The Embarrassment of Riches: Combining SGLT2 Inhibitors and Nonsteroidal Mineralocorticoid Antagonists for the Treatment of Diabetic Kidney Disease

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Diabetic kidney disease (DKD) is the leading cause of ESKD and associated with increased morbidity and mortality in diabetic patients. Extensive studies are being conducted to understand the pathophysiology of DKD and develop novel therapeutic strategies. Despite improvements in glycaemic control and blood pressure management with renin-angiotensin-aldosterone system blockade, the current therapy is insufficient and cannot prevent progression to ESKD. This imperfect situation has been lamented over for years. Only recently we have seen novel important treatment strategies for CKD which may change the landscape and improve the deleterious outcome for patients with DKD. Recently, 2 groups of novel drugs, sodium-glucose cotransporter 2 (SGLT2) inhibitors and finerenone, a mineralocorticoid receptor (MR) antagonist, were demonstrated to provide renoprotection [1–5]. Kolkhof et al. [6] in this issue of the journal provide evidence that combination of the 2 novel treatment strategies may be even more advantageous.

It seems that both new treatment strategies target different molecular mechanisms which play a role in the

pathogenesis of DKD. DKD is a heterogeneous disease entity in terms of its clinical manifestations, histopathology, and the rate of progression, which makes it difficult to develop effective therapeutics. The pathophysiology of DKD is complex and multifactorial, involving both metabolic and haemodynamic factors that trigger a complex network of pathological events activation of intracellular signalling pathways, oxidative stress, hypoxia, dysregulated autophagy, and epigenetic changes, which result in kidney inflammation and eventually fibrosis.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors prevent the renal tubular reabsorption of filtered glucose, thereby increasing glucosuria and lowering blood glucose levels. A substantial decrease in cardiovascular morbidity and mortality was observed in patients with type 2 diabetes who were treated with empagliflozin, and the drug was associated with a lower risk of incident or worsening nephropathy (EMPA-REG OUTCOME) [2]. Similar cardiovascular and kidney protection was reported in the CANVAS Program with canagliflozin [4] and in the studies with dapagliflozin [5]. What is remarkable about SGLT2 inhibitors is that their beneficial effects are not confined to DKD; a recent randomized controlled trial revealed that dapagliflozin significantly reduced the worsening of kidney function or

death in CKD patients both with and without type 2 diabetes (DAPA-CKD) [5].

There has been a considerable and sustained effort to uncover the mechanisms underlying these remarkable benefits of SGLT2 inhibitors on the development and progression of DKD. A leading hypothesis focuses on natriuresis resulting from inhibition of sodium and glucose reabsorption in the proximal tubules with activation of the tubuloglomerular feedback and subsequent vasoconstriction of the afferent arterioles and reduced intraglomerular pressure [7, 8]. SGLT2 inhibition also alters energy metabolism, which may contribute to renoprotection [9, 10].

In contrast, the MR antagonist finerenone has a direct effect on inflammatory processes in the kidney and the vasculature. Low-grade inflammation is a hallmark of cardiovascular and renal disease. In some patients' inflammatory biomarkers such as C-reactive protein or inflammatory cytokines (MCP-1) and their receptors are increased. These patients have a poor clinical outcome and prognosis [11]. Indeed, several experimental studies have shown that chronic activation of the MR enhances and stimulates a variety of different inflammatory mechanisms. Macrophages, dendritic cells, and T lymphocytes have been described as target cells for mineralocorticoids [12]. It has been demonstrated that the infiltration of the arterial wall and perivascular space by immune cells is a relatively early event after activation of the MR [13]. This pro-inflammatory effect of aldosterone can be abolished in monocyte/macrophage deficient animals [14]. Interestingly, oxidative stress and endothelial dysfunction are also reduced in these animals indicating that the effects of aldosterone on immune cells are centrally important in this "trio infernal" of oxidative stress, microinflammation, and fibrosis.

The important role of the MR in macrophage activation has been demonstrated in several studies with macrophage-specific MR KO mice [15]. Aldosterone may directly influence a switch in macrophage polarization and the differentiation of monocytes into an inflammatory phenotype. The expression of MR in myeloid cells plays an important role for both inflammation and fibrosis in the kidney and the heart, and knockout of the myeloid MR has been shown to suppress macrophage activity and protect the kidney in animal models. In preclinical models, overactivation of the MR is associated with elevated cardiovascular risk by driving inflammation and fibrosis, leading to damage to the heart, kidney, and peripheral vasculature. Possible mechanisms of MC overactivation include increased MR expression, cortisol-mediated MR activation, and ligand-independent MR activation (e.g., caused by oxidative stress). Finerenone is a novel, nonste-

roidal, selective MR antagonist (MRA), which, in the phase III FIDELIO-DKD study (Finerenone in Reducing Kidney Failure and Disease Progression in DKD), significantly reduced the risk of kidney and cardiovascular events in patients with CKD and T2D.

Both novel treatment strategies for (diabetic) kidney disease have not been approved by FDA yet, but questions abound. Which of the 2 treatment strategies will work better? Which patient groups will respond more favourably and will be able to define these patients using novel diagnostic tools? And last but not least: is combination therapy the answer?

Kolkhof and colleagues [6] are the first to describe the effects of combination therapy using both an SGLT2 inhibitor and finerenone. So far only anecdotal reports have demonstrated that the combination of the 2 drugs may be of value. Most studies have concentrated on either finerenone or SGLT2 inhibitors or their individual effects on the diabetic kidney. The most important finding in the present study is that combining SGLT-2 inhibition and finerenone has an additive positive effect on kidney function, proteinuria, and renal histology. The authors also used a robust rat model with severe renal damage induced by hyperglycaemia. The combination of the 2 drugs showed additional benefit beyond their individual effects on the diabetic kidney. These findings argue for a positive interaction of the 2 compounds, a complementary molecular mechanism and support future clinical studies with combination therapy.

There are several other noteworthy aspects of the study. Interestingly, it is not the highest concentration of the 2 drugs, which exerted the best beneficial effect. In this study, it is a combination of modest drug concentrations which results in most benefits. This is interesting because it is yet unclear whether the 2 drugs interfere with different mechanisms. While finerenone has been mostly associated with the reduction in inflammatory mechanisms, less monocyte infiltration and less fibrosis, the molecular mechanisms of SGLT2 inhibitors seem to be more complex. While anti-inflammatory effects have been observed with SGLT2 inhibitors, it seems that their molecular target is the energy metabolism of renal cells. A shift from glucose utilization to fatty acid oxidation seems to be of importance. It will be of interest to investigate whether the 2 classes of agents influence different pathways, and therefore, a combined therapeutic approach may be feasible in humans. In addition, several aspects of combining the 2 drugs which have not been addressed in this first animal study, that is, effects of SGLT2 inhibition on finerenone-induced hyperkalaemia

or the complex interaction of the 2 drugs on renal hemodynamics should be investigated in the future. After a long time with no new therapeutic strategies in patients with diabetes, there is now light on the horizon, and we can expect a better view and more therapeutic possibilities in diabetic nephropathy.

Conflict of Interest Statement

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