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MECHANISMS AND OUTCOMES OF SGLT2 INHIBITORS IN CARDIO RENAL PROTECTION: A NARRATIVE REVIEW

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Abstract:

T2DM is a complex metabolic disorder that increases the risk of death in patients with CVD and kidney diseases. Initially, lifestyle modifications and metformin therapy are prescribed. For patients contraindicated for metformin, sulfonylureas are prescribed, but still control was lost. Hence, a new class of drugs is introduced, including SGLT2 inhibitors. Phlorizin is the main drug, and other drugs are derived from phlorizin, including dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, sotagliflozin, etc. SGLT2 inhibitors block SGLT2 receptors present in PCT and reduce glucose and sodium reabsorption, finally leading to a reduction of blood glucose levels. SGLT2 inhibitors result in natriuresis & glucosuria that reduces BP and albuminuria. SGLT2 inhibitors also reduce inflammation & fibrosis, SNS & RAAS activity and serum uric acid, adipokine production, arterial contractility and stiffness and also promote renal haemodynamic action. These agents reduce heart failure hospitalisation and MACE, slow the progression of CKD, and preserve eGFR, as explained by main trials including EMPA-REG, CANVAS, DECLARE-TIMI, DAPA-HF, CREDENCE, DAPA-CKD, etc. Genital mycotic infections, diabetic ketoacidosis, urinary tract infections, polyuria, nausea and constipation are common ADRs of SGLT2 inhibitors. Guidelines like KDIGO, ESC, and ADA/EASD explain the prescribing patterns of SGLT2 inhibitors. The use of SGLT2 inhibitors promotes benefits in both CKD and CVD patients, but patients with severe decline in eGFR need further study.

KEY WORDS

Type2 Diabetes Mellitus; SGLT2 Inhibitors; Diabetic kidney disease; Cardiovascular disease .

INTRODUCTION

Type 2 diabetes mellitus is a complex metabolic disorder involving different organs characterised by insulin resistance in skeletal muscle and liver (1). T2DM is a very common condition that leads to serious health problems and increased risk of death in patients with cardiovascular and kidney diseases. T2DM is the main cause of CKD (2). CKD and CVD are the complications of diabetes (3). A more disturbing miracle occurring now is the combination of cardiac and renal dysfunction known as cardio-renal disease (4). Diabetes-related issues that affect small blood vessels, like diabetic ketoacidosis, are a major public health concern. In fact, almost 40% of people with T2DM develop DKD. DKD is one of the main causes of CKD and ESKD. Also, much of the increased risk of death seen in people with diabetes is likely because of DKD (5). CKD is defined by functional declines in GFR <60 ml/min/1.73 m^2 that persist beyond 3 months, regardless of the underpinning cause. The frequency of CKD is steadily rising, and it has become one of the leading causes of morbidity & mortality. CKD affects more than 10% of grown-ups worldwide (6). CKD affects 700 million people. According to WHO, CKD accounts for 12.2 deaths among 100,000 people, and the death rate from CKD is increasing (7). T2DM causes a 2- to 4-fold increase in the risk of CVD (8). 50% of mortality in people with T2DM is caused by CVD, including IHD, CAD, HF, stroke, and peripheral artery disease; this percentage increases when CKD is present (3). Guidelines for treatment operation include lifestyle modifications, followed by metformin monotherapy as a first-line pharmacological treatment in most cases. Still, for cases where metformin is contraindicated, sulfonylureas can be used as an indispensable first-line pharmacological intervention. Still, the progressive nature of T2DM means that ultimately complaint control will be lost and treatment intensification or fresh agents will be needed. The class of treatment certified for use in combination with SUs within the EU (European Union) includes DPP-4 inhibitors, GLP-1 analogues, thiazolidinediones, and a new class of agent, SGLT2 inhibitors (9). Phlorizin is the first drug in the SGLT2 inhibitor class, isolated from the root bark of an apple tree in 1835, and it exhibits a glycosuric effect (1). Several gliflozins are derived later from phlorizin, including dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, ipragliflozin, sotagliflozin, remogliflozin etabonate, luseogliflozin, and tofogliflozin (10). Since the preface of the first SGLT2 asset in 2012, the class has grown to include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin in Europe and America, with fresh members of the class getting established in other regions (11). SGLT2 inhibitors are a fairly new class of oral medications, first developed as anti-diabetics for T2DM, and they have clear benefits in lowering blood glucose (6). SGLT2 inhibitor therapy is advised for pts with T2DM who are at high risk of CVD in order to lower cardiovascular and renal events as well as hospitalisation for HF, according to the most recent 2019 European Society of Cardiology guidelines created in partnership with the European Association for the Study of Diabetes (12).

The objective of this study is to elaborate on the mechanisms of SGLT2 inhibitors in cardiorenal protection, to evaluate the outcomes of prescribing SGLT2 inhibitors in cardiac- and renal-impaired patients, and to describe the safety and adverse drug reactions of SGLT2 inhibitors.

OVERVIEW

SGLT2 inhibitors show their action by competitively binding to SGLT2 receptors present in the first and second segments of the PCT reversibly. This blocks glucose reabsorption from PCT to blood, thereby reducing blood glucose levels, and this effect is minimal, so the risk of hypoglycaemia is less with SGLT2 inhibitors (11). SGLT2 shows glucose lowering only in hyperglycaemic conditions but, unlike other hypoglycemic agents, is not associated with hypoglycemia. A 0.79% reduction in HbA1C is seen in normal renal subjects, whereas in patients with GFR 30-59 ml/min/1.73 m² a 0.3-0.4% reduction in HbA1C (10). SGLT2 inhibitors cause glucosuria and reduce glucotoxicity, which leads to improved insulin sensitivity in skeletal muscle and adipose tissue, thus resulting in enhanced beta cell function. These agents result in hypoglycaemia when used with SUs or insulin therapy (13). The non-glycaemic effects of SGLT2 inhibitors are BP lowering, renal haemodynamic modulation, decreased albuminuria, and uric acid lowering (14). The pharmacodynamic effect of SGLT2 inhibitors is inducing glycosuria by decreasing both the maximum renal glucose reabsorptive capacity (TmG) and the threshold for glucose resorption. The pharmacokinetics of SGLT2 inhibitors are that these are given orally and mostly eliminated through the renal and faecal routes (1). SGLT2 inhibitors confer cardiovascular and renal protection that goes beyond what's anticipated by enhancement in glycaemic control (15).

MECHANISMS OF CARDIORENAL PROTECTION:

1.RENAL PROTECTIVE MECHANISMS:

a. Modulation of tubuloglomerular feedback and reduction in albuminuria:

The glucosuric effect of SGLT2 inhibitors is well known; simultaneously, sodium gets excreted with glucose. The increased natriuresis is sensed by Na+-K+-2Cl- cotransporters of macula densa cells (16). Macula densa cells are present at the top of the ascending limb. As a result, ATP is generated from the membrane of macula densa cells due to osmotic gradient-mediated swelling of cells and leakage of ATP from the membrane. This ATP is converted to adenosine by the enzyme nucleotidase. This adenosine binds to A1 receptors of afferent vascular smooth muscle and alters calcium fluxes, which results in vasoconstriction. The adenosine in turn inhibits secretion of renin from JG cells, which causes efferent arteriole vasoconstriction (11). The entire process results in afferent arteriole vasoconstriction and decreased intraglomerular pressure, hyperfiltration and albuminuria. Finally reduces progression of CKD. This reduction in hyperfiltration causes an initial decrease in eGFR, i.e., 3-6 ml/min/1.73 m² (16).

b. Reduction in renal inflammation and fibrosis:

SGLT2 inhibitors inhibit mTORC1, which causes sodium and glucose reabsorption. Hence, oxygen reaches the DCT and also prevents production of hypoxia-inducible factor (HIF-1alpha) but promotes HIF-2alpha production and protects tubular function. Gluconeogenesis, fatty acid oxidation, and ketogenesis are activated in a starvation signalling pathway to compensate for calories lost through glucosuria. Additionally, SGLT2 inhibitors upregulate adenosine monophosphate-activated protein kinase (AMPK) and sirtuin-1 metabolism and stress response regulator. This increases FGF21/PGC-1 alpha activity, leads to restoration of impaired autophagic flux, reduces inflammation, and decreases cellular stress. The produced HIF-2alpha resulted in an increase in erythropoietin production (17). SGLT2 inhibitors reduce inflammatory and fibrotic factors like nuclear factor-kB, IL-6, TNFR1, matrix metalloproteinase 7, fibronectin-1 and monocyte chemoattractant protein 1 (MCP-1) (11).

c. Reducing SNS and RAAS activity:

Generally in CKD and hypertensive patients, the sympathetic nervous system is elevated, leading to the release of norepinephrine that activates the RAAS system and finally causes the release of renin. Renin in turn increases angiotensin II; this results in the release of aldosterone. Finally leads to constriction of the efferent arteriole. Simultaneously, IGP rises, and plasma filtration increases. Hence, plasma proteins present in the glomerulus raise oncotic pressure; this draws water and sodium into the capillary. Sodium and water retention occur, resulting in high blood pressure. SGLT2 inhibitors cause SNA suppression by preventing production of norepinephrine and tyrosine hydroxylase, thereby reducing sodium and fluid retention and finally decreasing blood pressure (6).

d. Uric acid excretion:

SGLT2 inhibitors eliminate renal uric acid due to competition of extra glucose for the urate transporter GLUT9b, resulting in reduced nephrolithiasis (11). In heart failure xanthine oxidase activity is increased, which produces uric acid through purine metabolism. Hence, SGLT2 inhibitors are prescribed in heart failure patients. SGLT2 inhibitors have been shown to reduce UA in pts with diabetes and without diabetes, although the exact mechanism is not known (18).

e. Tubular oxygenation and erythropoiesis:

Decrease in glucose and sodium reabsorption reduces stress on tubular cells. SGLT2 inhibitors cause suppression of hepcidin, a peptide that inhibits erythropoiesis. Erythropoietin levels rise by SGLT2 inhibition, resulting in erythropoiesis. Finally, it increases haematocrit value and oxygen delivery to distal parts. These effects are seen both in normal and reduced kidney function. Among CKD, the risk of anaemia is also reduced (10).

2. CARDIAC MECHANISMS

a. osmotic diuresis and natriuresis:

As detailed above, SGLT2 inhibitors block SGLT2 receptors in the proximal convoluted tubule, leading to a reduction in glucose and sodium reabsorption. This finally results in osmotic diuresis and natriuresis. Simultaneously excess fluid is also eliminated, resulting in volume depletion, which ultimately lowers blood pressure and vascular resistance. In patients with Type 2 DM, SGLT2 inhibitors reduce systolic BP by 5 mmHg and diastolic BP by 2 mmHg (14).

b. Reduce fibrosis and adipokine production:

Cardiac fibrosis involves deposition of extracellular matrix proteins from cardiac fibroblasts, resulting in impeded ventricular compliance that elevates heart failure risk. Dapagliflozin activates M2 macrophages and inhibits myofibroblast differentiation.

Deposition of fat on the epicardial layer and pericardium leads to altered paracrine regulation of adipokines in the myocardium. SGLT2 inhibitors reduce levels of adipocyte leptin, which regulates sodium and cardiac inflammation and fibrosis, along with the production of the anti-inflammatory adipokine adiponectin (19).

c. Reducing arterial contractility & arterial stiffness

Increased SNS & RAAS lead to vasoconstriction, and endothelial dysfunction and prostaglandin deficiency lead to vasodilation. Dapagliflozin induces vasorelaxation by inhibiting smooth muscle Kv7 ion channels associated with reduced arterial contractility and arterial stiffness (6).

d. Haemodynamic function:

T2DM leads to glucose reabsorption, which reduces oxygen supply to distal parts, leading to hypoxaemia, resulting in afferent renal neural activity. This causes less baroreflex response, leading to fluid retention and an increase in HR & vasoconstriction, resulting in an increase in afterload and preload and a shortening of diastole. This results in cardiomyopathy, CHD, and finally HF. SGLT2 inhibitors reduce this by glucose reabsorption (20).

e. Weight lowering:

SGLT2 inhibitors result in glycosuria, which leads to depletion of glucose in blood. Hence, calories are decreased, and the starvation signalling pathway is activated. Loss of calories results in decreasing weight. However, weight lowering accounts for 40% of BP lowering (6). SGLT2 inhibitors account for weight loss due to reduction in visceral fat rather than urinary glucose excretion (21).

f. Tubular energetics and Na+-H+ exchange:

In T2DM, excess glucose reabsorption in PCT causes a shift from fatty acid oxidation to glycolysis, resulting in accumulation of intracellular lipid, leading to cellular damage and fibrosis. SGLT2 inhibitors cause glycosuria, which results in fatty acid oxidation and reduces lipotoxic cell damage. SGLT2 inhibitors suppress activity of sodium hydrogen exchanger-3 (NHE-3); this influences renal sodium handling, acid-base balance and metabolic activities (11).

CARDIO-RENAL PROTECTIVE EFFECTS OF SGLT2 INHIBITORS—CLINICAL EVIDENCE AND MAJOR TRIALS

1. Cardiovascular protective effects

a. Reduction in Heart Failure Hospitalisation

SGLT2 inhibitors significantly reduce heart failure (HF) hospitalisation by 27–35% in patients with HFrEF, HFpEF, and type 2 diabetes at high cardiovascular risk. Major trials demonstrated consistent benefits: EMPA-REG OUTCOME (↓35%), CANVAS (↓33%), DECLARE-TIMI 58 (↓27%), DAPA-HF (↓30%), EMPEROR-Reduced (↓31%), VERTIS CV, EMPEROR-PRESERVED, SCORED, and SOLOIST-WHF (Sotagliflozin), with many showing reduced cardiovascular death.

b. Reduction in Major Adverse Cardiovascular Events (MACE)

SGLT2 inhibitors also reduce MACE, including CV death, nonfatal myocardial infarction, and stroke. The EMPA-REG OUTCOME and CANVAS trials reported a 14% reduction in MACE, highlighting their protective role in patients with established atherosclerotic cardiovascular disease.

Table 1. Outcomes of trials explaining cardiovascular protective effects

TRIAL	DRUG	POPULATION	KEY OUTCOMES
EMPA-REG Outcome (22)	*Empaglifozin*	T2DM,high CV risk	Reduced HF hospitalization 35%, reduced CV death 38%, reduced MACE 14%
Canvas program(23)	*Canaglifozin*	T2DM,high CV risk	Reduced HF hospitalization 33%, reduced MACE 14%
Declare-Timi 58(24)	*Dapaglifozin*	T2DM,high CV risk	Reduced HF hospitalization 27%, no significant MACE reduction
DAPA -HF(25)	*Dapaglifozin*	HfrEF	Reduced HF hospitalization 30%, reduced CV death 18%
EMPEROR-REDUCED(26)	*Empaglifozin*	HfrEF	Reduced HF hospitalization 31%
VERTIS-CV(27)	*Ertuglifozin*	T2DM,high CV risk	Reduced HF hospitalization,13%-No significant difference In 3-point MACE
EMPEROR-PRESERVED(28)	*Empagliflozin*	HfpEF	Reduced HF hospitalization, 21% Reduction in composite outcome (CV death or HHF); 30% reduction HHF
SOLOIST-WHF(29)	*Sotagliflozin*	T2DM,HF	33% reduction in composite (CV death or HHF)
SCORED(30)	*Sotaglifozin*	DM2, CKD and high CV risk	16% reduction in composite (CV death or HHF)

2. Renal Protective Effects

a. Slowing Progression of CKD

By reducing intraglomerular pressure via tubuloglomerular feedback, SGLT2 inhibitors slow CKD progression. Trials including CREDENCE (↓ESRD 32%), DAPA-CKD (↓renal composite 39%), EMPA-REG OUTCOME, CANVAS, DAPA-HF renal subgroup, and EMPA-KIDNEY demonstrated slower eGFR decline and reduced risk of kidney failure.

b. Reduction in Albuminuria

SGLT2 inhibitors significantly reduce urinary albumin excretion. Evidence from Cherney et al., 2014 (Empagliflozin), Heerspink et al., 2020 (Dapagliflozin), and the CANVAS-Renal subgroup confirmed reduced albuminuria across patient populations.

c. Preservation of eGFR

Despite an initial small drop, SGLT2 inhibitors preserve long-term kidney function. Key studies—CREDENCE (Perkovic et al., 2019), EMPA-REG OUTCOME (Wanner et al., 2016), and EMPEROR-Preserved—show sustained renal protection in both diabetic and HFpEF patients.

Table 2. Outcomes of trials explaining renal protective effects

TRIAL	DRUG	POPULATION	KEY OUTCOMES
CREDENCE(31)	Canaglifozin	T2DM with CKD	30% reduction in composite outcome
DAPA-CKD (32)	Dapaglifozin	CKD ± T2DM	44% reduction in composite outcome
EMPA-REG OUTCOME(renal) (33)	Empaglifozin	T2DM	39% reduction of incident or worsening nephropathy 46% reduction of post hoc renal composite outcome
CANVAS(renal) (23)	Canaglifozin	T2DM	40% reduction in eGFR, renal replacement therapy, or renal death
DAPA-HF (renal subgroup) (25)	Dapaglifozin	HFrEF ± T2DM	29% reduction in eGFR decline, ESKD or renal Death
EMPA-KIDNEY (34)	Empaglifozin	CKD ± T2DM	28% reduction in Progression of kidney disease or CV outcomes
EMPEROR - Preseved(renal) (28)	Empaglifozin	HFpEF ± T2DM	5% - no significant effect on major renal outcome
EMPEROR -REDUCED (26)	Empaglifozin	Chronic HF with reduced EF ± T2DM	30% reduction in composite renal outcome
SCORED (30)	Sotaglifozin	T2DM with CKD & CV risk	29% reduction in composite renal outcome

SAFETY PROFILE & ADVERSE EFFECTS

SGLT2 inhibitors are generally well-tolerated, but several adverse effects have been reported. The most common include genital mycotic infections, urinary tract infections (UTIs), polyuria, nausea, and constipation. These adverse events are usually mild and manageable, but serious complications may occur in select patients (35).

1.Genital Mycotic Infections

These infections include vulvovaginal candidiasis, vulvovaginitis, vulval abscess, and bacterial vaginitis. Female sex and a history of recurrent infections are the main risk factors. Preventive strategies include good glycaemic control and hygiene. Most cases are mild and resolve with short-course topical or oral antifungal therapy; discontinuation of SGLT2 inhibitors is rarely required (36).

2. Urinary Tract Infections and Pyelonephritis

SGLT2 inhibitors increase urinary glucose, potentially raising the risk of UTIs. While meta-analyses show a dose-dependent increase in risk, real-world studies suggest that severe infections like urosepsis are uncommon and comparable to other antidiabetic therapies. Caution is advised in patients with impaired urinary flow (37).

3. Diabetic Ketoacidosis (DKA)

SGLT2 inhibitors are associated with a 2–3-fold increased risk of DKA, including euglycemic DKA. Risk is higher with canagliflozin, followed by empagliflozin and dapagliflozin. Clinicians should assess individual risk factors and consider temporary discontinuation during acute illness, surgery, or reduced oral intake (38).

4. Acute Kidney Injury (AKI)

Initiation of SGLT2 inhibitors may rarely precipitate AKI due to volume contraction, particularly in older adults, patients on diuretics, or those with renal impairment. Monitoring of volume status and renal function is recommended (39).

5. Hypoglycemia

SGLT2 inhibitors alone have a low risk of hypoglycaemia; however, the risk increases when combined with insulin or sulfonylureas. Dose adjustment of concomitant agents is recommended, especially in older patients (40).

6. Lower-Limb Amputation

Risk factors include peripheral vascular disease, neuropathy, prior diabetic foot ulcer, or previous amputation. Canagliflozin is most strongly associated with increased amputation risk, while dapagliflozin may increase toe amputation risk. Patients with active foot ulcers or infections should not use SGLT2 inhibitors (41).

GUIDELINES

a. KDIGO

SGLT2 inhibitors are recommended for adults with type 2 diabetes and chronic kidney disease (CKD) with an eGFR ≥20 mL/min/1.73 m². Treatment may be continued even if eGFR declines below this threshold unless intolerance or dialysis occurs. These agents are also indicated in CKD patients with significant albuminuria or in those with heart failure, irrespective of albuminuria. Temporary discontinuation is advised during prolonged fasting, surgery, or critical illness to reduce ketosis risk. Routine CKD monitoring is sufficient, and the initial reversible decline in eGFR is not an indication for therapy withdrawal (42).

b. ESC

According to the European Society of Cardiology (ESC) guidelines, SGLT2 inhibitors are recommended in patients with type 2 diabetes and heart failure to reduce heart failure hospitalisation and cardiovascular mortality. Dapagliflozin, empagliflozin, or sotagliflozin are advised in heart failure with reduced ejection fraction (HFrEF), alongside early initiation of guideline-directed heart failure therapy. In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, as well as those with HFmrEF or HFpEF, SGLT2 inhibitors further reduce heart failure hospitalisation and adverse cardiovascular outcomes (43).

c. ADA/EASD

According to the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus, SGLT2 inhibitors with proven benefit are recommended in patients with type 2 diabetes and heart failure, chronic kidney disease, or established cardiovascular disease to reduce heart failure hospitalisation and major adverse cardiovascular events and improve renal outcomes, independent of baseline HbA1c or metformin use (44).

FUTURE DIRECTIONS / EMERGING RESEARCH

SGLT2 inhibitors (SGLT2is) are expected to continue transforming the management of chronic kidney disease (CKD), with compelling evidence supporting cardiovascular and renal benefits in diabetic or albuminuric patients. However, their efficacy in non-diabetic patients without albuminuria and in patients with eGFR below 20 mL/min/1.73 m² remains uncertain, with ongoing trials such as RENAL LIFECYCLES and others in dialysis and transplant populations aiming to address these gaps.

Emerging strategies include combining SGLT2is with mineralocorticoid receptor antagonists (MRAs), such as finerenone, which may provide additive benefits in proteinuria reduction and CKD progression, as investigated in trials like CONFIDENCE. Additionally, combining SGLT2is with endothelin receptor antagonists (ERAs) may enhance albuminuria reduction while mitigating side effects such as sodium retention, being evaluated in the ZENITH-CKD trial.

These studies highlight the potential of SGLT2is in combination therapy, targeting multiple CKD pathways to improve renal and cardiovascular outcomes and expand the patient populations who may benefit from these agents (45).

CONCLUSION:

Type 2 diabetes mellitus is the risk factor for hypertension, chronic kidney disease and even heart failure. SGLT2 inhibitors reduce the blood glucose levels without causing hypoglycaemia compared to biguanides and sulfonylureas. In addition to this, SGLT2 inhibitors are proven to reduce blood pressure and weight, reduce renal inflammation and fibrosis, and eliminate uric acid. This additive action makes these drugs useful in CKD, HTN and even heart failure. Various trials are also conducted to evaluate the efficacy of these agents, like EMPA-REG Outcome, CANVAS, DECLARE-TIMI, DAPA-HF, EMPEROR-reduced, VERTIS-CV, EMPEROR-PRESERVED, SCORED, and SOLOIST-WHF. Still, studies are ongoing to evaluate the safety of using SGLT2 inhibitors in dialysis patients and patients with eGFR < 20 ml/min/1.73 m². This study provides evidence that SGLT2 inhibitors slow the progression of CFD and preserve kidney health. SGLT2 inhibitors are also associated with ADRs like genital mycotic infections and UTIs as sugars are eliminated, DICA, AICI, hypoglycaemia, and lower limb amputation. SGLT2 inhibitors are proven safe for prescribing to patients with T2DM with HTN, CKD, or HF but without UTI.

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