SGLT-2 inhibitors: from bench to bedside for patients with cardiorenal disease

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The strong connection between chronic kidney disease (CKD) and cardiovascular disease prompted the need to focus on both issues simultaneously. Addressing this task brought multiple challenges since many trials either failed to meet renal endpoints, or numerous adverse effects hampered the implementation of the investigated drugs.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors were initially introduced as glucose-lowering agents acting by preventing the re-uptake of glucose that is normally filtered and reabsorbed in the proximal tubule. Blocking the SGLT-2 transporter leads to glucosuria, and subsequently decreases blood glucose levels. It was discovered, however, that these drugs have considerable renoprotective properties as well. Large cardiovascular outcome trials (EMPA-REG, CANVAS, DECLARE) showed a 40% reduction in composite renal endpoints, and this effect was confirmed in the CREDENCE trial, which particularly focused on renal outcomes. Interestingly, these results were not limited to people with diabetes but also appeared in those without diabetes-related CKD.

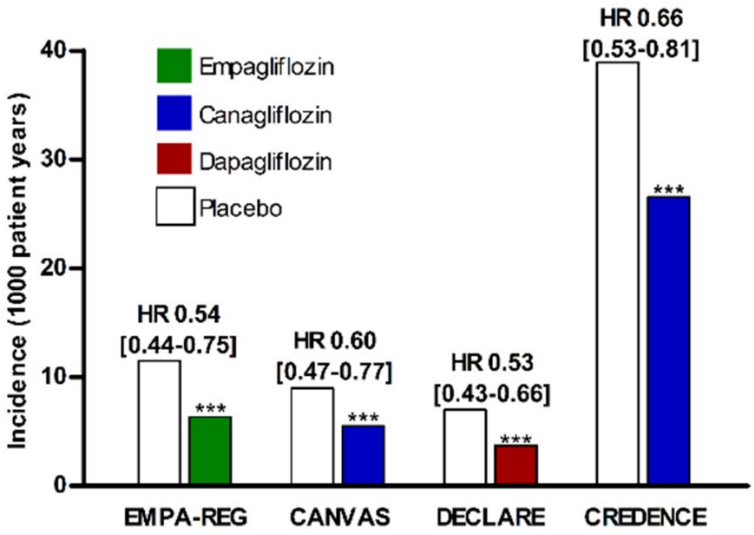

Figure 1. SGLT-2 inhibitors improve kidney outcomes in T2DM

The renoprotective mechanisms of SGLT-2 inhibitors are not completely understood, but clinical trials show an initial acute decline of glomerular filtration rate (GFR) followed by a subsequent stabilization of renal function compared to the placebo groups. Upon cessation of treatment, the GFR values quickly return to the baseline, which proves the renal hemodynamic effect of these therapeutics. Cherney et al. suggested that in patients with type 1 diabetes mellitus (T1DM) this effect might result from attenuation of renal hyperfiltration, most probably through tubular-glomerular feedback (TGF) mechanisms. With normal kidney function, in cases of conditional increase of GFR, the macula densa

senses higher sodium delivery in the distal tubule and adjusts the afferent and efferent tone through an autoregulatory response, thus balancing eGFR. Under chronic hyperglycemic conditions, increased proximal SGLT2-mediated reabsorption of sodium and glucose impairs this feedback mechanism. Thus, despite increased GFR, the macula densa is exposed to lowered sodium concentrations. This impairment of TGF signaling likely leads to inadequate arteriole tone and increased renal perfusion. SGLT-2 inhibitors block proximal tubule sodium and glucose reabsorption, thus causing a larger sodium flux into the macula densa, thereby restoring the TGF via modulation of arteriolar tone. This intense afferent arteriole constrictive response was recognized as the underlying renoprotective mechanism of SGLT-2 inhibitors.

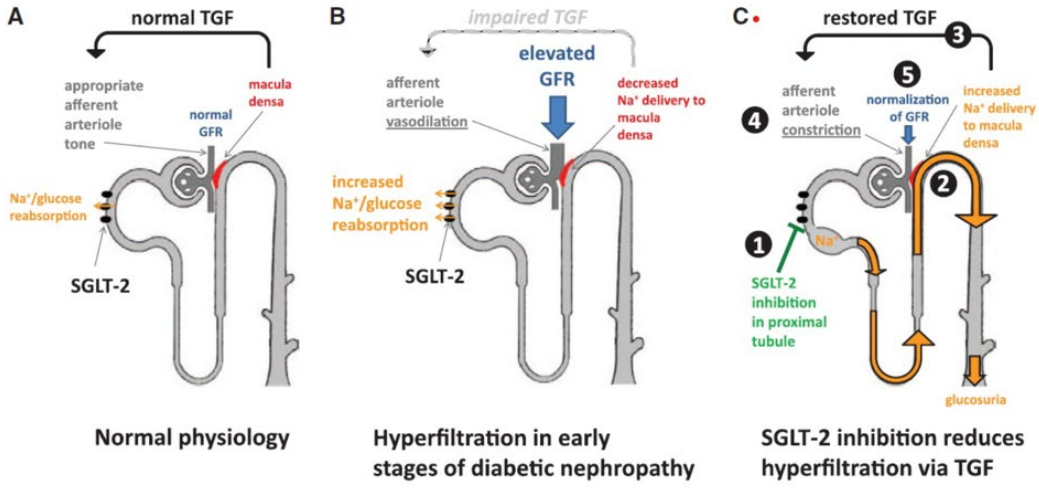

Figure 2. SGLT-2 inhibitors induce afferent renal vasoconstriction in T1DM

Other research also concluded that the SGLT-2 inhibitors induce post-glomerular vasodilation causing a GFR decline in persons with T2DM, similar to renin-angiotensin-system (RAS) blockers. A trial conducted by the German group, led by Ott and Schmieder, observed a reduction in glomerular vascular resistance and concluded that post-glomerular vasodilation is the mechanism that alters renal hemodynamics in T2D patients.

The Amsterdam trial led by Van Bomel compared the use of dapagliflozin and gliclazide in patients with type 2 diabetes (T2DM) on metformin monotherapy aiming to assess whether renal protective effects of SGLT-2 inhibitors are independent of glucose levels. In this cohort, dapagliflozin reduced GFR, while gliclazide did not consistently alter renal hemodynamic parameters. Dapagliflozin also reduced filtration fraction without increasing renal vascular resistance and increased urinary adenosine and prostaglandin concentrations. Both agents similarly improved glycoregulation.

Two additional potential renoprotective mechanisms associated with renal energy metabolism and oxygen availability are currently being investigated. Metabolic adaptations to urinary glucose loss induced by SGLT2-inhibitors include reduced fat mass and more ketone bodies as additional fuel. Thus, the SGLT-2 inhibitors shift the metabolism toward the utilization of ketones from fatty acids rather than glucose, suggesting that they promote higher energy efficiency in the kidney. Another hypothesis of SGLT-2 inhibitors' beneficial cardiovascular impact focuses on hematocrit as a marker of circulatory volume. Since SGLT-2 inhibitors block proximal sodium reabsorption, it is believed that they induce natriuresis and osmotic diuresis, thus reducing plasma volume and causing elevated hematocrit as a

marker of increased hemoconcentration. However, there is numerous evidence that calls this hypothesis into question.

Patients with diabetes also often require diuretic therapy. Therefore, Wilcox et al. looked at whether there is a diuretic interaction between dapagliflozin and bumetanide. In their study on healthy volunteers on a fixed dietary sodium intake, randomized to dapagliflozin or bumetanide, there was a transient increase in sodium excretion in the dapagliflozin group, which was much smaller than the increase seen with bumetanide and had no effect on cardiorenal disease. First-dose sodium excretion with bumetanide and dapagliflozin was not additive, but the weekly administration of one diuretic enhanced the initial sodium excretion with the other, thereby demonstrating a mutual adaptive natriuretic synergy.

The DAPASALT study included patients with T2D with preserved kidney function on a controlled standardized sodium diet (150 mmol/day). It evaluated the effects of dapagliflozin on sodium excretion, 24-h blood pressure, and extracellular, intracellular, and plasma volumes. The patients on dapagliflozin demonstrated reduced blood pressure without clear changes in urinary sodium excretion during standardized sodium intake, suggesting that factors other than natriuresis and volume changes may contribute to the blood pressure-lowering effects.

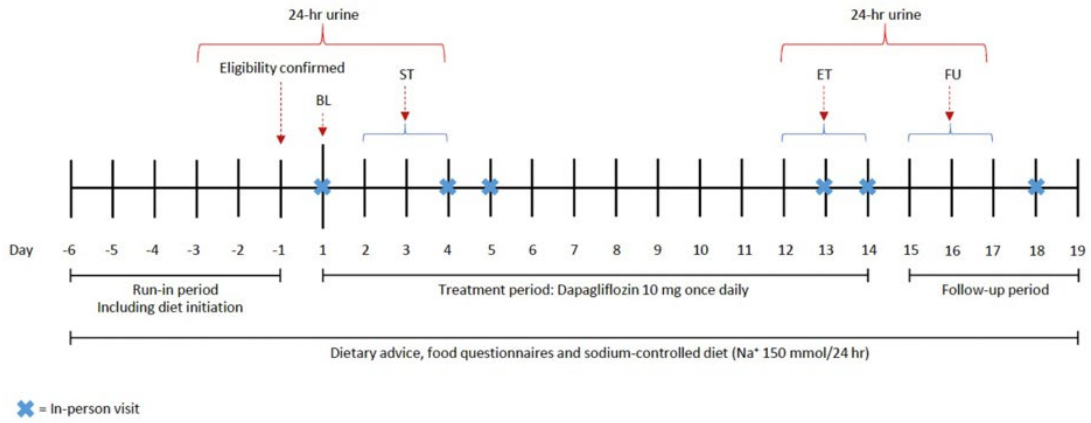

Figure 3. DAPASALT study

Future research into the effects of SGLT-2 inhibitors on cardiorenal illness is anticipated to focus on combination therapy involving finerenone, GLP-1 receptor agonists, and endothelin receptor antagonists, to put together combined medication guidelines. Another unmet need is the use of SGLT-2 inhibitors to protect the kidneys in T1DM, with an emphasis on euglycemic diabetic ketoacidosis mitigation strategies.

Key points

1. SGLT-2 Inhibitors brought huge success in improving kidney and cardiovascular outcomes.
2. SGLT-2 inhibitors' effect on renal hemodynamics has been suggested as the underlying mechanism for kidney benefits. Research into oxygenation effects is underway.
3. Although the SGLT-2 inhibitors provide an immense cardiovascular benefit, the mechanisms behind that effect are still poorly understood. It is still speculated whether natriuresis is the key factor yielding favorable cardiovascular outcomes.

Further reading

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