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Saudi Consensus on the Usage of Sodium-Glucose Cotransporter-2 Inhibitors on the Management of Chronic Kidney Diseases

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Abstract

According to recent epidemiological data, chronic kidney diseases (CKDs) affect approximately 10% of the global population. Like many countries, CKD is a significant public health issue in Saudi Arabia. The prevalence of CKD in Saudi Arabia is estimated to be around 4.5% of the adult population, with a higher prevalence in older age groups. Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are a class of oral medications used to treat type 2 diabetes mellitus (T2DM). In addition to their glucose-lowering effects, SGLT2i have been shown to have beneficial effects on kidney function in patients with or without T2DM. Therefore, a Saudi task force gathered to develop an explicit, evidence-based consensus on SGLT2i use in CKD Saudi patients. A panel of 14 experts made up a task force. An initial concept proposal was obtained. The proposal was divided into several topics discussed on 24 May 2023. A literature review was carried out. The literature search was completed on 3rd

June 2023. A drafted report was distributed to the entire panel. Approval of the recommendations required consensus, defined as a majority approval (*i.e.* above 75%). The recommendations were revised to accommodate any differences of opinion until a consensus was reached. Recommendations were finally formulated on 21st June 2023. Subsequently, the panel reviewed and discussed the supporting rationale of the revised recommendations. This article presents these practical recommendations.

Keywords

Chronic Kidney Disease, Sodium-Glucose Cotransporter-2 Inhibitors, Adverse Effects, Monitoring, Canagliflozin, Dapagliflozin, Empagliflozin

1. Introduction

1.1. Chronic Kidney Disease and Its Prevalence

Chronic kidney disease (CKD) is a common and serious health problem characterized by the gradual loss of kidney function over time [1]. According to recent epidemiological data, CKD affects approximately 10% of the global population, with an estimated 800 million people worldwide living with the condition [2]. CKD is more common in older adults and is often associated with other chronic conditions such as diabetes (DM) and hypertension. A comprehensive systematic review and meta-analysis of 100 studies comprising almost seven million patients reported a global prevalence of 13.4% for CKD stages 1 - 5 and 10.6% for CKD stages 3 - 5. The prevalences of the individual CKD stages were 3.5% (stage 1), 3.9% (stage 2), 7.6% (stage 3), 0.4% (stage 4), and 0.1% (stage 5), respectively [3].

Like many countries, CKD is a significant public health issue in Saudi Arabia [1]. The prevalence of CKD in Saudi Arabia is estimated to be around 4.5% of the adult population, with a higher prevalence in older age groups. The study also found that DM and hypertension were the most common risk factors for CKD, with rates of both conditions increasing in recent years [4].

More efforts are needed to prevent and manage the tremendous burden of CKD. Therefore, efforts to prevent and manage CKD in Saudi Arabia and around the world include early detection and treatment of risk factors such as DM and hypertension, lifestyle modifications such as healthy diet habits and regular exercise, and medication management to slow the progression of CKD [1] [5].

1.2. Brief Overview of SGLT2 Inhibitors

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are a class of oral medications used to treat type 2 diabetes mellitus (T2DM). They work by inhibiting glucose reabsorption in the kidneys, increasing urinary glucose excretion, and lowering blood glucose levels. By promoting glucose excretion, SGLT2is lead to

modest weight loss and lower blood pressure. The first SGLT2i, canagliflozin, was approved by the US Food and Drug Administration (FDA) in 2013. Since then, several other SGLT2is have been approved, including dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin. These medications are typically taken once daily, usually in the morning, and can be used alone or in combination with other antidiabetic medications such as metformin or insulin [6] [7] [8].

In addition to their glucose-lowering effects, SGLT2is have been shown to have beneficial effects on cardiovascular (CV) outcomes and kidney function in patients with T2DM and established cardiovascular disease (CVD) or CKD [6] [7]. These benefits have led to the use of SGLT2is in patients at high risk for CVD or kidney complications.

While generally well-tolerated, SGLT2is can cause adverse effects such as genital mycotic infections, urinary tract infections, and an increased risk of diabetic ketoacidosis in certain populations [8]. As with any medication, the benefits and risks of SGLT2is should be weighed carefully before initiating therapy.

Therefore, a Saudi task force, including nephrologists, endocrinologists, diabetologists, and internal medicine experts, gathered to develop an explicit, evidence-based consensus on SGLT2is use in Saudi patients with CKD, when to use this class, why, and how to monitor its impact on the progression of CKD? This article has the recommendations of this expert panel.

2. Methods

Fourteen experts, including nephrologists, endocrinologists, diabetologists, and internal medicine experts from 14 centers with more than 15 years of experience, made up the task force. An initial concept proposal included the definition of CKD, population, scope, and prevalence in Saudi Arabia. The proposal was divided into several topics discussed in two meetings. The meetings panel approved that the consensus will include diagnosis, management, monitoring of CKD and special populations, and finally, among the entire Saudi population. An expert writer searched the literature based on their search strategies, and they determined their databases. The included literature; guidelines, RCTs, consensus, and systematic reviews, were screened for relevance, quality and evidence. A draft report was written and distributed electronically to the expert panel. Approval of the recommendations required consensus, defined as a majority approval. The recommendations were revised to accommodate any differences of opinion until a consensus was reached. Recommendations were finally formulated. Subsequently, the panel reviewed and discussed the revised recommendations and tried to develop a consensus statement to be valid for the Saudi society and health care professionals (HCPs).

3. SGLT2 Inhibitors, a Multi-Indications Class

SGLT2 Inhibitors for Indications Other than DM

The success of SGLT2is in DM and the ongoing research in other indications

paved the way for their utilization as a multi-indication therapy. SGLT2is have been shown to have several benefits beyond glycemic control, including cardiovascular [9] [10] [11] and renal benefits [7] [12] and reduction in heart failure hospitalizations [13] [14] [15] [16]. These benefits have led to the use of SGLT2 inhibitors in patients with T2DM and high CV or renal risk and CKD patients apart from DM.

Both the dapagliflozin and prevention of adverse outcomes in heart failure (DAPA-HF trial) and the empagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction (EMPEROR-reduced study) proved SGLT2is benefits for patients with heart failure with reduced ejection fraction (HFrEF). In the DAPA-HF and EMPEROR-Reduced trials, SGLT2is reduced the composite of CV death or HF hospitalization by approximately 25%, compared to placebo. The benefit in reduction of hospitalization was 30% greater than standard of care in both trials. The risk of CV death was significantly lower (18%) with dapagliflozin, as was the risk of all-cause mortality (17%). Although no significant CV mortality benefit was observed with empagliflozin in a meta-analysis of DAPA-HF and EMPEROR-Reduced trials, SGLT2is therapy was associated with reducing all-cause mortality and CV death. The benefits in both trials were seen irrespective of baseline DM status [17]. Therefore, the 2022 AHA/ACC/HFSA guideline suggests that SGLT2 inhibitors may be beneficial in patients with HFrEF and some patients with HFpEF [18].

After their success in patients with HFrEF, SGLT2 inhibitors have emerged as a promising class of medications for treating heart failure with mildly reduced EF, preserved ejection fraction (HFpEF) and CKD as the mechanism of action of SGLT2is is beneficial in patients with HF or CKD, who often have comorbidities such as DM and hypertension [16] [19].

4. SGLT2 Inhibitors and CKD

4.1. Current Options for CKD Management and Their Limitations

The available options for CKD management include lifestyle interventions (healthy diet, exercise, weight management, and quitting smoking), control of hypertension and blood glucose, and lipid-lowering therapies. These measures can help prevent the onset or slow the progression of CKD and the development of CV complications [20] [21].

Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), which block the renin-angiotensin-aldosterone system (RAAS), have long been the recommended medications for treating hypertension and proteinuria [21] [22]. The lowering of T2DM endpoints with the angiotensin II antagonist losartan and irbesartan was detailed in different trials [23] [24]. Despite the beneficial effects of these drugs, there is still a sizable residual risk of kidney function decline and the emergence of CV problems [21] [22]. Patients with CKD benefit from CV benefits of lipid-lowering treatments but do not have renoprotective effects [21]. Endothelin receptor antagonists, at the cost of unac-

ceptable high side effects risk, can reduce proteinuria, arterial stiffness, and blood pressure in patients with CKD [23]-[28].

The effects of bardoxolone methyl, a synthetic triterpenoid with antioxidant and anti-inflammatory properties, on the risk of kidney failure or death from CV causes were examined in the Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes (BEACON) trial, which included 2185 patients with T2DM and stage 4 CKD. The study was terminated because the intervention was linked to a greater rate of CV events than the placebo [29]. Other strategies, such as treating anemia and acidosis and reducing uric acid, haven't been 100% successful [30]. As a result, patients with CKD continue to have a significant absolute risk of CV and renal morbidity and death. Therefore, it is highly desired to develop novel therapeutics for reducing renal problems [21].

4.2. Potential Pharmacologic Mechanisms of Renal Effects of SGLT2i

The potential mechanism of the renal benefits of SGLT2is is an area of ongoing investigation (**Figure 1**). Increased proximal tubular glucose and sodium reabsorption in DM may be due to overexpression of SGLT2 mRNA and increased transporter activity. As a result, decreased sodium transport to the macula densa inhibits tubuloglomerular feedback, which decreases the estimated glomerular filtration rate (eGFR) by causing afferent arteriolar vasodilation, hyperfiltration, and hyperperfusion. Therefore, SGLT2is decrease the workload on the glomeruli and tubules. Additionally, SGLT2is prevent proximal sodium and glucose reabsorption, which causes natriuresis. Acute reductions in BP and body weight, as

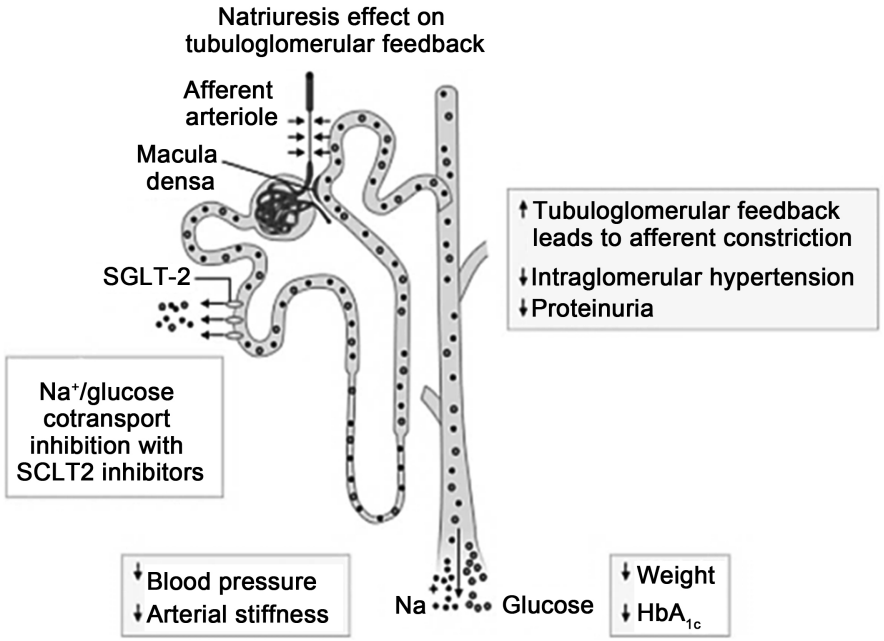

Figure 1. The potential effects of SGLT2is on renal structure and function: underlying mechanism [33].

well as contraction of the plasma volume, are linked to increased sodium excretion. SGLT2is reduce arterial stiffness, an indicator of both renal and cardiovascular risk. In addition to promoting anti-inflammatory and antifibrotic pathways, SGLT2i enhances the positive effects of decreased glomerular hypertension, hyperfiltration, and renal oxygenation. Therefore, SGLT2is have also been shown to reduce albuminuria [31] [32] [33].

Additionally, there is less histologic evidence of nephropathy when SGLT2i is present. There are assessments elsewhere, and more recent studies are shedding more insight into the mechanism underlying SGLT2i's advantageous effects [34] [35] [36].

4.3. Effectiveness of SGLT2 Inhibitors in CKD

The beneficial effects of SGLT2is on kidney function have been demonstrated in several large clinical trials, including the CREDENCE and DAPA-CKD trials [7] [12]. In these trials, patients with CKD treated with SGLT2is had a significantly lower risk of progression to end-stage kidney disease (ESKD) and a lower risk of cardiovascular events and mortality.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (**CREDENCE**) trial was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of canagliflozin, an SGLT2i, in patients with T2DM and albuminuric CKD. The trial demonstrated a significant reduction in the risk of the primary composite outcome of ESKD, doubling of serum creatinine, and renal or cardiovascular (CV) death in the canagliflozin group compared to the placebo group [7]. Canagliflozin also reduced the risk of secondary CV outcomes.

The "Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease" (**DAPA-CKD**) trial was a multinational, multicenter, event-driven, randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of dapagliflozin, an SGLT2i, in patients with CKD, with or without T2DM. The trial demonstrated a significant reduction by 39% (resulting in a number needed to treat of 19) in the risk of the primary composite outcome of sustained decline in eGFR, ESKD, or death from renal or CV causes in the dapagliflozin group compared to the placebo group. Dapagliflozin also reduced the risk of secondary outcomes, including all-cause mortality (reduced by 31%; HR, 0.69; 95% CI, 0.53 to 0.88; P = 0.004) and a composite of cardiovascular death and hospitalization for heart failure (reduced by 29%; HR, 0.71; 95% CI, 0.55 to 0.92; P = 0.009). The benefit was consistent for the primary endpoint regardless of the T2DM status, emphasizing the central principle that dapagliflozin benefits were independent of glycemic status, *i.e.*, dapagliflozin showed a kidney protective effect in patients with or without T2DM [12] [37].

The Study of Heart and Kidney Protection with Empagliflozin trial (**EMPA-KIDNEY**) was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of empagliflozin, an SGLT2i, in patients with CKD, with or without T2DM. The trial demonstrated a significant reduction in the risk

of the primary composite outcome of sustained decline in eGFR, renal death, or ESKD in the empagliflozin group compared to the placebo group [38]. Progression of kidney disease or death from CV causes occurred in 13.1% of the empagliflozin group and in 16.9% of the placebo group (HR, 0.72; 95% CI, 0.64 - 0.82; $P < 0.001$). Results were consistent among patients with or without diabetes and across subgroups defined according to eGFR ranges. However, there were no significant differences between the two groups in hospitalization for heart failure or death from CV cause (composite outcome) (4.0% of the empagliflozin group and 4.6% of the placebo group; HR, 0.84; 95% CI, 0.67 - 1.07; $P = 0.15$) or with respect to death from any cause (4.5% and 5.1%, respectively; HR, 0.87; 95% CI, 0.70 - 1.08; $P = 0.21$) [38].

These trials provide strong evidence for the efficacy of SGLT2is in managing CKD, particularly in patients with T2DM and albuminuria. The results of these trials have led to the inclusion of SGLT2is in guidelines for managing CKD in patients with DM [8].

Therefore, among the different available molecules of SGLT2is, only dapagliflozin is recommended by the NICE for CKD with or without T2DM. It is recommended for those with albuminuria (urine albumin: creatinine ratio (ACR) ≥ 22.6 mg/mmol and eGFR 25 - 75 ml/min/1.73m^2), either attributed to diabetic or non-diabetic causes. Also, dapagliflozin is recommended for those with ACR < 22.6 mg/mmol and eGFR 25 - 75 ml/min/1.73m^2 [39].

5. Safety and Side Effects

Although SGLT2is have demonstrated efficacy in reducing glucose levels and cardiovascular events in patients with T2DM [37], their safety profile in patients with CKD has been a topic of concern due to the potential adverse effects.

Although SGLT2is could cause volume depletion, previous studies believed that patients receiving SGLT2i may have a lower risk of acute kidney injury [40] [41].

Previous studies recommended that the concern of SGLT2is causing acute kidney injury should not impact the decision of healthcare professionals to prescribe or continue SGLT2is. However, some experts advise patients to temporarily withhold these agents during any illness that increases the risk of dehydration and to carefully monitor the patient's volume status by physical examination, blood pressure measurements, and laboratory tests, including haematocrit and electrolytes [42].

Previously, potential concerns of SGLT2i adverse effects existed in CKD patients, including hypoglycemia, urinary tract infections, and lower limb amputations. However, the later was a historical concern that was proven wrong by many studies as shown in the following paragraphs [43] [44].

However, no increase in serious hypoglycemia was observed with canagliflozin and dapagliflozin in the CREDENCE or DAPA-CKD trials, respectively [7] [12].

In addition, despite initial concerns, routine use of SGLT2 inhibitors was not found to increase urinary tract infections, as observed in a previous meta-analysis

(RR, 1.02; 95% CI, 0.95 - 1.09; I2 = 0.0%) [45].

Regarding the risk of lower limb complications, only patients receiving canagliflozin showed an increased risk of amputation (OR = 1.60; 95% CI, 1.04 - 2.46) and peripheral arterial disease development (OR = 1.53; 95% CI, 1.14 - 2.05) [44]. However, whether this constitutes a class effect or is strictly related to canagliflozin is unknown. Therefore, it is important to counsel patients with diabetes on routine preventative foot care.

6. Clinical Considerations

6.1. Patient Selection and Monitoring for SGLT2 Inhibitor Therapy in CKD

The use of SGLT2is in patients with CKD requires careful consideration due to the potential adverse effects. Patient selection and monitoring are critical in ensuring the safe and effective use of SGLT2is in CKD. Patient selection involves identifying patients most likely to benefit from SGLT2is therapy while minimizing the potential risks. SGLT2is should not be initiated in CKD patients with an eGFR of less than 20 mL/min/1.73m^2 or patients with ESKD requiring dialysis [46].

However, according to the 2022 KDIGO guidelines, once patients with CKD start SGLT2i treatment, it is favorable to continue on the prescribed agent even if the eGFR falls below 20 ml/min per 1.73 m^2 unless it is intolerable or KRT is initiated [47].

Additionally, patients with a history of AKI, hypotension, or dehydration should be closely monitored if SGLT2 inhibitors are used. Generally, regular monitoring is essential for patients with CKD who are receiving SGLT2is. Patients should monitor their eGFR and serum creatinine levels before initiating therapy and periodically thereafter to assess renal function [37]. In patients with eGFR < 60 mL/min/1.73m^2, the risk of AKI may be increased, and close monitoring is recommended [48].

Additionally, patients should be monitored for signs and symptoms of volume depletion, including orthostatic hypotension and electrolyte abnormalities, such as hyponatremia and hyperkalemia [39].

High-risk patients with CKD should be closely monitored with the presence of risk factors, including prior acute kidney injury [49], risk of volume depletion [39], exposure to nephrotoxic agents (such as nonsteroidal anti-inflammatory drugs (NSAIDs), contrast agents, and aminoglycoside antibiotics) [50], and other comorbidities (such as liver disease, heart failure, and sepsis) [39]. These risk factors should be considered when evaluating the potential use of SGLT2is in patients with CKD. Close monitoring of renal function is also recommended in those patients [51].

6.2. Dosage Adjustments for Patients with CKD

SGLT2is are renally cleared medications, and therefore, dosage adjustments are

necessary for patients with impaired kidney function to reduce the risk of adverse effects [37]. According to the Saudi FDA, the recommended starting dose of dapagliflozin is 10 mg once daily and empagliflozin is 10 mg once daily in CKD patients [52]. According to the Saudi FDA recommendations, for patients with an eGFR 60 to <90 or CrCl 60 to <90, the recommended starting dose of canagliflozin is 100 mg or 300 mg. In patients with an eGFR 45 to <60 or CrCl 45 to <60, the dose of is limited to 100 mg once daily. Canagliflozin should not be initiated in patients with an eGFR < 45 or CrCl < 45. Canagliflozin should be discontinued when eGFR is persistently < 45 or CrCl < 45. Canagliflozin should also not be used in patients with end stage renal disease (ESRD) or in patients on dialysis [52].

Dosage adjustment for SGLT2is is generally not required in elderly patients with CKD. Previous studies observed that body weight decreased more with higher doses of SGLT2 inhibitors, especially dapagliflozin [53].

However, patients with a higher body weight may require higher doses of some SGLT2i agents, such as canagliflozin, to achieve therapeutic efficacy [54]. Caution should also be exercised with the coadministration of certain medications, such as diuretics and angiotensin-converting enzyme inhibitors (ACEIs), which may affect renal function and increase the risk of hypovolemia [9]. Patients with hepatic impairment may require dosage adjustments of SGLT2is due to their effects on metabolism and clearance [55]. SGLT2is are not recommended during pregnancy and breastfeeding due to limited data on their safety and efficacy in these populations [8].

6.3. Potential Drug-Drug Interactions in Patients with CKD

SGLT2is can interact with other medications commonly used in CKD patients, potentially leading to adverse effects. They may enhance the diuretic effect of loop diuretics, leading to dehydration and electrolyte imbalances [56] [57]. NSAIDs can reduce renal blood flow and impair renal function, and concomitant use with SGLT2is may increase the risk of AKI [58]. Although only a few case studies were reported, SGLT2is could be linked to an increasing the risk of statin-induced myopathy, as they can increase the plasma concentration of statins [59]. However, these interactions should be handled in an individual base while monitoring fluid status, electrolytes status, renal functions, and myopathy. Also, this topic needs more investigation.

7. Conclusion

In conclusion, the role of SGLT2is in CKD is self-evident. Therefore, their utilization in CKD, DM or non-DM cases is recommended (use dapagliflozin, empagliflozin, then canagliflozin in sequence). Patient selection is one important factor when prescribing SGLT2is.

8. Recommendations

Recommendations
Assess all individuals with T2DM for established CVD and/or CKD or risk for them using standard diagnostic criteria. Initate SGLT2i in those with established CVD and/or CKD and in those with three or more CVD and/or CKD risk factors without established CVD and/or CKD.
Assess all CKD patients for risk of progression. Those with stages 3 - 5 CKD and high progression risk (urine albumin-to-creatinine ratio: UACR > 300 mg/g) should be considered for SGLT2i Adults with CKD and heart failure or eGFR ≥ 20 mL/min/1.73m^2 with UACR ≥ 200 mg/g should be treated with an SGLT2 inhibitor. Adults with eGFR ≥ 20 - 45 mL/min/1.73m^2 with UACR < 200 mg/g should be treated with an SGLT2 inhibitor.
Do not initiate SGLT2i if eGFR is below 20 mL/min/1.73m^2 but continue SGLT2i if the patient is already on it.
Regular monitoring is also essential for patients with CKD who are receiving SGLT2is.
Patients with a history of AKI, hypotension, or dehydration should be monitored closely if SGLT2 inhibitors are used.
Patients on SGLT2is should have their eGFR and serum creatinine levels monitored before initiating therapy and periodically thereafter to assess renal function. Close monitoring is recommended in patients with eGFR < 60 mL/min/1.73m^2.
Patients should be monitored for signs and symptoms of volume depletion, including orthostatic hypotension and electrolyte abnormalities, such as hyponatremia and hyperkalemia.
Assess for risk factors for AKI while on SGLT2is.
Use SGLT2i with caution in those with a history of genital or urinary tract infections.
Counseling for patients with regards genital infections, and volume status is recommended for those on SGLT2is.
Patients should be advised to withhold SGLT2is during an acute illness that can lead to dehydration.
Drug-to-drug interactions should be considered when prescribing SGLT2is with loop diuretics, ACEIs, ARBs, other anti-DM medications, NSAIDs, and statins.
Dosage adjustments are necessary. The recommended dosage adjustments for SGLT2is in patients with impaired kidney function are as follows: - Dapagliflozin is 10 mg once daily, and it should not be used in patients with an eGFR less than 25 mL/min/1.73m^2. - The recommended starting dose of Empagliflozin is 10 mg once daily, and it should not be used in patients with an eGFR less than 20 mL/min/1.73m^2. - The recommended starting dose of Canagliflozin is 100 mg once daily, and it should not be used in patients with an eGFR less than 45 mL/min/1.73 m^2.
Future directions and ongoing research in this field.
More research is needed to establish the role of SGLT2is therapy in specific populations with kidney diseases, such as kidney transplant recipients, those with lower grades of proteinuria (A2, e.g. those with chronic interstitial nephritis or CKD of unknown etiology), and those with lower eGFR.
Saudi cost-benefit analyses need to be undertaking to define the place of SGLT2is in standard treatment algorithms.
More research studies are needed to highlight the drug-drug interaction of SGLT2is in different population.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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