Author’s response to reviews

Title: Biphasic Insulin Aspart 30 vs. NPH plus Regular Human Insulin in Type 2 Diabetes Patients: A Cost-Effectiveness Study

Authors:

Amir Farshchi (farshchi.pharm@gmail.com;r-aghili@razi.tums.ac.ir)
Rokhsareh Aghili (aghili.r@tak.iums.ac.ir)
Maryam Oskuee (m.okuee.g103@gmail.com)
Sina Noshad (sina.noshad@gmail.com)
Marjan Rashed (marji.rashed@yahoo.com)
Abbas Kebriaeezadeh (kebriaee@tums.ac.ir)
Maryam Kia (Mkia220@yahoo.com)
Alireza Esteghamati (esteghamati@tums.ac.ir)

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Author’s response to reviews:

Dear Editor-in-Chief;

We are very grateful to your and the reviewers' comments and thoughtful suggestions. Based on these comments and suggestions, we have made careful modifications to the original manuscript, and carefully proof-read the manuscript to minimize typographical and grammatical errors.

We believe that the manuscript has been greatly improved and hope it has reached your standards.

Once again, we acknowledge your comments very much, which are valuable in improving the quality of our manuscript.

Sincerely yours,

Alireza Esteghamati
Here are our responses to the reviewers' comments and list of corrections.

Reviewer #1

1. Please describe a randomisation method
Response: Patients were randomly divided into two groups by using a random number generator.

2. How VAS was used as a second method of QALY calculations? Directly? VAS is a part of EQ-5D.
Response: Yes, VAS is a part of EQ-5D, but the authors preferred to report it separately because the results extracted from VAS were somehow different.

3. How disutilities from hypoglycaemias were calculated?
Response: Disutilities from hypoglycaemias were calculated indirectly. These disutilities have a significant impact on QALY and has reflected in this score indirectly [ref. 51 of the text].

4. Have you considered using country-specific population utilities (if available)?
Response: No, unfortunately in Iran we have not “specific population utilities” and we used UK TTO standard score.

5. Don't you think that lack of cost differences in the number of visits is a consequence of a study protocol (the same number of visits in both arms)?
Response: Yes, you are right, it was according to the study protocol.

6. What method of indirect costs calculations was used? Human capital approach? Based on GDP per capita or salary lost? Friction cost method?
Response: The method of indirect costs calculations was human capital approach.

7. Final utility values from the results section needs more explanations (in discussion?) due to unexpectedly big differences

Response: It has been discussed in discussion: “… Brod et al found that patients who were treated with BIAsp 30 reported improved treatment satisfaction after 26 weeks and that was large enough to be considered clinically meaningful to the patients [ref. 50 of the text]. It should also be noted that occurrence of major hypoglycemic episodes and weight gain both have detrimental effects on patients’ HRQOL and enhanced QALYs of the patients receiving BIAsp 30 could in part be accounted for by its superior profile in this regard [ref. 51 of the text]”.

8. How hypoglycaemias were included in QALY measures?

Response: As I explained earlier, occurrence of major hypoglycemic episodes have detrimental effects on patients’ HRQOL and enhanced QALYs of the patients receiving BIAsp 30 could in part be accounted for by its superior profile in this regard [51]. Therefore, the results extracted form QALY scores included hypoglycaemia effect.

9. In abstract: the last sentence in methodology section not finished; in the results section-abbreviation FPG and PPG should be introduced; in conclusions: "offers the same glucose control” not supported as it is dose-dependent, the drug was titrated

Response: Many thanks for your comments, they were changed in the text.

10. Please decide if HbA1c or A1c is used. Harmonise in the text

Response: Thanks, all A1cs were changed to HbA1c.

11. Spelling / spaces (p-page, l-line)
- p.6 l.29 "clinical of trial". "of" not needed
- p.6 l.48 "estimated" not "Estimated"
- p.9 l.7 space missing after L
- p.9 l.26, l.29 space after full stop and before [..] needed
- p.15 l.26 space after full stop needed
- p.16 l.31 space before [..] needed
- p.16 l.34 space after full stop needed
- p.17 l.29 space after full stop needed
- p.17 l.56 space before [..] needed
- p.9 l. 28

Response: Many thanks, all of them were corrected.

Reviewer #2: This is a well performed and presented cost-effectiveness study, which compares two medical interventions of treatment persons with T2DM with two types of insulin: Biphasic Insulin Aspart 30 (BIAsp 30) and NPH plus Regular Human Insulin (NPH/Reg) in single-center, parallel-group, randomized, open-label clinical trial.

Authors concluded that treating persons with T2DM with BIAsp 30 is more effective in almost all outcomes measured in the study (among others, in terms of experiencing less frequently hypoglycemic events than the group receiving human insulin and achieving improved health related quality of life). In addition, treatment with BIAsp 30 caused in the analyzed period less total costs than in the group treated with NPH/Reg. As a result BIAsp 30 insulin was found to be cost-saving in the trial groups. A cost-effectiveness and cost-utility framework was used correctly, but details of costs calculations methods were not sufficiently presented (reference article was given) and some clarifications are needed. The study is appropriately situated in the context. The manuscript is well written and the objectives, interventions, and results are clearly described. The conclusions appear to be robust.

The methods applied are appropriate and mostly well described.

Effectiveness data: Authors should state which value set have been used to convert the health states derived by the EQ-5D-3L instrument to a single score (between 1 and 0). In the absence of a set of Iranian national population-based utility weights, probably a set of utility weights for a population that most closely approximates it have been selected, or in the absence of a suitable candidate - the most robust valuation set (the UK TTO set).

Response: Unfortunately utility score of EQ-5D-3L has not been validated yet; therefore, we used standard UK score.
Costs: The mean direct costs (medical and non-medical) and production lost during trial period of 48 weeks have been presented. Some clarifications of the costs estimation methods are necessary. From the published paper, where the costs calculation methods are explained (and Authors are referring to) is not clear if the production lost is calculated considering only the working age time lost or entire time lost due to T2DM; is there unemployment rate in the Iran economy used to correct the real production lost to the society? What is the method of valuation time lost for someone being on disability retirement? It seems (from the paper Authors have referred to) that indemnity claims are also applied (which are rather transfer payments, not costs) instead of average wage in the economy.

Response: Because of socioeconomic level of Iranian people, working age has been shifted to 55-60 years old. Although it is not published formally, we had to consider it in our patients. therefore, we calculated entire time lost due to T2DM.

In addition, we did not consider unemployed patients in our calculations.

We calculated production lost only in patients who were employed and worked actively, so retirement disability was not calculated.

Indemnity claims were applied because there was not difference between these claims and average wage in the community.

Statistical analyses: Data base is not available to reviewer; however the statistical analyses chosen seem appropriate. I am not able to see calculations, but I have one recommendation to the table 3: please present results as "mean frequency of hypoglycemic events per 100 person-years" instead of "mean frequency of hypoglycemic events reported as percent per person year". Please look at the results in table 5, where the same values are named as: "Hypoglycemia event per person year".

Response: Thank you for your suggestion, tables 3 and 5 were harmonized and the results were presented as “Hypoglycemia event per person-year”.

Discussion section: The limitations of the study and the transferability of the results to the entire Iranian population are not discussed, adding these will be valuable for this paper.

Response: Many thanks for your comment, it was added to the text.