Received: 19 September 2022 | Revised: 30 September 2022 | Accepted: 13 October 2022

DOI: 10.1111/nep.14124

NEPHROLOGY WILEY

EDITORIAL

Complementary actions of finerenone and SGLT2-i on renal outcomes?: An urgent need for more information

The treatment of heart failure and chronic kidney disease (CKD) has been implemented in the recent years with the introduction of the sodium-glucose cotransporter 2 inhibitors (SGLT2-i) in the clinical practice. Currently, more than 850 million people are affected by CKD worldwide, a condition linked to substantially increased mortality and impaired quality of life.[1] These numbers in combination with the low awareness of CKD, and the projection that renal replacement therapy will increase substantially in the next few decades, make CKD a major health problem.

In two recently published phase III trials, the FIGARO-DKD and FIDELIO-DKD, it was shown that addition of finerenone, a novel, non-steroidal, selective mineralocorticoid receptor antagonist on top of optimal medical treatment led to reduction of heart failure-associated events, composites of time to cardiovascular death as also in renal outcomes compared to placebo.[2,3] Together in these trials a substantial number of participants were already on treatment with SGLT2-i and were randomized in the finerenone treatment arm.

Previous evidence has suggested that the combination of mineralocorticoid receptor antagonists and SGLT2-i may result in more pronounced renal benefits. In particular, in a rat model of hypertension-induced end-organ damage co-administration of finerenone with SGLT2-i led to more pronounced renal protection compared to monotherapy with each drug alone,[4] and a previous study in patients with CKD has shown an additive effect in the co-administration of the SGLT2-i dapagliflozin and the steroidal mineralocorticoid receptor antagonist, eplerenone in reducing urine albumin-to-creatinine ratio.[5] Thus, whether co-administration of finerenone and SGLT2-i leads to complementary renal protection in humans warranted investigation.

Indeed, in the recently published analysis "In the Finerenone in Chronic Kidney Disease and type 2 diabetes combined with FIDELIO-DKD and FIGARO-DKD trial program analysis (FIDELITY)," the investigators merged the two previous studies in order to assess the effect of finerenone and the interaction with SGLT2-i use on the prespecified cardiovascular (CV) and kidney composite outcomes.[6] In the FIDELITY population, 877 patients (6.7% of the population) were on a SGLT2-i at baseline, with 438 of them receiving finerenone and 439 on the placebo group, whereas during the on-treatment period 1113 patients (8.5% of the population) started a SGLT2-i (520 of them were on finerenone and 593 on placebo). With this new analysis, it was shown that finerenone reduced the risk of CV and kidney outcomes compared with placebo, but concomitant treatment with an SGLT2-i at baseline or at any time concomitant with study treatment did not result in additional benefits.[6] This interesting and clinically important analysis, suffers though the pitfalls of a post hoc analysis. In particular, there were differences in the characteristics of patients receiving SGLT2-i at baseline, and the analysis lacked statistical power for the composite kidney and CV outcomes because of the relatively small number of patients receiving SGLT2-i at baseline and the small number of clinical events in these patients. Interestingly, co-administration of SGLT2-i and finerenone seemed to protect from hyperkaliemia. This finding is in line with the meta-analysis of Lin et al.[7] where 10 eligible studies with a total of 71 553 participants were included, showing that SGLT2-i offer protection from hyperkaliemia. Finally, in the FIDELIO analysis additional adverse events were not noted by the combination treatment. Thus, it could be already concluded that combination of finerenone with SGLT2-i is a safe option that the clinicians should consider in patients with type 2 diabetes and CKD.

Ultimately, whether the combination of finerenone with SGLT2-i has any complementary actions will be rigorously addressed with the results from the ongoing trial on the combination of finerenone and empagliflozin (A Study to Learn How Well the Treatment Combination of Finerenone and Empagliflozin Works and How Safe it is Compared to Each Treatment Alone in Adult Participants With Long-term Kidney Disease [Chronic Kidney Disease] and Type 2 Diabetes [CONFIDENCE]). According to the online published project plan there will be three treatment arms with patients receiving either combination of finerenone and empagliflozin, finerenone with placebo, or empagliflozin with placebo for 6 months, and the results of this study are expected for 2024. Patients with CKD are a category of especially vulnerable patients and studies assessing novel treatments that may decelerate the progression to end-stage renal disease and the need for renal replacement therapy are expected with great interest from the scientific community.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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