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LETTER

Ertugliflozin, renoprotection and potential confounding by muscle wasting

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Abbreviations

$eGFR_{Cr}$	Creatinine-based eGFR
SGLT2	Sodium–glucose cotransporter 2
VERTIS CV	eValuation of ERTugliflozin effIcacy and Safety Cardio Vascular outcomes

To the Editor: The eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes (VERTIS CV) trial reported that ertugliflozin reduced the risk of the composite exploratory endpoint of sustained 40% decline in baseline creatinine-based eGFR ($eGFR_{Cr}$), chronic renal replacement therapy and death from renal causes [1]. Moreover, treatment with ertugliflozin was associated with a decreased urinary albumin/creatinine ratio and attenuation of deterioration in $eGFR_{Cr}$. Use of $eGFR_{Cr}$-based endpoints is endorsed by the National Kidney Foundation and the US Food and Drug Administration, provided that interventions do not affect creatinine generation from muscle [2]. These authorities recommend that potential effects of interventions on determinants of serum creatinine other than GFR (including muscle mass) are excluded, when $eGFR_{Cr}$ is used to approximate renal function. However, this condition is not satisfied by studies investigating the effect of sodium–glucose cotransporter 2 (SGLT2) inhibitors on renal outcomes, since these studies do not account for the fact that the pharmacological mechanism of action of SGLT2 inhibitors likely promotes loss of muscle mass [3, 4]. This mechanism involves induction of glucosuria through inhibition of SGLT2 in the renal proximal tubule. Loss of glucose molecules with urine can stimulate hepatic gluconeogenesis, which uses amino acids from skeletal muscle as primary substrates to endogenously produce new glucose molecules [3]. In this respect, excess loss of glucose is replenished at the expense of muscle tissue. Indeed, numerous studies investigating the effect of SGLT2 inhibitors on body composition have demonstrated that SGLT2 inhibition is associated with a substantial loss of muscle mass (an overview of these studies has been published previously [4]). Although no such study has been conducted for ertugliflozin to date, it is highly plausible that the observed weight reduction following treatment with ertugliflozin [5] is, at least in part, attributable to loss of muscle mass, given that ertugliflozin has the same pharmacological mechanism of action as the other SGLT2 inhibitors. Clearly, the effect of SGLT2 inhibitors on muscle mass involves a slow process that affects outcomes in the long term, which must be discriminated from the acute effects of SGLT2 inhibitors [4, 6]. The acute effects of SGLT2 inhibitors include enhancement of renal tubuloglomerular feedback through increased sodium concentrations at the macula densa, which induces afferent vasoconstriction and explains the characteristic acute drop in eGFR that occurs upon initiation of treatment with SGLT2 inhibitors [7]. In the VERTIS CV trial, this acute drop in eGFR was accompanied by a simultaneous drop in urinary albumin/creatinine ratio [1], a combination generally considered reflective of a change in glomerular haemodynamics [8]. Importantly, reduced muscle mass unequivocally leads to reduced serum creatinine, independently of underlying renal function [9]. Since serum creatinine is reciprocally related to the GFR [10], a reduced muscle mass implies overestimation of GFR (operating through reduced serum creatinine) when such estimates are based on creatinine measures. This line of thought fuels the belief that the surmised renoprotective

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effects of ertugliflozin (i.e. reduced risk of the composite endpoint of sustained 40% decline in baseline $eGFR_{Cr}$, chronic renal replacement therapy and death from renal causes, as well as attenuation of $eGFR_{Cr}$ deterioration) [1] are, at least in part, confounded by ertugliflozin-related loss of muscle mass. A second concern resulting from therapy-related muscle wasting is deferred initiation of dialysis or (re)transplantation, as the decision to do so principally relies on the eGFR [11]. If the eGFR is based on creatinine measures, therapy-related muscle wasting may, through overestimation of $eGFR_{Cr}$, conceal the necessity to proceed to renal replacement therapy. Another mechanism through which SGLT2 inhibitors may cause deferral of dialysis, is through mitigation or even prevention of fluid overload; glucosuria resulting from SGLT2 inhibition causes osmotic diuresis and hence mitigates (or even prevents) fluid overload, which may otherwise develop [12]. Finally, the use of $eGFR_{Cr}$ in circumstances under which therapy-related muscle wasting occurs compromises the detection, evaluation and management of acute and chronic kidney disease, as well as risk stratification for clinical procedures and selection of the correct dosage of drugs that are excreted by the kidney [13].

In summary, accurate assessment of renoprotective properties of interventions using $eGFR_{Cr}$ requires that the generation of creatinine from muscle is not affected by the intervention under study. Obviously, circumstances under which this condition cannot be met, which is likely to hold true for ertugliflozin (and other SGLT2 inhibitors), provide sound reasons for modification of endpoints of the current or future trials [14]. The VERTIS CV trial could benefit from analyses adjusted for muscle wasting or through utilisation of alternative GFR-based endpoints [2]. We, therefore, invite the authors to report on the effect of ertugliflozin after having adapted the renal endpoint, specifically via use of alternative filtration markers insensitive to changes in muscle mass, preferably cystatin C [10].

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References

1. Cherney DZI, Charbonnel B, Cosentino F et al (2021) Effects of ertugliflozin on kidney composite outcomes, renal function and albuminuria in patients with type 2 diabetes mellitus: an analysis from the randomised VERTIS CV trial. Diabetologia 64(6):1256–1267. https://doi.org/10.1007/s00125-021-05407-5
2. Levey AS, Inker LA, Matsushita K et al (2014) GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the national kidney foundation and the US food and drug administration. Am J Kidney Dis 64(6):821–835. https://doi.org/10.1053/j.ajkd.2014.07.030
3. Post A, Eisenga MF, Bakker SJL (2019) Canagliflozin and renal outcomes in diabetic nephropathy. N Engl J Med 381(11):1089. https://doi.org/10.1056/NEJMc1909687
4. Post A, Groothof D, Eisenga MF, Bakker SJL (2020) Sodium–glucose cotransporter 2 inhibitors and kidney outcomes: true renoprotection, loss of muscle mass or both? J Clin Med 9(5):1603. https://doi.org/10.3390/jcm9051603
5. Liu J, Tarasenko L, Terra SG et al (2019) Efficacy of ertugliflozin in monotherapy or combination therapy in patients with type 2 diabetes: a pooled analysis of placebo-controlled studies. Diabetes Vasc Dis Res 16(5):415–423. https://doi.org/10.1177/1479164119842513
6. Marton A, Kaneko T, Kovalik JP et al (2021) Organ protection by SGLT2 inhibitors: role of metabolic energy and water conservation. Nat Rev Nephrol 17(1):65–77. https://doi.org/10.1038/s41581-020-00350-x
7. Cherney DZI, Perkins BA, Soleymanlou N et al (2014) Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 129(5):587–597. https://doi.org/10.1161/CIRCULATIONAHA.113.005081
8. Cherney DZI, Zinman B, Inzucchi SE et al (2017) Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 5(8):610–621. https://doi.org/10.1016/S2213-8587(17)30182-1
9. Groothof D, Post A, Polinder-Bos HA, Hazenberg BPC, Gans ROB, Bakker SJL (2021) Muscle mass versus body mass index as predictor of adverse outcome. J Cachexia Sarcopenia Muscle 12(2):517–518. https://doi.org/10.1002/jcsm.12686
10. Stevens LA, Coresh J, Greene T, Levey AS (2006) Assessing kidney function-measured and estimated glomerular filtration rate. N Engl J Med 354(23):2473–2483. https://doi.org/10.1056/NEJMra054415
11. Lin X, Zeng XZ, Ai J (2016) The glomerular filtration rate (GFR) at dialysis initiation and mortality in chronic kidney disease (CKD) in east asian populations: a meta-analysis. Intern Med 55(21):3097–3104. https://doi.org/10.2169/internalmedicine.55.6520
12. Eickhoff MK, Dekkers CCJ, Kramers BJ et al (2019) Effects of dapagliflozin on volume status when added to renin-angiotensin system inhibitors. J Clin Med 8(6):779. https://doi.org/10.3390/jcm8060779
13. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3(1):1–150
14. Evans S (2007) When and how can endpoints be changed after initiation of a randomized clinical trial? PLoS Clin Trials 2(4):e18. https://doi.org/10.1371/journal.pctr.0020018