Routine care data and the benefits of GLP1 receptor agonists on slowing kidney function decline

Xu, Y.; Faucon, A.L.; Fu, E.L.; Carrero, J.J.

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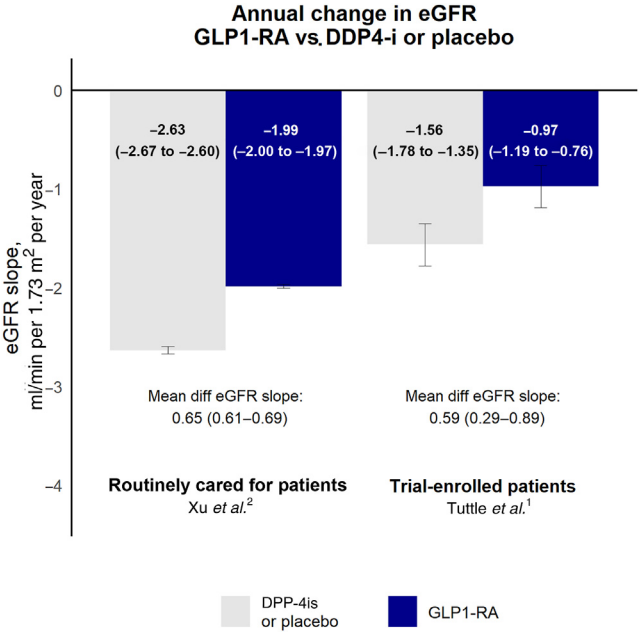

Figure 1 | Comparison of the annual change in estimated glomerular filtration rate (eGFR) in patients with type 2 diabetes treated with glucagon-like peptide-1 receptor agonist (GLP1-RA), dipeptidyl peptidase-4 inhibitor (DPP-4i), or placebo for patients enrolled in clinical trials or undergoing routine care. diff, difference.

To the editor: In the analysis of SUSTAIN-6 (the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes)/PIONEER-6 (the Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes) trials by Tuttle *et al.*,[1] semaglutide, a glucagon-like peptide-1 receptor agonist (GLP1-RA), was associated with a slower estimated glomerular filtration rate (eGFR) decline versus placebo, with a mean difference in eGFR slope of 0.59 ml/min per 1.73 m^2 per year. These trials included collectively 6480 patients with type 2 diabetes and high cardiovascular risk, followed up for 2.0 and 1.3 years, respectively.

The effects on eGFR slope are remarkably similar to those found in our earlier observational study,[2] which included 19,766 patients initiating GLP1-RAs (predominantly liraglutide) or DPP4-is (dipeptidyl peptidase-4 inhibitors, predominantly sitagliptin) from routine clinical practice. During a median of 2.9 years, initiation of GLP1-RAs was associated with a mean difference in eGFR slope of 0.65 ml/min per 1.73 m^2 per year slower versus DPP4-is (Figure 1).

Compared with the trials, our routinely cared for population had a lower prevalence of cardiovascular disease, less albuminuria, and higher eGFR (Supplementary Table S1). Their eGFR slope (e.g., –1.99 ml/min per 1.73 m^2 per year among GLP1-RA users) is biologically plausible and consistent with their high risk for chronic kidney disease progression, but more frequent testing among the sickest patients may bring down the absolute eGFR decline.[3] The eGFR slope in the trials was unexpectedly low (e.g., –0.97 ml/min per 1.73 m^2 per year for GLP1-RA users) and close to normal kidney aging, possibly attributed to the uniform monitoring of participants, as per trial protocols, and the strict inclusion and exclusion criteria applied.

Although we see collectively these results as reassuring and clearly in favor of kidney-protective effects for GLP1-RAs, they may also be a testimony that carefully conducted observational studies can extend and/or be a complement to clinical trial evidence.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Table S1. Comparison of baseline characteristics in the observational study by Xu *et al.*[2] and the pooled SUSTAIN-6/PIONEER-6 clinical trials by Tuttle *et al.*[1]

1. Tuttle KR, Bosch-Traberg H, Cherney DZI, et al. *Post hoc* analysis of SUSTAIN 6 and PIONEER 6 trials suggests that people with type 2 diabetes at high cardiovascular risk treated with semaglutide experience more stable kidney function compared with placebo. *Kidney Int*. 2023;103:772–781.
2. Xu Y, Fu EL, Clase CM, et al. GLP-1 receptor agonist versus DPP-4 inhibitor and kidney and cardiovascular outcomes in clinical practice in type-2 diabetes. *Kidney Int*. 2022;101:360–368.
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The authors reply: We thank Xu *et al.* for their viewpoint on the benefits of glucagon-like peptide-1 (GLP-1) receptor agonists for preserving kidney function in type 2 diabetes.[1] Their routine clinical practice data[2] are reassuring and confirmatory of our clinical trial findings[3] about the effects of a GLP-1 receptor agonist to slow loss of estimated glomerular filtration rate (eGFR). Both studies analyzed patients selected for type 2 diabetes, most of whom did not have chronic kidney disease (CKD).[2,3] Collectively, these results raise the intriguing possibility that GLP-1 receptor agonists could have a primary prevention role, because eGFR decline is a pathway to CKD and, ultimately, to kidney failure. However, our data suggest that they may slow eGFR decline more in patients with lower eGFR (<60 ml/min per 1.73 m^2). The estimated treatment difference in eGFR slope between semaglutide and placebo groups was 1.06 ml/min per 1.73 m^2 per year (95% confidence interval, 0.45–1.67 ml/min per 1.73 m^2 per year) in participants with eGFR 30 to <60 ml/min per 1.73 m^2 at baseline in contrast to 0.46 ml/min per 1.73 m^2 per year (95% confidence interval, 0.12–0.80 ml/min per 1.73 m^2 per year) in those with higher eGFR.[3]

This is a pivotal time for new therapies to address enormous unmet needs to improve CKD care.[4] Clinical (FLOW [A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease]; NCT03819153) and mechanistic (REMODEL [A Research Study to Find Out How Semaglutide Works in the Kidneys Compared to Placebo, in People With Type 2 Diabetes and Chronic Kidney Disease (the REMODEL Trial)]; NCT04865770) studies are underway to test if GLP-1 receptor agonists preserve kidney function. For comparative purposes, clinical practice data can inform therapeutic efficacy and safety across broad populations. Such work is also critical to identify patients with or at risk of CKD who may benefit from therapeutic advances and track progress in CKD awareness, detection, and intervention.

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Relative excess mortality risk after kidney transplantation: Eve's loss or Adam's win?

To the editor: We read with interest the recent study by Vinson *et al.*,[1] which reveals that after kidney transplantation, females face a greater risk of excess mortality compared with