Sodium glucose co-transporter 2 inhibition: a new avenue to protect the kidney

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Increasing knowledge on the role of the kidneys in maintaining optimal glucose homeostasis has led to the development of pharmacologic agents that block the sodium glucose co-transporter 2 (SGLT2) in the proximal tubule of the kidney. The SGLT2 transporter is responsible for the reabsorption of virtually all filtered glucose. Blockade of the transporter with SGLT2 inhibitors induces glycosuria of approximately 70–80 g/day and decreases HbA1c by 0.5–0.8% [1]. As a result of the glycosuric effects, and accompanied net calorie loss, SGLT2 inhibition leads to sustained reductions in body weight of 2–3 kg [2].

SGLT2 transporters reabsorb not only glucose but also sodium in a 1:1 stoichiometry. This leads to enhanced sodium excretion of ~25 mmol/day. As a result of the increased natriuresis, and concurrent osmotic diuresis, owing to glycosuric effects, SGLT2 inhibitors decrease blood pressure, plasma volume and increase haematocrit. In addition, SGLT2 inhibition decreases albuminuria by 30–40% [3, 4]. These combined effects render SGLT2 inhibitors promising agents for the management of diabetic kidney disease (DKD).

The long-term benefits of SGLT2 inhibitors are demonstrated in three large cardiovascular outcome trials [5–7]. These trials reported reductions in cardiovascular risk as well as strong and consistent reductions in risk for heart failure. The trials also suggested improvements in kidney outcomes, but these effects were mainly based on creatinine-based outcomes. The number of dialysis or kidney transplantation endpoints was very small. This is not surprising since the cardiovascular outcome trials were not designed to test the effects of SGLT2 inhibitors on slowing progressive kidney function loss. However, they provide a strong rationale to test the efficacy and safety of SGLT2 inhibitors in patients with kidney disease.

According to the label of the registered SGLT2 inhibitors in the USA and Europe—dapagliflozin, canagliflozin, empagliflozin and ertugliflozin—they should not be used in patients with severe kidney impairment due to reduced efficacy. Indeed, various studies have shown that the glycaemic efficacy of these drugs attenuates at lower glomerular filtration rate (GFR) levels [8, 9]. However, effects on other cardiovascular risk markers, such as body weight, blood pressure and albuminuria, persist even in patients with moderate-to-severe kidney impairment, suggesting that long-term benefits on clinical endpoints remain present in this population. This notion is supported by subgroup analyses from cardiovascular outcome trials demonstrating that SGLT2 inhibitors slow progression of kidney disease and reduce the risk of clinical endpoints in the subgroup of patients with an estimated GFR (eGFR) between 30 and 60 mL/min/1.73 m² [10, 11]. Against this background, the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial was designed and initiated in 2014. The objective of the trial was to examine the efficacy and safety of the SGLT2 inhibitor canagliflozin 100 mg/day in patients with type 2 diabetes, macroalbuminuria and eGFR between 30 and 90 mL/min/1.73 m². The trial was stopped early due to overwhelming efficacy. Although the results are not yet available, it is expected that the trial represents a new landmark in the management of DKD and will improve the outlook of many patients with DKD for whom no new treatment strategy has become available in the last 18 years.

What could be the mechanism of action giving rise to the benefits of SGLT2 inhibitors in slowing progression of DKD? It is unlikely that the long-term beneficial effects on kidney function are explained by improvements in glycaemic control as the HbA1c reductions observed in most trials were modest. Furthermore, active controlled studies have shown that at equal glycaemic control, eGFR decline was significantly less in SGLT2 inhibitor-treated compared with control-treated patients [12]. Other mechanisms have been described, as reviewed in detail elsewhere [13]. These include improving renal proximal tubule oxygenation, suppressing anti-inflammatory and anti-fibrotic pathways, and restoration of tubuloglomerular feedback. With respect to the latter, it is assumed that decreased sodium delivery to the macula densa, as may occur in type 2 diabetes due to increased SGLT2 expression, results in suppression of tubuloglomerular feedback resulting in afferent vasodilation, increased renal blood flow and hyperfiltration, which is the first clinical manifestation of DKD. A clinical trial in patients with type 1 diabetes demonstrated reductions in intra-glomerular pressure and acute reductions in the GFR, reflecting diminished...
The magnitude of the effect may be somewhat smaller compared to slow progression of kidney function decline in non-DKD, albeit Simulation studies have also suggested that SGLT2 inhibitors inhibition remain present in patients without diabetes [15].

However, the study also demonstrated a large variation in albuminuria response between individual patients, indicating that some patients showed a marked reduction in albuminuria, whereas others did not and remained at high risk of end-stage kidney disease. Thus, although SGLT2 inhibitors have brought us to the entrance of a new era for renal protective medicine, the search for new agents to further improve our pharmacological armamentarium should continue in order to protect every patient from progressive kidney function loss in the future.

CONFLICT OF INTEREST STATEMENT

Dr H.J.L.Heerspink is member of the steering committees of the CREDENCE and DAPA-CKD trials. He is consultant to Abbvie, AstraZeneca, Boehringer Ingelheim, Janssen, Gilead, Fresenius, Merck, Mundipharma and Mitsubishi Tanabe.

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Received: 3.1.2019; Editorial decision: 17.1.2019