

## PEER-REVIEW REPORT

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

**Manuscript NO:** 67845

**Title:** Role of dipeptidyl peptidase 4 inhibitors in the new era of antidiabetic treatment

**Provenance and peer review:** Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 04094091

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Associate Professor, Consultant Physician-Scientist

**Reviewer's Country/Territory:** Italy

**Author's Country/Territory:** Greece

**Manuscript submission date:** 2021-05-05

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-05-11 07:27

**Reviewer performed review:** 2021-05-12 06:00

**Review time:** 22 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

## SPECIFIC COMMENTS TO AUTHORS

The authors reviewed the mechanism of action, CV safety and current place of DPP-4 inhibitors in the management of type 2 diabetes. The review is well written, but there are some major issues that should be fixed in order to make it suitable for publication.

**MAJOR CONCERNS** - In the abstract, the authors state that DPP4i do not require dose titration. However, the dose of some of these agents actually needs to be reduced in patients with impaired renal function - In the introduction, the authors state that GLP-1 RA decrease heart failure and progression of renal disease. However, SGLT-2i are known to be more effective on HF, while GLP-1 RA reduce non-fatal stroke. Both classes may slow the progression of renal disease, although use of SGLT2-I is supported by stronger evidence. The authors should be more precise in describing the beneficial effects of these two classes of drugs - In the section "Mechanism of action and characteristics of DPP-4 inhibitors", referring to DPP-4i, the authors state that "These drugs inhibit incretin hormones" However, please note that DPP-4i do not inhibit the incretins GIP and GLP-1: as the authors correctly state later in the manuscript, they inhibit dipeptyl peptidase 4, i.e. the enzyme that degrades incretins, thereby prolonging the incretins' half-life. Please amend. - In the same section, the authors state that "DPP-4 inhibitors stimulate insulin secretion from pancreatic  $\beta$ -cells independently of blood glucose, thus overcoming the risk of hypoglycemia" However, 1) it is not DPP-4i that stimulate insulin secretion, but rather native GLP-1, whose action is prolonged by the inhibition of the degrading enzyme DPP-4 and 2) GLP-1 stimulates glucose-dependent insulin secretion, therefore both DPP-4i and GLP-1 RA are rarely associated with hypoglycemia. Please amend. - The part on "non-glycemic favorable effects" ("interestingly [...] underlying mechanisms") is not pertinent to the section on

the mechanism of action and should be removed from this section. The authors could report some of this information in the section "The place of DPP-4 inhibitors in the therapeutic algorithm of hyperglycemia" - When describing CVOTs, the authors should choose whether they need to report the HbA1c inclusion criterion: HbA1c values are provided only for some trials. - In the description of CVOTs, the authors mention pancreatitis: "Interestingly, acute pancreatitis.... Did not differ significantly"). However, the readers would not understand why this finding is interesting unless they know that this had been a safety concern. A brief section on the safety of DPP-4 inhibitors should be added to provide a more complete picture. Some of the information already in the text could be moved to this new section, in order not to make the manuscript too lengthy - In the section on the current use of DPP4-is, the authors need to make their arguments clearer: They state that "the abovementioned change in the prescription...." But then they quote cross-sectional data, which do not describe a change (no comparison with previous data), and DPP-4i appears to be the most prescribed. Also, drugs assessed in the epidemiologic studies mentioned should be listed. At the time of the US study [48], GLP-1 RA and SGLT-2 were not available and therefore were not included in the analysis. Also, the study in Germany [49] was conducted in nursing homes, i.e. in elderly people, for whom DPP-4i may be preferred over other drugs due to the good safety profile. - Adding a table summarizing DPP-4i's 1) HbA1c lowering efficacy, 2) available doses 3) dose adjustment in renal / hepatic impairment 4) risk of hypoglycemia 5) effect on body weight 5) CV safety and 6) contraindications would improve the quality of the manuscript. MINOR CONCERNS - Please do not use the word "diabetic" as a noun. Rather use "people first language" (e.g. patients with diabetes), in order not to identify people with their disease. - Please change "glycated hemoglobin" to "glycated hemoglobin"

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**Peer-review model:** Single blind

**Reviewer's code:** 04214085

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Instructor, Postdoctoral Fellow, Research Assistant Professor,  
Research Associate

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** Greece

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

<b>Peer-reviewer statements</b>	Peer-Review: [ <input checked="" type="radio"/> ] Anonymous [ <input type="radio"/> ] Onymous Conflicts-of-Interest: [ <input type="radio"/> ] Yes [ <input checked="" type="radio"/> ] No
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## SPECIFIC COMMENTS TO AUTHORS

In this review, the author reviewed the current role of DPP-4 inhibitors in antidiabetic treatment. The manuscript is likely to be helpful to a wide readership, but several important points are required to be addressed. The specific comments are listed below:

1. The author should make some tables or figures to summarize the characteristics and function of DPP-4 inhibitors, as well as the detail mechanism.
2. The author used the number of people with diabetes is 2014, it is too old. The newly number in 2019 has been reported.
3. The conclusion session should be re-drafted. There is quite duplicated information already mentioned above in the main text. This session is supposed to be summary of the manuscript and more importantly to provide the authors' perspective for the field.
4. There are some typos and abbreviations misuse. The author should check it carefully.