SGLT2 Inhibitors for Nephrologists

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Abstract

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are the mainstay of therapy for the prevention of progressive renal damage in diabetic and non-diabetic kidney diseases, especially glomerulonephritides. Sodium-glucose co-transporter-2 inhibitors are a relatively new class of oral antidiabetic drugs. Early evidence suggests that there are renal and cardiovascular benefits of this class of drugs that extend beyond glycaemic control for patients both with and without diabetes. With each and every trial, the limit for the glomerular filtration rate has been set lower, making the drugs more suitable from the perspective of nephrologists. This drug class has the potential to become the mainstay of reno-protective strategies used by nephrologists, in addition to angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. This article reviews the evidence and reports that are already published regarding the use of sodium-glucose co-transporter-2 inhibitors to treat non-diabetic glomerular disease.

Key Points

1. Early evidence for the antidiabetic sodium-glucose co-transporter-2 inhibitors (SGLT2i) suggests that there are renal and cardiovascular benefits of this class of drugs that extend beyond glycaemic control for patients both with and without diabetes.

2. Recent studies have shown benefits of SGLT2i in patient groups with lower GFR cut-offs (>25 mL/min), in both diabetic nephropathy and non-diabetic proteinuric primary renal diseases.

3. Anticipated upcoming studies consider the effect of SGLT2i in patient groups with GFR >20 mL/min, and in non-proteinuric primary renal diseases, as this drug class may become a mainstay in management and prevention in primary renal diseases beyond the scope of diabetic nephropathy.

SGLT2 INHIBITORS FOR NEPHROLOGISTS

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers are the mainstay of nephroprotective strategies both for diabetic and non-diabetic renal diseases. Nephrologists are in search of novel therapeutic modalities that can positively affect the progressive course of renal diseases and decline in glomerular filtration rate (GFR). Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are a newer class of oral hypoglycaemic drugs that was initially developed to treat patients with diabetes. The mechanism of action of SGLT2i involves the inhibition of the absorption of glucose in the proximal tubular cells, thereby inducing glycosuria and a reduction in plasma glucose levels. There is early evidence regarding the renoprotective and cardioprotective properties of SGLT2i beyond glycaemic control.[1,2] This article presents the existing evidence regarding the role of SGLT2i from a nephrologist's perspective.

Initial trials conducted on SGLT2i had cardiac primary endpoints and demonstrated beneficial effects, not only on the cardiovascular system but also on the renal system, as secondary endpoints. Major trials in this regard are summarised here.

In 2015, the EMPA-REG OUTCOME trial was published. This randomised trial included patients with Type 2 diabetes who had a GFR of 60–90 mL/min. The primary end-points of cardiovascular mortality, all-cause mortality, myocardial infarctions, and strokes were all shown to be reduced in the treatment arm compared with the placebo. Patients managed on empagliflozin were also shown to have reduced rates of renal dysfunction, progressive renal impairment, and worsening albuminuria as secondary outcomes.[3]

The CANVAS trial, published in 2017, was similarly based on cardiovascular primary endpoints such as strokes, myocardial infarctions, and cardiac deaths in patients with Type 2 diabetes and a GFR ranging from 60–90 mL/min. Outcomes related to kidneys, such as reduction in albuminuria, and a composite renal outcome of a reduction in GFR, dialysis, and death from renal failure, were secondary in nature. Both primary and secondary outcomes were reduced in the canagliflozin arm in comparison with the placebo.[4]

The DECLARE–TIMI trial, published in 2019, was a randomised controlled trial (RCT) that compared dapagliflozin with a placebo. This trial studied major adverse cardiovascular events, cardiovascular death, and hospitalisation as primary end-points in patients with Type 2 diabetes and a GFR ranging between 60–90 mL/min. Effects on the kidneys were studied as a secondary composite outcome of: decrease in estimated GFR (eGFR) of >40%, new end-stage renal disease (ESRD), and death from renal causes. Dapagliflozin decreased cardiovascular deaths and heart failure-associated hospitalisations, but not major adverse cardiovascular events. Renal composite outcomes were also lower in the dapagliflozin group when compared with a placebo.[5]

The DAPA-HF trial included patients with Type 2 diabetes with a lower GFR cut-off of >30 mL/min. Its composite primary outcome was worsening heart failure and cardiovascular death, while the secondary composite renal outcome was a decline in GFR of >50%, ESRD, dialysis, or transplantation. This trial showed a significant improvement in the primary cardiovascular outcome in the intervention arm compared with the placebo group; however, the secondary composite renal outcome was similar in both groups.[6]

The EMPEROR-Reduced (ejection fraction: <40%) and EMPEROR-Preserved (ejection fraction: >40%) trials suggested the renoprotective effects of SGLT2i in patients with reduced, but not preserved, cardiac function, although cardiac outcomes were improved in both trials.[7,8]

Subsequent trials were primarily conducted with renal primary endpoints. The first of these was the CREDENCE study, a placebo-controlled RCT that was published in 2019. Baseline characteristics of included patients were: Type 2 diabetes, a urine albumin-to-creatinine ratio (ACR) of >300 mg/g, and a GFR of 30–90 mL/min. The primary renal endpoints in this trial included renal or cardiovascular

deaths, doubling of creatinine, and ESRD. The trial was stopped before study completion as a significant improvement was demonstrated in the doubling of creatinine and in ESRD, the primary outcomes.[9]

The DAPA-CKD trial was published in 2020. This RCT included 4,304 patients with baseline characteristics of an even lower GFR of 25–75 mL/min and a urine ACR of 200–5,000 mg/g. This trial was the first to include patients without diabetes as well as patients with diabetes. The patients who were not diabetic were mostly comprised of patients with proteinuric nephropathies, such as hypertensive nephropathy (16%), IgA nephropathy (6%), and focal segmental glomerulosclerosis (FSGS; 3%). Notably, patients with polycystic kidney disease, lupus nephritis, vasculitis, and Type 1 diabetes were excluded from this study.

Patients were randomised to receive either dapagliflozin or a placebo, while a majority were maintained on ACEi (97%). Primary outcome measures included renal endpoints, such as a 50% decline in renal function (measured by the GFR), end-stage renal disease, and renal or cardiovascular death. This trial was stopped prematurely as it demonstrated the beneficial effects of dapagliflozin on the primary outcome: 9.2% in dapagliflozin versus 14.9% in the placebo arm (hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.51–0.72; p<0.001). The renal benefits were similar between patients with or without diabetes, patients with a GFR of < or >45 mL/min, and patients with albuminuria < or >1000 mg/g.[10,11]

The DIAMOND was a double-blind, randomised, placebo-controlled trial with a crossover design that was published in 2020. It included 53 adult patients (mean age: 51 years) with proteinuric renal disease (proteinuria: 500–3,500 mg/24 hours; mean baseline proteinuria: 1,110 mg/24 hours) and decreased renal function (GFR: >25.0 mL/min; baseline mean GFR: 58.3 mL/min). The study included patients with IgA nephropathy, FSGS, hypertensive nephropathy, and other pathologies. All patients had stable renin–angiotensin–aldosterone system blockade. In this trial, dapagliflozin (10 mg) was compared with a placebo in a crossover fashion, with a treatment period lasting for 6 weeks. There was no statistically significant difference in proteinuria reduction between the two groups. Systolic and diastolic blood pressure also did not differ between the two groups. The dapagliflozin arm showed a significant reduction in GFR (−6.6 mL/min) compared with the placebo group, which was reversible with drug discontinuation. The adverse events were also similar between the two groups. This trial concluded that, in contrast with previous evidence, dapagliflozin did not reduce proteinuria in patients with non-diabetic chronic kidney disease (CKD), emphasising the lack of understanding of this fascinating drug class and the need for further studies.[12]

Evidence of the benefit of SGLT2i in primary renal, non-diabetic kidney diseases is emerging in the form of small case reports. A summary of these findings is presented here.

In a case series of six patients with hereditary FSGS (*NPHS2* and *INF2* mutations) and X-linked Alport syndrome, the addition of SGLT2i to ACEi was shown to reduce proteinuria by 40%, while GFR stabilised after an early decline.[13] In a small case series, which included nine patients (mean age: 10.4 years) with both proteinuric glomerulopathy (including five patients with Alport syndrome) and normal renal function (GFR: 104.9 mL/min), dapagliflozin was used in addition to fosinopril. The authors reported a proteinuria reduction of 33% and 22% at 4 and 12 weeks, respectively.[14] Other studies have produced negative results for SGLT2i when used in patients with FSGS. In a small study conducted on humans and rodents, dapagliflozin was not found to induce changes in GFR or proteinuria in patients with FSGS after 8 weeks of therapy.[15] Dapagliflozin did not reduce proteinuria in the 11 patients with FSGS that were included in the DIAMOND study mentioned above.[16] For 104 patients with FSGS that were included in the DAPA-CKD study, the rate of chronic decline of GFR was lower in the dapagliflozin arm compared with a placebo.[17]

The DAPA-CKD trial included 270 patients with IgA nephropathy. Nearly half of patients were either randomised to dapagliflozin or a placebo and followed for up to 2 years. The mean eGFR was 43.8±12.2 mL/min/1.73m^2. The mean urinary ACR was 900 mg/g. Primary renal and cardiac composite outcomes were significantly

reduced in the dapagliflozin arm compared with the placebo arm (4% versus 15%; HR: 0.29; 95% CI: 0.12–0.73; p=0.005), including for ESRD (4% versus 12%; HR: 0.30; 95% CI: 0.11–0.83; p=0.014), eGFR decline (−3.5 versus −4.7 mL/min/1.73m^2/year, respectively; 95% CI: −0.12–2.51), and ACR decline (26% in dapagliflozin arm; 95% CI: −0.37, −14.00; p<0.001). Adverse events, including hypoglycaemic episodes and ketoacidosis, were similar between the two groups.[18,19] However, nearly 14% of patients with IgA nephropathy also had diabetes mellitus, and the analysis lacks information regarding the optimisation of ACEi doses in these patients, necessitating further studies.[20]

POSSIBLE MECHANISMS OF RENAL PROTECTION BY SGLT2 INHIBITORS

Normally, glycosuria appears when blood glucose levels exceed the 180 mg/dL threshold.[21] Hyperglycaemia with an increased intrarenal synthesis of angiotensin II promotes increased proximal tubule SGLT2 expression. This in turn contributes to an increase in tubular glucose reabsorption, with an increase in the threshold of glycosuria to 200–240 mg/dL, as seen in patients with diabetes.[22] In diabetes, higher proximal tubule sodium reabsorption due to increased SGLT2 expression reduces the delivery of sodium to the macula densa, which in turn activates tubuloglomerular feedback, ultimately causing afferent arteriolar vasodilation, increased intraglomerular pressure, and glomerular hyperfiltration.[23,24] This glomerular hyperfiltration is considered to be one of the major factors responsible for progressive renal damage in both diabetic and non-diabetic renal diseases. SGLT2i block proximal tubular sodium reabsorption, increasing distal sodium delivery, thereby acting to reduce the intraglomerular pressure, which prevents renal damage caused by hyperfiltration injury.[25]

Other mechanisms include: anti-inflammatory and antifibrotic effects by suppressing reactive oxygen species and inhibiting inflammatory and fibrotic mediators; increased sensitivity of muscles to insulin (counter to insulin resistance associated with uraemia and acidosis); blood pressure reduction, possibly through diuretic and natriuretic effects; possible action on the intrarenal renin-angiotensin system; direct effects of SGLT2i receptors on endothelial and mesangial cells; inhibition of epithelial–mesenchymal transformation; and reduction of uric acid levels.[26-33] Studies have also shown improvements in histological changes, such as glomerular capillary dilatation, mesangial expansion, glomerular adhesions to Bowman's capsule, preservation of the podocyte foot process ultrastructure, and prevention of podocyte depletion.[34]

Considering the early benefits of SGLT2i, even in patients with non-diabetic CKD, these agents may have a place in the treatment of patients with CKD in the future. While SGLT2i may not affect the primary inciting injury, these agents may have an impact on glomerular hyperfiltration and interstitial fibrosis, which are the final pathways of progressive renal damage.

The EMPA-KIDNEY trial is currently undergoing and includes patients with CKD and with a lower GFR cut-off limit of 20 mL/min/1.73 m^2.[35] This trial is expected to shed more light on the renoprotective effects of SGLT2i in patients with CKD who have a primary renal disease independent of diabetes.[36]

CONCLUSION

SGLT2i are a relatively new class of oral hypoglycaemic agents. Multiple trials have suggested the renoprotective properties of these agents in patients with diabetic nephropathy, as well as non-diabetic proteinuric primary renal diseases. Studies conducted with primary cardiac endpoints had a GFR cut-off of more than 60 mL/min. Later, primary renal studies attempted to reduce the cut-off to 25 mL/min, making a case for use of these agents in relatively advanced renal impairment. The ongoing EMPA-KIDNEY trial has further reduced the GFR cut-off to 20 mL/min, and, depending on the results of this trial, SGLT2i may also find a role in the management of patients with advanced renal impairment.

All of the previous trials focused on the renal benefits of SGLT2i in proteinuric renal diseases. The EMPA-KIDNEY trial will also clarify the role of SGLT2i in non-proteinuric primary renal

diseases. Nephrologists eagerly await the results of this study, which could add SGLT2i to the armamentarium of agents used to prevent progressive primary renal diseases. New research is expected to shed more light on novel indications for this newer class of agents; the preliminary results are encouraging, especially in patients with IgA nephropathy and Alport syndrome. Nephrologists throughout the world await further studies and new data regarding use of SGLT2i in primary renal diseases beyond the scope of diabetic nephropathy.

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