

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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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.⁵¹ 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 Qiu, 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, Qiu 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](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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