SGLT2 inhibitors for treatment of chronic kidney disease

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Abstract

There are several mechanisms underlying chronic kidney disease progression and they can be categorised in three major pathways: haemodynamic, metabolic, and inflammatory or fibrotic.[1] Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce glomerular hyperfiltration,[1] improve energy utilisation and mitochondrial function,[2] and lower inflammatory mediators, resulting in nephroprotective effects in both diabetic as well as non-diabetic patients.[3] Although SGLT2 inhibitors are well-tolerated with a low risk of serious adverse effects, patients need to be counselled on expected adverse events such as the increased risk for genital and urinary infections and how to prevent these, as well as the need to withhold SGLT2 inhibitors during periods of acute illness with vomiting and diarrhoea to prevent volume depletion.[4]

Keywords: chronic kidney disease, sodium-glucose cotransporter-2

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Introduction

Chronic kidney disease (CKD) of any aetiology is on the rise on a global scale.[5] An estimated 840 million people worldwide have chronic kidney disease, which was responsible for 1.2 million deaths and 35.8 million disability-adjusted life years in 2017.[6] Canagliflozin, dapagliflozin and empagliflozin have shown reduced risk of kidney-specific outcomes and death from kidney-related causes.[7] Of these, only dapagliflozin is currently registered for treatment of CKD in South Africa.[8] This article will discuss the role of SGLT2 inhibitors in patients with CKD.

Chronic kidney disease (CKD)

Damage to the kidney can result in a variety of clinical manifestations, ranging from asymptomatic haematuria to kidney failure requiring dialysis, depending on how the kidney responds to injury.[9] The kidney adapts to damage by increasing the glomerular filtration rate (GFR) in undamaged nephrons which is called adaptive hyperfiltration. Although initially beneficial, adaptive hyperfiltration eventually causes damage to the glomeruli of the remaining nephrons which may manifest as proteinuria and progressive kidney failure.[9]

The gradual decline in kidney function in CKD is initially asymptomatic. However, different signs and symptoms may only be observed with advanced kidney failure, including volume overload, hyperkalaemia, metabolic acidosis, hypertension, anaemia, and mineral and bone disorders.[9] The majority of individuals with CKD are therefore only diagnosed at the advanced stage of disease.[7] The onset of end stage kidney disease (ESKD) results as a constellation of signs and symptoms referred to as uraemia. Uraemia may manifest as anorexia, nausea, vomiting, pericarditis, peripheral neuropathy, and central nervous system abnormalities such as loss of concentration, lethargy, seizures, coma, and death.[9]

To prevent late diagnosis of CKD, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend monitoring for CKD progression by assessing both eGFR (estimated GFR) and urine albumin-creatinine ratio (UACR) at least annually and more frequently for those at higher risk (patients with hypertension, cardiovascular disease and diabetes).[7]

Initiating treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blocker (ARB) and sodium-glucose cotransporter-2 (SGLT2) inhibitors, can slow progressive disease and even preserve kidney function. Treatment provides most benefit if started before much irreversible scarring has occurred.[9]

Mechanism of action of SGLT2 inhibitors

It is difficult to pinpoint a single mechanism responsible for the protective effect of SGLT2 inhibitors on CKD progression. The most probable hypothesis is that a combination of factors has led to the benefits on renal function observed in clinical trials.[2]

Inhibition of SGLT2 reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption, leading to urinary excretion of glucose (without causing hypoglycaemic events) and osmotic diuresis.[8] Lower glycaemia and improvement of insulin resistance lead to a reduction in microvascular complications in the long term.[2]

Additional metabolic changes contribute to the renal protective effects. The higher glucagon/insulin ratio increases production of ketone bodies that may improve energy utilisation and mitochondrial function. The reduction in glucose reabsorption at the tubular level leads to a reduction in energy expenditure to maintain the sodium gradient necessary for luminal cotransport.[2] This conservation of energy may attenuate renal hypoxia.[4]

SGLT2 inhibitors increase the delivery of sodium to the distal tubule which increases tubulo-glomerular feedback.[8] This, combined with osmotic diuresis, leads to a reduction in volume overload, reduced blood pressure, lower preload and afterload, and results in restoration of intraglomerular pressure.[2,8] These changes can cause an initial dip in GFR when patients initiate SGLT2-inhibitor treatment that should be seen as an indication of haemodynamic efficacy rather than representing a matter of concern, since the dip in GFR is transient with no short- or long-term negative consequences.[2,5]

The cardio-renal benefits are not solely dependent on the blood glucose lowering effect and not limited to patients with diabetes mellitus. In addition to the osmotic diuretic and related haemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis, adipokines and uric acid may be mechanisms underlying the cardio-renal beneficial effects.[8]

Efficacy

The DAPA-CKD trial included 4 304 diabetic and non-diabetic patients to determine whether the nephroprotection conferred by SGLT2 inhibitors could also extend to CKD patients without diabetes.[2] Patients with CKD (eGFR of 25–75 ml/min/1.73 m^2) were on a stable dose of renin-angiotensin system (RAS) blockers for at least four weeks before enrolment. Treatment with dapagliflozin reduced the risk of GFR decline of > 50%, ESKD or death from renal or cardiovascular causes by 39%.[2] Dapagliflozin was equally effective in diabetic and non-diabetic patients.[2] SGLT2 inhibitors are the most effective class of drugs for the prevention of CKD progression since the discovery of the RAS inhibitors. The trial was stopped early after a median follow-up of 2.4 years after demonstrating overwhelming efficacy.[6] Trial-level estimates from DAPA-CKD estimated that for a 50-year-old patient until the age of 75, the drug combination of RAS inhibitors and SGLT2 inhibitors provided a 7.4 year gain in kidney-failure-free survival compared to a theoretical control not receiving any treatment.[2]

Recently published results from the EMPA-KIDNEY trial confirmed and expanded these findings. The trial enrolled 6 609 patients on background RAS inhibition which included 3 569 non-diabetic patients and patients with advanced CKD. The trial was stopped at a median follow-up of two years because empagliflozin demonstrated clear benefits in reducing eGFR of ≥ 40% from baseline, ESKD or death from renal causes and cardiovascular death. Empagliflozin was equally effective in diabetic and non-diabetic patients and confirmed that even patients with advanced CKD benefit from SGLT2 inhibitors.[2]

A recent meta-analysis of 13 randomised controlled trials extracted data from 90 413 patients from available reports and unpublished information provided by trial investigators. The authors reported that treatment with SGLT2 inhibitors reduced the risk of CKD (defined by sustained eGFR decrease of ≥ 50% or < 15 ml/min/1.73m^2, ESKD or death from kidney failure) by 37%. SGLT2 inhibitors conferred protection from CKD progression of 40% in diabetic kidney disease, 30% in patients with ischaemic/hypertensive kidney disease, 40% in patients with glomerulonephritis and 26% in patients with CKD of unknown aetiology. SGLT2 inhibitors also conferred protection from acute kidney injury and cardiovascular events.[2]

Adverse effects

SGLT2 inhibitors are well-tolerated with a low risk of serious adverse effects.[3]

Due to the excretion of glucose in urine, one of the first safety signals reported was a higher rate of mycotic genital infections and patients who are prescribed SGLT2 inhibitors are 3.57 times more likely to develop this adverse event.[2] There was also a significant but modest increase in the risk of urinary tract infections, particularly in female patients.[2,4,10] Necrotising fasciitis of the perineum, called Fournier's gangrene, is a significant adverse event, although post-marketing case reviews show a lower incidence than initially reported.[10] It is prudent though to use SGLT2 inhibitors with caution in patients with a history of complicated or recurrent urinary tract infections including those with chronic indwelling Foley catheters.[4] In most cases, either a topical or an oral course of antifungal therapy is sufficient to treat the infection effectively, thus termination of therapy may not be necessary.[3] Patients should be informed to maintain genital hygiene and to keep the genital region dry to prevent infections.[4]

In patients with a very low GFR, the initial dip in GFR associated with initiation of SGLT2 inhibitors could accentuate the risk of an acute adverse event[11] and therefore guidelines do not recommend initiation of an SGLT2 inhibitor for treatment of CKD if eGFR is < 20 ml/min/1.73 m^2. If eGFR falls below 20ml/min/1.73 m^2 after initiation of treatment, SGLT2 inhibitors may be continued for kidney protection unless it is not tolerated or kidney replacement therapy is initiated.[7] However, relevant studies in the meantime have shown that SGLT2 inhibitors greatly decrease the risk for acute kidney injury.[5]

Another concern for clinicians has been the presumed higher risk of hypoglycaemia. However, no significant hypoglycaemia events were noted in large randomised controlled trials that included patients without diabetes. This is because SGLT2 inhibitors only reduce plasma glucose levels by blocking the reabsorption of glucose and this is reduced as plasma levels fall. Thus, the risk of hypoglycaemia is low in the absence of other hypoglycaemic therapies.[3]

Although euglycaemic diabetic ketoacidosis is among the most concerning adverse effects associated with the use of SGLT2

inhibitors, the risk among patients without diabetes is minimal with only one event noted in a large meta-analysis during 30 000 participant years of follow-up.[3]

Practical recommendations for the use of SGLT2 inhibitors

SGLT2 inhibitors are recommended for treatment of CKD in patients who are stable on RAS inhibitor treatment and can be initiated in patients with an eGFR > 20 ml/min/1.73m^2.[7,10] They are effective in both diabetic and non-diabetic patients.

Dapagliflozin is indicated for treatment of CKD if eGFR ≥ 25 ml/min/1.73 m^2.[12] The package insert for dapagliflozin recommends a dose of 10 mg taken orally once daily, at any time of the day regardless of meals.[8]

Patients should be monitored for early signs of genital and urinary tract infection. Monitoring of blood pressure at home, volume status, weight, and blood glucose levels is also recommended. Patients should be counselled on maintaining proper hygiene when commencing an SGLT2 inhibitor. Patients should also be advised to withhold their SGLT2 inhibitor for two to three days before scheduled surgery, during episodes of acute illness, vomiting, diarrhoea, or inability to eat or drink for any reason. SGLT2 inhibitors may typically be resumed 24 to 48 hours following recovery.[4]

Conclusion

SGLT2 inhibitors have emerged as a key therapy in the treatment of CKD,[4] offering a myriad of direct and indirect renoprotective effects, halting the progression of CKD even in patients without diabetes and reducing the risk of all-cause mortality.[1,5]

References

1. Mende CW. Chronic kidney disease and SGLT2 inhibitors: A review of the evolving treatment landscape. Advances in Therapy. 2022;39:148-164. https://doi.org/10.1007/s12325-021-01994-2.
2. Podestà MA, Sabiu G, Galassi A, Ciceri P, Cozzolino M. SGLT2 inhibitors in diabetic and non-diabetic chronic kidney disease. Biomedicines. 2023;11(2):279. https://doi.org/10.3390/biomedicines11020279.
3. Krishnan A, Shankar M, Lerma EV, Wiegley N, Team GE. Sodium Glucose Cotransporter 2 (SGLT2) inhibitors and CKD: are you a# flozinator? Kidney Medicine. 2023;5(4):100608. https://doi.org/10.1016/j.xkme.2023.100608.
4. Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 inhibitors in patients with CKD: expanding indications and practical considerations. Kidney International Reports. 2022;7(7):1463-76. https://doi.org/10.1016/j.ekir.2022.04.094.
5. Skrabic R, Kumric M, Vrdoljak J, et al. SGLT2 inhibitors in chronic kidney disease: from mechanisms to clinical practice. Biomedicines. 2022;10(10):2458. https://doi.org/10.3390/biomedicines10102458.
6. Garcia Sanchez JJ, Thompson J, Scott DA, et al. Treatments for chronic kidney disease: a systematic literature review of randomized controlled trials. Advances in Therapy. 2022;39(1):193-220. https://doi.org/10.1007/s12325-021-02006-z.
7. Elkeraie AF, Al-Ghamdi S, Abu-Alfa AK, et al. Impact of Sodium-Glucose Cotransporter-2 inhibitors in the management of chronic kidney disease: A Middle East and Africa perspective. International Journal of Nephrology and Renovascular Disease. 2024:17;1-16. https://doi.org/10.2147/IJNRD.S430532.
8. Forxiga (dapagliflozin propanediol) film coated tablets. Package insert. Astra Zeneca. Bryanston. 8 October 2023.
9. Rosenberg M. Overview of the management of chronic kidney disease in adults. In: UpToDate[Internet]. 2022.
10. Kansara A, Mubeen F, Shakil J. SGLT2 inhibitors in patients with chronic kidney disease and heart disease: a literature review. Methodist DeBakey Cardiovascular Journal. 2022;18(4):62. https://doi.org/10.14797/mdcvj.1120.
11. Bailey CJ, Day C, Bellary S. Renal protection with SGLT2 inhibitors: effects in acute and chronic kidney disease. Current Diabetes Reports. 2022;22(1):39-52. https://doi.org/10.1007/s11892-021-01442-z.
12. Di Costanzo A, Esposito G, Indolfi C, Spaccarotella CAM. SGLT2 inhibitors: a new therapeutical strategy to improve clinical outcomes in patients with chronic kidney diseases. International Journal of Molecular Sciences. 2023;24(10):8732. https://doi.org/10.3390/ijms24108732.