A NARRATIVE REVIEW: EXPANDING THERAPUTIC ROLES OF SGLT2 INHIBITORS BEYOND GLYCEMIC CONTROL

By

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A Thesis submitted to the School of Pharmacy in partial fulfillment of the requirements of the degree of

Bachelor of Pharmacy (Hons.)

School of Pharmacy
BRAC UNIVERSITY

June 2026

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

This project does not involve any kind of animal or human trial.

Abstract

Persistent hyperglycemia causes type 2 diabetes mellitus (T2DM) which is a metabolic disorder that eventually leads to increased cardiovascular and renal complications. A newer class of antidiabetic medication, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors, helps to lower blood sugar by excreting extra glucose in urine, rather than relying on insulin. This narrative review explores how these inhibitors do a lot more than just controlling blood glucose. Studies show SGLT2 inhibitors can slow down chronic kidney disease and lower the risk of heart failure and heart related death-even in people who do not have diabetes. They provide these benefits by easing the physical strain on heart and kidneys. Promoting weight loss and lowering blood pressure. Overall. SGLT2 inhibitors have completely changed how previously we treated diabetic conditions, though further studies required to fully understand their long-term safety and their use in non-diabetic patients.

Keywords: SGLT2 inhibitors; Type 2 diabetes mellitus; Chronic-kidney disease; Cardiovascular mortality; Hemodynamics; Cardiorenal; Natriuresis.

Dedication

Dedicated to my Supreme Creator, beloved parents, and my little siblings Sara & Tasfim. Also, my friends who constantly support me on this journey.

Acknowledgement

I would like to express my gratitude to my respected supervisor, Nashrah Mustafa, Senior Lecturer of School of Pharmacy in Brac University, for her consistent support, insightful advice and constructive feedback throughout this project. I was able to overcome the obstacles and finish this thesis successfully because of her patience and wise guidance. Also, I want to sincerely thank all of the School of Pharmacy faculty members for their assistance during this journey.

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List of Acronyms

IL-6: Interleukin-6

MACE: Major adverse cardiovascular events

NAFLD: Nonalcoholic fatty liver disease

NASH: Nonalcoholic steatohepatitis

NHE: Sodium-hydrogen exchanger

NHE1: Sodium-hydrogen exchanger 1

PAD: Peripheral artery disease

PCT: Proximal convoluted tubule

RAAS: Renin-angiotensin-aldosterone system

ROS: Reactive oxygen species

SGLT: Sodium-glucose co-transporters

SGLT1: Sodium-glucose cotransporter 1

SGLT2: Sodium-glucose cotransporter 2

T2DM: Type 2 diabetes mellitus

TGF-B: Transforming growth factor-beta

TNF-a: Tumor necrosis factor-alpha

Chapter 1

Introduction

Type 2 diabetes mellitus remains a leading global health issue in the twenty-first century. The characteristics of type 2 diabetes are such as resistance to insulin, reduced secretion of insulin, and chronic hyperglycemia are linked to substantial increases in morbidity, mortality, and healthcare expenditures globally (Miller & Shubrook,2015; Ferrannini et al.,2014). The fast rise of sedentary lifestyles, obesity, urbanization and ageing populations has led to a greater prevalence of diabetes in both developed and developing countries (Miller & Shubrook,2015; Popoviciu et al.,2024). International epidemiological forecasts indicate that the incidence of diabetes in the coming decades is expected to increase more (Nugraha & Susanto,2025). The number of persons affected worldwide is in the hundreds of millions today (Lunder & Janic,2025). Importantly, type 2 diabetes is commonly associated with macrovascular and microvascular issues, includes coronary artery disease, heart failure, stroke, diabetic nephropathy and retinopathy, which go well beyond glycemic abnormalities (Verma & McMurray,2018; Bhatt et al.,2024). Cardiovascular disease remains the primary cause of death in persons with type 2 diabetes while chronic kidney disease is a main contributor to long-term impairment and health care expenses (Steiner,2016; Perkovic et al.,2019).

The emphasis of diabetes management for many years has been on tight glycemic control to prevent complications (Miller & Shubrook,2015; Popoviciu et al.,2024). Conventional antihyperglycemic medications that successfully lowered blood glucose levels include metformin, sulfonylureas, insulin, and thiazolidinediones, but many of these medications had drawbacks concerning cardiovascular safety, risk of hypoglycemia, weight gain, or durability of therapeutic effect . Although strict glycemic control has been shown to reduce multiple microvascular complications, several clinical studies demonstrate that glucose lowering alone did not significantly reduce cardiovascular mortality or progression of heart failure in many

individuals with type 2 diabetes (Steiner,2016;Shah et al.,2025). In response, it became increasingly clear that the treatments of diabetes should target more broad pathophysiological pathways than hyperglycemia per se (Bhatt et al.,2024;Verma & McMurray,2018).

The improvement of SGLT2 inhibitors marked a significant therapeutic advancement. About 90% of the filtered glucose from the glomerular filtrate is reabsorbed by sodium-glucose cotransporter 2, which is mostly expressed in the kidney's proximal convoluted tubules (Defronzo et al., 2013; Ferrannini et al., 2014) . When SGLT2 is inhibited, it decreases renal glucose reabsorption which raises urine glucose excretion and lowers plasma glucose levels. In contrast to many conventional treatments, SGLT2 inhibitors have a glucose-lowering impact that is independent of insulin production or insulin sensitivity, which makes them especially useful in the advanced phases of type 2 diabetes that are marked by β-cell failure.

Early mechanistic studies demonstrated that SGLT2 inhibition leads to reductions in blood pressure, osmotic diuresis, natriuresis, calorie loss and modest weight loss, and improved glycaemic management (Ferrannini et al., 2014; Verma & McMurray, 2018) . These physiological effects opened the door to benefits beyond decreasing blood sugar (Bhatt et al., 2024; Verma & McMurray, 2018). Later seminal cardiovascular outcome research has dramatically changed the understanding of this drug class. The EMPA-REG OUTCOME research showed that empagliflozin significantly reduced hospitalisation for heart failure, all-cause mortality and cardiovascular mortality in patients with T2DM and established cardiovascular disease (Steiner, 2016; Zinman et al., 2015). Similar results were confirmed later in the DECLARE-TIMI 58 research and the CANVAS Program, indicating the cardioprotective role of SGLT2 inhibitors in different types of patients (Neal et al., 2017; Wiviott et al., 2019).

Recent findings from heart failure and renal outcome trials have shown that SGLT2 inhibitors are useful for more than just treating diabetes (McMurray et al., 2019; Yaribeygi et al.,2024). Both the DAPA-HF study and the EMPEROR-Reduced trial demonstrated significant reductions in worsening heart failure and cardiovascular death in patients with heart failure with reduced ejection fraction, including those without diabetes (McMurray et al., 2019; Packer et al., 2020) . Furthermore, renal outcome trials such as CREDENCE, DAPA-CKD and EMPA-KIDNEY trials have established the renoprotective properties of these medications in lowering the occurrence of renal failure and in retarding the progression of chronic kidney disease (Perkovic et al., 2019; Heerspink et al., 2020; The EMPA-KIDNEY Collaborative Group,2023).

These findings have resulted in changes in glucose-centric diabetes therapy to combined cardiorenal-metabolic protection. According to available data, the advantages of SGLT2 inhibitors are mediated by a number of interrelated mechanisms, such as improved cardiac energy metabolism, natriuresis, reduction of preload and afterload, attenuation of oxidative stress, modulation of inflammatory pathways, restoration of tubuloglomerular feedback, and reduction of intraglomerular pressure (Verma & McMurray, 2018; Bhatt et al., 2020). Due to the pleiotropic nature of these actions, there is a great deal of interest in this medication class's wider therapeutic potential (Hasan et al., 2024; Anker et al., 2021) .

With this rapidly evolving data base, a detailed examination of both mechanistic and clinically proven data is required. Therefore, the aim of this narrative review is to objectively analyse the physiological mechanisms, evidence of cardiovascular and renal outcomes, and emerging therapeutic applications of SGLT2 inhibitors in type 2 diabetes. Special focus is given to the understanding of how these medications have revolutionised diabetic care beyond glycaemic control, and their implications for future cardiorenal-metabolic therapy (Nugraha & Susanto.,2025; Anker et al.,2021).

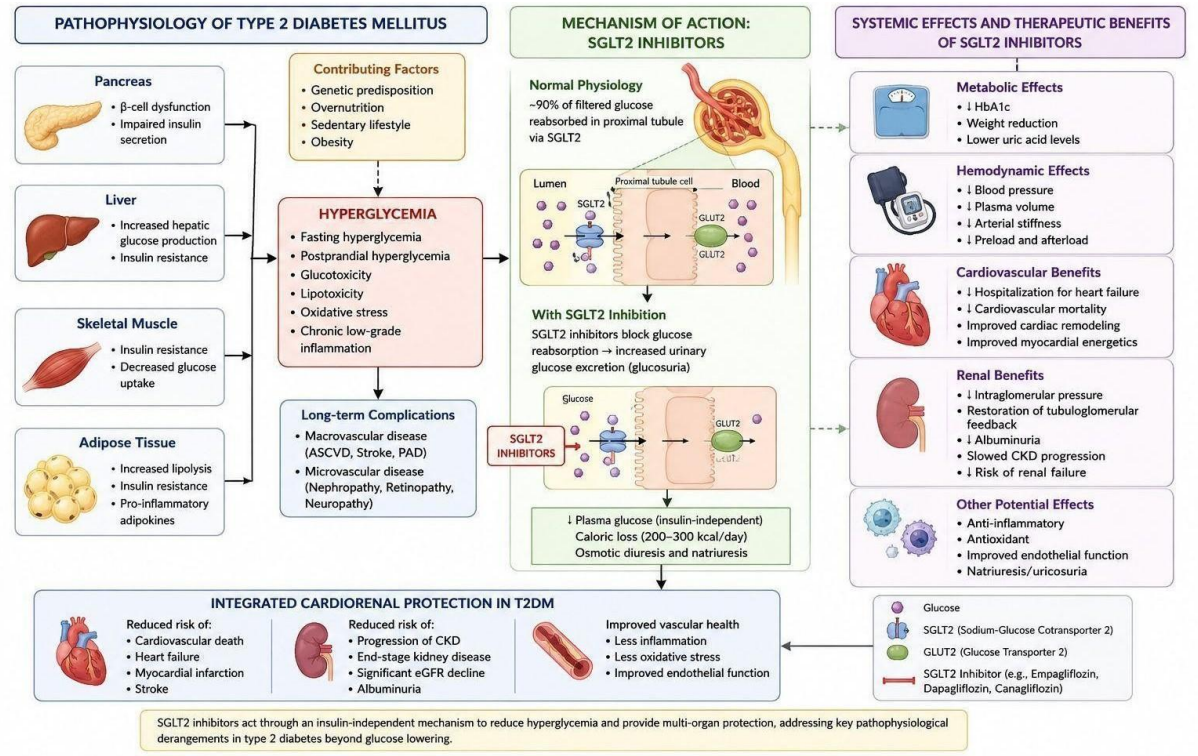

Figure 1. *Pathophysiology of type 2 diabetes mellitus and therapeutic goals of sodium-glucose co-transporter 2 (SGLT2) inhibitors Also multi-organ mechanisms of hyperglycemia depicted in the diagram: β-cell failure, hepatic glucose overproduction, insulin resistance in muscle and adipose tissue and systemic metabolic stress. It also illustrates the effect of SGLT2 inhibition to reduce glucose reabsorption in the kidney. SGLT2 inhibitors have additional metabolic, cardiovascular, and renal benefits, offering integrated cardiorenal protection in people with T2DM, beyond improving diabetic control.*

Chapter 2

Methodology

This narrative review discusses the significance of SGLT2 inhibitors in the management of Type 2 Diabetes Mellitus (T2DM), with a focus on cardiovascular, renal and metabolic outcomes as well as glycemic control (Popoviciu et al., 2024). This review draws on data from major clinical trials, mechanistic studies and key literature reviews about SGLT2 inhibitors (SGLT2 inhibitors: Beyond glycemic control, 2024)(Bhatt et al., 2024; Verma & McMurray, 2018).

Four major electronic databases was carried out for a literature search in such as PubMed, Scopus, Web of Science and Google Scholar (Hasan et al., 2024; Miller & Shubrook, 2015). Additional relevant research was identified by manually searching reference lists of included papers (Hasan et al., 2024; Verma & McMurray, 2018). The search period was from 2010 to 2025 and sixty articles/papers were used; the target papers included mechanistic investigations, cardiovascular outcome trials (CVOTs), renal outcome trials, heart failure trials as well as systematic or narrative reviews (Popoviciu et al., 2024; Neal et al., 2017).

The key search terms used were “SGLT2 inhibitors”, “type 2 diabetes mellitus”, “cardiovascular outcomes”, “renal protection”, “heart failure”, and “chronic kidney disease”, either alone or in combination (Hasan et al., 2024; Miller & Shubrook, 2015) . Other drug-specific and mechanism related words such as “empagliflozin”, “dapagliflozin”, “canagliflozin” and “cardiorenal protection” were also utilised to ensure the entire coverage of the literature (Steiner, 2016; Wiviott et al., 2019).

Inclusion criteria were original research papers, randomised controlled trials, meta-analyses, large-scale outcome trials and mechanistic studies that have been peer-reviewed and are relevant to SGLT2 inhibitors in T2DM (Hasan et al., 2024; Verma & McMurray, 2018). The choice of landmark trials such as EMPA-REG OUTCOME, CANVAS Program, DECLARE-

TIMI 58, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, CREDENCE, DAPA-CKD, and EMPA-KIDNEY was based on the impact that they have made in the current understanding of cardiorenal benefits (Steiner, 2016; Neal et al., 2017; Wiviott et al., 2019).Studies were excluded if they were not published in English, were not full text, were conference abstracts only, or did not contain enough methodological or accurate data.The studies in animals only and publications without well-defined clinical goals were also excluded (Miller & Shubrook, 2015).

Data extraction was performed for the following study features: authors, year of publication, study design, patient population, interventions, primary and secondary outcomes, cardiovascular and renal endpoints, mechanistic results and major clinical conclusions (Hasan et al., 2024; Miller & Shubrook, 2015). The underlying physiology and mechanisms are based on experimental evidence (DeFronzo et al., 2013; Ferrannini et al., 2014), and the broader mechanistic interpretations are informed by comprehensive reviews (Heerspink et al., 2016; Verma & McMurray, 2018).

The extracted data was analysed to summarize the physiological mechanisms, cardiovascular benefits, renal protection and metabolic effects of SGLT2 inhibitors beyond simply controlling glucose (Hasan et al., 2024; Verma & McMurray, 2018).

Chapter3

Renal Physiology and Molecular Mechanisms of SGLT2 Inhibition

It is essential to understand the renal baseline role in glucose regulation and the specific molecular pathways altered by these agents to fully appreciate the therapeutic impact of SGLT2 inhibitors. This section outlines the normal physiology of renal glucose reabsorption, the targeted mechanism of SGLT2 inhibition & the pleiotropic effects that occur beyond simple glycemic control.

3.1 Physiology of Renal Glucose Reabsorption

The kidneys play a crucial function in regulation of glucose by means of glucose filtration and reabsorption. The glomeruli filter about 180 g of glucose every day under normal physiological settings. Thus, practically all of the glucose is reabsorbed in the proximal convoluted tubule and urine glucose excretion is low (DeFronzo et al., 2013;Ferrannini et al.,2014).

The reabsorption of glucose is preeminently mediated by sodium-glucose co-transporters (SGLTs), predominantly SGLT2 and SGLT1, in the renal function (DeFronzo et al., 2013;Wang & Zuo et al.,2025). SGLT2 transporters are mostly located in the S1 section of the proximal tubule and responsible for reabsorbing about ~90% of filtered glucose. These transporters operate by a lower affinity and higher capacity mechanism. In contrast, SGLT1 transporters are expressed in the S3 segment and reabsorb the remaining 10% of glucose via a high affinity low capacity system .

In T2DM, persistent hyperglycemia results in an overexpression of SGLT2 and an increase in reabsorption of renal glucose level (DeFronzo et al., 2013;Ferrannini et al., 2014) . This maladaptive response raises the renal threshold for excreting glucose which worsens chronic hyperglycemia (DeFronzo et al., 2013; Hasan et al., 2024). Increased salt and glucose

reabsorption also reduces sodium transport to the macula densa inducing glomerular hyperfiltration and intraglomerular hypertension, major drivers of the progression of diabetic renal disease (Heerspink et al., 2020;Perkovic et al.,2019)

3.2 Mechanism of Action of SGLT2 Inhibitors

SGLT2 inhibitors disrupt SGLT2 transporters in the proximal renal tubules, leading to decreased reabsorption of blood sugar and increased urine sugar excretion (DeFronzo et al., 2013;Ferrannini et al., 2014). This procedure decreases the plasma glucose levels regardless of insulin secretion or insulin sensitivity, making these medicines beneficial even in individuals with insulin resistance (DeFronzo et al., 2013;Ferrannini et al.,2014).

Glucosuria occurs due to blockage of glucose reabsorption. About 60 – 80 g of glucose are ejected every day. This loss of glucose in urine results in a caloric deficit of around 200-300 kcal/day that explains the slow weight loss observed after therapy (Ferrannini et al., 2014;Verma & McMurray,2018).

The sodium-dependence of glucose transport through SGLT2 means that blockage of this transporter also decreases sodium reabsorption and induces natriuresis (Heerspink et al.,2020;Verma & McMurray,2018). More salt transport to the macula densa restores tubuloglomerular feedback, decreases vasodilation of the afferent arteriole and lowers intraglomerular pressure. These effects have important renal protective effects and delay the evolution of diabetic nephropathy (Heerspink et al., 2020;Perkovic et al.,2019).

SGLT2 inhibitors also lead to osmotic diuresis due to increased glucose content in urine (McMurray et al., 2019; Verma & McMurray, 2018). This causes a modest reduction in plasma volume which decreases both cardiac preload and afterload. These haemodynamic changes likely contribute to the early cardiovascular benefits observed in trials such as EMPA-REG OUTCOME and DAPA-HF (McMurray et al., 2019; Zinman et al., 2015).

3.3 Pleiotropic Mechanisms Beyond Glycemic Control

In addition to glucose control, SGLT2 inhibitors offer cardiovascular & renal protection through various metabolic, inflammatory, and hemodynamic pathways (Bhatt et al., 2024; Verma & McMurray, 2018). A key mechanism is the reduction of oxidative stress (Verma & McMurray, 2018; Yaribeygi et al., 2024). Chronic hyperglycemia increases generation of reactive oxygen species (ROS), which leads to endothelial dysfunction and damages tissues. SGLT2 inhibitors reduce glucotoxicity and oxidative stress, increasing vascular and cellular function.

These medicines also have anti-inflammatory effects due to decreases in inflammatory mediators such as interleukin-6 and tumour necrosis factor-alpha (Verma & McMurray, 2018;Adamska-Patruno et al.,2025). Inhibition of inflammatory pathways may decrease vascular injury, cardiac remodelling and renal fibrosis associated with diabetes and chronic kidney disease (Heerspink et al., 2020; Verma & McMurray, 2018).

A very important protective mechanism is the betterment of endothelial function (Verma & McMurray, 2018; Bhatt et al., 2024). SGLT2 inhibitors can make an improvement for endothelial integrity and vascular reactivity through lowering oxidative stress, inflammation and blood pressure. These changes may in part explain the reduction in major cardiovascular events shown in big outcome trials (Zinman et al., 2015;Wang & Zuo.,2025).

Moreover, SGLT2 inhibitors may enhance mitochondrial efficiency by facilitating the use of ketone bodies as an alternative energy source. This technique may increase energy generation in the cardiac cells and lower the cellular stress, especially in heart failure (Verma & McMurray, 2018;McMurray et al.,2019).

Another key method of cardiorenal protection is haemodynamic regulation(Verma & McMurray, 2018; Hasan et al., 2024) . SGLT2 inhibitors reduce plasma volume by natriuresis and osmotic diuresis, resulting in decreased blood pressure and glomerular

hyperfiltration(Verma & McMurray, 2018; Heerspink et al., 2020) . These synergistic actions result in a reduction in hospitalisations for heart failure and renal function preservation as evidenced in trials such as CREDENCE, DAPA-CKD, and EMPA-KIDNEY (Heerspink et al., 2020; Herrington et al., 2023; Perkovic et al., 2019).In summary, the diverse physiological effects of SGLT2 inhibitors extend far beyond glucose lowering making them a cornerstone of modern cardiorenal-metabolic therapy (Hasan et al., 2024; Verma & McMurray, 2018).

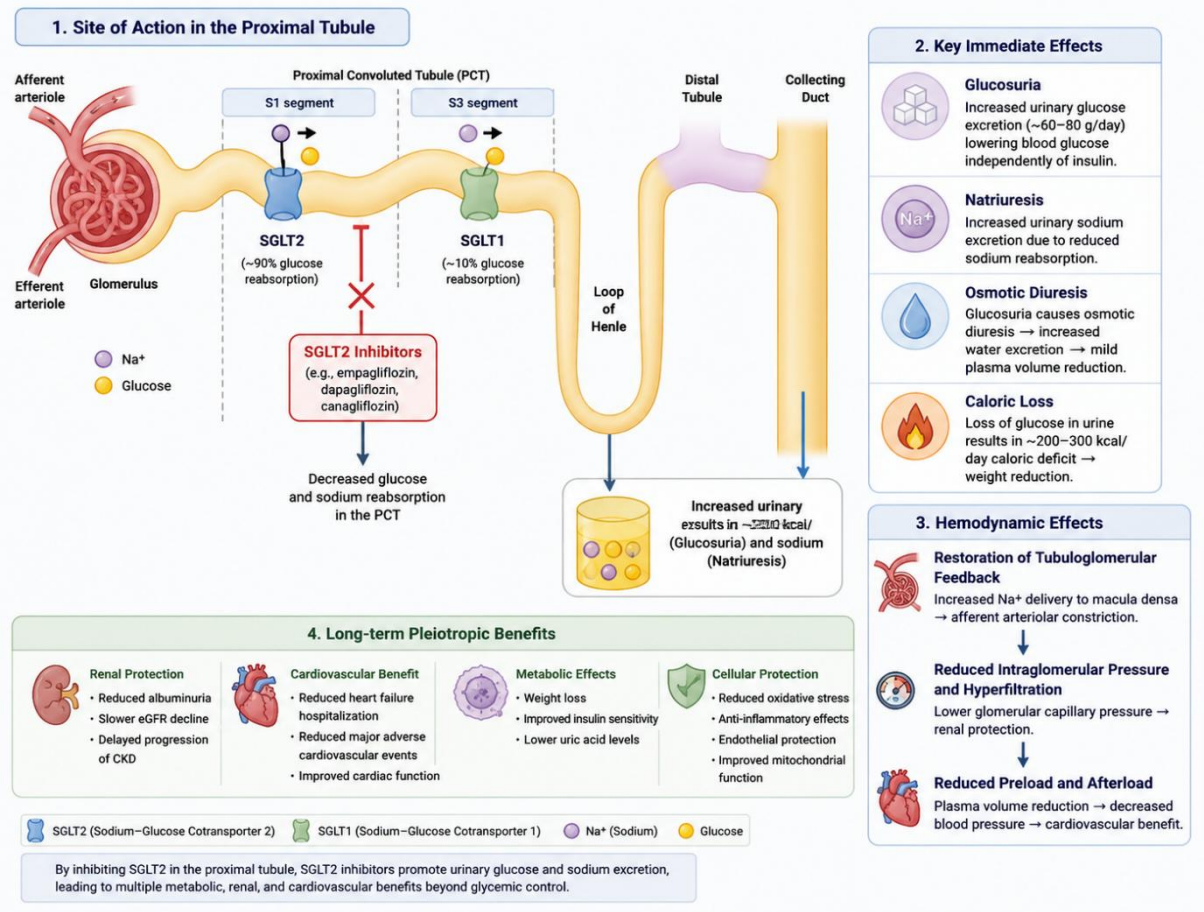

Figure 2. Mechanism of Action of SGLT2 inhibitors in the kidney.
SGLT2 inhibitors inhibit sodium-glucose co-transporter 2 in the proximal convoluted tubule, thus reducing reabsorption of glucose and sodium. This induces glucosuria, natriuresis and osmotic diuresis and contributes to better glycemic control, weight loss and decrease in blood pressure.Also some pleiotropic advantages include reduction of oxidative stress, anti-inflammatory action, endothelial protection, and improved cardiovascular and metabolic results

Drug	FDA Approval year	Selectivity	Half-life	Major Indications	References
Empagliflozin	2014	Highly selective for SGLT2 over SGLT1 (~2500-fold)	~12 hours	Type 2 Diabetes Mellitus (T2DM), Heart Failure (HFrEF & HFpEF), Chronic Kidney Disease (CKD), reduction of cardiovascular mortality	(Steiner, 2016; Hasan et al., 2024)
Dapagliflozin	2014	Highly selective for SGLT2 over SGLT1 (~1200-fold)	~12–13 hours	T2DM, Heart Failure (HFrEF & HFpEF), CKD	(Wiviott et al., 2019; Hasan et al., 2024)
Canagliflozin	2013	Selective for SGLT2 over SGLT1 (~250-fold)	~10–13 hours	T2DM, Diabetic Kidney Disease, reduction of cardiovascular risk	(Neal et al., 2017; Hasan et al., 2024)
Ertugliflozin	2017	Highly selective for SGLT2 over SGLT1 (~2000-fold)	~16–17 hours	T2DM, glycemic control improvement	(Hasan et al., 2024)

Table 1: FDA approved SGLT2 inhibitors & their pharmacological characteristics

Chapter 4

Glycemic and Metabolic Effects in Type 2 Diabetes Mellitus

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have emerged as a new class of therapeutic agents for the therapy of Type 2 Diabetes Mellitus (T2DM) with the ability to improve glycaemic control as well as to confer metabolic, cardiovascular and renal advantages(Miller & Shubrook, 2015; Hasan et al., 2024). Unlike conventional antidiabetic drugs that mainly act by enhancing insulin secretion or insulin sensitivity, SGLT2 inhibitors decrease blood glucose via an insulin-independent mechanism by blocking renal glucose reabsorption in the proximal tubules, resulting in increased urinary glucose excretion DeFronzo et al., 2013; Ferrannini et al., 2014).

A key metabolic impact of SGLT2 inhibitors is a decrease of glycated haemoglobin (HbA1c) (Ferrannini et al., 2014;Nugraha & Susanto., 2025). Clinical trials demonstrate an HbA1c reduction of roughly 0.5 -- 1.0% depending on the patients baseline glycemic state and concomitant treatment (Ferrannini et al., 2014). Their mechanism is independent of pancreatic beta-cell function and so these medications are effective even in advanced T2DM. They have a comparatively minimal risk of hypoglycemia when administered alone as well (Miller & Shubrook, 2015; Ferrannini et al., 2014).

SGLT2 inhibitors are also linked to substantial weight loss(Ferrannini et al., 2014; Verma & McMurray, 2018). Increased urine glucose excretion causes a daily loss of 200-300 kcal, leading to gradual reductions in body weight and adiposity (Ferrannini et al., 2014;Hasan et al., 2024). This effect is of therapeutic relevance, because obesity is closely connected with the resistance of insulin and cardiovascular issues. Unlike insulin and sulfonylurea, SGLT2 inhibitors improve overall metabolism beyond lowering blood glucose and do not typically cause weight gain (Steiner, 2016;Verma & McMurray,2018).

Another favourable consequence is an increase in insulin sensitivity(Heerspink et al., 2020; Verma & McMurray, 2018) . By reducing glucotoxicity and visceral fat, SGLT2 inhibitors indirectly improves peripheral insulin sensitivity and metabolic flexibility (Verma & McMurray, 2018; Hasan et al., 2024). Also they provide blood pressure lowering properties through natriuresis and osmotic diuresis leading to modest plasma volume contraction and improved hemodynamic state (Verma & McMurray, 2018; Hasan et al., 2024).

SGLT2 inhibitors are often given in conjunction with metformin, insulin, DPP-4 inhibitors, and GLP-1 receptor agonists . Combination treatment improves glycaemic control by complementing mechanisms with less deleterious metabolic consequences SGLT2 inhibitors have demonstrated greater cardiovascular and renal protective effects compared to metformin, especially in lowering hospitalizations for heart failure and development of chronic kidney disease (McMurray et al., 2019; Perkovic et al., 2019). SGLT2 inhibitors are more favourable in heart failure and renal outcomes although GLP-1 receptor agonists may have more weight reduction than GLP-1 receptor agonists (Bhatt et al., 2024; Verma & McMurray, 2018).

Importantly, the cardiovascular advantages of SGLT2 inhibitors are not limited to lowering blood sugar (Steiner, 2016; Verma & McMurray, 2018) . Large outcome trials such as EMPA-REG OUTCOME, DECLARE-TIMI 58, and CANVAS demonstrated rapid reductions in cardiovascular mortality and heart failure hospitalization shortly after treatment began, even before significant HbA1c reductions occurred (Neal et al., 2017; Wiviott et al., 2019; Zinman et al., 2015). This implies that other mechanisms such as hemodynamic regulation, reduction in oxidative stress, anti-inflammatory effects and improvement in myocardial energy metabolism play a substantial role in cardiorenal protection (Verma & McMurray, 2018; Hasan et al., 2024).

Moreover, the most recent data underlines that SGLT2 inhibitors are now more than a glucose lowering drug class, but a multi-functional therapy with broad spectrum uses in contemporary day cardiorenal-metabolic medicine (Popoviciu et al., 2024; Verma & McMurray, 2018).

Chapter 5

Cardiovascular Benefits of SGLT2 Inhibitors

Though SGLT2 was initially developed for glycemic control, it has shown cardiovascular benefits that reshaped the modern clinical standards. This section explores these advantages by reviewing landmark cardiovascular outcome trials (CVOTs), detailing their specific efficacy in cardiac issues or failure & examining the underlying management, also the mechanism of action that drives to cardio protection.

5.1 Cardiovascular Outcome Trials (CVOTs)

The cardioprotective effects of SGLT2 inhibitors have changed the treatment of T2DM (Steiner, 2016; Hasan et al., 2024). SGLT2 inhibitors were originally developed as glucose lowering medicines (DeFronzo et al., 2013; Miller & Shubrook, 2015). The large cardiovascular outcome trials (CVOTs) showed unexpected and considerable reductions in cardiovascular morbidity and mortality (Neal et al., 2017; Wiviott et al., 2019).

The EMPA-REG OUTCOME trial program was the big experiment to show significant cardiovascular benefits of SGLT2 inhibition (Steiner, 2016; Verma & McMurray, 2018). The EMPA-REG OUTCOME trial found that empagliflozin significantly decreased cardiovascular mortality, all-cause mortality and hospitalization for heart failure in patients with T2DM and existing cardiovascular disease (Steiner, 2016; Verma & McMurray, 2018). After commencement of therapy, reductions in CV events were observed early indicating mechanisms beyond glycemic control alone (Steiner, 2016; Hasan et al., 2024).

The CANVAS Program further implies the cardioprotective effects of SGLT2 inhibitors (Neal et al., 2017; Hasan et al., 2024) showed that canagliflozin was cooperating with a lower risk of serious adverse cardiovascular events, including cardiovascular death, nonfatal myocardial

infarction, and nonfatal stroke (Neal et al., 2017; Hasan et al., 2024). The data also indicated significant renal protective effects additionally reductions in hospitalization for cardiac failure (Neal et al., 2017; Perkovic et al., 2019).

Likewise, the DECLARE-TIMI 58 trial assessed dapagliflozin in a broad population of individuals with T2DM, with and without preexisting atherosclerotic cardiovascular disease (Wiviott et al., 2019; Hasan et al., 2024). Dapagliflozin significantly reduced hospitalization for heart failure and improved renal outcomes, with a less apparent reduction in MACE (Wiviott et al., 2019; Heerspink et al., 2020).

The major trials showed that SGLT2 inhibitors protect the heart regardless of blood glucose levels, shifting the focus of the treatment toward protecting both the heart and the kidney (Steiner, 2016; Verma & McMurray, 2018).

5.2 Benefits in Heart Failure

SGLT2 inhibitors and their function in the therapy of heart failure is one of the noteworthy clinical developments(McMurray et al., 2019; Packer et al., 2020). There have been steady improvements in both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), even in those without diabetes (Anker et al., 2021; Hasan et al., 2024).

The DAPA-HF study indicated that dapagliflozin significantly reduced the risk of worsening heart failure and cardiovascular death in HFrEF patients irrespective of diabetes status (McMurray et al., 2019; Shah et al., 2024). Improvements in symptoms, functional capacity and quality of life were also seen, supporting the use of SGLT2 inhibitors as foundational therapy in the management of heart failure (McMurray et al., 2019; Packer et al., 2020).

The EMPEROR-Reduced study also demonstrated that empagliflozin reduced cardiovascular death and hospitalization for heart failure in patients with HFrEF (Packer et al., 2020; Heerspink et al., 2024). Importantly, empagliflozin also delays renal, damage which highlights

the strong link between cardiovascular and renal protection (Packer et al., 2020; Heerspink et al., 2020).

Most recently, the EMPEROR-Preserved study has extended the therapeutic role of SGLT2 inhibitors to HFpEF, a disease that has hitherto been linked with limited treatment options (Anker et al., 2021; Hasan et al., 2024) showed that empagliflozin dramatically reduces heart failure hospitalizations in patients with preserved ejection fraction, representing a major breakthrough for HFpEF treatment (Anker et al., 2021; Shah et al., 2024).

Consequently this research solidified SGLT2 inhibitors as a profound therapy for heart failure and altered international cardiovascular treatment guidelines (McMurray et al., 2019; Packer et al., 2020).

5.3 Mechanism of Cardio protection

The cardiovascular impact of SGLT2 inhibitors are mediated by numerous interrelated physiological and molecular pathways. Importantly, these protective effects cannot be fully explained by reductions in blood glucose levels (Verma & McMurray, 2018; Bhatt et al., 2024). One prominent one is the hemodynamic regulation by natriuresis and osmotic diuresis (Verma & McMurray, 2018; Yaribeygi et al., 2020). Increased excretion of sodium and water decreases plasma volume and, thus, decreases cardiac preload and afterload (Verma & McMurray, 2018; Heerspink et al., 2020). Reducing stress on the ventricular wall increases the efficiency of the heart and reduces the likelihood of heart failure aggravation (Verma & McMurray, 2018; Heerspink et al., 2020).

Changes in myocardial energy metabolism may potentially contribute to cardio protection (Verma & McMurray, 2018; Hasan et al., 2024). SGLT2 inhibitors induce moderate ketogenesis and increase the availability of ketone bodies providing the myocardium with a more energy-efficient substrate for ATP synthesis (Verma & McMurray, 2018; Hasan et al.,

2024). Enhanced cardiac energy utilization may enhance myocardial function, particularly in failing hearts (Verma & McMurray, 2018; McMurray et al., 2019).

Another possible mechanism is suppression of the sodium-hydrogen exchanger (NHE), especially the NHE1 isoform in cardiomyocytes (Verma & McMurray, 2018; Hasan et al., 2024). NHE overactivity leads to intracellular sodium and calcium overload, which lead to myocardial damage and unfavorable cardiac remodelling (Verma & McMurray, 2018; Shah et al., 2024). Evidence suggests that SGLT2 inhibitors may not directly but indirectly limit the activity of NHE which then reduces cellular stress and improves myocardial function (Verma & McMurray, 2018; Hasan et al., 2024).

SGLT2 inhibitors also have anti-inflammatory and antifibrotic properties (Verma & McMurray, 2018; Heerspink et al., 2020). Chronic inflammation and myocardial fibrosis are key determinants of progression of heart failure and diabetic cardiovascular disease (Verma & McMurray, 2018; Heerspink et al., 2020). SGLT2 inhibitor therapy has been demonstrated to reduce inflammatory mediators, oxidative stress and profibrotic signalling pathways (Heerspink et al., 2020; Verma & McMurray, 2018). These actions may have beneficial impacts on endothelial function, reduced vascular stiffness and maintenance of heart structure (Heerspink et al., 2020; Verma & McMurray, 2018).

Furthermore, SGLT2 inhibitors lower blood pressure, decrease arterial stiffness and induce mild weight reduction, all of which play a role in long-term cardiovascular protection (Verma & McMurray, 2018; Ferrannini et al., 2014). The early and consistent cardiovascular advantages found in several trials provide compelling evidence to support the hypothesis that SGLT2 inhibitors are multifunctional cardiorenal-metabolic medicines, not only glucose-lowering drugs (Steiner, 2016; Bhatt et al., 2024).

In recent evaluations, it has been confirmed that the emerging cardiovascular indications for SGLT2 inhibitors are very important therapeutic advances for modern diabetes and cardiac issue solvers (Adamska-Patruno et al.,2025;Heerspink et al.,2020).

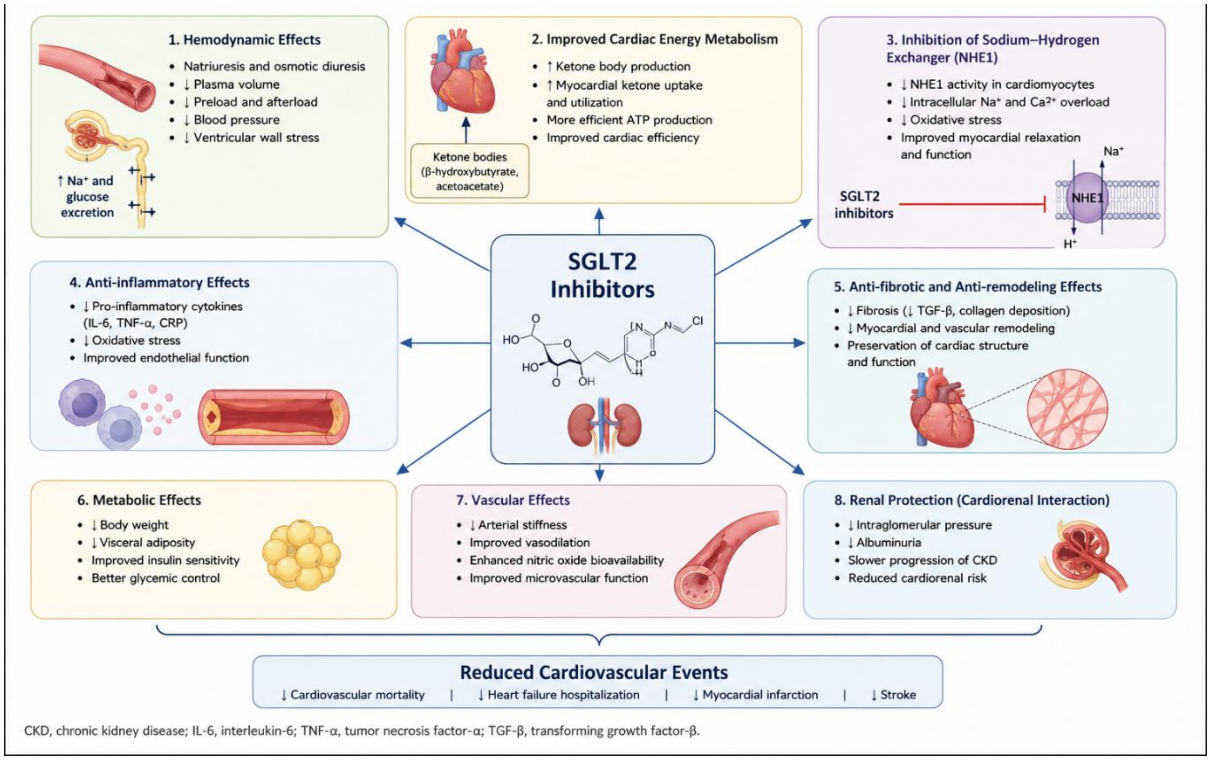

Figure 3. Proposed Cardiovascular Protective Effects of SGLT2 Inhibitors.
The cardio vascular preventive effects of SGLT2 inhibitors are mediated by several interrelated hemodynamic, metabolic and molecular pathways. Natriuresis and osmotic diuresis decrease plasma volume, preload, afterload and ventricular wall stress. Better utilisation of ketone bodies enhances cardiac energy metabolism and improves cardiac energy efficiency. Other cardioprotective effects are inhibition of sodium–hydrogen exchanger (NHE1), reduction of oxidative stress and inflammatory cytokines, attenuation of myocardial fibrosis and cardiac remodelling, improvement of endothelial and vascular functions, and preservation of renal function through cardiorenal interaction. The pathways together decrease cardiovascular mortality, heart failure hospitalisation, myocardial infarction and overall cardiorenal risk

Trial	Drug	Population	Primary Outcome	Major Findings	References
EMPA-REG OUTCOME	Empagliflozin	T2DM + established CVD	3-point MACE	↓ CV mortality, ↓ all-cause mortality, ↓ HF hospitalization	(Steiner, 2016; Verma & McMurray, 2018)
CANVAS Program	Canagliflozin	T2DM + high CV risk	3-point MACE	↓ MACE, ↓ renal disease progression	(Neal et al., 2017; Hasan et al., 2024)
DECLARE-TIMI 58	Dapagliflozin	T2DM with/at risk of ASCVD	CV death or HF hospitalization	↓ HF hospitalization, improved renal outcomes	(Wiviott et al., 2019; Hasan et al., 2024)
DAPA-HF	Dapagliflozin	HFrEF patients ± diabetes	HF worsening or CV death	↓ HF hospitalization & CV mortality	(McMurray et al., 2019; Hasan et al., 2024)
EMPEROR-Reduced	Empagliflozin	HFrEF patients ± diabetes	CV death or HF hospitalization	↓ HF hospitalization, slower renal decline	(Packer et al., 2020; Hasan et al., 2024)
EMPEROR-Preserved	Empagliflozin	HFpEF patients	CV death or HF hospitalization	↓ HF hospitalization in HFpEF	(Anker et al., 2021; Hasan et al., 2024)

Table 2. Major Cardiovascular Outcome Trials of SGLT2 Inhibitors

Chapter 6

Renoprotective Effects and Chronic Kidney Disease

A significant change in the treatment of chronic kidney disease (CKD) has resulted from the significant renoprotective advantages of sodium-glucose co-transporter 2 inhibitors, which go beyond decreasing glucose. Restoring tubuloglomerular feedback is one of the main protective measures for the kidneys (Heerspink et al., 2020; Perkovic et al., 2019). Afferent arteriolar vasodilation and glomerular hyperfiltration are caused by excessive glucose and sodium reabsorption in the proximal tubules in Type 2 Diabetes Mellitus (T2DM), which lowers sodium supply to the macula densa (Heerspink et al., 2020; Perkovic et al., 2019). Intraglomerular hypertension and gradual renal damage are caused by continuous hyperfiltration (Heerspink et al., 2020; Perkovic et al., 2019). SGLT2 inhibitors help in lowering glomerular hyperfiltration and restoring tubuloglomerular feedback when it blocks the proximal tubular salt and force reabsorption of glucose (Wang & Zuo., 2025).

Another significant mechanism underpinning renal protection is the decrease in intraglomerular forces (Heerspink et al., 2020; Perkovic et al., 2019). So, decreased intraglomerular pressure reduces the development of diabetic nephropathy which is by reducing mechanical strain on the barrier of glomerular filtration (Heerspink et al., 2020; Perkovic et al., 2019). The prolonged maintenance of renal function is greatly aided by this impact(LI et al.,2025).

Additionally, SGLT2 inhibitors reduce albuminuria which is a significant indicator of renal impairment and cardiovascular risk (Perkovic et al., 2019; Heerspink et al., 2020). According to clinical investigations, urinary albumin excretion has been significantly decreasing after

therapy, which suggests more glomerular integrity and reduced renal inflammation (Perkovic et al., 2019; Heerspink et al., 2020).

SGLT2 inhibitors have anti-inflammatory and anti-fibrotic qualities in addition to haemodynamic effects (Verma & McMurray, 2018; Hasan et al., 2024). The improvement of CKD is influenced by fibrosis and chronic inflammation (Verma & McMurray, 2018; Hasan et al., 2024). According to experimental data, SGLT2 inhibitors reduce structural kidney damage which is by lowering oxidative stress, inflammatory cytokines, and profibrotic signalling pathways (Verma & McMurray, 2018; Hasan et al., 2024).

Another significant advantage of SGLT2 inhibitor therapy is the glomerular filtration rate(eGFR) estimation (Heerspink et al., 2020; Perkovic et al., 2019).Even if the hemodynamic alterations may cause a temporary drop in eGFR following treatment initiation, long-term medication lowers the risk of end-stage kidney disease and slows the overall rate of renal function decline, (Li et al., 2025; Perkovic et al., 2019).

6.1 Landmark Renal Trials

The renoprotective function of SGLT2 inhibitors has been demonstrated by a number of valuable clinical trials (Perkovic et al., 2019). Canagliflozin was recommended to patients with diabetic nephropathy and type 2 diabetes in the CREDENCE study . The trial showed a significant decrease in renal or cardiovascular death, doubling of blood creatinine, and progression to end-stage kidney disease while compared to a placebo (Perkovic et al., 2019; Heerspink et al., 2020).

The DAPA-CKD experiment increased the use of SGLT2 inhibitors in the treatment of chronic kidney disease (Heerspink et al., 2020; Hasan et al., 2024). Regardless of whether a patient had diabetes or not, Heerspink et al. (2020) shown that dapagliflozin dramatically decreased

cardiovascular mortality, end-stage kidney disease, and declining renal function in CKD patients (The EMPA-KIDNEY Collaborative Group,2023).

Similarly, empagliflozin was incorporated in the EMPA-KIDNEY trial, which had a large number of individuals who did not have diabetes (Empagliflozin in Patients with Chronic Kidney Disease, 2023; Hasan et al., 2024). SGLT2 inhibitors are important treatments for CKD, as evidenced by the study's notable reductions in cardiovascular death (Empagliflozin in Patients with Chronic Kidney Disease, 2023).

6.2 Use beyond Diabetes

The use of SGLT2 inhibitors in CKD populations without diabetes is a significant new advancement (Heerspink et al., 2020; Hasan et al., 2024). Traditionally chronic kidney disease treatments mainly focused on diabetic neuropathy; however, evidence shows that SGLT2 inhibitors give real renal benefits independent of blood glucose level management (Heerspink et al., 2020; Hasan et al., 2024). Their therapeutic use in CKD patients with or without diabetes has expanded because they improve glomerular haemodynamics, lower inflammation, and maintain renal function (Heerspink et al., 2020; Empagliflozin in Patients with Chronic Kidney Disease, 2023).

Overall, through a variety of haemodynamic, metabolic, and anti-inflammatory mechanisms, SGLT2 inhibitors have revolutionised the treatment of chronic kidney disease (Perkovic et al., 2019; Hasan et al., 2024). Their increasing importance as vital treatments for maintaining kidney function and lowering cardiorenal risk in both diabetic and non-diabetic individuals is supported by the consistent results of large renal outcome trials (Heerspink et al., 2020; Empagliflozin in Patients with Chronic Kidney Disease, 2023). Recent evaluations shows SGLT2 inhibitors are a wonderful achievement in modern nephrology and cardiovascular medicine. Their therapeutic value goes far beyond reducing blood glucose level (Hasan et al., 2024; Verma & McMurray, 2018).

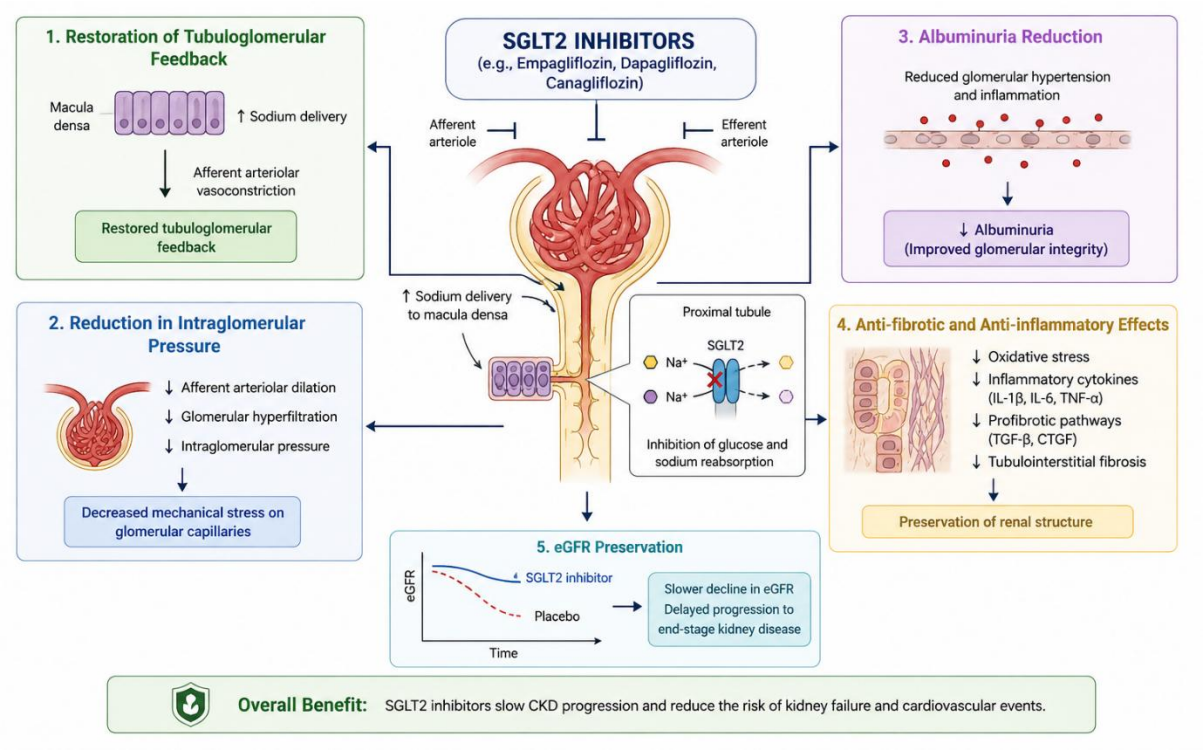

Figure 4. *Reno protective Mechanisms of SGLT2 Inhibitors.*
SGLT2 inhibitors exert renoprotection by diverse hemodynamic, metabolic and antiinflammatory pathways. Inhibition of proximal tubular sodium and glucose reabsorption restores tubuloglomerular feedback, increases sodium supply to the macula densa and lowers glomerular hyperfiltration and intraglomerular pressure. These results lead to a reduction in mechanical stress on glomerular capillaries and a reduction in albuminuria. Other preventive strategies include mitigation of oxidative stress, generation of inflammatory cytokines and profibrotic signalling pathways, hence minimizing tubulointerstitial fibrosis and preserving kidney structure. Long-term therapy decreases the rate of decline in estimated glomerular filtration rate (eGFR), delays progression to end-stage kidney disease and reduces overall cardiorenal risk in diabetic and non-diabetic chronic kidney disease populations.

Trial	Drug	Population	Renal Outcome	Findings	References
CREDENCE	Canagliflozin	T2DM with diabetic nephropathy and albuminuric CKD	ESKD, doubling of serum creatinine, or renal/CV death	Reduced kidney failure risk, slowed CKD progression, and reduced renal/CV events	(Perkovic et al., 2019; Hasan et al., 2024
DAPA-CKD	Dapagliflozin	CKD patients with or without T2DM	Sustained eGFR decline, ESKD, or renal/CV death	Reduced CKD progression and renal/CV mortality regardless of diabetes status	(Heerspink et al., 2020; Hasan et al., 2024)
EMPA-KIDNEY	Empagliflozin	Broad CKD population with or without diabetes	Kidney disease progression or CV death	Reduced CKD progression and supported use in non-diabetic CKD	(Empagliflozin in Patients with Chronic Kidney Disease, 2023; Hasan et al., 2024)

Table 3: Major Renal Outcome Trials of SGLT2 Inhibitors

Chapter 7

Safety Profile and Clinical Challenges

The SGLT2 inhibitors offer considerable cardiovascular, renal, and metabolic benefits, but are linked with multiple significant adverse effects and clinical problems that necessitate careful selection and monitoring of patients (Miller & Shubrook, 2015; Popoviciu et al., 2024). The safety profile and challenges of these agents is crucial to understand for getting therapeutic benefit while decreasing potential risk (Miller & Shubrook, 2015.

Genital mycotic infection is one of the most prevalent side events observed with SGLT2 inhibitors. The increased urinary glucose excretion provides a good habitat for fungal development, especially Candida species, resulting in a higher frequency of genital infection in both men and women (Miller & Shubrook, 2015; Hasan et al., 2024). Urinary tract infections may occur occasionally. Most infections are mild to moderate in severity and can be successfully treated with conventional antifungal or antibiotic medication (Neal et al.,2017; Popoviciu et al.,2024).

Another important but very rare consequence is euglycemic diabetic ketoacidosis (euDKA). Unlike classical diabetic ketoacidosis, euDKA may develop with just modestly raised or even normal blood glucose levels, perhaps resulting in a delayed diagnosis. SGLT2 inhibitors stimulate ketogenesis by increasing glucagon secretion, decreasing insulin levels and promoting oxidation of fatty acid (Verma & McMurray, 2018; Hasan et al., 2024). The risk factors such as fasting for a lengthy period, serious illness, surgery, alcohol excess even severe insulin insufficiency (Miller & Shubrook, 2015; Popoviciu et al., 2024). For this, clinicians must educate the patients to recognize and understand the symptoms including nausea, vomiting, stomach pain and dyspnoea (Miller & Shubrook, 2015).

Other problems are volume depletion and hypotension associated with the osmotic diuretic and natriuretic actions of SGLT2 inhibitors (Miller & Shubrook, 2015; Verma & McMurray, 2018). Elderly people, who are receiving diuretics and patients with decreased renal function may be especially sensitive to dehydration, dizziness and orthostatic hypotension (Miller & Shubrook, 2015; Hasan et al., 2024). Hence, appropriate hydration and close monitoring of blood pressure also renal function is advised at the start of therapy even during dose titration (Nugraha & Susanto.,2025).

Concerns about fractures and lower-limb amputations were initially voiced following the CANVAS Program, which demonstrated an elevated risk of amputation in individuals treated with canagliflozin (Neal et al., 2017; Hasan et al., 2024). Contributing variables may include volume depletion, peripheral vascular dysfunction and poor wound healing (Neal et al., 2017; Hasan et al., 2024). However, the results from subsequent research and meta-analyses have been conflicting and the overall class effect remains unknown (Hasan et al., 2024; Verma & McMurray, 2018). However, caution is suggested in patients with severe peripheral vascular disease, diabetic foot ulcers or previous amputations (Hasan et al., 2024).

The safety of SGLT2 inhibitors in senior populations has also been a great focus (Miller & Shubrook, 2015; Hasan et al., 2024). Older patients often have many co-morbidities, greater susceptibility to dehydration and hypotension (Miller & Shubrook, 2015; Hasan et al., 2024). However, the clinical trials have shown better tolerability profiles in the elderly patient population with adequate monitoring and individualization of treatment procedure.

SGLT2 inhibitors are increasingly used in patients with chronic kidney disease (CKD) because they exert reno protective effects (Heerspink et al., 2020; Perkovic et al., 2019). Glycemic effectiveness declines with decreasing estimated glomerular filtration rate (eGFR) although renal and cardiovascular protective advantages continue to be shown even in people with moderate chronic kidney disease (Heerspink et al., 2020; Hasan et al., 2024). In large trials like

DAPA-CKD and EMPA-KIDNEY, very satisfying results were observed in CKD patients with or without diabetes (Heerspink et al., 2020; Empagliflozin in Patients with Chronic Kidney Disease, 2023). Renal function, electrolyte balance and volume status should, nevertheless, be checked from time to time throughout treatment (Heerspink et al., 2020; Hasan et al., 2024).

The risk-benefit assessment is still of paramount importance in SGLT2 inhibitors clinical practice (Miller & Shubrook, 2015; Hasan et al., 2024). In most patients with T2DM, heart failure or CKD, the CV and renal advantages are far greater than the possible hazards (Hasan et al., 2024; Verma & McMurray, 2018). SGLT2 inhibitors are highly safe when paired with patient education, customized treatments and early monitoring side effects (Miller & Shubrook, 2015; Hasan et al., 2024). Recent evaluations further emphasize that despite some adverse effects, SGLT2 inhibitors are a major breakthrough for modern cardiorenal-metabolic therapeutic advancements (Hasan et al., 2024; Verma & McMurray, 2018).

Adverse Effect	**Proposed Mechanism**	**Clinical Significance**	**Management**	**References**
Genital mycotic infections	Increased urinary glucose promotes fungal growth	Common but usually mild; more frequent in females	Personal hygiene, antifungal therapy, patient education	(Miller & Shubrook, 2015; Hasan et al., 2024)
Urinary tract infections	Glucosuria may facilitate bacterial growth	Usually mild; severe infections are uncommon	Antibiotic treatment and hydration	(Miller & Shubrook, 2015; Hasan et al., 2024)
Euglycemic diabetic ketoacidosis (euDKA)	Increased ketogenesis, reduced insulin levels, enhanced glucagon secretion	Rare but potentially serious metabolic complication	Temporary drug discontinuation during illness/surgery; patient education	(Verma & McMurray, 2018; Hasan et al., 2024)

Volume depletion and hypotension	Osmotic diuresis and natriuresis causing plasma volume reduction	Dizziness, dehydration, orthostatic hypotension	Monitor hydration, blood pressure, and renal function	(Miller & Shubrook, 2015; Verma & McMurray, 2018)
Fracture risk	Possible mineral imbalance and volume depletion	Increased fracture concern mainly reported with canagliflozin	Fall-risk assessment and monitoring in high-risk patients	(Neal et al., 2017; Hasan et al., 2024)
Lower-limb amputation	Reduced perfusion and impaired wound healing in susceptible individuals	Higher risk in patients with peripheral vascular disease or diabetic foot disease	Careful foot monitoring and avoidance in high-risk patients	(Neal et al., 2017; Hasan et al., 2024)
Acute decline in eGFR	Hemodynamic reduction in intraglomerular pressure	Usually transient and reversible	Monitor renal function after therapy initiation	(Heerspink et al., 2020; Perkovic et al., 2019)
Safety concerns in elderly patients	Increased susceptibility to dehydration and hypotension	Higher risk of falls and volume depletion	Individualized dosing and close clinical monitoring	(Miller & Shubrook, 2015; Hasan et al., 2024)
Safety in CKD populations	Reduced glycemic efficacy at low eGFR levels	Cardiorenal benefits generally persist despite lower glucose-lowering effect	Regular monitoring of renal function and electrolytes	(Empagliflozin in Patients with Chronic Kidney Disease, 2023; Heerspink et al., 2020)

Table 4. SGLT2 Inhibitors Adverse Effects and Safety Considerations

Chapter 8

Expanding Therapeutic Applications Beyond Diabetes

The therapeutic role of sodium glucose co-transporter 2 (SGLT2) inhibitors has expanded well beyond glucose level lowering in Type 2 Diabetes Mellitus (T2DM) (Hasan et al., 2024; Verma & McMurray, 2018).The increasing clinical evidence is showing these medicines have considerable cardiovascular, renal and metabolic benefits even in non-diabetic persons and their wider uses in modern medicine is becoming evident (McMurray et al., 2019; Anker et al., 2021).

One of the most notable advancements is the use of SGLT2 inhibitors in heart failure patients without diabetes (McMurray et al., 2019; Packer et al., 2020). Landmark trials such as DAPA-HF and EMPEROR-Reduced showed that dapagliflozin and empagliflozin significantly reduced hospitalizations for heart failure and cardiovascular death in patients with heart failure with reduced ejection fraction (HFrEF), regardless of diabetic status (McMurray et al., 2019; Packer et al., 2020). Likewise, in the EMPEROR-Preserved study, significant improvements were shown in heart failure with preserved ejection fraction (HFpEF), a disease state that has had few treatments until now (Anker et al., 2021; Hasan et al., 2024). These results assure that SGLT2 inhibitors as a keystone of heart failure treatment independent of glycemic control (Anker et al., 2021; McMurray et al., 2019).

SGLT2 inhibitors have also shown considerable advantages in chronic kidney disease (CKD) without diabetes (Heerspink et al., 2020; Hasan et al., 2024). Furthermore, trials such as EMPA-KIDNEY and DAPA-CKD revealed significant decreases in progression of CKD, end-stage kidney disease and cardiovascular mortality in both diabetic and non-diabetic populations (Heerspink et al., 2020; Empagliflozin in Patients with Chronic Kidney Disease, 2023). Their reno protective effects are mostly related to restoration of tubulo-glomerular feedback,

reduction in intraglomerular pressure and anti-inflammatory effects (Heerspink et al., 2020; Verma & McMurray, 2018).

Also there is more evidence for possible applications in metabolic syndrome and obesity (Ferrannini et al., 2014; Hasan et al., 2024). SGLT2 inhibitors trigger glucosuria and loss of calory resulting in moderate but clinically relevant weight loss and improvements in insulin resistance (Ferrannini et al., 2014; Verma & McMurray, 2018). Reduction in visceral adiposity, blood pressure and metabolic stress may aid in improving overall cardiometabolic health status, making these drugs suitable adjuncts in the management of metabolic syndrome (Verma & McMurray, 2018; Bhatt et al., 2024).

Another area of burgeoning attention is nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) (Verma & McMurray, 2018). Experimental & clinical investigations show that SGLT2 inhibitors may reduce hepatic fat formation, cell damage, and inflammation in the liver (Hasan et al., 2024; Verma & McMurray, 2018). This means they could help treat hepatic steatosis and delay the onset of liver fibrosis through improvements in body weight, insulin sensitivity and lipid metabolism, but additional large-scale trials are needed (Hasan et al., 2024; Verma & McMurray, 2018).

SGLT2 inhibitors are also being studied for potential neuro protective and anti-aging benefits (Hasan et al., 2024; Verma & McMurray, 2018). Clinical evidence shows that some of these compounds may reduce oxidative stress, cell damage, rapid mitochondrial function and reduce chronic inflammation, all processes here strongly linked to neuro degeneration and aging (Hasan et al., 2024; Verma & McMurray, 2018). The studies also show possible benefits in cognitive decline and age-related cardiovascular dysfunction (Hasan et al., 2024; Verma & McMurray, 2018). These need further clinical confirmation for clinical advancement (Hasan et al., 2024; Verma & McMurray, 2018).

In summary, the rising therapeutic applications of SGLT2 inhibitors underscore their evolution from glucose-lowering drugs to multi-target cardiorenal-metabolic medicines (Hasan et al., 2024; Verma & McMurray, 2018). Their benefits extend well beyond diabetes treatment and may impact future treatment plans in several chronic diseases, as highlighted in recent studies (Hasan et al., 2024; Verma & McMurray, 2018).

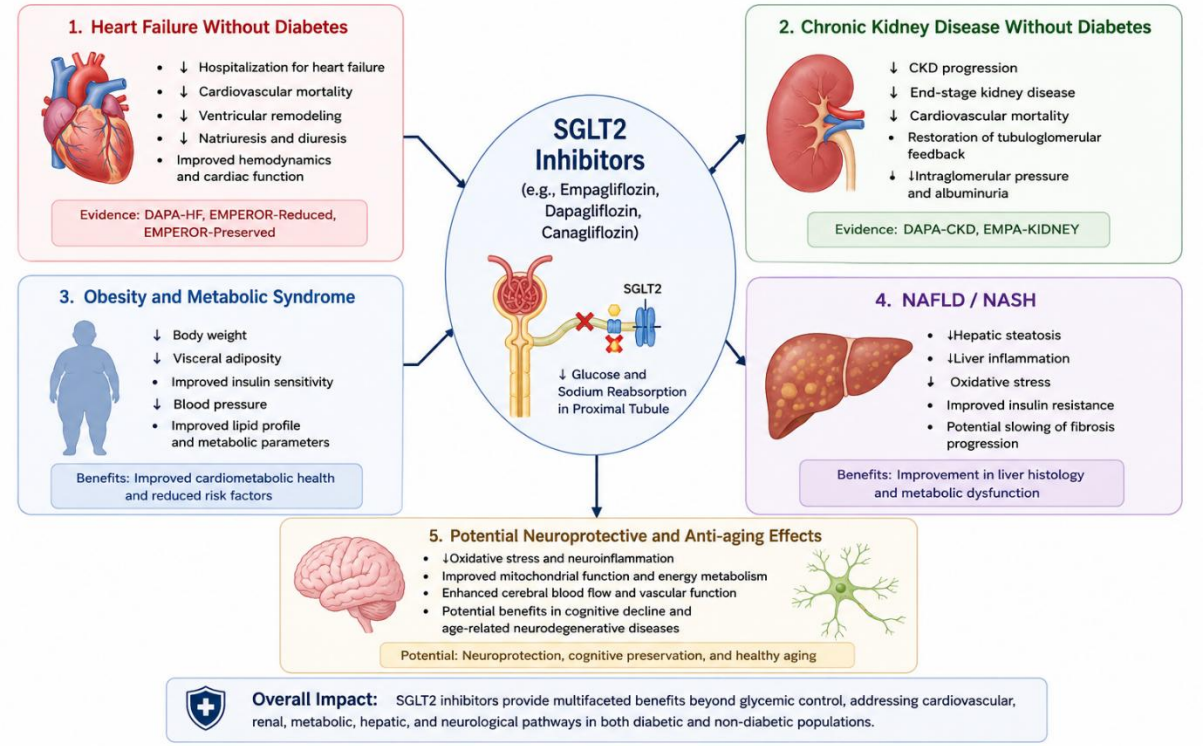

Figure 5. Expanding Therapeutic Uses of SGLT2 Inhibitors Outside Diabetes.

SGLT2 inhibitors have wide-ranging therapeutic promise outside glycemic control via numerous cardiovascular, renal, metabolic, hepatic and possibly neuroprotective pathways. In clinical trials, large advantages have been found in heart failure and chronic renal disease populations regardless of diabetic status, including decreases in hospitalisation for heart failure, cardiovascular mortality, chronic kidney disease progression, and end-stage kidney disease. Other metabolic benefits are weight loss, increased insulin sensitivity, and beneficial effects on obesity and metabolic syndrome. Data also supports possible roles in non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), neuroprotection, and healthy aging by reducing oxidative stress, inflammation, and mitochondrial dysfunction.

Chapter 9

Current Research Gaps and Unsolved Controversies

Several critical research gaps and clinical obstacles remain, despite the impressive cardiovascular, renal, and metabolic benefits of sodium-glucose co-transporter 2 (SGLT2) inhibitors (Hasan et al., 2024; Miller & Shubrook, 2015). More studies are required to optimize their therapeutic use, improve patient selection and better understanding of their long-term safety also mechanistic consequences (Hasan et al., 2024; Verma & McMurray, 2018).

One big area of concern is long term protection (Miller & Shubrook, 2015; Hasan et al., 2024). Though present data pointed to generally good safety profiles, uncertainties still exist about the long-term implications of acute SGLT2 inhibition, mostly in the elderly and in advanced chronic kidney disease (CKD) patients (Heerspink et al., 2020; Hasan et al., 2024). Adverse effects are seen such as recurring vaginal infections, volume depletion, euglycemic diabetic ketoacidosis even potential fracture or amputation concerns needed in the long term in different patients (Miller & Shubrook, 2015; Neal et al., 2017). Hence, it is important to do further post-marketing surveillance and real-world analysis (Hasan et al., 2024; Verma & McMurray, 2018).

Another intriguing future avenue is precision therapeutic approaches (Hasan et al., 2024; Verma & McMurray, 2018). Individual reactions to SGLT2 inhibitors are dependent on genetic background, comorbidities, renal function and cardiovascular risk profiles (Hasan et al., 2024; Verma & McMurray, 2018). Additional studies may reveal patient-related factors associated with excellent therapy response or sensitivity to harmful effects (Hasan et al., 2024; Verma & McMurray, 2018). These individualized treatment options may improve efficacy while reducing problems (Hasan et al., 2024; Verma & McMurray, 2018).

There is also increased interest in combination therapeutic options (Miller & Shubrook, 2015; Hasan et al., 2024). SGLT2 inhibitors are widely used alongside metformin, insulin, glucagon-like peptide-1 (GLP-1) receptor agonists and renin-angiotensin-aldosterone system (RAAS) inhibitors (Miller & Shubrook, 2015; Hasan et al., 2024). Recent research suggests that combination cardiorenal-metabolic therapy may have synergistic effects through complementary pathways (Hasan et al., 2024; Verma & McMurray, 2018). The combined use of SGLT2 inhibitors and GLP-1 receptor agonists in particular may further improve weight loss, cardiovascular protection and metabolic regulation (Hasan et al., 2024; Verma & McMurray, 2018). However, further studies are needed to define the appropriate sequence, dosing strategies and long-term safety of combination therapy (Hasan et al., 2024; Miller & Shubrook, 2015).

Biomarker-guided treatment is another area of interest in building (Hasan et al., 2024; Verma & McMurray, 2018). Biomarkers identification related with inflammation, fibrosis, oxidative stress or kidney injury may improve early prediction of therapy response and disease progression (Hasan et al., 2024; Verma & McMurray, 2018). Biomarker-based techniques may assist doctors in identifying individuals most likely to respond to SGLT2 inhibitor therapy, and enable more personalized treatment planning (Hasan et al., 2024; Verma & McMurray, 2018). Pharmacoeconomic issues also are still significant (Miller & Shubrook, 2015; Hasan et al., 2024). Despite the reductions in hospitalizations and long-term cardiorenal problems achieved with SGLT2 inhibitors, their relatively high cost may limit availability in low- and middle-income nations (Miller & Shubrook, 2015; Hasan et al., 2024). Future research should investigate long-term cost-effectiveness, healthcare resource utilization and economic effects in various healthcare systems and patient demographics (Miller & Shubrook, 2015; Hasan et al., 2024).

Another key research gap is that different populations are under-represented in clinical trials (Hasan et al., 2024; Verma & McMurray, 2018). Many landmark research have largely included people from specific regional and racial backgrounds which may limit generalizability of findings (Hasan et al., 2024; Verma & McMurray, 2018). More study in other racial, ethnic, socioeconomic, and age cohorts is needed to better understand population-specific responses and to guarantee equitable therapeutic use (Hasan et al., 2024; Verma & McMurray, 2018).

9.1 Efficacy and Safety Limits in Advanced CKD

Initiation of SGLT2 inhibitors provide a transient hemodynamic "dip" in the estimated glomerular filtration rate (eGFR) due to afferent arteriolar vasoconstriction (Heerspink et al., 2020). While large renal outcome trials have proved that long-term eGFR preservation outweighs this temporary decline, an unresolved controversy surrounds their safety limits in advanced chronic kidney disease (stage 4 or 5 CKD with eGFR < 20–25 mL/min/1.73m²) (The EMPA-KIDNEY Collaborative Group, 2023). Because the primary glucose-lowering efficacy of these drugs significantly decreases alongside dropping renal function defines the exact fact where metabolic futility meets long-term cardiorenal protection remains highly debated in modern nephrology (Wang & Zuo, 2025).

9.2 Long-Term Durability in Non-Diabetic Populations

The physiological long-term durability of SGLT2 inhibition in non-diabetic populations is still unknown, despite the fact that trials like DAPA-CKD and EMPA-KIDNEY unquestionably extended the therapeutic landscape to people without diabetes (The EMPA-KIDNEY Collaborative Group, 2023; Li et al., 2025). Unlike diabetic patients, who possess an overexpressed baseline of SGLT2 cotransporters, non-diabetic cohorts display different baseline metabolic shifts, meaning the precise molecular differences in systemic anti-inflammatory responses and cellular protection outside of glucotoxicity require deep, prolonged surveillance (Nugraha & Susanto, 2025).

9.3 Optimization of Combination Therapy with GLP-1 Receptor Agonists

Combination therapy of SGLT2 inhibitors with glucagon-like peptide-1 (GLP-1) receptor agonists has become a desirable dual approach as the management of cardiorenal-metabolic syndrome moves toward a holistic care model (Lunder & Janić, 2025). The precise sequencing, ideal patient profiles, and long-term economic scalability of this combination therapy are still mainly unknown, despite the fact that both medication classes lower major adverse cardiovascular events (MACE) through unique, complimentary mechanisms (Nugraha & Susanto, 2025). There are still unanswered problems regarding whether immediate dual initiation provides better multi-organ protection than sequential step-up therapy, necessitating more precise recommendations in clinical practice (Popoviciu et al., 2024).

9.4 Unsolved Controversies

While the cardiac & renal benefits of SGLT2 inhibitors are well-established, many clinical controversies and unsolved questions continue to challenge practitioners regarding their optimization, safety limits, and dual-therapy boundaries.

9.4.1 Amputation Risk and Safety Controversies with Canagliflozin

One of the most noteworthy debates occurred from the CANVAS Program, which revealed an unanticipated rise of lower-limb amputations and fractures largely associated with canagliflozin medication (Neal et al., 2017). Though later studies with other class agents could not strongly reproduce this specific hazard, analyzing the underlying mechanism—whether caused by acute volume depletion, localized hypovolemia, or tissue perfusion constraints—remains an unsolved clinical challenge (Popoviciu et al., 2024). Clinicians still encounter ambiguity regarding whether this risk is a rigorous canagliflozin-specific event or a latent class impact that warrants aggressive consideration in patients with advanced peripheral vascular disease or history of diabetic foot ulceration (Watts et al., 2018).

Chapter 10

Conclusion And Future Direction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors is one of the most important therapeutic breakthroughs in contemporaneous diabetes and cardiorenal therapies (Hasan et al., 2024; Verma & McMurray, 2018).Which was originally designed as glucose-lowering agents for T2DM, these medications have manifested large cardiovascular, renal and metabolic advantages much beyond glycemic management (Hasan et al., 2024; Verma & McMurray, 2018). SGLT2 inhibitors exert multimodal protection across various organ systems through mechanisms such as glucosuria, natriuresis, restoration of tubulo-glomerular feedback, decrease in oxidative stress and anti-inflammatory actions (Perkovic et al., 2019).

Major outcome trials including EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, DAPA-HF, CREDENCE, DAPA-CKD, and EMPA-KIDNEY have consistently shown reductions in cardiovascular mortality, heart failure hospitalizations and chronic kidney disease progression also the overall cardiorenal risks (Perkovic et al., 2019; McMurray et al., 2019). More importantly, these benefits frequently occur independently of a patient's diabetes status, solidifying the role of SGLT2 inhibitors treating heart failure and chronic renal disease in both diabetic and non-diabetic populations (Packer et al., 2020; Heerspink et al., 2020).

The emergence of SGLT2 inhibitors represents a fundamental change in the control of glucose level (Steiner, 2016; Hasan et al., 2024). Now, the treatment approaches are increasingly targeting incorporated cardiorenal-metabolic protection rather than just glycemic control (Hasan et al., 2024; Verma & McMurray, 2018). This revolution has had a major effect on international clinical recommendations and has changed the way diabetes, heart failure and chronic renal disease patients are treated (McMurray et al., 2019; Packer et al., 2020).

They have significant therapeutic efficacy, but further study is needed to address long-term safety issues, optimize the strategy of combination therapy, improve biomarker-guided treatment, and evaluate the effectiveness in different groups (Miller & Shubrook, 2015; Hasan et al., 2024). The potential of SGLT2 inhibitors in obesity, fatty liver disease, neurodegenerative illnesses and healthy aging needs to be studied further (Hasan et al., 2024; Verma & McMurray, 2018).

Ultimately, SGLT2 inhibitors have evolved from antidiabetic medications into indispensable, multifunctional therapies with wide therapeutic value (Hasan et al., 2024; Verma & McMurray, 2018). They are predicted to play a significant role in determining the future of diabetes, nephrology, cardiovascular medicine and precision-based cardiorenal care through their continuing growth (Popoviciu et al., 2024; Verma & McMurray, 2018)

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