Response to [Challenging the Restrictive Approach: Reconsidering SGLT-2 Inhibitor Use in CKD]

The Author Replies: Dear editors, we would like to respond to the questions raised by Helvaci *et al.*[1] regarding the beneficial effects of sodium-glucose cotransporter 2 inhibitors (SGLT2is) in the absence of renin-angiotensin-aldosterone system inhibitors (RAASi) and in the absence of albuminuria when estimated glomerular filtration rate (eGFR) is >45. Use of SGLT2i in these 2 clinical settings remains debatable based on all data available. For the first clinical setting, although subgroup analyses of the EMPA-KIDNEY trial showed beneficial effects of SGLT2i regardless of RAASi use,[2,3] there were fewer patients recruited (18%) who were not on RAASi. This small sample size resulted in a wide confidence interval of the effect size for subgroup without RAASi in the randomized controlled trial (RCT) (absolute difference in mean slope for eGFR: 0.81, 95% confidence interval: 0.21–1.40). One could argue that other analyses have also shown consistent benefit of SGLT2i in patients with chronic kidney disease (CKD) not on RAASi.[4] However, we would like to highlight that most of the RCTs of SGLT2i summarized in our article[S1] recruited fewer "high risk" patients with CKD who were at more than 20% 5-year risk of kidney failure. This CKD subgroup is particularly difficult to treat given the higher rates of adverse events from renoprotective treatments. For example, in the EMPA-KIDNEY trial, RAASi use was 91% in participants with eGFR >45 and 82% in participants with eGFR <30.[2,3] Although the RCTs did not report significant differences in adverse events from SGLT2i use in the high-risk CKD subgroup,[S1] the protocol implemented in RCTs is difficult to implement in real-world patients. From one perspective, in CREDENCE and many other RCTs, SGLT2i was not stopped even after eGFR decline met the eligibility criteria, and often continued until dialysis dependence; this strict protocol adherence resulted in >70% of participants using SGLT2i at 2 years.[S1] Conversely, recent publications from real-world patients show high discontinuation rates for SGLT2i prescriptions; 25% at 1 year and up to 50% at 5 years.[S2,S3] Furthermore, one of the risk factors for high discontinuation rates of SGLT2i prescriptions was comorbid CKD,[S4] a clinical setting where SGLT2i is likely to benefit these patients. Taken together, there are paradoxical risks associated with beneficial treatments in patients with CKD, that is, people who are more likely to benefit from a treatment might also be the ones who do not tolerate them. For the second clinical setting, patients with nonalbuminuric CKD with eGFR >45, there are not enough data regarding efficacy of SGLT2i. The EMPA-KIDNEY trial included patients with nonalbuminuric CKD with eGFR <45, where efficacy of SGLT2i is clear even in the absence of albuminuria.[S5] In our review article,[S1] we have highlighted this eGFR cut-off from CKD subgroups where there is lack of clear evidence, that is, patients with eGFR >45 and albuminuria <200 mg/g of creatinine. Therefore, we recommend SGLT2i only for those receiving RAASi and for CKD subgroups with no albuminuria if eGFR is <45 until more data become available.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

1. Helvaci O, Yasar E, Helvaci B. Challenging the restrictive approach: reconsidering sodium-glucose transport protein 2 inhibitor use in CKD. *Kidney Int Rep*. 2024;9:1935.
2. The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, et al. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388:117–127. https://doi.org/10.1056/NEJMoa2204233
3. EMPA-KIDNEY Collaborative Group. Effects of empagliflozin on progression of chronic kidney disease: a prespecified secondary analysis from the empa-kidney trial. *Lancet Diabetes Endocrinol*. 2024;12:39–50. https://doi.org/10.1016/S2213-8587(23)00321-2
4. Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2019;7:845–854. https://doi.org/10.1016/S2213-8587(19)30256-6

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