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Integrating Sglt-2 Inhibitors into the Clinical Management of Type 2 Diabetes Mellitus and Chronic Kidney Disease: Current Evidence and Future Outlook

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Objective and Background: The prevalence of type 2 diabetes mellitus (T2DM) is steadily increasing globally. A significant complication of T2DM is diabetic kidney disease, which contributes to increased morbidity and mortality. Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors are a class of oral antidiabetic agents that effectively lower blood glucose levels and provide protective benefits for kidney health.
Methods: A comprehensive review of studies was conducted focusing on the use of SGLT-2 inhibitors in patients with T2DM, including those with chronic kidney disease (CKD), defined as a

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glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m², or urine albumin/creatinine ratio ≥ 30 mg alb/g creatinine. The studies evaluated clinical outcomes such as cardiovascular events, kidney disease progression, and mortality.

Results: Research findings demonstrate that SGLT-2 inhibitors significantly reduce the risk of hospitalization due to heart failure, myocardial infarction, and stroke. Additionally, these medications lower the incidence of cardiovascular-related and all-cause mortality. Renal-specific benefits include slowing the progression of albuminuria, reducing the decline in GFR, lowering the need for renal replacement therapy, and decreasing kidney-related deaths.

Keywords: Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors; type 2 diabetes; chronic kidney disease.

1. INTRODUCTION

"Type 2 diabetes mellitus is a major global health issue, affecting more than 90% of individuals with diabetes. According to data from the International Diabetes Federation (IDF), the prevalence of diabetes continues to rise each year. In 2021, the global prevalence of diabetes among adults aged 20-79 years was estimated at 537 million, with projections indicating an increase to approximately 643 million by 2030 and 783 million by 2045. Indonesia, the prevalence of diabetes mellitus ranks 5th globally, with 19.5 million cases in 2021, expected to rise to 28.6 million by 2045. Indonesia also ranks 3rd in the world with 14.3 million individuals living with undiagnosed diabetes mellitus (73% of the population)" (Magliano et al. 2021) "The increased expression of Sodium-Glucose Co-Transporter-2 (SGLT-2) in the proximal tubules of the kidneys is one of the pathophysiological mechanisms of hyperglycemia in patients with diabetes mellitus, as well as hyperfiltration in diabetic kidney disease. Various mechanisms of SGLT-2 inhibitors can provide renal protection" (Magliano et al. 2021, Davidson 2019). "Several studies on SGLT-2 inhibitors (such as canagliflozin, dapagliflozin, and empagliflozin) in patients with type 2 diabetes mellitus, including EMPA-REG OUTCOME, CANVAS/CANVAS-R, DECLARE-TIMI 58, CREDENCE, DAPA-CKD, and EMPA-KIDNEY, have focused on cardiovascular and renal outcomes" (Giorgino et al. 2020, Krishnan et al. 2023).

2. METHODS

This review article examines the integration of Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors into the clinical management of type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). A systematic approach was employed to analyze peer-reviewed studies, clinical trials, and meta-analyses published in the last decade. Key databases such as PubMed, Scopus, and clinical trial registries were searched using keywords including "SGLT-2 inhibitors," "type 2 diabetes," "chronic kidney disease," "renal protection," and "cardiovascular outcomes." (Krishnan et al. 2023, Yetti and Sukmarini 2019, ElSayed et al. 2023).

"The inclusion criteria were studies involving adult patients with T2DM or CKD, reporting on the efficacy and safety outcomes of SGLT-2 inhibitors. Data extracted included effects on glycemic control, renal outcomes (e.g., progression of albuminuria, glomerular filtration rate decline, need for renal replacement therapy), and cardiovascular endpoints (e.g., heart failure hospitalization, stroke, and myocardial infarction). Additional focus was placed on subgroup analyses involving patients with varying degrees of CKD" (Davidson 2019, ElSayed et al. 2023).

"A narrative synthesis was conducted to summarize the current evidence, emphasizing the clinical benefits, mechanisms of action, and future implications of SGLT-2 inhibitors in these patient populations. Limitations of existing studies and areas for future research were also identified to guide clinical decision-making and research priorities" (Indonesia 2015, Hoogeveen 2022).

The PICO method was used to analyze the research question. PICO is an acronym for Population, Intervention, Comparison, and Outcome (Mathes et al. 2017). The PICO components for this article are as follows: (Horton et al. 2015).

Population: Adult patients with Type 2 Diabetes Mellitus (T2DM), including those who also have Chronic Kidney Disease (CKD), defined as a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m², or a urine albumin/creatinine ratio ≥ 30 mg alb/g creatinine.

Intervention: The use of Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors, a class of oral antidiabetic medications that not only lower blood glucose levels but also provide protective benefits for kidney health.

Comparison: This article does not explicitly mention comparisons with other interventions, but in some of the included studies, comparisons may be made between SGLT-2 inhibitors and control group without treatment.

Outcome: Cardiovascular outcomes: Reduction in the risk of hospitalization due to heart failure, myocardial infarction, and stroke.

Mortality: Reduction in the incidence of cardiovascular-related mortality and all-cause mortality.

Renal outcomes: Slowing the progression of albuminuria, reducing the decline in GFR, decreasing the need for renal replacement therapy, and reducing kidney-related deaths.

Using the PICO approach, this article clearly evaluates the effectiveness and safety of SGLT-2 inhibitors in the management of T2DM and CKD, as well as their impact on clinical outcomes related to both renal and cardiovascular health. A total of 140 articles were obtained from the search (Mancini et al. 2022). After excluding duplicate articles, 140 articles remained. Inclusion and exclusion criteria were applied, resulting in 68 articles that met the criteria. A critical review was conducted based on the inclusion and exclusion criteria, and articles for review were selected through researcher consensus, focusing on articles discussing the extraglycemic cardiovascular mechanisms of this class of drugs. Ten articles were included in this review, as shown in Fig. 1.

3. MECHANISMS INVOLVED IN THE PATHOGENESIS OF DIABETIC KIDNEY DISEASE (DKD)

Type 2 Diabetes Mellitus (T2DM) is a form of diabetes that occurs due to the progressive loss of insulin secretion, not caused by autoimmunity, as seen in Type 1 diabetes. In Type 2 DM, patients typically have a background of insulin resistance and metabolic syndrome (Kumar et al. 2020). Insulin resistance means that the body is unable to use insulin effectively, even though insulin levels may initially be normal or high (Petersen and Shulman 2018). To compensate for this, the pancreas produces more insulin. Over time, however, the pancreas becomes fatigued, and its ability to secrete insulin decreases (Galicia-Garcia et al. 2020). Metabolic syndrome refers to a group of conditions that increase the risk of heart disease, stroke, and Type 2 diabetes. These conditions include abdominal obesity (excess fat around the abdomen), hypertension (high blood pressure), hyperlipidemia (high cholesterol and triglyceride levels), and glucose intolerance (including insulin resistance or prediabetes) (Silveira Rossi et al, 2022). Other risk factors contributing to the development of Type 2 DM include genetic predisposition, an unhealthy lifestyle (such as poor diet and lack of physical activity), and increasing age. In Indonesia, the rising prevalence of obesity and unhealthy eating habits has contributed to the growing number of Type 2 diabetes cases. It is important to make lifestyle changes, such as adopting a healthy diet, engaging in regular physical activity, and managing body weight, in order to prevent or effectively manage Type 2 DM (Artasensi et al. 2020).

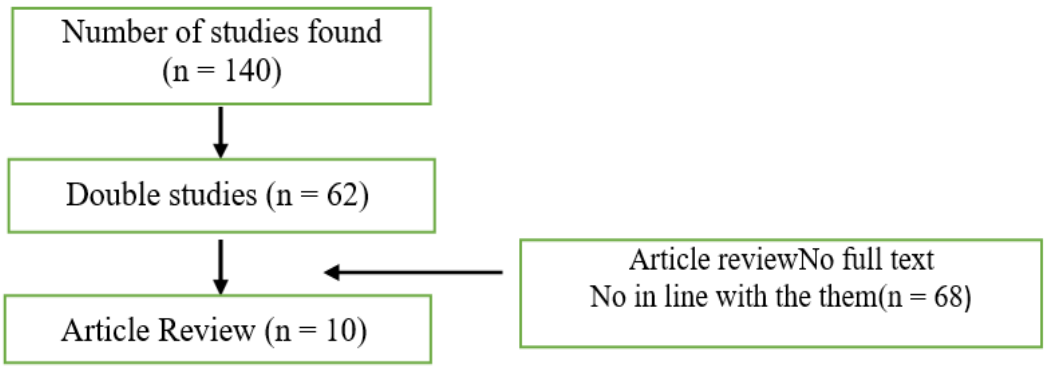

Fig. 1. Data extraction (Articles relevant to the purpose of research) (Munn et al. 2014)

"The pathogenesis of hyperglycemia in type 2 DM can include beta-cell pancreatic failure, pancreatic alpha-cell dysfunction, fat cell resistance to insulin's antilipolytic effects, impaired insulin action in muscle cells, increased glucose production by the liver, increased food intake due to insulin resistance in the brain, changes in the gut microbiota composition, glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) deficiencies, decreased amylin levels, low-grade systemic inflammation, and increased expression of Sodium-Glucose Co-Transporter-2 (SGLT-2), which causes increased glucose reabsorption in the renal tubules" (Alsahli and Gerich 2010, Grover et al. 2021).

"Type 2 DM can lead to macrovascular complications such as coronary artery disease, stroke, peripheral artery disease, heart failure, and microvascular complications including neuropathy, retinopathy, and nephropathy" (Margonato et al. 2021).

Diabetic kidney disease (DKD) is a clinical diagnosis defined by the presence of chronic kidney disease characterized by persistent (at least 3 months) urinary albumin excretion (albumin-to-creatinine ratio [ACR] ≥ 30 mg/g) or low estimated glomerular filtration rate (< 60 mL/min/1.73 m²) in patients with diabetes melitus (Nayak et al. 2014, Samsu 2021). Diabetic nephropathy, on the other hand, is based on histological changes in the glomerulus (glomerular basement membrane thickening, mesangial expansion with or without nodular sclerosis/Kimmelstiel–Wilson lesions, podocyte loss, endothelial damage) observed in kidney biopsies (Khoury et al. 2020). Diabetic kidney disease can occur in nearly half of patients with type DM throughout their lifetime. Approximately 20% of patients with type 2 diabetes will have an estimated glomerular filtration rate < 60 mL/min/1.73 m², and 28% will develop albuminuria (de Boer et al. 2022, Galicia-Garcia et al. 2020). If type 2 diabetes occurs at ages 15-24 years, the risk of developing moderate albuminuria is nearly 100%. Globally, Diabetic Kidney Disease is the leading cause of chronic kidney disease and end-stage kidney disease (ESKD) (Neal et al. 2017, Wiviott et al. 2019). "According to the 2018 Indonesian Renal Registry data, diabetic kidney disease/ nephropathy ranks second, accounting for 27%, as the cause of CKD stage 5, following hypertensive kidney disease which accounts for 36%" (Margonato et al. 2021).

"The pathogenesis of DKD in patients with type 2 DM begins with the presence of hyperglycemia and dyslipidemia, which act as promoters of glomerular hyperfiltration and hyperperfusion. Glomerular hyperfiltration, an increase above the physiological value of glomerular filtration rate (120-180 mL/min/1.73 m²), is estimated to occur in 40-50% of patients with type 2 DM" (Perkovic et al. 2019). "The mechanisms underlying glomerular hyperfiltration are not fully understood, but one considered mechanism is the increased glucose reabsorption in the proximal tubules through Sodium-Glucose Co-Transporter-2 (SGLT-2), which reduces solute levels in the distal tubules, particularly sodium chloride at the macula densa. The decrease in tubuloglomerular feedback can lead to the dilation of the afferent arteriole, increasing glomerular perfusion. Simultaneously, activation of the renin-angiotensin system leads to an increase in local angiotensin II production at the efferent arteriole, causing vasoconstriction (Fig. 2)" (Alicic et al. 2017, DeFronzo et al. 2021, Wiviott et al. 2019).

In addition, there is an increase in endothelin-1, a vasoconstrictor of the efferent arteriole, which, similar to the renin-angiotensin- system, plays a role in hypertension, endothelial dysfunction, inflammation, and activation of receptors that directly increase glomerular permeability and fibrosis (Neal et al. 2017). Other factors contributing to the development of DKD include an increase in the production of advanced glycation end products, reactive oxygen species, intracellular nicotinamide adenine dinucleotide hydrogen, and transforming growth factor-β (Zinman et al. 2015). Additionally, there is an increase in pro-fibrotic factors such as connective tissue growth factor and vascular endothelial growth factor, which play a role in the survival of endothelial cells, podocytes, and mesangial cells. These various factors can activate intracellular signaling pathways, such as protein kinase C, Janus kinase/signal transducers and activators of transcription (JAK/STAT), and NF-κB. (Perkovic et al. 2019, Jardine et al. 2018).

Protein kinase C increases levels of prostaglandin E2 and nitric oxide, causing vasodilation of the afferent arteriole, amplifying the effects of angiotensin II on the efferent arteriole, and increasing vascular endothelial growth factor, transforming growth factor-β, and connective tissue growth factor. (Jalal et al. 2011, Lytvyn et al. 2015). Janus kinase 2 is

activated by reactive oxygen species and is linked to mesangial cell hypertrophy. NF-κB, a transcription factor, regulates various genes associated with inflammation, immunity, and apoptosis (Zhao et al. 2020). “The activation of NF-κB correlates with the occurrence of proteinuria and interstitial cell infiltration in the kidneys. Proteinuria contributes to the stimulation of NF-κB, and like a cycle, it can lead to persistent proteinuria” (Ziyadeh and Wolf 2008).

“The pathophysiology of diabetic kidney disease in patients with type 2–DM is more complex, as cardiovascular risk factors such as hypertension, obesity, and hyperuricemia also contribute to the development of microvascular damage. Systemic hypertension and obesity can lead to glomerular hyperfiltration through increased systemic blood pressure passing through the glomerulus and glomerular hypertrophy” (Petersen and Shulman 2018). “Additionally, in patients with diabetes mellitus DM and obesity, there is reduced autophagic activity (a mechanism that maintains homeostasis during oxidative stress) in podocytes and proximal tubular epithelial cells in the kidneys. This makes patients more vulnerable to kidney injury. Increased uric acid contributes to diabetic kidney disease through endothelial dysfunction, enhanced renin-angiotensin activity, induction of the inflammatory cascade, and the production of cytokines such as transforming growth factor-β” (Jalal et al. 2011).

4. MECHANISMS OF ACTION OF SGLT-2 INHIBITORS AND RESULTS OF DIFFERENT RECENT STUDIES

“Sodium-Glucose Co-Transporter-2 (SGLT-2) is a membrane protein located in the renal tubule cells that simultaneously transports sodium and glucose for reabsorption” (Kaplan et al. 2018). “SGLT-2 is predominantly found in the first and second segments of the proximal tubules of the kidneys, where it plays a crucial role in the reabsorption of approximately 90% of the filtered glucose” (Salvatore et al. 2022). “Any remaining glucose is reabsorbed through the Sodium-Glucose Co-Transporter-1 (SGLT-1) in the distal segment of the proximal tubule” (Horton et al. 2015). “In individuals with normal glomerular filtration rate (GFR), all glucose is reabsorbed in the proximal renal tubules. However, in cases of hyperglycemia, such as in patients with DM , a greater-than-normal amount of glucose is filtered into the proximal renal tubules, leading to increased glucose reabsorption. This process is associated with an upregulation of both SGLT-2 and SGLT-1 expression” (Group 2023). “SGLT-2 inhibitors are oral anti-diabetic medications that work by inhibiting glucose reabsorption in the proximal renal tubules, thus promoting the excretion of glucose through urine. By blocking the SGLT-2 transporter, these medications help lower blood glucose levels in patients with type 2 DM and provide additional benefits such as weight loss, improved blood pressure control, and kidney protection” (Jung et al. 2020).

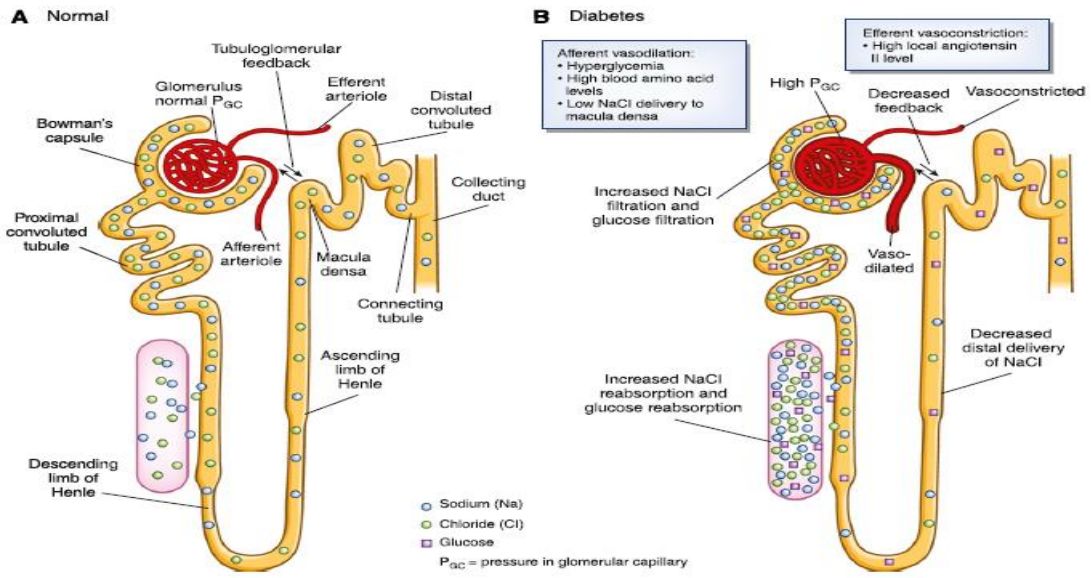

Fig. 2. Renin-angiotensin system activation and its effect on efferent arteriole vasoconstriction (Alicic et al 2017, Harrison-Bernard 2009)

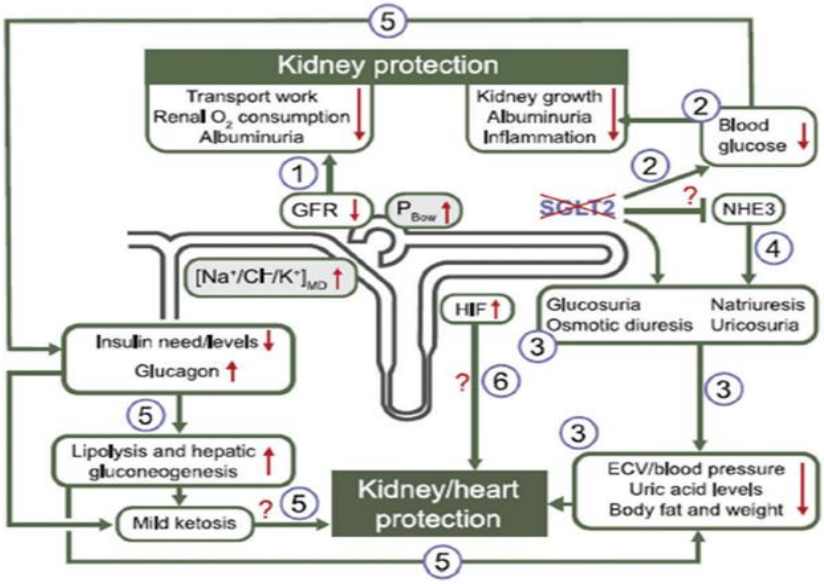

Fig. 3. Mechanism of Kidney Protection by Sodium-Glucose Co-Transporter-2 Inhibitors (Sen and Heerspink 2021, Davidson 2019)

The kidney protection effects of Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors are attributed to several mechanisms, including (a) Reduction of renal glucose and sodium reabsorption in the proximal renal tubules: This leads to a decrease in hyperfiltration by increasing sodium transport to the macula densa, thereby activating the tubuloglomerular feedback and causing vasoconstriction of the afferent arteriole. (b) Lower blood glucose levels: This reduces the potential for glucose toxicity to the kidneys (such as hypertrophy, inflammation, and injury) and other organs, thereby helping to protect kidney function. (c) Due to a decrease in plasma volume and sodium, as well as weight loss, SGLT-2 inhibitors contribute to lowering blood pressure. (d) Sodium-Glucose Co-Transporter-2 and Na+/H+ exchanger 3 (NHE3) co-expression: Inhibition of SGLT-2 leads to natriuresis, which contributes to a reduction in blood pressure and other beneficial renal effects. (e) Increased glucagon levels This causes vasodilation and increases renal blood flow, glomerular filtration rate, and electrolyte excretion. At the same time, a reduction in insulin levels leads to increased lipolysis and gluconeogenesis. (f). A reduction of kidney injury due to ischemia through the increased activation of transcription factors, particularly those induced by hypoxia, which are involved in kidney repair processes. (g) Reduction in arterial stiffness, vascular resistance, uric acid levels: SGLT-2 inhibitors also modulate the renin-angiotensin-aldosterone system, contributing to improved kidney function and cardiovascular protection. These mechanisms work synergistically to protect kidney function and provide broader cardiovascular benefits for patients with diabetes and chronic kidney disease (Perkovic et al. 2019, Zinman et al. 2015).

Various studies on Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors in patients with type 2 diabetes melitus DM have been conducted. The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) study, involving 7,020 patients with type 2 diabetes, showed that administering 10 mg/25 mg of empagliflozin compared to placebo resulted in a lower risk of death from cardiovascular causes (hazard ratio 0.62; 95% CI 0.49-0.77; p<0.001), death from all causes (hazard ratio 0.68; 95% CI 0.57-0.82; p<0.001), and hospitalization for heart failure (hazard ratio 0.65; 95% CI 0.50-0.85; p=0.002) (Zinman et al. 2015). Similarly, the Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk (Davidson 2019). The administration of 100 mg/300 mg canagliflozin, compared to placebo, was associated with a lower risk of death from cardiovascular causes, myocardial infarction, and stroke (hazard ratio 0.86; 95% CI 0.75-0.97; p<0.001), progression of albuminuria (hazard ratio 0.73; 95% CI 0.67-0.79), a 40% decline in glomerular filtration rate,

the need for renal replacement therapy, and death from renal causes (hazard ratio 0.60; 95% CI 0.47-0.77) (Neal et al. 2017).

“In the Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE-TIMI 58) study, involving 17,160 patients, the administration of 10 mg dapagliflozin, compared to placebo, showed a lower risk for hospitalization due to heart failure (hazard ratio 0.73; 95% CI 0.61-0.88), a 40% decline in glomerular filtration rate, the occurrence of end-stage kidney disease, and death from renal causes (hazard ratio 0.76; 95% CI 0.67-0.87)” (Mosenzon et al. 2022, Wiviott et al. 2019).

“The Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) study involving 4,401 patients with type 2 diabetes and a mean glomerular filtration rate of 56 mL/min/1.73 m², demonstrated that 100 mg of canagliflozin, compared to placebo, was associated with a lower risk of end-stage kidney disease, doubling of serum creatinine, and death from renal causes (hazard ratio 0.66; 95% CI 0.53-0.81; p<0.001), as well as cardiovascular death, myocardial infarction, and stroke (hazard ratio 0.80; 95% CI 0.67-0.95; p=0.01), and hospitalization due to heart failure (hazard ratio 0.61; 95% CI 0.47-0.80; p<0.001)” (Mahaffey et al. 2019, Perkovic et al. 2019).

“The Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) study, involving 4,304 patients with a glomerular filtration rate of 25-75 mL/min/1.73 m², of which 67.5% had type 2 diabetes, showed that the administration of 10 mg dapagliflozin, compared to placebo, resulted in a lower risk for a ≥50% decline in glomerular filtration rate, end-stage kidney disease, and death from renal causes (hazard ratio 0.56; 95% CI 0.45-0.68; p<0.001), as well as death from cardiovascular causes or hospitalization due to heart failure (hazard ratio 0.71; 95% CI 0.55-0.92; p=0.009)” (Heerspink et al. 2020).

“The Empagliflozin in Patients with Chronic Kidney Disease (EMPA-KIDNEY) study, which involved 6,609 patients with a glomerular filtration rate of 20-45 mL/min/1.73 m² or 45-90 mL/min/1.73 m² with albumin-to-creatinine ratio ≥200, and 46% of whom had type 2 diabetes, demonstrated that the administration of 10 mg empagliflozin, compared to placebo, resulted in a lower risk of progression of kidney disease or death from cardiovascular causes (hazard ratio 0.72; 95% CI 0.64-0.82; p<0.001). These results were consistent in both patients with diabetes and those without diabetes” (The EMPA-KIDNEY Collaborative Group. 2023).

5. CONCLUSION

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are oral antidiabetic medications with potential renal protective effects. The administration of SGLT-2 inhibitors in patients with type 2 diabetes has been shown to reduce the risk of cardiovascular and renal complications. These medications work by inhibiting glucose reabsorption in the kidneys, promoting glucose excretion through urine, and improving glycemic control. Additionally, SGLT-2 inhibitors have been shown to offer benefits beyond glucose control, such as reducing the risk of heart failure, slowing the progression of chronic kidney disease, and lowering the risk of cardiovascular events."

DATA AVAILABILITY

All relevant data are included in the paper and its supporting information files. This study aims to inform researchers to identify integrating SGLT-2 Inhibitors into the Clinical Management of Type 2 Diabetes and Chronic Kidney Disease: Current Evidence and Future Outlook.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

The authors hereby state that no generative AI tools such as large language models (ChatGPT, COPILOT, etc.) or text-to-image generators were utilized in the creation or editing of this work.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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