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PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes

Manuscript NO: 47997

Title: Novel pharmacological therapy in type 2 diabetes mellitus with established cardiovascular disease: Current evidence

Reviewer's code: 00506298

Reviewer's country: Spain

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-04-06 10:53

Reviewer performed review: 2019-04-06 11:22

Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The review by Pozo el al, on Novel Pharmacological approach in the management of type 2 diabetic patients with cardiovascular disease is very interesting from a clinical practice point of view. I recommend the paper publication in the WJD

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INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes

Manuscript NO: 47997

Title: Novel pharmacological therapy in type 2 diabetes mellitus with established cardiovascular disease: Current evidence

Reviewer's code: 03470699

Reviewer's country: Greece

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-04-07 19:00

Reviewer performed review: 2019-04-18 17:50

Review time: 10 Days and 22 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is a well written mini review paper on the CV outcomes of novel antidiabetic drugs in people with type 2 diabetes. I have some minor comments that could further improve the accuracy of presented data. General comments I suggest that the authors

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should mention the updated role that these agents have in the T2D management algorithm, according to the recently published ADA/EASD consensus statement. It would be useful to be mentioned that evidence for CV benefits are available for other antidiabetic drugs apart from SGLT-2i and GLP-1 agonists, albeit these data are not derived from CVOTs (see UKPDS for metformin and PROACTIVE for pioglitazone). Specific comments Abstract: It is too long for an abstract. It could be more concise. Abstract: "The aim for the regulation is is not only" The second "is" should be deleted. Abstract: "Additionally, Sodium-Glucose Co-transporter 2 inhibitors (SGLT2i) have a benefit in patients with congestive heart failure and diabetic kidney disease" There is evidence for beneficial outcomes on HF and kidney disease for GLP-1 agonists as well, though not so strong as for SGLT2 inhibitors. Introduction: It would be useful to mention here the incidence of established atherosclerotic disease among people with T2D (approximately 20%). Introduction: "They have shown non-inferiority in atherosclerotic cardiovascular disease yet have potential risk in congestive heart failure". This is applicable only for specific agents, saxagliptin in particular. Other DPP-4 inhibitors (e.g. sitagliptin) have not been shown to increase hospitalization for HF rates in relevant trials. Please clarify. Current evidence: "It also raised safety concerns by showing increased risk for amputations, fractures, mycotic infections…." Increased rates of mycotic infections have been reported not only in CANVAS, but in other SGLT2i CVOTs, as well. Please rephrase. Renal effects: "For now, dulaglutide remains the only novel therapy that can be used in moderate to severe CKD given the evidence provided by the Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7) trial" This is not accurate. In LEADER trial 20.7% of participants had moderate and 2.4% had severe renal impairment. No differences in safety or efficacy were demonstrated in these patients compared to those with normal renal function. According to liraglutide's product monograph, the

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drug can be administered in patients with eGFR up to 15 ml/min/1.73 m2. Please clarify. Additional considerations: "Most drugs demonstrated CV benefit after several years of median follow up." This is true only for GLP-1 agonists. Divergence in the survival curve for MACE was observed at 3 months in the EMPA-REG study. Please rephrase. Conclusion: "GLP-1RAs have been associated with both acute and chronic pancreatitis". This is quite debatable in the literature. A recent meta-analysis of available evidence (Storgaard et al. Diabetes Obes Metab, 2017) showed no increased risk for acute pancreatitis in T2D patients treated with GLP-1 agonists. I think that limiting the use of GLP-1 agonists due to increased concerns for pancreatitis is the wrong message to clinicians, since this is not supported by strong data.

INITIAL REVIEW OF THE MANUSCRIPT

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