Editor
World Journal of Diabetes

Re: Novel Pharmacological Therapy in Type 2 Diabetes Mellitus with Established Cardiovascular Disease: Current Evidence

Dear Sir/Madam,

Attached, please find the revised version which we hope that your readership with benefit and enjoy reading it. We like to thank the editorial team and reviewer for their comments. We thank them for that. Please feel free to call us with any questions.

Sincerely,

Salim Surani, MD

Response to Reviewers Comments

Reviewer 1:

Comments: 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

Response: We appreciate the reviewer nice comments and appreciate his time and effort.

Reviewer 2:

Comments: 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 should mention the updated role that these agents have in the T2D management algorithm, according to the recently published ADA/EASD consensus statement.

Response: We appreciate the reviewer time and comment and agree with that. We have added the statement regarding the recently published ADA/EASD consensus.

Comment: 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).

Response: We appreciate and agree with the reviewer comment but adding the drugs as metformin and pioglitazone would be beyond the scope of this review and may be a separate topic for another review. We have focused our review on SGLTi2 and GLP-1RA.

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.

Response: We appreciate the reviewer comment and has been modified as suggested.

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.

Response: We appreciate the reviewer comments. Modification and clarification have been done as suggested. Have clarified the point regarding the CANVAS and other trial

Comment: 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 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.

Response: We appreciate the reviewer insight and comment. The manuscript has been modified to clarify these points.

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.

Response: We modified the conclusion acknowledging those points. We thank the reviewer for their insight and vigilance.