International Journal of Medical Sciences And Clinical Research

VOLUME Vol.05 Issue10 2025
PAGE NO. 17-21
DOI 10.37547/ijmscr/Volume05Issue10-03

The Role Of SGLT-2 Inhibitors In Cardio-Renal Protection And The Management Of Type 2 Diabetes Mellitus

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Received: 12 August 2025; **Accepted:** 08 September 2025; **Published:** 10 October 2025

Abstract: In recent years, sodium-glucose cotransporter type 2 (SGLT-2) inhibitors, a class of medications originally developed for managing type 2 diabetes mellitus (T2DM), have demonstrated significant benefits beyond glycemic control. These drugs have shown protective effects on both renal and cardiovascular systems, even in patients without diabetes. Researchers suggests that metabolic reprogramming plays a critical role in the progression of chronic heart failure (CHF) and chronic kidney disease (CKD). This reprogramming is associated with impaired cardiac energy metabolism due to a mismatch between glucose uptake and its oxidation, leading to the accumulation of glucose-6-phosphate (G6P), glycogen deposition, and activation of the pentose phosphate pathway. The consequence is mitochondrial dysfunction, oxidative stress and decreased fatty acid oxidation.

Similar mechanisms occur in the proximal tubules of the kidneys in CKD, resulting in tubular injury, albuminuria, and interstitial fibrosis. By inhibiting glucose and sodium reabsorption in the proximal tubules, SGLT-2 inhibitors increase glucosuria, induce mild osmotic diuresis and promote natriuresis. These processes yield anti-inflammatory effects, reduce oxidative stress and apoptosis, and further stimulate autophagy.

The additional effects include lowered blood pressure, decreased myocardial workload and reduced sympathetic nervous system activity. Additionally, SGLT-2 inhibitors improve tubuloglomerular feedback, reduce glomerular hyperfiltration and enhance erythropoiesis by mimicking systemic hypoxia. These mechanisms form the basis of the cardio- and nephroprotective effects of SGLT-2 inhibitors.

Keywords: Heart failure, chronic kidney disease, metabolic syndrome, SGLT-2 inhibitor, organoprotection, cardioprotection.

Introduction: Type 2 diabetes mellitus (T2DM) is a widespread metabolic disease, marked by insulin resistance and impaired insulin production, resulting in persistent hyperglycemia. Over time, chronic elevated blood glucose can cause both microvascular (e.g., nephropathy, retinopathy, neuropathy) and macrovascular complications, particularly cardiovascular diseases. Therefore, the management of T2DM encompasses not only glycemic control but also prevention of these comorbid conditions.

Chronic kidney disease (CKD) is a common comorbidity in patients with heart failure and is also pathogenetically linked to its progression [1]. Studies show that individuals with CKD have a threefold increased risk of developing CHF compared to those with normal kidney function, and CKD progression accelerates as renal function declines. Recommended therapies for patients with symptomatic heart failure with reduced ejection fraction (HFrEF) typically include ACE inhibitors or angiotensin II receptor blockers (ARBs), or the combination of sacubitril and valsartan, along with beta-blockers, aldosterone antagonists, and SGLT-2 inhibitors as part of comprehensive therapy [2]. However, the exact mechanisms underlying the cardio-

and nephroprotective effects of SGLT-2 inhibitors remain under investigation [3].

Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors: Mechanism and Agents

SGLT-2 is a high-capacity sodium-glucose cotransporter located in the proximal tubules of the kidneys, responsible for reabsorbing over 91% of filtered glucose. Once reabsorbed, glucose is transported across the basolateral membrane via GLUT proteins into the bloodstream [4].

The multifaceted mechanisms by which SGLT-2 inhibitors exert cardio-renal protection have been increasingly recognized. These agents promote adenosine-mediated dilation of efferent arterioles even in patients with well-controlled renin-angiotensin system activity. They reduce sodium and glucose reabsorption in the proximal tubules, leading to glucosuria, modest osmotic diuresis, and natriuresis. As a result, blood pressure drops, cardiac preload and afterload decrease, and sympathetic nervous system activity is dampened. SGLT-2 inhibitors also restore tubuloglomerular feedback and reduce glomerular hyperfiltration, improving renal hemodynamics. Additionally, these drugs mimic a hypoxic state, stimulate erythropoiesis, exert anti-inflammatory effects, lower oxidative stress and apoptosis, and enhance autophagy. Their use is also associated with improved cardiac energy metabolism and reduced pathological remodeling [5].

The primary SGLT-2 inhibitors include:

- **Empagliflozin** (Jardiance, Synjardy)- The initial dose is 10 mg once daily; the dose may be increased to 25 mg daily to achieve the targeted glycemic goal. (Not recommended if eGFR < 30 mL/min/1.73 m² to improve glycemic control)
- **Dapagliflozin** (Farxiga, Xigduo XR)- initial dose is 5 mg once daily; increase to 10 mg once daily to achieve the targeted glycemic goal (Not recommended if eGFR< 45 mL/min/1.73 m² to improve glycemic control)
- **Canagliflozin** (Invokana, Invokamet)- the initial dose is 100 mg once daily and may be increased to 300 mg daily. (Not recommended if eGFR< 30 mL/min/1.73 m² to improve glycemic control)
- **Ertugliflozin** (Steglatro)- the initial dose is 5 mg once daily, which is increased to 15 mg daily to achieve the glycemic goal. (Not recommended if eGFR<45 mL/min/1.73 m² to improve glycemic control.)

These agents effectively improve glycemic control, support weight reduction, and help lower blood pressure [6].

Cardiovascular Benefits

SGLT-2 inhibitors have been shown to significantly reduce cardiovascular risk in patients with T2DM. A network meta-analysis of randomized controlled trials (RCTs) involving nearly 4304 patients with HFrEF revealed that dapagliflozin significantly lowered cardiovascular and all-cause mortality compared to placebo. Both dapagliflozin and empagliflozin reduced hospital readmissions for heart failure, although empagliflozin was linked to a slightly higher incidence of genital infections [7].

From a pool of 3,969 database records, 15 randomized trials involving 20,241 patients were selected; among them, 10,594 (52.3%) received SGLT2 inhibitors. Treatment with SGLT2 inhibitors was associated with a significant reduction in all-cause mortality (HR 0.86; 95% CI 0.79–0.94; p = 0.0007; I^2 = 0%) and cardiovascular mortality (HR 0.86; 95% CI 0.78–0.96; p = 0.006; I^2 = 0%) compared to placebo. Additionally, the combined outcome of cardiovascular mortality, heart failure hospitalizations, or urgent heart failure visits was significantly lowered by SGLT2 inhibitors across various subgroups, including males and females, those younger and older than 65, Black and White patients, individuals with estimated glomerular filtration rates (eGFR) below or above 60, patients classified as NYHA class II or NYHA class III and above, as well as those with heart failure with preserved ejection fraction[8].

Normally, in cardiomyocytes, over 95% of ATP is generated via mitochondrial oxidative phosphorylation, with glycolysis contributing around 5%. The primary energy source is beta-oxidation of fatty acids (40–60%), followed by carbohydrate metabolism (20–40%), and moderate use of ketone bodies or branched-chain amino acids (10–15%). Key metabolic pathways are regulated by nutrient-sensing molecules, including SIRT1, a NAD^+-dependent deacetylase, which also maintains mitochondrial integrity through downstream targets [9].

AMPK (AMP-activated protein kinase) is another crucial energy sensor that, under conditions of low energy, shifts metabolism toward catabolism and inhibits anabolic processes, including lipid and cholesterol synthesis and gluconeogenesis. AMPK activation also suppresses mTORC1, a central regulator of cell growth and proliferation [10].

Renal Protective Effects

SGLT-2 inhibitors have demonstrated clear benefits in protecting renal function, particularly in patients with diabetic kidney disease. The CREDENCE trial, focused on canagliflozin, showed a reduced risk of kidney disease progression and cardiovascular events in patients with T2DM and CKD. A total of 4,401 patients were randomized and followed for a median of 2.62

years. The risk of the primary outcome was reduced by 30% in the canagliflozin group compared to placebo, with event rates of 43.2 versus 61.2 per 1,000 patient-years (hazard ratio [HR] 0.70; 95% confidence interval [CI], 0.59 to 0.82; P = 0.00001). The risk of a kidney-specific composite outcome—including end-stage kidney disease, doubling of serum creatinine, or death due to renal causes—was 34% lower in the canagliflozin group (HR 0.66; 95% CI, 0.53 to 0.81; P < 0.001). Additionally, the risk of developing end-stage kidney disease alone decreased by 32% (HR 0.68; 95% CI, 0.54 to 0.86; P = 0.002). Patients treated with canagliflozin also experienced a lower risk of cardiovascular death, myocardial infarction, or stroke (HR 0.80; 95% CI, 0.67 to 0.95; P = 0.01), as well as fewer hospitalizations due to heart failure (HR 0.61; 95% CI, 0.47 to 0.80; P < 0.001). No significant differences were observed between groups in rates of amputation or fractures [11].

Similarly, the DAPA-CKD trial reported that dapagliflozin slowed kidney failure and reduced cardiovascular mortality in CKD patients, regardless of diabetic status. The independent data monitoring committee recommended early termination of the trial due to demonstrated efficacy. Over a median follow-up period of 2.4 years, the primary outcome occurred in 9.2% of participants receiving dapagliflozin (197 of 2,152) compared to 14.5% in the placebo group (312 of 2,152), yielding a hazard ratio (HR) of 0.61 (95% confidence interval [CI], 0.51 to 0.72; P < 0.001). The number needed to treat to prevent one primary outcome event was 19 (95% CI, 15 to 27). Regarding the composite outcome of sustained decline in estimated glomerular filtration rate (eGFR) of at least 50%, end-stage kidney disease, or death from renal causes, the HR was 0.56 (95% CI, 0.45 to 0.68; P < 0.001). For the composite endpoint of cardiovascular death or hospitalization for heart failure, the HR was 0.71 (95% CI, 0.55 to 0.92; P = 0.009). All-cause mortality occurred in 4.7% of the dapagliflozin group compared to 6.8% of the placebo group (HR 0.69; 95% CI, 0.53 to 0.88; P = 0.004). The beneficial effects of dapagliflozin were consistent among participants both with and without type 2 diabetes. The safety profile observed was consistent with prior reports [12].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as empagliflozin, dapagliflozin, and canagliflozin, are widely approved treatments for lowering blood glucose. Their distinct mechanism of promoting glucose excretion through urine also leads to weight loss. Additionally, their osmotic diuretic and natriuretic effects cause a reduction in plasma volume, contributing to decreases in systolic and diastolic blood pressure by approximately 4 to 6 mm Hg and 1 to 2 mm Hg, respectively. These effects likely play a role in the cardiovascular and renal benefits observed with these drugs. SGLT2 inhibitors also cause an immediate, dose-dependent drop in estimated glomerular filtration rate (eGFR) by about 5 mL/min/1.73 m² and reduce albuminuria by 30% to 40%. These changes reflect findings from preclinical studies, which suggest that increased sodium and chloride delivery to the macula densa triggers renal tubuloglomerular feedback, resulting in afferent arteriole vasoconstriction. In patients with chronic kidney disease (CKD) and an eGFR below 60 mL/min/1.73 m², the glucose-lowering and weight loss effects of SGLT2 inhibitors are diminished due to reduced filtration. However, the blood pressure-lowering, eGFR modulation, and albuminuria-reducing effects remain intact and may even be more pronounced in CKD. Regarding long-term outcomes, the EMPA-REG OUTCOME trial, which studied patients with type 2 diabetes and established cardiovascular disease, found that empagliflozin led to a 14% reduction in the primary composite endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke), along with over 30% reductions in cardiovascular mortality, overall mortality, and hospitalizations for heart failure—despite only minimal differences in HbA1c between the empagliflozin and placebo groups[13].

Cardiorenal Protection via Metabolic changing

A particularly notable finding is that SGLT-2 inhibitors trigger a transcriptional response akin to nutrient deprivation, activating the AMPK/SIRT1/PGC-1α signaling cascade while simultaneously inhibiting mTOR. This leads to increased fatty acid oxidation, gluconeogenesis, and ketogenesis—essentially simulating a fasting-like metabolic shift. Importantly, activation of the AMPK/SIRT1/PGC-1α axis improves mitochondrial performance, decreasing oxidative stress, endoplasmic reticulum stress, inflammation, and apoptosis [14].

These changes also promote autophagy in cardiac and renal cells, enabling recycling of intracellular components, restoring ATP production, and further reducing oxidative and ER stress [15].

In the EMPA-REG OUTCOME study, it was proposed that increases in hemoglobin and hematocrit following SGLT-2 inhibitor therapy accounted for approximately half of the observed cardiovascular protection, likely due to enhanced erythropoiesis. Recent meta-analyses also indicate that these drugs alleviate iron deficiency and anemia in patients with CHF and CKD, potentially through anti-inflammatory mechanisms (e.g., reduced IL-6) and increased autophagy via SIRT1 activation. Modulation of iron homeostasis may also partly explain

the cardiovascular and renal outcome improvements [16,17].

Hypoglycemic Effects

A total of 33 randomized controlled trials (RCTs) involving 8,496 participants met the inclusion criteria for this meta-analysis. The findings demonstrated that, compared to control groups, treatment with SGLT2 inhibitors significantly improved glycated hemoglobin (HbA1c) levels in patients, with a weighted mean difference (WMD) of −0.73% (95% confidence interval \[CI], −0.84 to −0.61). Additionally, the proportion of patients achieving HbA1c levels below 7% was significantly higher in the SGLT2 inhibitor group (risk ratio \[RR] 2.33; 95% CI, 1.74 to 3.12). The use of these agents also resulted in reductions in fasting plasma glucose (WMD −28.47 mg/dL; 95% CI, −32.86 to −24.08) and postprandial glucose levels (WMD −52.32 mg/dL; 95% CI, −67.67 to −39.96), as well as a decrease in body weight (WMD −1.73 kg; 95% CI, −2.28 to −1.17). Importantly, SGLT2 inhibitors were not associated with an increased risk of hypoglycemia (RR 1.27; 95% CI, 0.89 to 1.82) or urinary tract infections (RR 0.93; 95% CI, 0.68 to 1.27). However, there was a statistically significant increased risk of genital tract infections (GTIs) with SGLT2 inhibitor use (RR 1.73; 95% CI, 1.02 to 2.96). Stratified analyses indicated that patients presenting with higher baseline HbA1c levels experienced greater reductions in HbA1c following treatment, while those with elevated body weight or longer duration of diabetes exhibited a higher risk of developing GTIs [18].

Adverse Effects

Although generally well tolerated, SGLT-2 inhibitors are associated with several side effects, including:

- **Genital fungal infections**: Elevated glucose levels in urine promote fungal growth[18].
- **Urinary tract infections**: Glucosuria may predispose to bacterial infections[18].
- **Volume depletion**: Due to osmotic diuresis, especially in patients with low blood pressure or impaired renal function.
- **Euglycemic diabetic ketoacidosis (DKA)**: Though rare, it can occur, particularly in insulin-deficient states or during acute illness[19].

Meta-analyses of randomized controlled trials (RCTs) found no significant difference in the occurrence of urinary tract infections (UTIs) between patients treated with SGLT2 inhibitors and those in the control groups (2,526 out of 29,086 vs. 1,278 out of 14,940; risk ratio [RR] 1.05, 95% confidence interval [CI] 0.98 to 1.12; moderate-quality evidence). However, the analyses indicated a notably higher risk of genital infections among those receiving SGLT2 inhibitors compared to controls (1,521 out of 24,017 vs. 216 out of 12,552; RR 3.30, 95% CI 2.74 to 3.99; moderate-quality evidence). Subgroup analyses based on follow-up duration (interaction p = 0.005), type of control treatment (interaction p = 0.04), and specific SGLT2 inhibitors used (interaction p = 0.03) also revealed significant differences in genital infection rates. Future large-scale trials are expected to provide further clarity on UTIs, and additional research is necessary to compare the infection risks associated with individual SGLT2 inhibitors [20].

CONCLUSION

SGLT-2 inhibitors—such as empagliflozin, dapagliflozin, and canagliflozin—represent a significant advancement in T2DM treatment. Beyond blood sugar regulation, these agents provide robust cardiovascular and renal protection, making them essential in comprehensive diabetes management. However, careful monitoring is necessary due to potential side effects. Ongoing research is needed to clarify their long-term safety and broaden their use across various patient populations.

The pleiotropic cardio- and nephroprotective effects of SGLT-2 inhibitors form the basis for exploring their mechanisms beyond glucose lowering. Recent insights into how these drugs alter metabolism provide a new perspective on their organ-protective benefits. Notably, SGLT-2 inhibitors appear to induce a fasting-like metabolic state, shifting energy use from glucose to lipids and ketones. This metabolic reprogramming activates nutrient deprivation pathways and helps sustain cellular energy balance, offering a potential explanation for the cardiorenal benefits of this drug class.

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