Reviewer #1:

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.

Answer: We have added a table (Table 1) summarizing the characteristics, function and mechanism of DPP-4 inhibitors as suggested.

2. The author used the number of people with diabetes is 2014, it is too old. The newly number in 2019 has been reported.

Answer: We have updated the information regarding diabetes prevalence. Specifically, we added that "The global prevalence of DM in 2019 was estimated to be 9.3% (463 million people) with a projection to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045" (Page 4, lines 4-7, reference 1).

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.

Answer: Thank you for your comment. The conclusion section has now been re-drafted. (Pages 18-19)

4. There are some typos and abbreviations misuse. The author should check it carefully.

Answer: Corrections have been made throughout the text.

Reviewer #2:

The authors reviewed the mechanism of action, CV safety and current place of DPP-4 inihibitors 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 –

Answer: Thank you for the comment. We clarified that DPP-4 inhibitors do not require dose *up*titration. We also stated that they can be administered in patients with chronic kidney disease *after dose modification* (Page 2, lines 13-14).

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.

Answer: Thank you very much for the comment and clarifications. We have made appropriate corrections and added relevant data accordingly (Page 5, lines 3-7 and 10-11, references 11-15).

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. –

Answer: Thank you very much for the comment-correction. We now state that "These drugs inhibit DPP-4, i.e. the enzyme that degrades incretins, subsequently prolonging their half-life" (Page 5, lines 21-23).

In the same section, the authors state that "DPP-4 inhibitors stimulate insulin secretion from pancreatic β-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.

Answer: Thank you very much for the comments-corrections. We have now made appropriate amendments in the text (Page 5, lines 14-15 and 17-19).

- 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"

Answer: Thank you for your comment. The above-mentioned part has now been moved to the "The place of DPP-4 inhibitors in the therapeutic algorithm of hyperglycemia" section (Page 16, lines 15-18).

- When describing CVOTs, the authors should choose whether they need to report the HbA1c inclusion criterion: HbA1c values are provided only for some trials.

Answer: We added the HbA1c inclusion criterion in the studies that did not mention it.

- 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.

Answer: We added a short paragraph regarding previous concerns regarding increased risk of pancreatitis and pancreatic cancer with DPP-4 inhibitors and more recent data based on a meta-analysis of randomized controlled trials (Page 14, lines 13-19, references 51-52).

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.

Answer: We added the abovementioned paragraph about the risk of pancreatitis/pancreatic cancer and incorporated it in a section entitled "Safety of DPP-4 inhibitors". Some more data about safety is mentioned in several relevant parts of the manuscript. We believe it would be better to leave this data in the respective paragraphs, as moving it to a new paragraph about safety may alter the coherence of the manuscript. However, we briefly mention the safety concerns again in this new section (Pages 14-15).

- 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.

Answer: Thank you for your comments. The paragraph has been rephrased and new information has been added accordingly.

- 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.

Answer: Four tables addressing the issues raised by both reviewers have now been added.

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 hemoglobulin" to "glycated hemoglobin"

Answer: Thank you for your comments. Appropriate corrections have been made throughout the text.