

July 12, 2018

World Journal of Diabetes

Dear Dr. Fang-Fang Ji,

I would like to thank you and the reviewers for your concise and helpful comments and suggestions.

We will re-submit my revised manuscript entitled “A retrospective review of efficacy of anagliptin as compared to linagliptin on metabolic parameters over 2 years of drug consumption” to *World Journal of Diabetes*.

According to the reviewers' comments, we completely corrected our manuscript. We will show you the list of modification on the following pages. All the changes made to the manuscript appear as underlined text in the revised manuscript. We appreciate your re-consideration for the publication of my revised manuscript in your journal.

Sincerely yours,

Hidetaka Hamasaki, MD, PhD
Editorial board member of World Journal of Diabetes,
Hamasaki Clinic

The List of Modification

Reviewer No. 02913340

Overview of the study This study evaluates the comparative effectiveness of anagliptin and linagliptin on the glycemic control, blood pressure, lipid profile, and liver and renal function in Japanese patients with T2DM. As per my pubmed review the comparison of Anagliptin and linagliptin is not available before, representing novel work. Though the study is retrospective in nature, but it has potential to guide a good RCT in future. Limitations as inherent to retrospective study are there, but still authors have managed to present the data in a systematic manner. I find discussion a bit lengthy which authors can consider to shorten it and manuscript a bit unstructured especially results section and abstract, which I think should be done to improve the presentation of manuscript. Introduction and methods section are well written. Thank you very much for your time and efforts to review my manuscript.

Major revisions

1. *Abstract needs to be structured. Kindly see instructions for observational study.*

I have revised Abstract accordingly.

2. *Important findings can be objectively shown as in numbers like A1C, BP, Lipids*

In accordance with your comment, I have added specific values of HbA1c, blood pressure, and lipids to the Results section.

3. *Results should be structured. Para 1 should contain the baseline characteristics and demographics of enrolled patients. Para 2 should contain the important/number of changes made to the prescription in terms of drugs for glucose control, lipid and blood pressure medications. Para 3,4,5 should contain details separately for glucose parameters, blood pressure and lipid parameters respectively. Objective data can be included rather than straight statements. Para 6 should contain remaining information.*

In accordance with your comment, I have revised the Results section.

4. *Most important is that results have been compared from baseline to end of study period, whereas study was to compare the effectiveness of 2 drugs. Therefore change in 2 arms should be compared separately after adjusting for baseline parameters.*

Thank you for your helpful comment. In accordance with your comment, I have calculated %change in clinical parameters during the study period, and compared them between groups.

I have added the following sentences to the Results section:

HbA1c levels significantly decreased in both the anagliptin group (from 11.1 ± 2.8 mmol/L to 9.7 ± 1.9 mmol/L) and the linagliptin group (from 12 ± 3.3 mmol/L to 9.2 ± 1.8 mmol/L). However, the %change in HbA1c was lower in the anagliptin group than that in the linagliptin group (-5.6% vs. -17.4%, $p = 0.004$)...The %change in diastolic blood pressure was also larger in the anagliptin group than that in the linagliptin group (-9.7% vs. -4.9%, $p = 0.044$)...There was also a significant difference in %change in HDL-C levels between groups (2.8% vs. 5.6%, $p = 0.037$)...We also found a significant difference in %change in Cr levels between groups (6.8% vs. 22%, $p = 0.038$); however, there was no significant difference in %change in ALT levels between groups (-2.2% vs. -15.2%, $p = 0.088$).

5. *Data should be presented in SI units*

The applicable data have been presented in SI units.

6. *Flow of discussion is not smooth. I will suggest that most of the discussion should focus on the differences between two drugs rather than on GLP-1 or other DPP-4 inhibitors. Discussion should be streamlined so that one parameter is discussed followed by other and so on, and should not be intermingled like discussion on blood pressure followed by lipid and then back to blood pressure. It should be shortened a bit.*

In accordance with your comment, I have revised the Discussion section.

Specifically, I have deleted the text regarding the association between DPP-4 inhibitions and blood pressure. I have also deleted the text regarding the effect of GLP-1 receptor agonists on lipids. I tried to focus on the difference between anagliptin and linagliptin.

7. *Another major limitation is ensuring compliance and adjustment of medication changes in between.*

As you pointed out, we cannot completely ensure whether the study participants kept medication adherence during the study period because this study was a retrospective observational study.

I have added this concern to the study limitation:

Third, although we confirmed the medication adherence at every medical examination, we could not ensure whether the study participants kept medication adherence during the study period.

Minor

1. *Title needs revision. Can be made as "A retrospective review of efficacy of anagliptin as compared to linagliptin on metabolic parameters over 2 years of drug consumption"*
Wording can still be changed by authors so that title reflects what has been there in manuscript.

In accordance with your comment, I have changed the title to, "A retrospective review of efficacy of anagliptin as compared to linagliptin on metabolic parameters over 2 years of drug consumption".

2. *Type 2 diabetes [T2D] should be replaced by Type 2 diabetes mellitus [T2DM]*

I have replaced T2D by T2DM in the manuscript.

3. *Under study design: Where Hamasaki Clinic is mentioned [Page 5, Line 2], kindly add whether it is either primary care clinic or tackles patients who have been referred.*

Hamasaki Clinic is a diabetes-specialty clinic. We treat outpatients with diabetes ranged from mild to severe.

Reviewer No. 00503221

This manuscript on the Efficacy of anagliptin and linagliptin on metabolic parameters in the long-term management of type 2 diabetes: A comparative cohort study, does not contain new significant data or conclusion.

Thank you very much for your time and efforts to review my manuscript.

To our knowledge, this is the first study to compare the effectiveness of anagliptin and linagliptin.

Reviewer No. 00506397

Hamasaki and Hamasaki report the results of a 2-year retrospective study that was aimed at assessing the comparative effectiveness of anagliptin and linagliptin on the glycemic control, blood pressure, lipid profile, and liver and renal function in Japanese patients with T2D. Based on the data from 234 patients (anagliptin group, 117 patients; linagliptin group, 117 patients), the authors report that although both DPP-4 inhibitors had a salutary effect on glycemic control at 3, 6, 12, and 24 months, their clinical outcomes were not identical. While anagliptin treatment led to reduced diastolic blood pressure and total serum cholesterol, patients treated with linagliptin had increased HDL-cholesterol levels and reduced urinary albumin–creatinine ratio (UACR). Apparently, linagliptin also improved liver function. Based on these analyses, the authors suggested that anagliptin and linagliptin may be clinically differentiated with respect to their ability to affect blood pressure, lipid profile, and liver function. Although his suggestion is consistent with their overall findings of this rather preliminary study, the manuscript will benefit from making following changes to improve the presentation of these data:

Thank you very much for your helpful comments.

I appreciate the time and effort that was invested in reading the manuscript.

1. *In the Core tip the authors should explicitly point out that this study suffers from two limitations: First, for a retrospective study, this has rather small number of patients. Second caveat should be included with regard to a relatively short duration of patient follow-up.*

In accordance with your comment, I have mentioned these limitations in the Core tip.

2. *The authors need to articulate more clearly their concluding statements at the end of Discussion: "This study supports the hypothesis that there could be a drug-specific effect of DPP-4 inhibitors on metabolic parameters beyond their class effect. Thus, we cannot describe the utility of these drugs in clinical practice separately. However, a multicenter, randomized, open-label, parallel-group trial has been conducted previously to assess the comparative effectiveness of anagliptin and sitagliptin on LDL-C in patients with T2D and atherosclerosis [27]. Nevertheless, further investigations are warranted to validate the findings of this study." What were the findings of the multicenter, randomized, open-label, parallel-group Trial mentioned in Reference #27? Do these data support authors' conclusions based on the present study or not? If not, how was that study related to the overall design of the current study?*

Unfortunately, the paper [ref.27] is a study protocol of the REASON trial. According to the ClinicalTrial.gov, the results of this trial have not been reported yet. However, this trial aims to determine whether anagliptin or sitagliptin are effective in reducing LDL-C in patients with type 2 diabetes and cardiovascular risk factors on statin. If anagliptin do reduce LDL-C, and the effect is unique among DPP-4 inhibitors, the administration of anagliptin in patients with cardiovascular disease such as coronary artery disease is rational. To avoid misleading statement, I have removed the word "previously" from the text you mentioned.

3. *Under Medical History Recording, the sentence "In addition, we confirmed the medication adherence of study patients' at every medical examination." There is no need to put an apostrophe after patients.*

Thank you for your careful reading. I have deleted an apostrophe after patients.

4. *The data presented in Figure 1 and 2 are redundant. This information is already contained in Table 3. Both Figures should be removed and additional information contained in both Figures may be articulated in words in the Text.*

In accordance with your comment, I have removed Figure 1 and 2, and added some information represented in the Figures to the Results section.