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Editor  
World J Diabetes

Institutionen för kliniska vetenskaper Lund  
Professor Bo Ahrén

**Dear Editor,**

Please find enclosed the edited manuscript in Word format (file name: 6359-revised.doc).

**Title:** Insulin plus incretin: A glucose-lowering strategy for type 2 diabetes

**Author:** Bo Ahrén

**Name of Journal:** *World Journal of Diabetes*

**ESPS Manuscript NO:** 6359

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

1. The title has been shortened, key words have been inserted and a core summary of less than 100 words has been written.
2. Reviewer 1 raised two points:
  - a. Is there any evidence that incretin plus insulin is better than other formula such as sulfonylureas +/- metformin or DPP4 inhibitor? Besides, in it really a more commonly used glucose-lowering therapy (declare in your article page 3) formula in clinical setting?

**Response:** This is a relevant point raised by the reviewer since it is important to compare different treatment strategies in head-to-head studies. So far,

however, no head-to-head studies have been performed comparing the combination of incretin plus insulin therapy (+ metformin) with other three-drug combinations. In the revised version of the manuscript, this has clearly been stated and the need of such studies is high-lighted . Further, the reviewer asked about the evidence for the increased use of the incretin plus insulin combination. However, such evidence does not exist and what I meant in the article was the increased interest in this combination, which is evident from the increased number of studies and publications on this combination since 2011. To avoid this misunderstanding, the sentence on this has been rewritten.

- b. We know that DM is now thought as CAD equivalent disease. Therefore, is there any evidence illustrated that the combination therapy had long term CV events reduction effect which showed in patients treated with metformin?

**Response:** The reviewer is correct that important for the long-term benefit of glucose-lowering therapy is beneficial effects on CV events. Since no such studies have so far been done, or even started, with the three drug combination of incretin plus insulin therapy, there is a need for subanalysis of such patient groups in the on-going cardiovascular trials on incretin therapy and for more direct studies. This is now clearly stated in the article.

3. Reviewer 2 raised 2 major and several minor comments:

- a. In the Rationale section reviews and meta-analyses are cited, and only few original publications are being discussed. Especially regarding hypoglycemic events, there is a need for citing some of the first original studies.

**Response:** Thank you. In the revised version, original articles have been quoted in these sections on the rationale for the combination, particularly in the hypoglycemia section.

- b. The paragraph about the rationale for combining insulin and incretin therapy is highly relevant and

interesting. However, it would improve the manuscript if the Result section reflected the background. The main Result section does not read very well. It is just a list of study summaries, which makes it difficult for the reader to get an overview of the evidence. The Result section could be improved by focusing on the four topics from the rationale section (weight loss, hypoglycaemia, glycaemic control, disease modifying actions). References could also be added to Table 1, so it reflects current findings in addition to the theoretical background of the treatment modalities. Moreover, main findings in relation to the four main topics could be added to Table 2. 3. The conclusion could be clearer in terms of addressing the evidence related to the four topics mentioned in the background. Moreover, the author could suggest which types of studies are needed in the future.

**Response:** Thank you for this valuable point. As a response to this point, a new section has been introduced in which the different controlled trials which are compared along the topics from the rationale section, as suggested by the reviewer. With this new section, the concern raised by the reviewer that it was difficult to compare the trials hopefully is met. Furthermore, former Table 1 was deleted and new Tables 1 and 2 have both been improved with references and with information on effects of glucose, hypoglycemia and body weight, as requested. Finally, as requested, suggestions of further studies have been performed.

- c. Minor comments: 1. Title: "The promising glucose-lowering strategy for type 2 diabetes" could be changed to "A glucose-lowering strategy for type 2 diabetes", which is more objective. 2. Page 20: The statement "...it is advisable to reduce the basal insulin dose by 20% when starting incretin therapy..." should have a reference. 3. Page 20: "Further studies are required to examine the long-term beneficial effects of this initial combination". Consider deleting "beneficial", because adverse effects should also be examined in long-term studies.

**Response:** The title has been changed as suggested and the word “beneficial” has been deleted. In regard to hard evidence for a 20% reduction in basal insulin dose when starting combination therapy in patients with low HbA1c, such evidence is lacking and therefore no special percentage is given in the article.

4. Reviewer 3 raised 2 comments

- a. The kinds of insulin analogues, which were used in clinical trials, should be added in Table 2.

**Response:** Former Table 2 has been completely rewritten and include now much more information; it has therefore been split in Tables 1 (for GLP-1 receptor agonists) and Table 2 (for DPP-4 inhibitors); type of insulin is now given in the legend to the Tables.

- b. There were several spelling errors in this manuscript which were observed and listed by the reviewer.

**Response:** Thank you for finding these mis-spellings, which now have been corrected.

5. Reviewer 4 raised several comments

- a. The abstract needs revision of the language as some phrases are really long (several studies have also verified.....) while others are really short (the combination is also often ...)

**Response:** The abstract has been rewritten as suggested.

- b. Abbreviations mentioned for the first time need to be written in full (ADA, EASD).

**Response:** This has been done.

- c. A more detailed scientific analysis of GLP1 and DPP-4 inhibitors distribution of receptors and of their pharmacodynamics and kinetics would add value to the content of the article.

**Response:** A new paragraph has been written with a more detailed analysis of GLP-1 and DPP-4.

- d. A more thorough discussion of precautions and adverse effects of treatment by both groups is also necessary.

**Response:** A new paragraph has been written with a more detailed discussion on safety and adverse events.

- e. In all the mentioned studies, it is important to clarify whether the reduction in HbA1c was significant statistically with P values.

**Response:** This has been performed (with p-values and variations) throughout, as requested.

- f. Some spelling mistakes are present and require revisions

**Response:** Thank you. These misspellings (and others) have been corrected.

- g. A table comparison between a lot of the data mentioned about the various DPP-4 inhibitors and another one maybe for GLP1 preparations would clarify the differences and improve the readability of the material.

**Response:** More data have now been inserted in new Tables 1 and 2, as requested.

3 References and typesetting were corrected

Thank you again for publishing my manuscript in the *World Journal of Diabetes*.



*Bo Ahren, author*