Author's response to reviews

Title: Lower Risk of Hypoglycaemia and Greater Odds for Weight Loss with Initiation of Insulin Detemir Compared with Insulin Glargine in Turkish Patients with Type 2 Diabetes: local results of a multinational observational study

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Author's response to reviews: see over
For the attention of
The Editors Board
BMC Endocrine Disorders

24th April 2014

Dear Sirs

Thank you for your invitation to resubmit our manuscript entitled: “Lower risk of hypoglycaemia and greater odds for weight loss with initiation of insulin detemir compared with insulin glargine in Turkish patients with type 2 diabetes: local results of a multinational observational study”.

Global results of the study have already been published, in accordance with good Please find our point-by-point response to each of the 3 reviewers’ comments below.

An independent native English speaker has also reviewed the revision, as requested by the journal editor.

Sincerely,

Professor Taner Damci

On behalf of all co-authors
Prof Rifat Emral
Dr Tanzer Balkir
Anne Louise Svendsen MSc PhD
Prof Jiten Vora

Reviewer’s report
Reviewer: Michelangela Barbieri

Reviewer’s report:
Taner Damci et al evaluated the effectiveness of insulin initiation with either insulin detemir (IDet) or with insulin glargine (IGlar) in real-life clinical practice in Turkish patients with type 2 diabetes mellitus (T2DM). Authors concluded that initiation of basal insulin analogues, IDet and IGlar, were both associated with clinically significant glycaemic improvements. Indeed, a lower risk of minor hypoglycaemia, and greater odds of weight loss #1kg, was observed with IDet compared with IGlar.

The study is interestingly and adequately conducted. Indeed I have several major concerns.

Major Compulsory Revisions
1. The major flaw of the manuscript concern the statistical analysis and the congruency of results. In Figure 1a and figure 1c error bars, indicating 95% confidence intervals, are not statistically compatible with the p values reported. Odd ratio, 95% confidence intervals and p value should be accurately revised and reported in the figures.
We thank the reviewer for identifying this error. The p values in Figure 1a and 1b have now been corrected. The p values provided in Figure 1c are correct. All p values are now congruent with the 95% confidence intervals. There were no changes to the effect size or confidence interval for the parameters, and therefore no change to any of the conclusions.

2. The definition of major and minor hypoglycaemia is not clear. How the number of weeks (4 weeks for minor and 12 weeks for major hypoglycemia events) preceding the follow up visit could define the severity of hypoglycaemia?

Hypoglycaemia had been defined in the original submission as follows:

The definitions have been rewritten for clarity (page 8, line 1-6):
All episodes of hypoglycaemia were self-reported. Major hypoglycaemia was defined as any hypoglycaemia event requiring assistance from a third party. Minor hypoglycaemia was defined as a blood glucose measurement < 56 mg/dl (3.1 mmol/L) with or without symptoms. The period of recall for major hypoglycaemia and minor hypoglycaemia was 12-weeks and 4-weeks prior to the follow-up visit, respectively. Hypoglycaemic events were classified as nocturnal, if they occurred between bedtime and getting up in the next morning.

3. As stated by the authors other studies have previously compared insulin detemir and insulin glargine and an observational study with all related limitations does not provide any new incremental advance compared to a randomized, controlled clinical trial.

We disagree. Observational studies have played a key role in supplementing information gathered by randomized controlled trials (RCTs). This is recognized by regulatory bodies such as FDA (Food & Drug Administration), which often requests post-marketing observational studies for purposes of monitoring safety; as well as payer organizations such as NICE (National Institute of Clinical Excellence), in order to evaluate clinical effectiveness in more heterogeneous patient populations and under real-life conditions.

Once daily administration of insulin detemir and insulin glargine have only been directly compared in 3 studies, and in 1 of these studies the basal insulins were part of a basal-bolus regimen where it is difficult to tease apart the effects of each component of the regimen. We also recognize that all insulin RCTs are treat to target trials, which do not reflect real-life clinical management, and is a strategy no longer supported by the ADA/EASD consensus guidelines.

We believe that the results and conclusions presented and discussed are balanced, and that the limitations of the analysis have been clearly documented.

4. Authors stated: “Patients were recruited into the study after they were deemed to be candidates for once-daily insulin detemir or once-daily insulin glargine as add on therapies to OADs based on the decision of the study physician according to local clinical practice” and more “....... there is a lack of a uniform consensus as to which of the two available basal analogue insulin should be recommended to initiate insulin treatment and what the potential differences are, if any, in patients with T2DM”. Indeed, the local clinical practice of the population investigated show an uniform consensus for detemir treatment. How the authors could explain the high difference in number of patients assigned to detemir
therapy (n=2395) compared to glargine therapy (n=491)?

As the reviewer points out, “Patients were recruited into the study after they were deemed to be candidates for once-daily insulin detemir or once-daily insulin glargine as add on therapies to OADs based on the decision of the study physician according to local clinical practice” indicates that as in any observational study, it is not possible to exclude the possibility that the results could be explained by a selection bias and consequent confounding. The recruitment has been stated as a limitation in the original text, and in the revision, further emphasis has been placed on both the ‘recruitment’ and ‘loss to follow-up’ as forms of selection bias.

There are no specific recommendations for the preferential use of either insulin glargine or insulin detemir. In the present study, only 17% of patients were prescribed insulin glargine. This difference may reflect the involvement of the study sponsor, and contact with investigators who were known to prescribe insulin detemir.

In Table 1, we can see that patients treated with insulin detemir had a shorter duration of diabetes, higher HbA1c at baseline, and differed with respect to concurrent number and class of OAD treatment, compared to patients treated with insulin glargine. These differences do not appear to clearly indicate a specific patient phenotype (i.e. selection). As this is an observational study, we do expect to find differences between the subgroups. This is the reason why we have analyzed post-treatment results using models, which include a large number of clinically relevant and previously identified confounders.

5. The more sensitive analysis evaluating the independent effect of insulin type on final HbA1c is superfluous being the simpler model already not significant.

The reviewer is referring to the additional models presented in the online supplement. All 3 models were conceived prior to performing the analysis, and are models that have been used previously. It was agreed among the authors, that these models should be applied consistently. Both the expanded model (additional inclusion of macrovascular disease) and the restricted model (only including duration of diabetes, previous history of hypoglycaemia, and baseline HbA1c) are sensitivity analyses. The results show that the inclusion of more or less confounders does not change the effect size or direction associated with insulin type. These analyses are not more or less sensitive than the original model, but they do indicate that the effects of insulin type in the original model are robust.

Minor concerns.
1. Baseline and post treatment values should be reported in one table.

We disagree with the reviewer regarding the inclusion of baseline and post-treatment results within a single table.

In Table 1, we present baseline data for the two groups, and we also report p values comparing these subgroups. This comparison evaluates the extent to which we are dealing with the same population in the two groups.

In Table 2, we present the post-treatment results and intentionally do not include p values. The two treatment groups had differences at baseline and were also treated with different insulin in the study. Therefore a direct comparison of their final endpoints does not make sense; instead the final endpoints are analyzed in a model taking confounding into account.
2. All parameters included in each models should indicated in figure legend and through result section.

All the parameters are stated in the statistical section (page 9, lines 6-16) and are also presented in the figures. There are no additional parameters in the models.

Reviewer’s report
Reviewer: Giovanna Muscogiuri

Reviewer’s report:
The purpose of this study was to evaluate the effectiveness of insulin initiation with either insulin detemir (IDet) or with insulin glargine (IGlar) in real-life clinical practice in Turkish patients with type 2 diabetes mellitus (T2DM). The authors conclude that initiation of basal insulin analogues, IDet and IGlar, were associated with clinically significant glycaemic improvements. A lower risk of minor hypoglycaemia, and greater odds of weight loss #1kg, was observed with IDet compared with IGlar. The manuscript has poor novelty since many manuscripts have dealt with this topic.

Major Compulsory Revisions
1) The main issue of the manuscript is that the patients belonging to the two groups were not well randomized. Thus, the results should be revisioned considering also the background antidiabetic therapy.

This study is not a randomized trial, but an observational study of real-life clinical practice. Please refer to the reply to Reviewer 1 Comment 3. The type of study and the relationship of the analyses presented in relation to the total cohort, are described in the title. The limitations of this observational study have also been clearly documented (page 16, lines 13-24).

The reviewer’s concerns regarding concomitant OAD therapy are well taken. The regression analyses have been adjusted for a large number of possible confounders, including the number and change in OAD therapy at the time of insulin initiation (page 9, lines 6-16). The effects of OAD therapy on final HbA1c, hypoglycaemia and weight are also shown in Figures 1a-c.

2) The same patients should be switched to the opposite insulin, i.e. who took glargine should be switched to detemir and vice versa to see if the conclusion of the authors should be confirmed

The reviewer proposes an interesting crossover study design. Unfortunately, this study did not include crossover, as the primary endpoint was to assess the safety of once-daily insulin initiation in a real-life clinical setting.

3) All the patients were overweight. A normal weight population should be enrolled to see the “pure” effect of both insulin on weight.

Since this is an observational study of real-life clinical practice, inclusion and exclusion criteria were very broad, and there was no intent to recruit specific patient populations other than those seen in day-to-day clinical practice.
Minor Essential Revisions
Please report the lipid profile in Table.

The lipid data is provided below. As you can see there are no clinically meaningful differences between baseline or post treatment values. In our view, we think that the inclusion of this additional lipid data is irrelevant and shifts the focus away from the other interesting findings. After careful consideration, therefore, we have decided not to add this data to the table.

<table>
<thead>
<tr>
<th></th>
<th>Insulin detemir</th>
<th>Insulin glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cholesterol (mmol/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.4 ± 1.1</td>
<td>5.3 ± 1.1</td>
</tr>
<tr>
<td>Final visit</td>
<td>5.1 ± 1.0</td>
<td>4.7 ± 0.9</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.3 ± 1.3</td>
<td>2.3 ± 1.2</td>
</tr>
<tr>
<td>Final visit</td>
<td>2.0 ± 1.0</td>
<td>1.9 ± 0.9</td>
</tr>
</tbody>
</table>

Reviewer's report
Reviewer: Zeynep Osar Siva

Thank you for asking me to review the manuscript entitled 'Lower Risk of Hypoglycaemia and Greater Odds for Weight Loss with Initiation of Insulin Detemir Compared with Insulin Glargine in Turkish Patients with Type 2 Diabetes: local results of a multinational observational study ' by Damci et al. This article is a sub-analysis of a multinational open label observational study on insulin initiation in patients with T2DM. The authors have analysed the data of a local cohort in Turkey.

The question posed by the authors is well defined. The methods are appropriate and well described. The data are sound and the manuscript adheres to the relevant standards for reporting and data deposition.

Since the study was not randomized, it is not possible to differentiate between the effects of treatment and other study or demographic variables on clinical outcomes, and results should be interpreted with caution. These limitations of the work are clearly stated by the authors. The authors have acknowledged relevant published data in the discussion. The discussion and conclusion are well balanced and adequately supported by the data.

The article is one of the few studies directly comparing the effects of once-daily insulin detemir and insulin glargine initiation as add-on therapy to OAD in patients with type 2 diabetes. It is of importance in its field and acceptable without revision.
We thank the reviewer for their favorable appraisal of this manuscript.