Letter Regarding "Systematic Review of Cardiovascular Outcome Trials Using New Antidiabetic Agents in CKD Stratified by Estimated GFR"

To the Editor: In a systematic review[1] with meta-analysis recently published in the journal *KI Reports*, the authors identified that sodium-glucose cotransporter-2 inhibitors versus placebo significantly reduced major adverse cardiovascular events (MACE: a composite of nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death) in patients with type 2 diabetes (T2D) and estimated glomerular filtration rate <60 ml/min per 1.73 m^2, whereas glucagon-like peptide-1 receptor agonist (GLP1RA) failed to do it owing to the lack of sufficient power, as stated in the article of Arshad *et al.*[1]

In our opinion, the reason for the nonsignificant effect of GLP1RA was not the one given by Arshad *et al.*,[1] but it probably was that different types of GLP1RA had different effects on MACE in patients with T2D with estimated glomerular filtration rate <60 ml/min per 1.73 m^2, as suggested by substantial heterogeneity ($I^2 = 53\%$) in Figure 3b in the article of Arshad *et al.*[1]

To evaluate this possible reason, we did an exploratory subgroup analysis according to the structural homology of GLP1RA. Accordingly, we identified that exendin-4–based GLP1RA versus placebo did not significantly affect MACE (risk ratio 1.03, 95% CI 0.89–1.20) in patients with T2D with estimated glomerular filtration rate <60 ml/min per 1.73 m^2, whereas human GLP1RA significantly reduced MACE (risk ratio 0.78, 95% CI 0.64–0.95), with a significant between-group difference ($P_{subgroup} = 0.03$; Figure 1). This suggests that human GLP1RA but not exendin-4–based GLP1RA could reduce MACE in patients with T2D with chronic kidney disease. Thus, human GLP1RA, along with sodium-glucose cotransporter-2 inhibitors, should be recommended in patients with T2D and chronic kidney disease, to prevent atherosclerotic cardiovascular events.

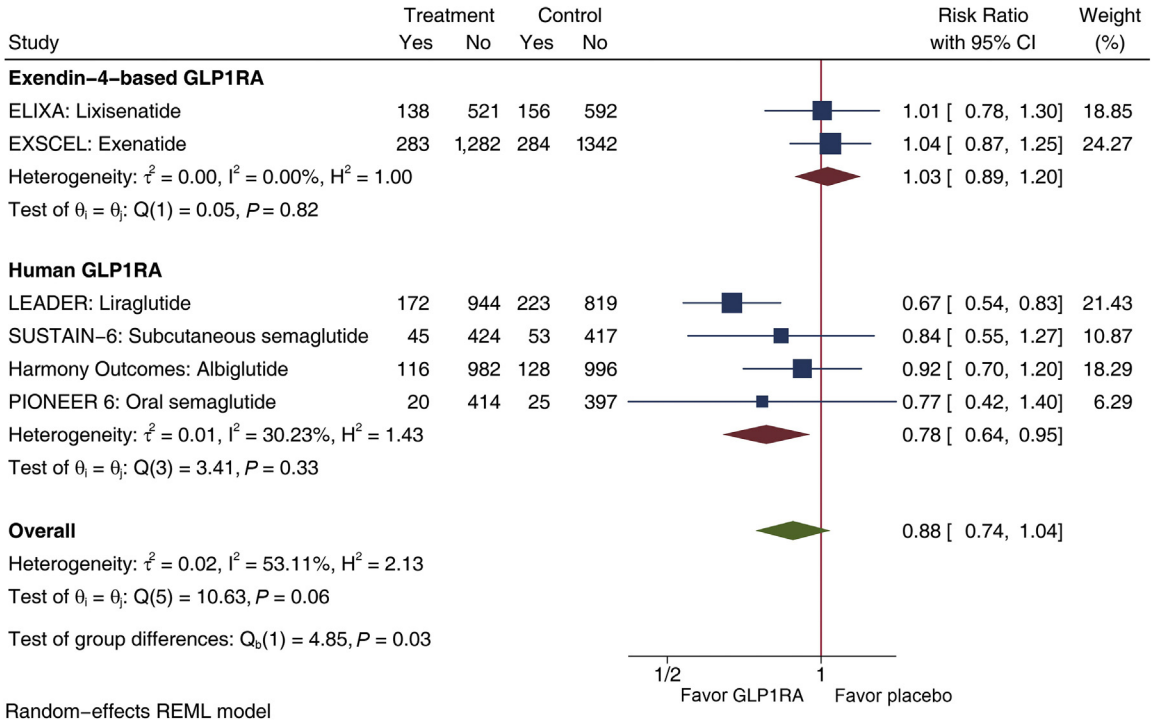

Figure 1. Meta-analysis revealing the effect of GLP1RA versus placebo on major adverse cardiovascular events in patients with T2D with eGFR <60 ml/min per 1.73 m^2, stratified by the structural homology of GLP1RA. eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes.

DISCLOSURE

All the authors declared no competing interests.

1. Arshad A, Sarween N, Sharif A. Systematic review of cardiovascular outcome trials using new antidiabetic agents in CKD stratified by estimated GFR. *Kidney Int Rep*. 2021;6:2415–2424 Published online July 1, 2021 https://doi.org/10.1016/j.ekir.2021.06.029.

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Received 15 September 2021; accepted 17 September 2021; published online 7 October 2021

Kidney Int Rep (2021) **6,** 2934–2935; https://doi.org/10.1016/j.ekir.2021.09.014

Author Replies: I appreciate the interest from Zhao and Qiu in our manuscript exploring major adverse cardiovascular events with new antidiabetic agents in patients with chronic kidney disease.[1] In their letter,[2] they provide insightful subanalyses revealing stratified effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) based on structural homology, with significant benefit found with human-based but not exendin-4–based GLP-1RA. This is consistent with data from the original cardiovascular outcome trials. In a meta-analysis by Kristensen *et al.*,[3] which analyzed clinical outcomes of GLP-1RA in patients with diabetes, patients randomized to human-based GLP-1RA were found to have significant protection from major adverse cardiovascular events (hazard ratio 0.84; 95% CI 0.79–0.90), but not exendin-based GLP-1RA (hazard ratio 0.95; 95% CI 0.85–1.06). The study authors also observed that heterogeneity of the effect of the 2 GLP-1RA types was nearly significant ($P = 0.06$). This trial evidence is in keeping with real-world observations in a general population setting.[4]

The mechanisms of cardiovascular protection by GLP-1RA are only partially known. Members of the GLP-1RA class differ for molecular structure, half-life, and administration schedule.[S1] It can be postulated that GLP-1RA based on the sequence of the endogenous human GLP-1 may activate the GLP-1 receptor in a more physiological way than exendin-4–based GLP-1RA. However, no head-to-head trial has directly compared human-based versus exendin-based GLP-1RA in terms of cardiovascular outcomes, and none are planned. Therefore, aligned with currently available evidence from the general population and the additional analysis from Zhao and Qui, it may be reasonable to advocate stratified selection of human-based GLP-1RA for patients with chronic kidney disease.

1. Arshad A, Sarween N, Sharif A. Systematic review of cardiovascular outcome trials using new antidiabetic agents in CKD stratified by estimated GFR. *Kidney Int Rep*. 2021;6:2415–2424. https://doi.org/10.1016/j.ekir.2021.06.029.
2. Zhao LM, Qui M. Letter: regarding "systematic review of cardiovascular outcome trials using new antidiabetic agents in CKD stratified by estimated GFR". *Kidney Int Rep*. 2021;6:2934–2935.
3. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7:776–785. https://doi.org/10.1016/S2213-8587(19)30249-9.
4. Longato L, Di Camillo B, Sparacino G, et al. Cardiovascular effectiveness of human-based vs. exendin-based glucagon like peptide-1 receptor agonists: a retrospective study in patients with type 2 diabetes. *Eur J Prev Cardiol*. 2021;28:22–29. https://doi.org/10.1093/eurjpc/zwaa081.

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Received 22 September 2021; accepted 24 September 2021; published online 7 October 2021

Kidney Int Rep (2021) **6,** 2935; https://doi.org/10.1016/j.ekir.2021.09.015