope of this article.

3) Early insulin is presented as a "more realistic" approach than oral therapies for reaching and maintaining glycemic targets in type 2 diabetes. While this may well be the case, it should be recognized (in the Discussion) that the introduction of new classes of drugs (e.g., GLP-1 receptor agonists), and the growing use of triple combinations, could change the scenario, providing physicians with some more valid alternative to insulin therapy. The data published by Calvert et al. on which this study bases the time to delay of insulin initiation does include patients on two or more oral therapies but still demonstrates poor glycaemic control for much of the time. However, we completely agree with the reviewer that the portfolio of therapeutic agents for the treatment of type 2 diabetes when properly prescribed together with appropriate monitoring of glycaemic control is likely to offer very real alternatives to insulin. We have updated the discussion to reflect this.

Minor Essential Revisions
1) Ref. 13 is the epidemiological analysis of the UKPDS; the main analysis (UKPDS 33) is a more appropriate reference. This has been altered in the manuscript.
2) Ref. 15 is a meta-analysis of observational studies, and not of RCTs; this should be specified in the text. This has been included in the manuscript.
3) Ref. 14 is not by Patel et al. (it is the ADVANCE study) 
The PubMed citation includes Patel as authors and the referencing software included this in the manuscript. This has been changed to report “The ADVANCE Collaborative Group” as the author of the publication.

4) Ref. 18 could be changed with the more recent (2008) edition of the ADA/EASD Consensus Algorithm by Nathan et al. The most recent statement from the ADA and EASD by Nathan et al. has been included.

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 (Ely 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: 1 Date: 12 January 2009
Reviewer: James Sowers

Reviewer's report:
This is a study based on modeling of the long term benefits of early insulin therapy. This is largely based on the UKDPS. There is no inclusion or discussion of the ACCORD and other recent studies. This needs to be corrected.
The author is correct in his assertion that the model used in this analysis incorporates data from the UKPDS largely because it remains the largest and most comprehensive single longitudinal study of type 2 diabetes available. However, it should be highlighted that it is not the only data source used to construct the diabetes model employed here.

Dealing with the reviewers specific concern regarding ACCORD. We have not incorporated evidence from ACCORD into the model currently as the results from the study, are to a large degree, at odds with the majority of studies in the treatment of type 2 diabetes, i.e. improved glycaemic control leads to improved clinical outcomes. The reason(s) for these differences have not been elucidated yet and it would not seem prudent to ignore the evidence accumulated so far on the benefits of improved glycaemic control because of the results from a single trial. The speculations that increased mortality in the intensively controlled group of ACCORD may have been due to hypoglycaemia and associated MI, the use of TZD’s, patients already at a high risk of cardiovascular disease, etc. are awaiting confirmation and an explanation of the underlying clinical relationships between risk and outcome. We are currently in the process of validating the model against outcomes from ACCORD, ADVANCE, the VADT and UKPDS(80). This may allow us to empirically derive the summary outcomes reported by the studies but this would not represent a valid method and approach for modelling outcomes based on other diabetes studies. We are happy to include brief discussion of this within the manuscript in relation to the model outcomes and practical management of type 2 diabetes and hope that this response is sufficient for the reviewer.

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 declare that I have no competing interests'
Reviewer's report

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

Version: 1 Date: 8 January 2009
Reviewer: Andreas Pfützner

Reviewer's report:

In general, this appears to be a well performed hypothetical modelling study regarding early use of insulin in patients with type 2 diabetes. The authors calculate a longer survival and later onset of diabetes complications in favor of early insulin use.

I have several comments:

There need to be be some more clarification on the baseline model in the method section, or these points need to be discussed as limitations in the discussion section:

- what OADs were considered to be used instead of insulin in the late insulin group (co-medications in the UK in previously published trials may not necessarily represent current state of the art).

We performed the analyses under the premise that the data establishes that patients were poorly controlled on OADs alone according to their HbA1c levels and therefore they should have progressed to the next recommended therapeutic option. The data showed that for insulin this delay is protracted despite the high HbA1c values and our intention was to examine the potential consequences of insulin initiation earlier than observed. The publications by Calvert et al. did not provide details on specific OAD use and although we agree with the reviewer that the regimens may not represent state of the art (and may reflect compliance issues) our study investigated insulin use only and not better OAD management. As we have mentioned briefly in the discussion, we could have chosen to present a more general “what if” analysis with hypothetical improvements in glycaemic control not linked to specific interventions. However, given the published data available (which was the inspiration for performing this analysis) we feel that specifically addressing insulin use is more appropriate. If other data become available we would be very happy to repeat this analysis from a more general perspective. It is possible, however, to interpret the study from a more general point of view, as an investigation into the benefits of improved control in general (with adverse events appropriate for insulin use), especially as a purely clinical outlook has been taken and no costs have been accounted. We have included further discussion of this general point in the manuscript to address the possibility that clinical benefits could be derived from better management of type 2 diabetes and a specific reference to the use of OADs (and modern therapies such as DPP-IV and GLP-1 analogues).

- The model is based on conventional therapy only - this needs to be more clearly stated

We are unsure exactly what the reviewer is referring to. The model is based on what we consider to be the best available evidence for projecting long-term clinical outcomes from typically reported intermediate endpoints and risk factors e.g. HbA1c, blood pressure, serum lipids, use of other medications such as aspirin, statins, etc. The model incorporates findings from both the UKPDS and DCCT (for type 1 diabetes) with arms described as conventional and intensive in each referring to their differing treatment targets. In terms of “intensive” therapy (as opposed to conventional therapy) as examined in the ACCORD study, which resulted in increased mortality for those subjects who were set lower HbA1c targets, as the underlying cause of these results hasn’t been demonstrated yet and these results largely disagree with all other data we have not attempted to capture this effect. We have, however, discussed this situation in the manuscript and highlighted the fact that there is an ongoing debate into the pivotal perception that the goal of improved glycaemic control may not as simple as first thought and may not be appropriate for all patients. If the reviewers comment refers to the incorporation of data from studies examining more modern interventions (DPP-IV, GLP-1, etc.), pending long-term outcomes from those studies we are unable to capture those intervention specific effects.

- according to the EASD guidelines early use of basal insulin is common in the EU (a factor limiting the transferability of the results into current practice)

The generalisability or transferability of the outcomes from this and any other hypothetical study are limited by many factors including, as the reviewer correctly points out, current practices. However, the data from the UK (an EU country) on which this analysis was based details the
typical delay to insulin and as such in this setting we feel the results can be considered appropriate. We have, however, included additional discussion concerning interpretation of these results in other settings for which data on the length of time with uncontrolled glycaemia on OADs alone is unavailable.

- political company statements are not contributing to the quality of the paper and should be entirely left out. (E.g., the speculation regarding thiazolidinedione use and increased mortality in the ACCORD study in the discussion section: A. only rosiglitazone was used in ACCORD, B. all analyses show that mortality was not associated with TZD use in ACCORD, C. The whole discussion is questionable anyway because of study selection bias in the original meta-analyses. One could rather speculate that increased mortality in the intensive arm in ACCORD may have been induced by the high insulin doses leading to increased hypoglycemia frequency and stimulation of growth hormone effects by endothelial MAPK-1 activation, both factors contributing to an increased mortality). We included a discussion of the results from ACCORD as they cast doubt on the assertion that lowering HbA1c levels in whatever fashion necessary would produce better outcomes. We have restructured the manuscript to avoid inadvertent implications of a political nature (it was not our intent to do so).

**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:** In the past five years, I have received research support, consultancy fees, speaker fees and travel support from insulin producing companies (Eli Lilly, Sanofi-Aventis, NovoNordisk, Biodel, Halozyme, Mannkind, and Pfizer)
Reviewer's report
Title: The consequences of delaying insulin initiation in UK type 2 diabetes patients failing oral hyperglycaemic agents: a modelling study
Version: 1 Date: 19 January 2009
Reviewer: Hirotaka Watada
Reviewer’s report:
This manuscript contains very important messages. I cannot find any points to be improved.
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests