Review Article

Role of Sodium-Glucose Co-Transporter 2 Inhibitors in Chronic Kidney Disease Management

Sangeeta Anand Gamre*, Shweta Dattatreya Sawant, Inayat Isak Kabir, Ritesh Hetram Bisen

1. B. Pharm, Director, Amethys Insights Private Limited, U No. 504, Marathon Max, Link Road, Mulund West Mumbai, Maharashtra, India, 400080.
2. M. Pharm (Pharmacology), Medical Writer, Amethys Insights Private Limited, U No. 504, Marathon Max, Link Road, Mulund West Mumbai, Maharashtra, India, 400080.
3. M. Pharm (Pharmacology), PV Manager, Amethys Insights Private Limited, U No. 504, Marathon Max, Link Road, Mulund West Mumbai, Maharashtra, India, 400080.
4. M. Pharm, PGDM, Team Lead HEOR, Amethys Insights Private Limited, U No. 504, Marathon Max, Link Road, Mulund West Mumbai, Maharashtra, India, 400080.

***Corresponding author's E-mail:** Sangeeta_G@amethysinsights.com

Received: 04-11-2024; **Revised:** 27-01-2025; **Accepted:** 08-02-2025; **Published online:** 20-02-2025.

ABSTRACT

Chronic Kidney Disease (CKD) poses a significant global public health challenge, affecting an estimated 850 million people worldwide, primarily due to diabetes and hypertension. Early recognition of CKD is necessary for harnessing the significant advances in staging, prognosis, and treatment. Progressive CKD leads to the requirement for kidney replacement therapy with transplantation or dialysis. Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2 inhibitors), initially developed as glucose-lowering agents for type 2 diabetes, have emerged as pivotal therapeutic agents in CKD management. Beyond their primary metabolic effects, SGLT2 inhibitors have demonstrated pleiotropic benefits in clinical trials, including reduced mortality and delayed CKD progression in both diabetic and nondiabetic populations. Key trials, such as DAPA-CKD, CREDENCE, and EMPA-KIDNEY, have substantiated these renal benefits, leading to their endorsement as first-line therapy in recent Kidney Disease: Improving Global Outcome (KDIGO) guidelines. This review synthesizes current evidence on CKD epidemiology, clinical manifestations, and the evolving role of SGLT2 inhibition in renal protection. Mechanistically, SGLT2 inhibitors act by inhibiting renal glucose reabsorption, improving metabolic parameters, and providing direct renal benefits. The article also discusses the efficiency of SGLT2 inhibitors in CKD management and their integration into clinical practice following recent guideline updates. In conclusion, the recognition of SGLT2 inhibitors as key players in CKD treatment marks a paradigm shift in nephrology, offering substantial benefits beyond glycemic control. By advocating for their broader implementation, this review aims to improve global CKD outcomes and reduce the burden of kidney failure on healthcare systems and patient quality of life.

Keywords: Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2 Inhibitors), Chronic Kidney Disease (CKD), Empagliflozin, Dapagliflozin.

INTRODUCTION

Chronic kidney disease (CKD) is defined as having a low glomerular filtration rate or high proteinuria, which affects around 15%– 20% of adults worldwide.[1] The Global Burden of Disease Consortium projects that CKD will rank among the top five conditions contributing to years of life lost by 2040.[2]

The incidence of CKD and its impact on mortality and cardiovascular outcomes increase with age.[3] The most frequent causes are diabetes mellitus, hypertension, chronic glomerulonephritis, obstructive nephropathy, intestinal nephritis recurrent kidney infections, prolonged acute renal disease, and long-term use of certain medications.

Current CKD standard treatment involves renin-angiostatin system (RAS) blockade by angiostatin receptor blockers (ARB) and angiostatin-converting enzyme inhibitors (ACEi).

The treatment of CKD focuses on managing underlying causes, slowing the disease progression, and addressing complications to enhance quality of life. Treatment strategies may differ depending on the specific stage of CKD and the individual's health status.[4]

In recent years, there has been growing interest in exploring the role of SGLT2 inhibitors in managing kidney diseases.[4]

This review summarizes the evidence for current paradigms of disease identification and classification, epidemiology, nephroprotective effect of SGLT2 inhibitors in CKD patients, and the major guidelines in CKD.

Epidemiology

CKD is a global public health crisis. Approximately 850 million patients in the world have CKD, with ~4 million receiving kidney replacement therapy. Diabetic kidney disease (DKD) is the foremost cause of CKD globally.[5] In 2015, there were ~415 million people living with diabetes mellitus with the prevalence predicted to rise to 642 million by 2040, largely driven by an aging population and lifestyle factors.[5,6] In 2016, this disease was 13th on the list of causes of death on a world scale.[5] In Sri Lanka, Central America, Egypt, and Central India, defined geographic areas exist where many cases of CKD of unknown cause have been identified.[7] Many countries have developed national registries of patients with kidney failure, allowing comparison of incidence across ages and countries.[2,8]

In India, diabetes and hypertension today account for 40–60% of cases of CKD.[9] According to the Global Burden of

Disease (accessed on 26 October 2024), the prevalence of CKD in India is 9.23%.

Jafar et al. noted that approximately 1 in 5 adults in India has CKD.[10] Diabetes is the leading cause of the CKD/ESKD burden in India, accounting for one-third of CKD patients., while other etiologies such as hypertension (13%), glomerulonephritis (14%), and undetermined causes (16%). The high burden of CKD and associated risk factors have serious implications for a country of 1.35 billion, especially in rural areas where 66.4% of India's total population resides, literacy rates are low at 65%, and 58% live on less than $3.10 (purchasing power parity) daily.[10]

Classification of Chronic Kidney Disease

CKD is a worldwide public health problem, with adverse outcomes of kidney failure, CVD, and premature death.[11]

KDIGO conducted a survey and sponsored a controversies conference to (1) provide a clear understanding to both the nephrology and nonnephrology communities of the evidence base for the definition and classification recommended by Kidney Disease Quality Outcome Initiative (K/DOQI), (2) develop global consensus for the adoption of a simple definition and classification system, and (3) identify a collaborative research agenda and plan that would improve the evidence base and facilitate implementation of the definition and classification of CKD.[11]

Specifically, diagnosis of CKD requires one or more of the following: albuminuria, defined as an albumin-to-creatinine ratio (ACR) ≥30 mg/g of creatinine (approximately ≥3 mg/mmol) or albumin excretion of ≥30 mg/day; GFR <60 mL/min/1.73 m^2; abnormalities on urine sediment, histology, or imaging; electrolyte or other abnormalities attributed to tubular disorders; or history of kidney transplantation.[2]

Clinical manifestations of CKD

Albuminuria

Albumin is one type of plasma protein found in the urine in normal subjects and in larger quantities in patients with kidney disease. Recent recommendations for the measurement of urine proteins emphasize quantification of albuminuria rather than total protein.[11]

The greater the urinary albumin excretion, the worse the prognosis.[12] Again, recent practice has been to categorize patients based on the severity of urinary albumin excretion as shown in Table 1.

Table 1: Persistent Albuminuria Categories

A1	uACR < 30 mg/g	Mildly increased albuminuria
A2	uACR 30–300 mg/g	Moderately increased albuminuria
A3	uACR > 300 mg/g	Severely increased albuminuria

Abbreviations: uACR: Urinary albumin to creatinine ratio

GFR

The second axis for CKD classification focuses on GFR.[2] The GFR is one component of the excretory function. Still, it is widely accepted as the best overall index of kidney function because it is generally reduced after widespread structural damage and most other kidney functions decline in parallel with GFR in CKD.[13] The larger the reduction in eGFR below 60 mL/min/1.73 m^2, the greater the risk of poor health outcomes.[12]

Recent practice has shifted towards categorizing patients by specific stages for greater simplicity. Stage 3a denotes an eGFR of 45–59 mL/min/1.73 m^2, or moderately reduced kidney function; stage 3b denotes an eGFR of 30–44 mL/min/ 1.73 m^2, or moderate to severely reduced kidney function; stage 4 denotes an eGFR of 15–29 mL/min/1.73 m^2, or severely reduced kidney function and stage 5 denotes an eGFR of < 15 mL/min/1.73 m^2, or kidney failure.[12]

Cause

The third axis for classification is the cause of CKD. Classification of cause is typically based on the presence or absence of systemic disease (for example, obesity, diabetes, hypertension, systemic autoimmune disease) and the specific location of the kidney pathology (for example, glomeruli, tubulointerstitium, vasculature, or cystic/congenital abnormality). Molecular phenotyping and genetic testing are increasingly being used to assign the cause of disease.[2]

SGLT-2 inhibitors

One of the most significant advancements in CKD management over the past decade was the discovery that SGLT-2 inhibitors offer strong protective effects on the heart and kidneys in patients with and without diabetes.[2] Many studies have shown that SGLT2 inhibitors can reduce the risk of serious cardiac and renal outcomes in patients, improve the patient's cardiac and renal outcomes, and reduce the number of hospitalizations, thereby reducing medical expenses in this respect.[1]

SGLT2 inhibitors are a new group of drugs that became available after 2010, with their continuous rise in popularity reaching its peak today. The precursor to this class of drugs was phlorizin, an o-aryl glucoside derived from plant origin, discovered in the 19th century and identified as a nonselective sodium-glucose cotransporter inhibitor. However, due to its poor absorption from the gastrointestinal tract, researchers began searching for orally effective inhibitors of these co-transporters.[4]

In 1996, researchers in Japan at Kyoto University and Tanuba Seiygyu Co. developed phlorizin analogs, the first chemically engineered SGLT2 inhibitors.

In the United States, the first SGLT2 inhibitor approved for use was canagliflozin in 2013. Initially, these substances were thought to be primarily antidiabetic drugs because of their mechanism of action. As research has progressed,

additional properties of these drugs have been identified. In 2021, dapagliflozin was approved for use in CKD to slow disease progression. There are now more drugs from this group approved for use, and the most popular include drugs such as empagliflozin, dapagliflozin, canagliflozin, or ertugliflozin. [4,14]

Mechanism of action

SGLT2 inhibitors bind to the SGLT2 protein which includes the binding site for glucose and sodium. By binding to the SGLT2 protein, SGLT2 inhibitors form complexes that prevent the active transport of glucose and sodium. As a result, there is an increased excretion of glucose, sodium, and water in the urine, leading to a decrease in blood glucose concentration. Importantly, the mechanism of action of SGLT-2 inhibitors is independent of insulin regulation. [4,15] The mechanism of action is summarized in Figure 1.

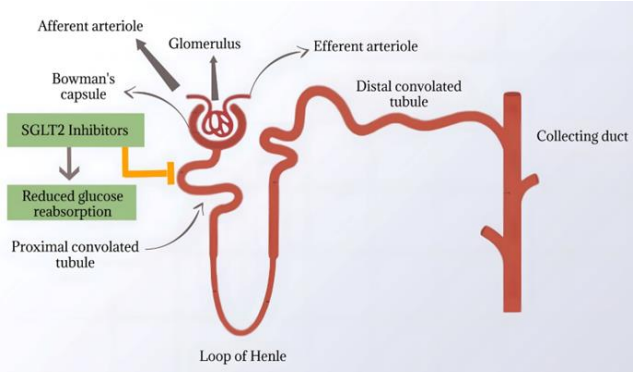

Figure 1: The mechanism of action of SGLT2 Inhibitors

Potential Mechanism of SGLT2 Inhibitors in Renal Protection

Tubuloglomerular Feedback (TGF)

One of the most important effects of SGLT2 inhibitors on the kidney is to decrease in glomerular hyperfiltration. A key process in the kidney that controls the GFR to preserve renal function and fluid-electrolyte balance is known as TGF.[4] Glomerular hyperfiltration is a common pathway of kidney injury in diabetic and nondiabetic patients.[16]

Various preclinical and clinical studies have shown that dapagliflozin and empagliflozin lower glomerular hyperfiltration without altering blood glucose levels. Canagliflozin has been shown to reduce GFR with proteinuria within 3 weeks of treatment in patients with Type 2 Diabetes Mellitus (T2DM).[3]

Effects of SGLT2 Inhibitors on Renal Energy Metabolism

In addition to improving renal energy metabolism, SGLT2 inhibitors enhance oxygen uptake and transformation at the mitochondrial level.[17] In contrast to the continuous glucose loss caused by increased glycosuria, SGLT2 inhibitors improve physiologic adaptive responses.[18] These response mechanisms induce an increase in endogenous glucose production by increasing glucagon and reducing insulin levels. These effects promote ketogenesis and lipolysis, leading to an increase in circulating ketone bodies among β-OH-butyrate. This mechanism provides a powerful synergistic effect that could ultimately protect kidney function.[3]

Effects of SGLT2 Inhibitors on Erythropoietin

A previous study with phlorizin has been shown to decrease oxygen levels in an in vivo study. These studies signify the role of SGLT2 inhibitors in mitigating the metabolic burden on proximal tubules, thereby increasing HIF-1α for erythropoietin production in patients with CKD.[3] Heerspink et al. showed that administration of SGLT2 inhibitors increased hematocrit, hemoglobin, and transiently elevated reticulocyte count and erythropoietin concentrations.[19]

Effects of SGLT2 Inhibitors on metabolic burden in nephrons

SGLT2 inhibitors lower the metabolic burden related to reabsorbed excessive sodium, protein, and other solutes in progressive CKD. The SAND trial had promising effects in patients with the Syndrome of Inappropriate Anti-Diuresis (SIAD). The study demonstrated a significant increase in plasma sodium levels as compared with placebo (10 vs. 7 mmol/L, respectively), indicating the reno-protective effects of empagliflozin. [3,20]

Other Reno-Protective effects of SGLT2 Inhibitors

The previous evidence has shown that SGLT2 inhibitors can exert nephroprotective effects by reducing oxidative stress, inflammation, fibrosis, sympathetic nervous system activation, intraglomerular hypertension, and improving myocardial efficiency and mitochondrial function. SGLT2 inhibitors promote weight loss and a reduction in the abdominal and peripheral fat and body weight through osmotic diuresis. Canagliflozin has shown to reduce weight, glycosylated hemoglobin, and blood pressure.[3]

Anti-inflammatory effect

SGLT2 inhibitors have been shown to reduce renal inflammation. SGLT2 inhibitors decrease various inflammatory signalling pathways and help to reduce the inflammatory response in the kidneys in various ways. First, they induce the activation of AMPK, which then suppresses the NF-κB and MAPK pathways, thereby reducing the synthesis of inflammatory mediators. Second, SGLT2 inhibitors upregulate sirtuin 1 (SIRT1), a NAD+-dependent deacetylase known for its anti-inflammatory effects, which further attenuates inflammation by inhibiting NF-κB activity. [3, 4,21]

Anti-fibrotic effect

Treatment with SGLT2 inhibitors may contribute to increased autophagia, decreased inflammation and thereby prevent fibrosis through their actions regarding ketone bodies. [3,4,19]

Effects of SGLT2 Inhibitors on metabolic parameters

Reduction of uric acid

Uric acid, the end product of purine metabolism in the human body, has been associated with the development of different diseases including CKD. Elevated serum levels of uric acid could be a result of increased production and/or reduced elimination and have been associated with increased oxidative stress, inflammation, decreased NO production, and consequent endothelial dysfunction. SGLT2 inhibitors have been shown to reduce uric acid concentrations.[21]

Stimulating Ketogenesis

Ketone bodies are an efficient fuel substrate representing a good source of energy and improving cardiac metabolic efficiency. Ketone bodies generate more ATP per molecule of oxygen consumed compared to glucose or free fatty acid (FFA). Increased fatty acid (FFA) transport to the liver enhances ketogenesis due to a lower insulin-to-glucagon ratio. In nondiabetic patients, treatment with SGLT2 inhibitors has resulted in a doubling of plasma ketone bodies, similar to levels observed in diabetic patients. This is accompanied by increased levels of ketone bodies and metabolites from ketogenesis in the urine.[19,21]

Improved mitochondrial energy supply

SGLT-2 inhibitors have been found to increase urinary glucose excretion, which results in a reduction of glucose levels in the body. This causes a shift in energy utilization, where fatty acid b-oxidation is employed as the main source of energy. The change in energy supply mainly accounts for the weight loss seen with SGLT-2 inhibitors. Increased b-oxidation leads to excess acetyl coenzyme A, which generates ketone bodies such as b-hydroxybutyrate, acetoacetate, and acetone. These ketone bodies serve as a fuel source for ATP production in the mitochondria, thus improving mitochondrial energy supply.[15]

Inhibition of the sympathetic nervous system (SNS)

Dapagliflozin has been shown to reduce the expression of tyrosine hydroxylase and norepinephrine levels in hypertensive mice. These findings suggest that the effect of SGLT-2 inhibitors in protecting renal function could be attributed to a decrease in renal sympathetic nerve activity.[15]

Improve vascular endothelial function

The reduced function of endothelial cells often leads to decreased nitric oxide production (NO). The over-expression of adhesion molecules and pro-inflammatory cytokines disrupt the normal ability of the endothelium to facilitate the dilation of blood vessels.[21] In diabetic rats, extended administration of SGLT-2 inhibitors effectively improved vascular endothelial dysfunction by enhancing NO diastolic function, reducing oxidative stress, and alleviating glucose toxicity in the aortic rings.[15] In another study, investigating endothelial dysfunction in diabetes, dapagliflozin was found to potentially facilitate the repair of vascular endothelial by decreasing the expression of vascular adhesion molecules, phosphorylated IkB expression, and infiltration of inflammatory macrophages in vivo.[15]

Antioxidative Stress

Oxidative stress plays an important role in the pathogenesis of CKD in DM, especially because the kidneys are particularly vulnerable to OS due to their high energy consumption and content of mitochondria (especially in proximal tubules).[22]

The effects of SGLT2 inhibitors on mitochondrial function and oxidative stress can occur through various mechanisms. One of the effects of SGLT2 inhibitors is the reduction of mitochondrial ROS production and reduction of Ca^{2+} overload in mitochondria, affecting vascular function in the diabetic milieu. Such a reduction of oxidative stress helps alleviate endothelial dysfunction and decreases the microvascular complications of diabetes mellitus in the myocardium. SGLT2 inhibitors can reduce the level of electron donors, such as NADH, by reducing the level of glucose. [21]

The beneficial effects of SGLT2 Inhibitors are summarized in Figure 2.

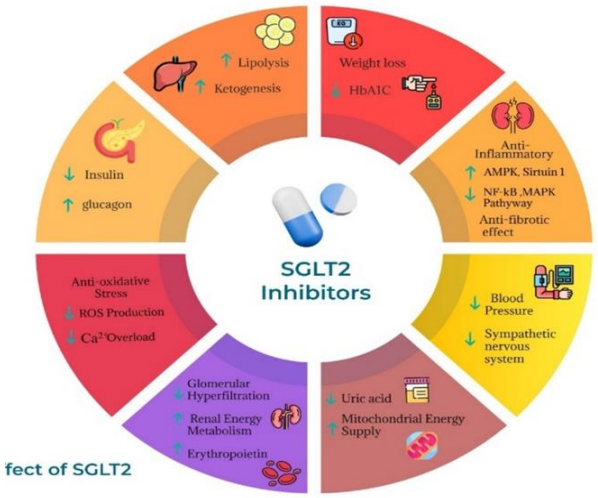

Figure 2: The beneficial effects of SGLT2 Inhibitors

Evidence of efficiency of SGLT2 Inhibitors in kidney diseases

The **CREDENCE trial** (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) was the first trial to examine the effect of an SGLT2 inhibitors on major renal outcomes in CKD.

The primary outcome was ESKD, defined as dialysis, transplantation, or sustained eGFR < 15 ml/min/1.73 m^2; doubling of serum creatinine; or death from renal or cardiovascular causes. Mean eGFR was 56.2 ml/min/1.73 m^2; median uACR was 927 mg/g; mean age of participants was 63 years; and 33.9% of patients were women. The trial was stopped early (median follow up: 2.62 years) when it became clear at a prespecified interim analysis that

participants receiving an SGLT2 inhibitor had benefits for the primary outcome (P < 0.01). At adjudication, the relative risk of the composite primary outcome (which includes doubling of serum creatinine, dialysis, kidney transplantation or death from kidney or CV causes) was 30% lower in the participants receiving canagliflozin (hazard ratio 0.70; 95% CI 0.59–0.82; P=0.00001). The key secondary kidney outcome (doubling of serum creatinine, end-stage kidney failure treated by dialysis or kidney transplantation, or death from kidney failure) was also reduced by 34% (hazard ratio 0.66; 95% CI 0.53–0.81; P < 0.001), and the relative risk of ESKD was lowered by 32% (hazard ratio 0.68; 95% CI 0.54–0.86; P=0.002) with canagliflozin treatment compared with placebo. The canagliflozin group also exhibited a reduced risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01) as well as hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001).

The renoprotective effects of canagliflozin were consistent across all trial subgroups, including patients with severely reduced eGFR. In addition, a post hoc analysis showed that canagliflozin treatment led to early sustained reductions in urinary albumin excretion, which were independently associated with improved long-term kidney and CV-related outcomes. [23,12, 24]

The **DAPA-CKD trial** evaluated the impact of dapagliflozin on renal outcomes and cardiovascular mortality in CKD patients. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, ESKD, or death from renal or cardiovascular causes.

The trial was also stopped early (median follow-up: 2.4 years) due to overwhelming efficacy. The primary endpoint occurred in 9.2% of participants in the dapagliflozin group compared to 14.5% in the placebo group (HR 0.61; 95% CI 0.51–0.72). The renal component of the primary composite outcome of ≥50% sustained decline in eGFR, ESKD, and renal death was reduced with dapagliflozin (HR 0.56; 95% CI, 0.45–0.68), which included reductions in each component of this renal composite. Dapagliflozin reduced geometric mean uACR by 29.3% (95% CI −33.1 to −25.2; P < 0.0001). a typical eGFR dip during the first 2 weeks was evident with dapagliflozin (−3.97 ± 0.15 vs. −0.82 ± 0.15 ml/min/1.73 m^2), which was followed by a smaller annual eGFR loss subsequently. (−1.67 ± 0.11 vs. −3.59 ± 0.11 ml/min/1.73 m^2). [23,12,25]

The **EMPA-KIDNEY trial** (Study of Heart and Kidney Protection with Empagliflozin), assessed the effect of once-daily empagliflozin treatment on the progression of kidney disease and CVD, and the safety profile. The study was carried out at 241 centers across eight different countries. The primary outcome was a composite of progression of kidney disease (defined as ESKD, a sustained decrease in eGFR to <10 ml per minute per 1.73 m^2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes.

This study was also stopped after a prespecified interim review identified unequivocal efficacy. At adjudication, treatment with empagliflozin was associated with a statistically significant reduction in the primary composite outcome of kidney disease progression or CV death (HR 0.72; 95% CI 0.64 to 0.82; P < 0.001). Reduction in all-cause hospitalization (HR 0.86; 95% CI 0.78, 0.95; P=0.003) was also reported. Finally, the decline rate in eGFR significantly slowed after treatment with empagliflozin, showing effectiveness across all subgroups, including those without severely elevated albuminuria. [12,26]

Another study, the **SCORED trial** was conducted to assess the safety of Sotagliflozin in 10,584 patients with T2DM (glycated hemoglobin level, ≥7%), CKD (eGFR, 25 to 60 ml per minute per 1.73 m^2 of body-surface area), and risks for CVD. The primary end point was modified during the trial to the composite of the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure. The trial ended early due to a loss of funding.

Nonetheless, after a median follow-up of 16 months, the primary composite outcome was reduced by Sotagliflozin compared with placebo (HR 0.74; 95% CI 0.63–0.88; P < 0.001). The MACE outcome (a composite of CV death, non-fatal myocardial infarction or stroke) was also reduced (HR 0.84; 95% CI 0.72–0.99), as was the composite outcome of death from CV causes or hospitalization for HF (HR 0.77; 95% CI 0.66–0.91). The composite kidney endpoint (a sustained decrease in the eGFR of ≥50%, dialysis, kidney transplantation or a sustained eGFR of 15ml/min/1.73m^2 was reduced by Sotagliflozin but failed to reach significance (HR 0.71; 95% CI 0.46–1.08) with a low number of events limiting the power of the trial. The decline in eGFR was halted by Sotagliflozin, while kidney function declined in the placebo group (Sotagliflozin 0.09 mL/min/1.73 m^2/year vs placebo −1.31 mL/min/1.73 m^2/year).[12,27]

Summaries of all the above trials has been mentioned in Table 2.

Recent Guideline – KDIGO

Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of CKD recently updated in 2024 heralds a new era in the care of people with kidney diseases.

These KDIGO 2024 guidelines are updated to the 2012 guideline, which was published in March 2024 in Supplement to Kidney International. The Executive Summary was published in the April 2024 issue of Kidney International.

Table 2: Summary of Clinical Trials [12,23,24,25]

Name of Study	**CREDENCE Trial**		**DAPA-CKD Trial**	
Drugs and comparator	**Drug**	**Comparator**	**Drug**	**Comparator**
	Canagliflozin 100 mg	Placebo	Dapagliflozin 10 mg	Placebo
Median follow-up, years	2.6		2.4	
Study design	Randomized, Double-blind, Placebo-controlled, Multicenter Clinical Trial		Randomized, Double-blind, Placebo-controlled, Multicenter Trial	
eGFR eligibility criteria, mL/min per 1.73 m^2	30-90		25–75	
Sample size	4401		4304	
Age, years	63.0 (9.2)		61.85 (12.1)	
Primary outcome	Composite of doubling of serum creatinine, ESKD, or death from kidney or cardiovascular causes: 0.70 (0.59 to 0.82)		Composite of sustained decline in eGFR of ≥50%, ESKD, or death from kidney or cardiovascular causes: 0.61 (0.51 to 0.72)	
Stage 4 CKD rate	4%(n=174)		14%(n=624)	
Primary composite outcome	HR 0.70 (0.59- 0.82) (95% CI), P Value 0.00001		HR 0.61 (0.51- 0.72) (95% CI), P Value <0.001	
Key Results	The risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years. These results indicate that canagliflozin may be an effective treatment option for renal and cardiovascular protection in patients with type 2 diabetes with chronic kidney disease.		Dapagliflozin significantly lowered the risk of CKD progression or death from renal/ cardiovascular diseases compared to placebo.	
Safety (*no./total no.)*	**1. Any adverse event**		**1. Discontinuation of regimen due to adverse event**	
	1784/2200	1860/2197	118/2149	123/2149
	2. Any serious adverse event		**2. Any serious adverse event**	
	737/2200	806/2197	633/2149	729/2149
	3. Serious adverse event related to trial drug		**3. Renal-related adverse event**	
	62/2200	42/2197	155/2149	188/2149
	4. Hyperkalemia		**4. Volume depletion**	
	151/2200	181/2197	127/2149	90/2149

Table 2: Summary of Clinical Trials [12,26,27]

Name of Study	**EMPA-KIDNEY Trial**		**SCORED Trial**	
Drugs and comparator	**Drug**	**Comparator**	**Drug**	**Comparator**
	Empagliflozin 10 mg	Placebo	Sotagliflozin 200 to 400 mg	Placebo
Median follow-up, years	2.0		1.33	
Study design	International Randomized Parallel Group Double-blind Placebo-controlled Clinical Trial		Phase 3, Randomized, Double-blind, Placebo-controlled Trial	
eGFR eligibility criteria, mL/min per 1.73 m^2	20-90		25-60	
Sample size	6609		10,584	
Age, years	63.9 (13.9)		69 (NA)	
Primary outcome	Composite of sustained decrease in eGFR to <10 mL/min/1.73 m^2 or by ≥40% from		Total number of deaths from cardiovascular causes, hospitalizations	

	baseline, ESKD, or death from kidney or cardiovascular causes: 0.72 (0.64 to 0.82)		for heart failure, and urgent visits for heart failure.	
Stage 4 CKD rate	34.2% (n=1131)		7.7%(n=813)	
Primary composite outcome	0.72 (0.64–0.82) P Value <0.001		0.74 (0.63-0.88) P value <0.001	
Key Results	Empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo		Sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo	
Safety no. (%)	**1. Serious urinary tract infection**		**1. Urinary tract infections**	
	52 (1.6)	54 (1.6)	610 (11.5)	585 (11.1)
	2. Serious hyperkalemia		**2. Diarrhea**	
	92 (2.8)	109 (3.3)	448 (8.5)	315 (6.0)
	3. Serious acute kidney injury		**3. Volume depletion**	
	107 (3.2)	135 (4.1)	278 (5.3)	213 (4.0)
	4. Bone fracture		**4. Bone fractures**	
	133 (4.0)	123 (3.7)	111 (2.1)	117 (2.2)
	5. Symptomatic dehydration		**5. Genital mycotic infections**	
	83 (2.5)	76 (2.3)	125 (2.4)	45 (0.9)

Abbreviations: eGFR- Estimated Glomerular Filtration Rate, ESKD: End-stage kidney disease, CKD: Chronic kidney disease, HR: Hazard Ratio, CI: Confidence Interval

The guidelines are organized into 6 chapters. A wide range of key topics is addressed in this guideline, including optimal CKD evaluation and classification, kidney disease risk assessment, management of complications, medication management and drug stewardship in CKD, and strategies for delivering patient-centered care across diverse clinical settings. Key highlights of the KDIGO CKD Guideline include guidance updates on the measurements of estimated glomerular filtration rate and albuminuria, utilization of CKD risk prediction equations, and personalized treatment recommendations for kidney and cardiovascular risk reductions customized to individual patient needs and preferences.

This comprehensive guidance document based on current best evidence indicates some exciting new approaches to management strategies and treatment options for people living with CKD, intending to improve symptom management, disease modification, and offer person-centered approaches, while also recognizing the heterogeneity of CKD. [28,29]

CONCLUSION

In conclusion, SGLT-2 inhibitors represent a significant advancement in the management of CKD, offering substantial cardiovascular and renal protective benefits across all CKD stages, regardless of diabetic status. Evidence from large, well-designed randomized controlled trials supports their efficacy, not only in achieving effective glycemic control, but also in slowing the CKD progression. SGLT2 inhibitors lower the risk of kidney failure and are now a cornerstone of CKD therapy due to their ability to activate TGF, lower the intraglomerular pressure and lowering of hyperfiltration-mediated kidney damage also promotes multiple other favorable physiologic pathways that contribute to kidney health. Additionally, these inhibitors suppress inflammation and fibrosis, improve oxidative stress, enhance EPO production, optimize mitochondrial energy supply, inhibit the SNS, and protect vascular endothelial cells. These mechanisms likely contribute to the observed renal protective effects of SGLT-2 inhibitors in advanced DKD.

In the future implications for SGLT2 inhibitors in renal health represent a comprehensive approach, providing new opportunities for prevention, intervention, and improved patient outcomes in the field of kidney-related diseases.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Chen X, Wang J, Lin Y, Yao K, Xie Y, Zhou T. Cardiovascular outcomes and safety of SGLT2 inhibitors in chronic kidney disease patients. Frontiers in Endocrinology. 2023 Nov 16;14:1236404. DOI:10.3389/fendo.2023.1236404; PMID:38047108.
2. Chen TK, Hoenig MP, Nitsch D, Grams ME. Advances in the management of chronic kidney disease. bmj. 2023 Dec 5;383. DOI:10.1136/bmj-2022-074216; PMID: 38052474.
3. Lv J, Guo L, Wang R, Chen J. Efficacy and safety of sodium-glucose cotransporter-2 inhibitors in nondiabetic patients with chronic kidney disease: a review of recent evidence. Kidney Diseases. 2023 Apr 11;9(5):326-41. DOI: 10.1159/000530395; PMID: 37901712.
4. Gajewska A, Wasiak J, Sapeda N, Młynarska E, Rysz J, Franczyk B. SGLT2 Inhibitors in Kidney Diseases—A Narrative Review. International Journal of Molecular Sciences. 2024 May 1;25(9):4959. DOI: 10.3390/ijms25094959; PMID: 38732178
5. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clinical journal of the American Society of Nephrology. 2017 Dec 1;12(12):2032-45. DOI: 10.2215/CJN.11491116; PMID: 28522654
6. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes research and clinical practice. 2019 Nov 1;157:107843. DOI: 10.1016/j.diabres.2019.107843; PMID: 31518657.
7. Johnson RJ, Wesseling C, Newman LS. Chronic kidney disease of unknown cause in agricultural communities. New England Journal of Medicine. 2019 May 9;380(19):1843-52. DOI: 10.1056/NEJMra1813869; PMID: 31067373.
8. Ng MS, Charu V, Johnson DW, O'Shaughnessy MM, Mallett AJ. National and international kidney failure registries: characteristics, commonalities, and contrasts. Kidney international. 2022 Jan 1;101(1):23-35. DOI: 10.1016/j.kint.2021.09.024; PMID: 34736973.
9. Varma PP. Prevalence of chronic kidney disease in India-Where are we heading? Indian journal of nephrology. 2015 May;25(3):133. PMID: 26060360
10. Jafar TH, Ramakrishnan C, John O, Tewari A, Cobb B, Legido-Quigley H, Sungwon Y, Jha V. Access to CKD Care in Rural Communities of India: a qualitative study exploring the barriers and potential facilitators. BMC nephrology. 2020 Dec;21:1-2. DOI: 10.1186/s12882-020-1702-6; PMID: 31996168.
11. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, Zeeuw DD, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney international. 2005 Jun 1;67(6):2089-100. DOI: 10.1111/j.1523-1755.2005.00365.x ; PMID: 15882252.
12. Thomas MC, Neuen BL, Twigg SM, Cooper ME, Badve SV. SGLT2 inhibitors for patients with type 2 diabetes and CKD: a narrative review. Endocrine Connections. 2023 Jul 31;12(8). DOI: 10.1530/EC-23-0005; PMID: 37159343.
13. Chapter 1: Definition and classification of CKD. *Kidney Int Suppl (2011)*. 2013;3(1):19-62. doi:10.1038/kisup.2012.64.
14. Brown E, Heerspink HJ, Cuthbertson DJ, Wilding JP. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. The Lancet. 2021 Jul 17;398(10296):262-76. DOI: 10.1016/S0140-6736(21)00536-5; PMID: 34216571.
15. Dai ZC, Chen JX, Zou R, Liang XB, Tang JX, Yao CW. Role and mechanisms of SGLT-2 inhibitors in the treatment of diabetic kidney disease. Frontiers in Immunology. 2023 Sep 21;14:1213473. DOI: 10.3389/fimmu.2023.1213473; PMID: 37809091.
16. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. Nature Reviews Nephrology. 2012 May;8(5):293-300. DOI: 10.1038/nrneph.2012.19; PMID: 22349487.
17. Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose-lowering effect. Cardiovascular Diabetology. 2020 Dec;19:1-0. DOI: 10.1186/s12933-020-01071-y; PMID: 32590982.
18. Sen T, Heerspink HJ. A kidney perspective on the mechanism of action of sodium glucose co-transporter 2 inhibitors. Cell metabolism. 2021 Apr 6;33(4):732-9. DOI: 10.1016/j.cmet.2021.02.016; PMID: 33691091.
19. Speedtsberg ES, Tepel M. Narrative review investigating the nephroprotective mechanisms of sodium glucose cotransporter type 2 inhibitors in diabetic and nondiabetic patients with chronic kidney disease. Frontiers in Endocrinology. 2023 Dec 20;14:1281107. DOI: 10.3389/fendo.2023.1281107; PMID: 38174341.
20. Refardt J, Imber C, Sailer CO, Jeanloz N, Potasso L, Kutz A, Widmer A, Urwyler SA, Ebrahimi F, Vogt DR, Winzeler B, Christ-Crain M. A randomized trial of empagliflozin to increase plasma sodium levels in patients with the syndrome of inappropriate antidiuresis. Journal of the American society of nephrology. 2020 Mar 1;31(3):615-24.

    DOI: 10.1681/ASN.2019090944; PMID: 32019783.
21. Schönberger E, Mihaljević V, Steiner K, Šarić S, Kurevija T, Majnarić LT, Bilić Ćurčić I, Canecki-Varžić S. Immunomodulatory effects of SGLT2 inhibitors—targeting inflammation and oxidative stress in aging. International journal of environmental research and public health. 2023 Aug 29;20(17):6671. DOI: 10.3390/ijerph20176671; PMID: 37681811.
22. Nabrdalik-Leśniak D, Nabrdalik K, Irlik K, Janota O, Kwiendacz H, Szromek-Białek P, Maziarz M, Stompór T, Gumprecht J, Lip GY. The influence of SGLT2 inhibitors on oxidative stress in heart failure and chronic kidney disease in patients with type 2 diabetes. Endokrynologia Polska. 2023;74(4):349-62. DOI: 10.5603/EP.a2023.0039 ; PMID: 37431873.
23. Mark PB, Sarafidis P, Ekart R, Ferro CJ, Balafa O, Fernandez-Fernandez B, Herrington WG, Rossignol P, Del Vecchio L, Valdivielso JM, Mallamaci F, Ortiz A, Nistor I, Cozzolino M. SGLT2i for evidence-based cardiorenal protection in diabetic and non-diabetic chronic kidney disease: a comprehensive review by EURECA-m and ERBP working groups of ERA.

Nephrology Dialysis Transplantation. 2023 Nov;38(11):2444-55. DOI: 10.1093/ndt/gfad112; PMID: 37230946.

24. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, Zeeuw Dd, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, , Mahaffey KW. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. New England journal of medicine. 2019 Jun 13;380(24):2295-306. DOI: 10.1056/NEJMoa1811744 ; PMID: 30990260.

25. Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JF, McMurray JJ, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC. Dapagliflozin in patients with chronic kidney disease. New England Journal of Medicine. 2020 Oct 8;383(15):1436-46. DOI:10.1056/NEJMoa2024816 ; PMID: 32970396.

26. EMPA-Kidney Collaborative Group. Empagliflozin in patients with chronic kidney disease. New England Journal of Medicine. 2023 Jan 12;388(2):117-27. DOI: 10.1056/NEJMoa2204233 ; PMID: 36331190.

27. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Inzucchi SE, Kosiborod MN, Cherney DZ, Dwyer JP, Scirica BM, Bailey CJ, Díaz R, Ray KK, Udell JA, Lopes RD, Lapuerta P, Steg PG. Sotagliflozin in patients with diabetes and chronic kidney disease. New England Journal of Medicine. 2021 Jan 14;384(2):129-39.

DOI: 10.1056/NEJMoa2030186; PMID: 33200891.

28. Levin A, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK, Herrington WG, Hill G, Inker LA, Kazancıoğlu R, Lamb E. Executive summary of the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease: known knowns and known unknowns. Kidney international. 2024 Apr 1;105(4):684-701.

DOI: 10.1016/j.kint.2023.10.016; PMID: 38519239

29. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease Volume 105, Issue 4S, April 2024.