Article published on 2025-6-23

Unlocking the Potential of Sotagliflozin in Diabetes Mellitus targeting SGLT 1 & SGLT 2: A Comprehensive Review

Manoj Kumbhare, Siddhi Chandak*, Arshad Shaikh, Sakshi Velhal, Aishwarya Dukare, Harshali gode, Nishant Pagere, Bhagwan Ide

Department of Pharmaceutical Chemistry, SMBT College of Pharmacy, Dhamangaon, Nashik – 422403, India

***Correspondence Author:**
Siddhi M. Chandak,
Department of Pharmaceutical Chemistry, SMBT College of Pharmacy, Dhamangaon, Nashik – 422403, Affiliated to Savitribai Phule Pune University, India
Email: siddhimchandak@gmail.com
ORCID ID: 0009-0006-7860-2388

Chinese Journal of Applied Physiology, 2025: e20250012

Abstract Sotagliflozin, a novel dual inhibitor of sodium-glucose cotransporters 1 and 2 (SGLT1/2), represents a promising therapeutic advancement for managing diabetes mellitus. By inhibiting SGLT1 in the small intestine and SGLT2 in the kidneys, sotagliflozin uniquely improves glycemic control through reduced postprandial glucose absorption and enhanced urinary glucose excretion. This dual mechanism has shown significant benefits for both type 1 and type 2 diabetes, including reduced insulin requirements, better glycemic control, weight loss, and improved cardiovascular and renal outcomes. Clinical trials have highlighted its potential to mitigate the risks of diabetic complications such as heart failure and chronic kidney disease. However, its use is associated with some side effects, including gastrointestinal disturbances, urinary tract infections, and an elevated risk of diabetic ketoacidosis. This review explores the chemistry, pharmacology, and therapeutic implications of sotagliflozin, emphasizing its unique dual-target approach and potential to address unmet needs in diabetes management.

Keywords Sotagliflozin, Diabetes mellitus, Pharmacological, Phytochemicals

Introduction

Diabetes mellitus (DM) of Types 1 and 2 impact millions of humans globally and poses serious health risks [1]. Chronically elevated blood sugar levels resulting from either insulin resistance, inadequate insulin production, or a combination of the two are characteristics of both kinds. Many people still struggle to achieve optimal blood sugar control, particularly those with type 1 diabetes, despite significant improvements in diabetes management in recent years [2]. Type 1 diabetes is usually treated with insulin therapy, but type 2 diabetes is usually treated with insulin, oral hypoglycemic drugs, and lifestyle changes [3]. However, these treatments have drawbacks such

DOI: 10.62958/j.cjap.2025.012
www.cjap.ac.cn

Published by CJAP editorial office and Asian BioMed Innovation Press

as poor blood glucose control, weight gain, and side effects like hypoglycaemia [4].

SGLT2 inhibitors have significantly transformed the treatment of diabetes, particularly for those with type 2 diabetes [5]. These drugs work by blocking glucose reabsorption in the kidneys, leading to increased glucose elimination via urine. They have been shown to enhance glycemic control, promote weight loss, and offer cardiovascular and renal benefits. Nevertheless, SGLT2 inhibitors come with certain drawbacks, such as reduced efficacy in type 1 diabetes and the possibility of side effects, including urinary tract infections and diabetic ketoacidosis (DKA.)[6].

Researchers have looked into developing dual SGLT1/2 inhibitors in response to these difficulties, which aim to enhance the efficiency of SGLT2 inhibition while mitigating some of its disadvantages [7]. Sotagliflozin, a novel dual inhibitor, targets both SGLT1 (located primarily in the small intestine) and SGLT2 (located in the kidneys). Comparing this dual-target strategy to SGLT2 inhibition alone, offers several advantages, especially when it comes to addressing the challenges associated with controlling type 1 and type 2 diabetes[8].

Because sotagliflozin inhibits both SGLT1 and SGLT2, it has a unique effect on the treatment of diabetes. On the one hand, SGLT1 inhibitors reduce the absorption of glucose in the small intestine, reducing glucose spikes after meals, whereas SGLT2 inhibitors help the excretion of glucose through urine [9]. Together, these benefits may improve glucose control overall, lessen the requirement for insulin in people with type 1 diabetes, and promote weight loss without the increased risk of severe hypoglycemia that is usually associated with insulin therapy[10].

This review aims to comprehensively analyse sotagliflozin pharmacological properties, chemical makeup, and therapeutic applications. Examining these facets will strengthen our understanding of how sotagliflozin could be a promising treatment for diabetes and its importance in improving patient outcomes, especially for those who are unable to achieve adequate glycemic control with current therapies [11].

Background on Diabetes and Treatment Limitations

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia or consistently high blood sugar levels. The two main forms of diabetes, type 1 diabetes (T1D) and type 2 diabetes (T2D), share many characteristics, including impaired glucose metabolism, although having different underlying causes [12].

Type 1 Diabetes

This autoimmune disease is characterized by a total lack of insulin because the immune system unintentionally targets and kills the pancreatic beta cells that produce insulin. People with T1D must therefore rely on exogenous insulin to control their blood sugar levels. Many T1D patients, however, still have difficulty achieving ideal glycemic control even after receiving insulin treatment [13]. These people are more likely to suffer from long-term problems such as renal disease, nerve damage, and heart disease, and many of them have high blood sugar levels after meals. Individuals with type 1 diabetes may also be at risk for hypoglycemia as a result of their insulin treatment, which can have major repercussions if left untreated[13], [14].

Type 2 Diabetes

Insulin resistance, a metabolic disorder that causes cells to become less responsive to insulin and ultimately results in an insulin shortage, is a hallmark of type 2 diabetes. Most people with T2D do not immediately need exogenous insulin treatment, unlike those with T1D.[15]. But as the illness worsens, the body's capacity to produce insulin frequently runs out of ways to combat insulin resistance, which raises blood sugar levels. Factors like obesity, a sedentary lifestyle, and unhealthy eating habits are strongly linked to type 2 diabetes. Despite the availability of numerous therapeutic alternatives, such as SGLT2 inhibitors, GLP-1 agonists, sulfonylureas, and metformin, many patients still have difficulty maintaining continuous glycemic control and experience consequences such as kidney, heart, and visual problems [16].

Diabetes is becoming more and more common worldwide, which emphasizes the pressing need to develop novel medicines that effectively control blood sugar levels while reducing the negative side effects frequently associated with existing therapy. In recent times, SGLT2 inhibitors have gained significant attention as a promising class of drugs [17].

SGLT2 Inhibitors: Mechanism of Action and Limitations

The protein known as sodium-glucose co-transporter 2, or SGLT2, is found in the kidneys' proximal tubules and reabsorbs most of the glucose that the kidneys filter. In normal conditions, 90% of glucose is recovered by SGLT2, preventing glucose loss in urine.

Glucose excretion through urine increases and blood glucose levels decrease when medications that target this transporter are used [18]. This class of drugs has shown great promise in the treatment of type 2 diabetes because it helps control blood sugar levels without depending on insulin production changes, reducing the risk of hypoglycaemia [19].

SGLT2 inhibitors have also shown additional benefits, including lowering blood pressure, protecting the kidneys and heart, and encouraging weight loss. SGLT2 inhibitors can slow the progression of renal disease, lower the risk of hospitalization for heart failure in diabetics, and prevent severe cardiovascular occurrences, according to clinical trials. However, despite these positive effects, it is crucial to recognize the drawbacks of SGLT2 inhibition [20].

First off, those with type 1 diabetes, whose main problem is inadequate insulin production rather than insulin resistance, do not respond as well to SGLT2 inhibitors. Furthermore, the way SGLT2 inhibitor function may result in adverse consequences including dehydration, vaginal infections, and infections of the urinary tract. Furthermore, diabetic ketoacidosis, a potentially fatal disease for those with type 1 diabetes, is increased by these drugs. When there is insufficient insulin, the body begins using fat as fuel, which results in diabetic ketoacidosis [21].

The Emergence of Dual SGLT1/2 Inhibitors

To improve overall glucose regulation and overcome the drawbacks of SGLT2 inhibitors, dual SGLT1/2 inhibitors have been developed. By targeting both SGLT1 and SGLT2, these drugs provide a more thorough approach to the treatment of diabetes. The small intestine is where SGLT1 is primarily expressed and is essential for the absorption of galactose and glucose. By inhibiting SGLT1, it lessens the intestinal absorption of glucose, hence reducing the post-meal rises in blood sugar [22]. Sotagliflozin and other dual inhibitors that block both SGLT1 and SGLT2 at the same time enhance glucose control by reducing intestinal glucose absorption as well as urine excretion. This technique can improve control over fasting blood glucose, which can lead to additional benefits for managing type 1 and type 2 diabetes [23].

A dual-target approach, like sotagliflozin, seems especially helpful for people with type 1 diabetes. Insulin therapy alone is generally insufficient for those with this syndrome, who frequently require high insulin dosages and show severe glycemic fluctuation, especially after meals. It is also anticipated to help reduce weight, which is a major problem for many people with type 2 diabetes, by preventing the absorption of glucose and promoting the outflow of calories through the urine [24].

The Promise of Sotagliflozin

Sotagliflozin's dual inhibition of SGLT1 and SGLT2 provides a fresh approach to the challenges of managing diabetes. Comparing the combined effects of reduced intestinal glucose absorption and higher urine glucose excretion to SGLT2 inhibitors alone, the former may result in better glycaemic management [25]. Promising results from clinical trials for sotagliflozin include improved renal function, decreased insulin needs, weight loss, and improved glycemic management. The development of sotagliflozin represents a promising breakthrough in the management of diabetes. Being a dual inhibitor of SGLT1 and SGLT2, it offers a unique mode of action that may be helpful for those with type 1 and type 2 diabetes. The goal of this review is to learn more about sotagliflozin's chemistry, pharmacology, and therapeutic applications [26].

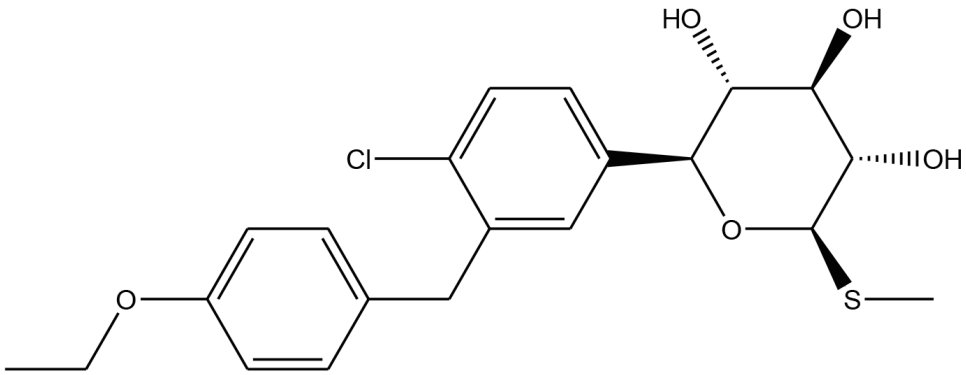
Chemistry of Sotagliflozin

By inhibiting SGLT-1 and SGLT-2, the small molecule sotagliflozin, sometimes referred to as LX4211, is taken orally. In human studies, it has around 20 times the selectivity for SGLT-2 compared to SGLT-1; the IC50 values for SGLT-2 and SGLT-1 are 0.0018 μM and 0.036 μM, respectively. The chemical formula for sotagliflozin is (2S, 3R, 4R, 5S, and 6R)-2-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]. 3, 4, 5-triol-6-methylsulfanyloxane. Although sotaglifozin is more than 10 times more effective than dapagliflozin and canagliflozin, which are selective SGLT-2 inhibitors, it is nonetheless equally effective as an SGLT-2 inhibitor. However, nothing is known about how it affects SGLT-1 in different tissues [27].

The information below indicates that sotagliflozin appears to have little effect on renal SGLT-1, suggesting that its low affinity is only useful as a treatment in tissues (such as the gut) where SGLT-1 is highly expressed. Another theory is that sotagliflozin functions as a strong inhibitor of intestinal SGLT-1 because it is more prevalent in the intestinal lumen than in the bloodstream [28].

Mechanism of action

Sotagliflozin is a type of sodium-glucose co-transporter 2 (SGLT2) inhibitor that was developed to treat diabetes. It inhibits the renal proximal convoluted tubule's sodium-glucose cotransporter-2 (SGLT2) enzymes. A good way to treat diabetes is



(2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-methylsulfanyloxane-3,4,5-triol

Structure of sotagliflozin

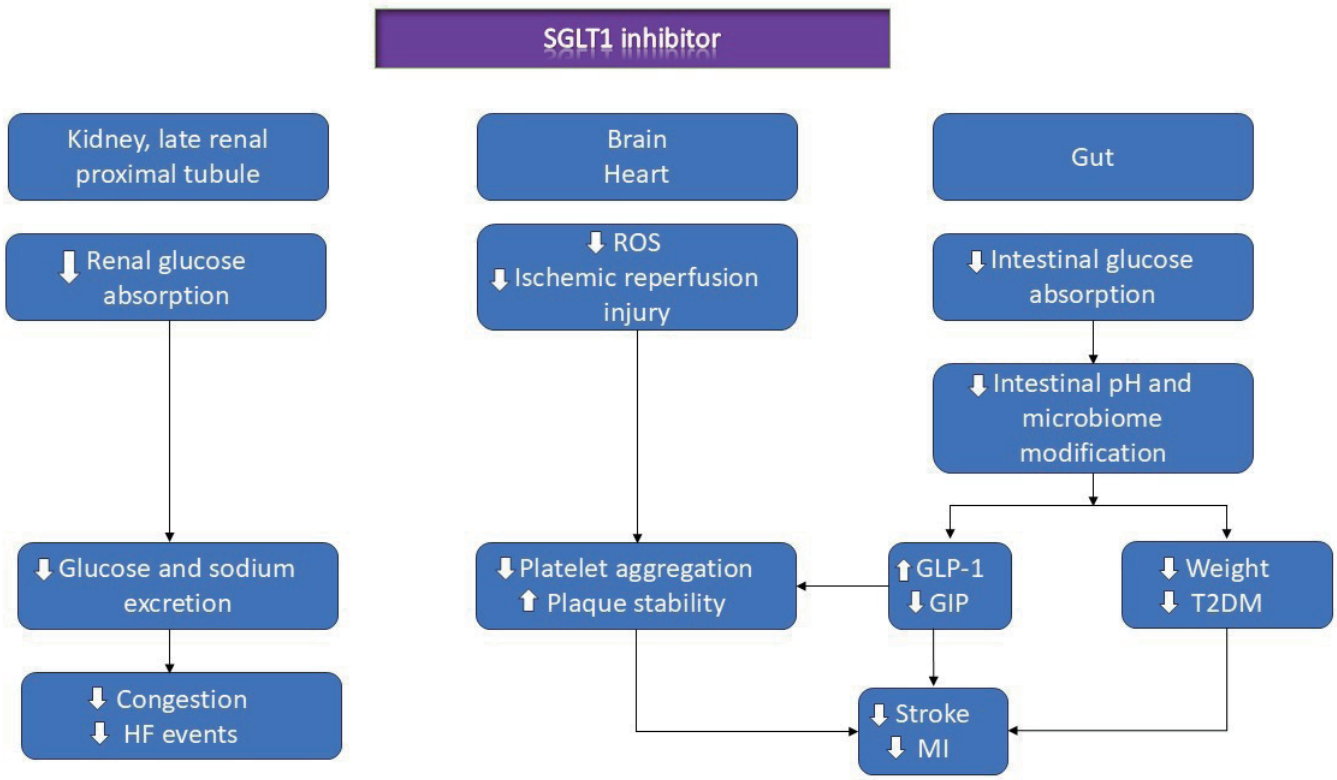


Figure 1: Mechanism of action of Sotagliflozin.

to target SGLT2, as this transporter is in charge of reabsorbing about 90% of the glucose that is filtered past the kidneys. Blood glucose levels of 180 mg/dL are generally considered to be the threshold for renal glucose reabsorption. Higher levels of SGLT2 are found in diabetics, though, and this could exacerbate hyperglycemia. In diabetic patients, better glucose control results from blocking the SGLT2 protein. This prevents glucose from being reabsorbed by the kidneys [29].

Sotagliflozin is a unique type of medication since it acts as an SGLT1 and SGLT2 inhibitor. Inhibiting the SGLT1 transporter, which primarily facilitates the absorption of glucose in the small intestine, can slow down the digestion of glucose after meals. Additionally, this may raise GLP-1 and GIP plasma levels. Since numerous studies have demonstrated how successfully SGLT2 inhibitors treat patients with cardiovascular issues, their advantages are not just for those with diabetes. Trials for cardiovascular disease patients, such as the Emperor-reduced study for Empagliflozin and the DAPA-HF trial for Dapagliflozin, support the

use of SGLT-2 inhibitors [30].

Both trials included patients with heart failure (HF) and reduced ejection fraction (EF), regardless of whether they had type 2 diabetes. According to both studies, patients on SGLT2 inhibitors who kept their heart rates steady had a decreased chance of dying from a heart attack or being admitted to the hospital for heart failure. However, no noteworthy randomized controlled trials have demonstrated that SGLT-2 has a positive impact just after a decompensated heart failure episode [31]. When SGLT2 inhibitors are started soon after such an incident, their safety and effectiveness are established, as shown in the SOLOIST-WHF trial. It is still unknown how sodium-glucose cotransporter 2 drugs affect the risk of stroke [32].

Despite studies from meta-analyses looking into the effect of SGLT2 inhibitors on stroke risk in people with type 2 diabetes showing no appreciable benefits, the SCORE study, which examined the use of sotagliflozin in diabetics with chronic kidney disease, found a significant reduction in stroke incidence among those taking sotagliflozin. Despite the paucity of studies in this area at the moment, it suggests that SGLT-1 inhibitors may have anti-ischemic properties [33]. The two main categories of glucose transporters involved in preserving glucose homeostasis are facilitated transporters, known as uniporters (GLUTs), and active transporters, called symporters (SGLTs).SGLTs use the sodium gradient across the cell membrane to generate the energy needed to actively transport glucose. It takes energy for the Na+/K+ pump to keep this sodium gradient going [34]. When the human SLC5 family was cloned in 1987, the intestinal sodium/glucose transporter SGLT1 was the first member to be identified. SLC5 is made up of 12 different components, including short-chain fatty acids, choline, myoinositol (SMIT1), salt cotransporters for sugars, and iodide (NIS). One, two, four, five, six, and SMIT1 are the six human SGLTs. Instead, SGLT3 acts as a glucose sensor rather than a glucose transporter [35].

The fact that SGLTs are widely expressed emphasizes how crucial a role they play in organs other than the kidney and intestine. The two most well-known roles of SGLTs are in the intestinal and renal absorption of glucose, which primarily involves SGLT1 and SGLT2, respectively. The absorption of galactose and glucose in the gut is principally controlled by SGLT1. The two stages of this absorption in adult enterocytes are traditionally recognized as follows: (i) glucose and galactose are absorbed at the apical side, also known as the brush border membrane; (ii) glucose leaves the cell and enters the bloodstream through GLUT2, which is located at the basolateral membrane. The precise biochemical process that causes SGLT1 to be overexpressed in diabetes is still unknown [36].

An inhibitor of the sodium-glucose co-transporter 2 (SGLT2), sotagliflozin, was developed to treat diabetes. The sodium-glucose cotransporter-2 (SGLT2) enzymes in the kidney's proximal convoluted tubule are affected by it. In diabetic treatment, it is beneficial to target the SGLT2 transporter because approximately 90% of filtered glucose must be reabsorbed for it to function [37]. At blood glucose levels of 180 mg/dL, the renal threshold for glucose reabsorption is normally reached. On the other hand, people with diabetes frequently have higher SGLT2 protein levels, which can make hyperglycemia worse. The kidneys are prevented from reabsorbing glucose when the SGLT2 protein is inhibited, which helps diabetics better control their blood sugar levels. Because sotagliflozin inhibits both SGLT1 and SGLT1, the primary glucose transporter in the small intestine, it has been shown to increase plasma levels of GLP-1 and GIP and delay the breakdown of glucose after meals. This makes sotagliflozin especially remarkable [37].

Dual Inhibition (Sglt1 and Sglt 2)

SGLT1 and SGLT2 are sodium-glucose cotransporter types that sotagliflozin targets. Inhibition of SGLT1 reduces and delays postprandial hyperglycemia by slowing down glucose absorption, which is mostly facilitated in the proximal tract. Reabsorbing glucose into the bloodstream from glomerular filtrate is primarily the function of SGLT2. Sotagliflozin lowers the renal threshold for glucose and decreases the renal reabsorption of filtered glucose by inhibiting SGLT2, CARDIOVASCULAR EFFECTS:

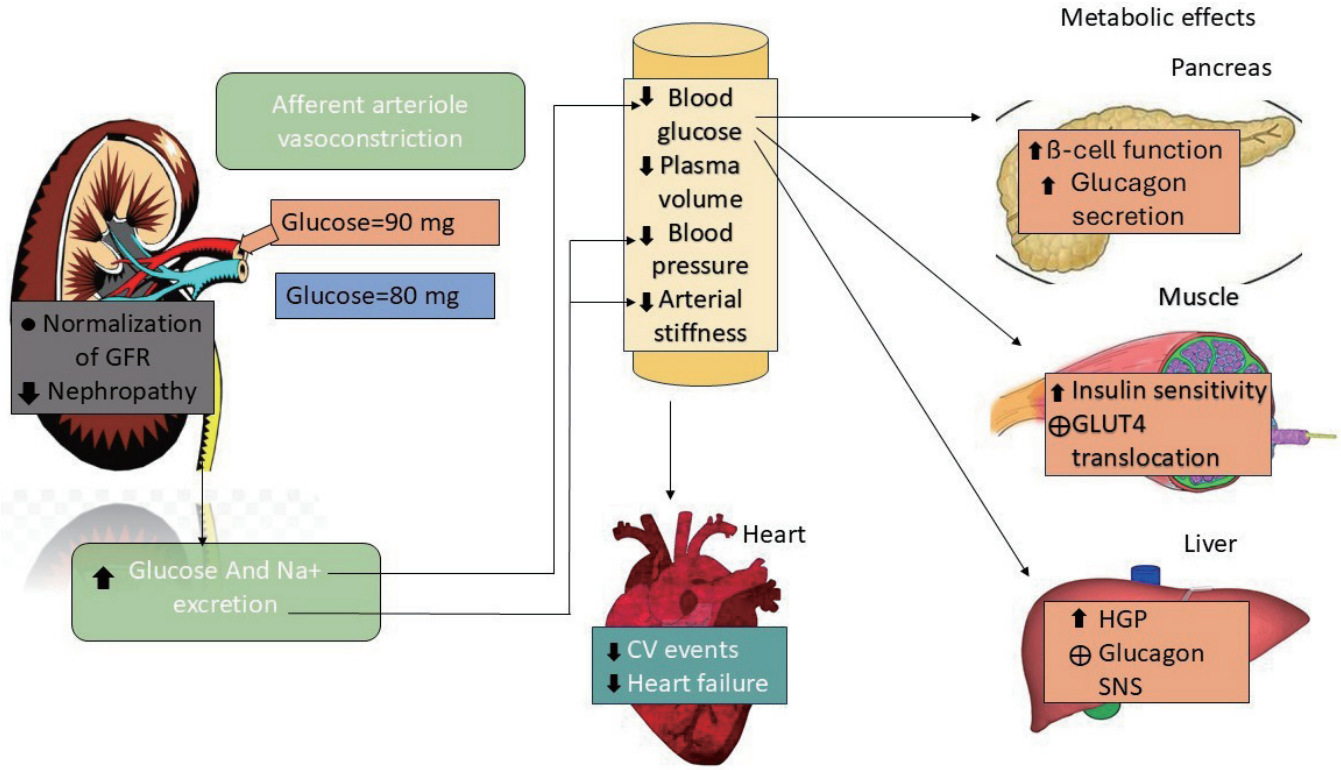


Figure 2: Integrated metabolic and hemodynamic effects of glucose and sodium modulation in the kidney and peripheral tissues.

This diagram illustrates the systemic effects of glucose and sodium excretion through the kidney. Afferent arteriole vasoconstriction and increased glucose/Na^+ excretion lead to normalization of glomerular filtration rate (GFR) and reduced nephropathy. These changes lower blood glucose, plasma volume, blood pressure, and arterial stiffness.

Recent research has shown that several sodium–glucose cotransporter-2 (SGLT2) inhibitors used to treat diabetic mellitus (DM) can reduce the risk of hospitalization for individuals with type 2 DM, who are more vulnerable to severe cardiac disease. Because sotagliflozin lowers the risk of cardiovascular death and heart failure (HF)-)-related hospitalizations, the US Food and Drug Administration (FDA) approved the medication in May 2023 for the treatment of diabetes mellitus. A lack of cardiac pumping capacity due to a variety of anatomical or functional flaws in ventricular filling can cause heart failure [38].

The heart's inability to pump blood quickly enough to meet the needs of the metabolizing tissues is the main cause of the symptoms associated with this illness. Patients with long-term health issues like diabetes and high blood pressure are particularly vulnerable to this insufficiency, which over time can put a strain on other organs [39]. The risk of cardiovascular disease is doubled for those who have diabetes. In the proximal (SGLT-2) and distal (SGLT-1) tubules, the designated transporter is prevented from reabsorbing glucose that has been filtered through the kidney glomerulus by SGLT inhibitors [40].

Nevertheless, there is mounting evidence that SGLT inhibition has cardiovascular benefits beyond glucose control, especially for those with diabetes and heart failure. Cardiomyocyte sodium levels, oxidative stress, endothelial inflammation, fibrosis, mitochondrial dysfunction, and cardiac energy metabolism are only a few of the many hypothesized sites of action (and interaction)[41].

Kidney Protection

Twenty to forty per cent of people with type 1 diabetes still have kidney problems as a result of the disease, even when traditional renal risk factors are effectively managed. By preventing glucose from being reabsorbed in the renal tubules, SGLT2 inhibitors cause glucose to be lost through urine; these drugs also lower body weight and HbA1c levels. In addition to causing glucosuria, SGLT2 inhibitors also enhance natriuresis, which lowers systolic blood pressure, decreases plasma volume, and raises serum albumin and hematocrit levels. By stimulating tubuloglomerular

feedback mechanisms, the natriuretic action also reduces intraglomerular pressure, which in turn reduces glomerular hyper filtration [41]. SGLT2 inhibition lowers the urine albumin-to-creatinine ratio (UACR), a clinical indicator of long-term cardiovascular and renal risk, and lowers the chance that both diabetic and non-diabetic patients will experience the progression of chronic kidney disease (CKD)[42], [43].

The possible mechanisms including hemodynamics, inflammation, and pathways linked to hypoxia are being studied but are still not fully understood, despite our imperfect understanding of how SGLT2 inhibitors lower UACR and protect end organs. UACR levels and associated risks are fundamentally related, and a decrease in UACR levels is associated with better long-term kidney and cardiovascular protection [44]. According to the ADA Standards of Practice Guidelines, a reduction of at least 30% in UACR is recommended as a primary therapeutic goal for people with diabetes and chronic kidney disease. A 25% to 40% decrease in UACR has been demonstrated by SGLT2 inhibitors in earlier research. The SCORED analysis showed that sotagliflozin significantly reduced UACR and improved UACR progression or regression in people with T2D and CKD [45].

Albuminuria was significantly reduced by sotagliflozin across the UACR spectrum; this reduction may be related to physiological effects resulting from the inhibition of both SGLT2 and SGLT1. The SCORED study found that UACR, a measure of kidney protection, was significantly impacted by baseline eGFR, HbA1c, and UACR levels, whereas prior cardiovascular outcome studies consistently showed benefits across varied levels of baseline renal risk. Patients with chronic kidney disease (CKD) have only been recruited into two trials thus far: SCORED and EMPA-Kidney [45].

Patients with T2D and CKD largely took sotagliflozin, which in clinical terms showed a safety profile similar to that of other SGLT inhibitors, except for a small increase in diarrhoea rates due to its partial blockage of SGLT1 in the gut. In a variety of T2D patients under the active supervision of primary care physicians and kidney, endocrine, and cardiovascular specialists, sotagliflozin increased UACR and altered the rates of UACR progression/regression [46].

Pharmacodynamics

Table 1: Effect of Sotagliflozin on Renal Glucose Filtration and Reabsorption.

Category	Details
Glucose Filtration & Reabsorption	Once filtered by the glomerulus, glucose is almost entirely reabsorbed by the proximal convoluted tubule (PCT).
Maximum Renal Glucose Reabsorption (TmG)	The renal threshold for glucose reabsorption (TmG) is 375 mg/min.
Normal Glucose Filtration Rate	The filtered glucose rate is 180 g/day or 125 mg/min (based on eGFR of 180 L/day and plasma glucose of 100 mg/dL).
Glycosuria in Normal Individuals	Does not occur unless blood glucose levels exceed 180 mg/dL.
Glycosuria in Diabetes	Develops when filtered glucose exceeds TmG, commonly in poorly managed type 1 or type 2 diabetes.

[47].

It is difficult for glucose to pass through the walls of the proximal convoluted tubule (PCT) due to its polarity, which causes it to be reabsorbed by glucose transport channels. The PCT's apical membrane has two sodium-glucose cotransporters. The PCT's first segment (S1) contains SGLT2, a low-affinity, high-capacity cotransporter that accounts for 90% of glucose reabsorption. Another transporter located in the S2 (the latter part of the PCT) and S3 (proximal straight tubule) segments has a limited capacity and a high affinity for glucose and galactose. The Na/K ATPase pump, located in the basolateral membrane, concurrently transports three sodium ions into the bloodstream from the lumen and takes in two potassium ions[48].

Consequently, a gradient in sodium concentration is created, and intracellular sodium levels are decreased. The SGLT proteins use the energy generated by this concentration gradient to transfer sodium ions across the apical membrane of the proximal convoluted tubule (PCT) and one glucose molecule against its gradient. This approach provides the greatest illustration of secondary active transport. The intracellular sodium-to-glucose cotransport ratios for SGLT1 and SGLT2 are 2:1 and 1:1, respectively. The glucose is subsequently released into the bloodstream by the GLUT1 and GLUT2 transporters on the basolateral membrane of the PCT. People and animals with poorly managed diabetes

have a 20% greater transport maximum for glucose (TmG) than those without the condition [49].

SGLT2 is overexpressed in the proximal convoluted tubule (PCT) of diabetics, according to early research involving human patients and animal models. However, not all investigations confirm this finding. Blocking SGLT2 will decrease renal glucose reabsorption and enhance glycemic management (e.g., lowering HbA1c levels), as this rise in renal glucose reabsorption is a part of the dangerous octet. SGLT2 inhibitors have a pharmacological activity that causes glycosuria because they lower the tubular maximum for glucose (TmG) and the threshold for glucose reabsorption. For example, in those with well-controlled type 2 diabetes mellitus (T2DM), the TmG decreased by 56%, from 420 mg/min to 184 mg/min [50].

Those without diabetes may also have glucose in their urine even when their blood sugar levels are normal due to a significant drop in the threshold for glucose reabsorption from 180 mg/dL to 40–80 mg/dL. While 90% of the glucose filtered by the kidneys is reabsorbed by SGLT2 (around 160 g/day in healthy individuals), SGLT2 inhibitors only raise the amount of glucose expelled in urine by 80 g/day, which is less than 50% of the total quantity filtered[51].

The SGLT1 makes this conundrum clear. Due to its more distant position in S2/S3 and the fact that SGLT2 has already reabsorbed 90% of the glucose, SGLT1 functions well below its maximum transport capacity of 80 g/day. When a significant amount of glucose reaches SGLT1, these transporters are operating at their maximal reabsorptive capacity, which explains why no more than 50% of the filtered glucose ends up in the urine. We conclude that SGLT1 can reabsorb around 40% of the previously filtered glucose, while SGLT2 can absorb up to 90% of the filtered glucose [52].

Pharmacokinetics

In 1835, the apple tree's root bark was discovered to have the first naturally occurring SGLT2 inhibitor, which was shown to cause glycosuria. Because phenazine breaks down quickly when taken orally and it's O-glucoside bond is vulnerable to digestive β-glucosidase, it was not developed as a treatment for high blood sugar. This is because it is not well absorbed in the gastrointestinal tract. Later, other treatments were developed, and currently, the FDA has approved only a few medications to treat people with type 2 diabetes: empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin. The world's first SGLT2 inhibitor to be approved was dapagliflozin. It can be used as a therapy on its own or in conjunction with saxagliptin and metformin [53].

5 mg is the initial dosage; if necessary, it can be increased to 10 mg. The selectivity of dapagliflozin for SGLT2 is around 1,200 times higher than that of SGLT1. Because of its 78% bioavailability and insensitivity to high-fat meals, it can be administered regardless of food intake. It is appropriate for once-daily use since dapagliflozin is well absorbed when taken orally, reaching its peak concentration (Tmax) 1–1.5 hours after administration, has 78% protein binding, and a half-life (T1/2) of 13 hours. Furthermore, no documented pharmacological interactions with other drugs frequently used to treat Type 2 Diabetes Mellitus (T2DM) have been documented [54].

Dialysis patients, those 75 years of age or older, patients with moderate to severe renal impairment, and women who are pregnant or nursing should not take this drug. Patients with severe hepatic impairment should begin taking 5 mg once daily. In the United States, canagliflozin was the first SGLT2 inhibitor to receive approval. It shows somewhat lower selectivity for SGLT2, with a 250-fold preference for SGLT2 over SGLT1. A 24-hour kidney glucose threshold is lowered by the medicine, depending on the dosage. Taken once a day before the first meal, the starting dosage is 100 mg, with the possibility of increasing it to a maximum of 300 mg per day [55].

At a dose of 300 mg, canagliflozin has a high plasma protein binding rate of 99% and an absolute bioavailability of 65%. Canagliflozin reaches its peak concentrations in 1–2 hours, and the 100 mg and 300 mg doses have apparent terminal half-lives of 11 and 13 hours, respectively. No noteworthy interactions between drugs have been noted. It is not advised to use canagliflozin in patients with significant hepatic impairment or an eGFR of less than 45 mL/min/1.73 m^2. It is under the category of category C medications for expectant mothers. The maximum dosage advised for senior citizens is 100 mg daily. The drug empagliflozin was approved in 2014[56].

Dialysis patients, those 75 years of age or older, patients with moderate to severe renal impairment, and women who are pregnant or nursing should not take this drug. Patients with severe hepatic impairment should begin taking 5 mg once daily. In the United States, canagliflozin was the first SGLT2 inhibitor to receive approval. It shows somewhat lower selectivity for SGLT2, with a 250-fold preference for SGLT2 over SGLT1. A 24-hour kidney glucose threshold is lowered by the medicine, depending on the dosage. Taken once a day before the first meal, the starting dosage is 100 mg, with the possibility of increasing it to a maximum

of 300 mg per day [57].

There have also been no reports of problems with other drugs that are often used to treat type 2 diabetes. The main routes of excretion for empagliflozin are the kidneys (55%), followed by faeces 40%. People with chronic renal disease (stages 2-3) usually tolerate this medicine well, while stage 4 patients occasionally experience hypoglycemia. It is not recommended to use it when pregnant or nursing. The most recently approved SGLT2 inhibitor by the FDA is ertugliflozin. There is currently little information on the pharmacokinetics and pharmacodynamics of this drug. Starting at 5 mg once daily, ideally in the morning with or without meals, is the recommended dosage. It can be raised to 15 mg once daily [58].

It is eliminated by the faecal and renal pathways in about equal proportions, and its oral bioavailability can reach 90%. There have been no notable drug-drug interactions documented, and its profile of precautions and contraindications is comparable to that of other SGLT2 inhibitors. Ertugliflozin should not be started by anybody with an eGFR of less than 60 mL/min/1.73 m^2, nor should it be taken by anyone with an eGFR of less than 30 mL/min/1.73 m^2. The first dual SGLT1/SGLT2 inhibitor, sotagliflozin, has advanced to phase-III clinical trials. It has a slightly greater affinity for the SGLT2 receptor than the SGLT1 receptor by a ratio of just 20. It has been shown that taking the medication just before breakfast improves its effectiveness [59].

There seems to be little increase in 24-hour urine glucose excretion compared to baseline when compared to the effects of SGLT2 inhibition alone. Most likely, this is because SGLT1 inhibition also reduces intestinal glucose absorption. Except for urine glucose excretion, which stabilizes after the 200 mg once-daily dosage, sotagliflozin's effects are dose-dependent. Up to 97.7% of plasma proteins can bind to it, and it takes three hours to reach its maximum concentration (Tmax). In people with type 2 diabetes mellitus (T2DM) who have normal kidney function, its quick absorption onset and half-life (T1/2), which vary from 13.5 to 20.7 hours, indicate once-daily dosing. Despite being mainly eliminated by the kidneys, sotagliflozin's plasma elimination is not considerably affected in people with kidney disease [60].

In the TANDEM studies, 1,406 individuals with type 1 diabetes mellitus (T1DM) were randomly assigned to receive 400 mg of sotagliflozin or a placebo. The group receiving sotagliflozin had a larger percentage of patients who achieved the primary objective, which was the percentage of patients who had HbA1c levels below 7% without any bouts of hypoglycemia or diabetic ketoacidosis (DKA). Without causing general hypoglycemia, sotagliflozin also decreased HbA1c and insulin consumption. For individuals with type 1 diabetes, these outcomes are probably going to help the medication get regulatory approval. However, the sotagliflozin group experienced more adverse events than the placebo group did, especially those who were given the higher dose of 400 mg once daily. The most frequent adverse effects were gastrointestinal problems, nausea, and diarrhoea, all of which are normal when intestinal SGLT1 is inhibited. Additionally, there was a trend in this research that greater doses were linked to more cases of diabetic ketoacidosis (DKA), especially among insulin pump users. All groups had a similar prevalence of hypoglycemic events, except insulin pump users, who had a higher frequency of severe hypoglycaemia [61].

Clinical Applications

In patients with type 1 diabetes, the combination of SGLT1 and SGLT2 inhibitors improved clinical indices of cardiorenal health. Changes in eGFR, UACR, blood pressure, hematocrit, serum albumin, and uric acid that can be measured are largely in line with what happens to people with type 2 diabetes who take SGLT2 inhibitors. These results are of therapeutic significance because SGLT2 inhibitors have been associated in multiple groups with a decreased risk of diabetic kidney disease, including severe renal outcomes. Although these positive effects on clinical outcomes were seen, it is important to keep in mind that the mechanisms behind these benefits are still unclear [62].

The available analyses of published cardiovascular outcome studies imply that mechanisms that are not dependent on glucose play a major role in the cardiorenal advantages linked to SGLT2 inhibitors. Clinical trials have demonstrated improvements in glycemic control and weight loss in people with type 1 diabetes, which is different from what is usually seen in those with type 2 diabetes. Given that type 1 and type 2 diabetes are likely to share many of the same factors that lead to end-organ damage, it is crucial to determine whether inhibiting SGLTs has comparable cardiorenal effects in individuals with type 1 diabetes to assess the potential for both primary and secondary end-organ protection with these treatments[63].

Table 2: Glucose-Lowering Actions of SOTA: Renal and Gut Effects.

Category	Details
SOTA Mechanism	Acts as both an SGLT1 inhibitor (SGLT1i) and an SGLT2 inhibitor (SGLT2i).
SGLT1 Inhibition in Kidneys	SOTA levels are insufficient to block SGLT1 in the kidneys.
SGLT1 Inhibition in Intestines	Half-maximally inhibits intestinal SGLT1, delaying and reducing glucose absorption, leading to lower postprandial glucose levels.
Gut Effects	Increases intestinal hormone production over time, enhancing insulin sensitivity and mitochondrial bioenergetics, contributing to kidney protection.
Renal Glucose Load Reduction	Lowers glucose load in renal tubules, reducing urine glucose excretion (UGE).
UGE Differences	SOTA shows different UGE patterns compared to specific SGLT2 inhibitors.
Glucose-Lowering Mechanisms	Reduces glucose levels by improving insulin sensitivity or decreasing glucose absorption.

[64].

Notably, SOTA was found to alter blood pressure, renal function, and blood volume indicators (such as albumin and hematocrit) due to SGLT inhibition-induced natriuresis. However, the clinical implications of different UGE rates and the corresponding natriuresis levels associated with different SGLT inhibitors are not fully understood. A decrease in estimated glomerular filtration rate (eGFR) is associated with the onset of SGLT2 inhibition in several investigations, including people with type 2 diabetes. The medicine can be stopped to halt this drop, which stabilizes with time. Tubuloglomerular feedback-induced hemodynamically mediated constriction of the afferent arteriole is the most plausible cause of this initial shift in eGFR. It is crucial to emphasize that the documented decrease in eGFR in this group is not as dramatic as that seen in younger persons with type 1 diabetes who are undergoing hyper filtration [65].

Hematocrit levels in those with type 2 diabetes increased 3–7% over baseline in previous studies, and this increase continued during long-term clinical evaluations. Hemoconcentration or possibly increased erythropoietin production was the likely source of this rise. In people with diabetes with type 2 diabetes, hematocrit increases were significantly associated with CV benefits, indicating the clinical importance of hematocrit changes within the EMPA-REG OUTCOME trial. Because they might be linked to benefits similar to those observed in SGLT2i trials in type 2 diabetic patients, the current analysis implies that the rise in hematocrit and levels of serum albumin observed in people with type 1 diabetes after SOTA, as well as the quick return to baseline following a 7-day washing out, might have clinical significance [67].

Adverse Effects and Safety Profile

In addition to heart failure (HF), sotagliflozin is used to treat both type 1 and type 2 diabetes. It has limitations when it comes to controlling blood sugar levels, just like any other medicine. For both men and women, sotagliflozin may raise the risk of yeast infections. Urinary tract infections, including kidney and bladder infections, can also result from it. Diabetic ketoacidosis (DKA) is a hazardous condition that can occur when sotagliflozin raises blood ketone levels. DKA symptoms include nausea, vomiting, rapid breathing, dizziness, and stomach pain. Because sotagliflozin promotes the excretion of glucose in the urine, which can result in fluid loss or more frequent urination, it also raises the risk of electrolyte imbalance or dehydration [68].

This can lead to electrolyte imbalance and dehydration, including hyponatremia (low blood sodium levels). Although it is less frequent than other diabetes drugs, sotagliflozin use might result in hypoglycemia or low blood sugar. Hypoglycemia can cause tremors, dizziness, shaking, confusion, and unconsciousness. Gastrointestinal problems like nausea and diarrhoea can occur in some people using sotagliflozin. The following are the most common adverse events linked to sotagliflozin: Diarrhea was the most commonly reported adverse effect, with a prevalence of 7% [69]. Five per cent of cases had urinary tract infections, but 1.5% and 4.1% of cases had more severe side effects, such as acute renal failure and ketoacidosis, respectively. When using this drug, it is important to stay hydrated because 4% of patients experience dehydration. The need for patient knowledge and monitoring for this particular side effect is highlighted by the fact that genital yeast infections had the greatest incidence at 10%. According to these findings, patients and healthcare professionals must keep an eye out for and take care of any possible side effects related to sotagliflozin. Diabetes may increase the risk of diabetic ketoacidosis,

and people with diabetes should be on the lookout for diseases like urethritis, bone fractures, and some cancers, such as breast and bladder cancer [70].

Comparison with Other SGLT Inhibitors

People on insulin pump therapy are more likely to experience issues if the infusion set fails. With the correct education, these tragedies may probably be prevented. The advantages of SGLTi treatment exceed the dangers, provided that patients and medical practitioners are aware of and appropriately manage the hazards. Additionally, by postponing the absorption of glucose, sotagliflozin may reduce the need for ultra-fast insulins in individuals with type 1 diabetes. In addition to the kidneys, HSGLT-1 controls the release of glucose from heart capillaries and the production of entero-endocrine cells, both of which may be advantageous to the cardiovascular system. However, it is yet unknown exactly what role SGLT-1 plays in these tissues [74].

Conclusion

Sotagliflozin stands out as the first dual SGLT1/2 inhibitor, offering a novel approach to diabetes management through its ability to target both intestinal glucose absorption and renal glucose reabsorption. Its dual mechanism provides significant clinical benefits, including improved glycemic control, weight loss, and cardiovascular and renal protection, especially for patients who struggle to achieve adequate glucose regulation with current therapies. Despite its potential, caution is warranted due to risks such as diabetic ketoacidosis and gastrointestinal side effects. Future research should focus on further optimizing its therapeutic profile, clarifying its long-term safety, and exploring its full potential in addressing complications related to diabetes. Sotagliflozin represents a meaningful step forward in advancing treatment options for diabetes, with a notable impact on improving patient outcomes.

Author contribution

Each author contributed significantly to the article's conceptualization, design, data collection, and interpretation. They also participated in the article's drafting or critical revision.

Data availability statement

Data is available on the demand.

Declaration of competing interest

According to the authors, they are unaware of any competing financial interests or personal ties.

Acknowledgements

The assistance of numerous data resource websites and journals for its open access is acknowledged by the authors. This has made it quite easy for us to compile a variety of references. Since this review is brief, no direct patient or animal data were used in this article.

References

1 D. Tomic, J. E. Shaw, and D. J. Magliano, "The burden and risks of emerging complications of diabetes mellitus," Nat Rev Endocrinol, vol. 18, no. 9, pp. 525–539, Sep. 2022, doi: 10.1038/s41574-022-00690-7.

2 M. C. Petersen and G. I. Shulman, "Mechanisms of Insulin Action and Insulin Resistance," Physiol Rev, vol. 98, no. 4, pp. 2133–2223, Oct. 2018, doi: 10.1152/physrev.00063.2017.

3 S. Y. Tan et al., "Type 1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention," Diabetes & Metabolic Syndrome: Clinical Research & Reviews, vol. 13, no. 1, pp. 364–372, Jan. 2019, doi: 10.1016/j.dsx.2018.10.008.

4 A. Chaudhury et al., "Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management," Front Endocrinol (Lausanne), vol. 8, Jan. 2017, doi: 10.3389/fendo.2017.00006.

5 D. L. Bhatt et al., "Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure," New England Journal of Medicine, vol. 384, no. 2, pp. 117–128, Jan. 2021, doi: 10.1056/NEJMoa2030183.

6 Z.-C. Dai, J.-X. Chen, R. Zou, X.-B. Liang, J.-X. Tang, and C.-W. Yao, "Role and mechanisms of SGLT-2 inhibitors in the treatment of diabetic kidney disease," Front Immunol, vol. 14, Sep. 2023, doi: 10.3389/fimmu.2023.1213473.

7 M. Nandave, "SGLT2 Inhibitors for Primary and Secondary Protection from Cardiovascular and Renal Diseases in Type 2 Diabetes," in Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors in Heart Failure, Singapore: Springer Nature Singapore, 2024, pp. 151–247. doi: 10.1007/978-981-97-7568-2_3.

8 T. Danne et al., "Improved Time in Range and Glycemic Variability With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: A Pooled Analysis of 24-Week Continuous Glucose Monitoring Data From the inTandem Program," Diabetes Care, vol. 42, no. 5, pp. 919–930, May 2019, doi: 10.2337/dc18-2149.

9 A. Alblooshi, "THE EFFECT OF LICOGLIFLOZIN (SGLT1/2 INHIBITOR) ON DIABETES AND CARDIAC COMPLICATIONS," Theses, Nov. 2022, Accessed: Jan. 25, 2025. [Online]. Available: https://scholarworks.uaeu.ac.ae/all_theses/1052

10 A. I. Adler, S. Ting, R. Dent, and N. Latimer, "NICE

guidance on dapagliflozin with insulin for type 1 diabetes," Lancet Diabetes Endocrinol, vol. 7, no. 10, pp. 750–751, Oct. 2019, doi: 10.1016/S2213-8587(19)30265-7.

11 A. Long and M. Salvo, "Sotagliflozin: Efficacy, Safety, and Potential Therapeutic Applications in Heart Failure," Annals of Pharmacotherapy, vol. 58, no. 9, pp. 935–946, Sep. 2024, doi: 10.1177/10600280231211179.

12 X. Lu et al., "Type 2 diabetes mellitus in adults: pathogenesis, prevention and therapy," Signal Transduct Target Ther, vol. 9, no. 1, p. 262, Oct. 2024, doi: 10.1038/s41392-024-01951-9.

13 G. Miceli et al., "The Potential Impact of SGLT2-I in Diabetic Foot Prevention: Promising Pathophysiologic Implications, State of the Art, and Future Perspectives—A Narrative Review," Medicina (B Aires), vol. 60, no. 11, p. 1796, Nov. 2024, doi: 10.3390/medicina60111796.

14 Z.-C. Dai, J.-X. Chen, R. Zou, X.-B. Liang, J.-X. Tang, and C.-W. Yao, "Role and mechanisms of SGLT-2 inhibitors in the treatment of diabetic kidney disease," Front Immunol, vol. 14, Sep. 2023, doi: 10.3389/fimmu.2023.1213473.

15 C. M. A. Cefalo et al., "Sotagliflozin, the first dual SGLT inhibitor: current outlook and perspectives," Cardiovasc Diabetol, vol. 18, no. 1, p. 20, Dec. 2019, doi: 10.1186/s12933-019-0828-y.

16 N. Lukic et al., "SGLT-2 Inhibitors: The Next-generation Treatment for Type 2 Diabetes Mellitus," Curr Med Chem, vol. 31, no. 30, pp. 4781–4806, Sep. 2024, doi: 10.2174/0109298673251493231011192520.

17 A. Caturano et al., "Modern Challenges in Type 2 Diabetes: Balancing New Medications with Multifactorial Care," Biomedicines, vol. 12, no. 9, p. 2039, Sep. 2024, doi: 10.3390/biomedicines12092039.

18 Y. Oe and V. Vallon, "The Pathophysiological Basis of Diabetic Kidney Protection by Inhibition of SGLT2 and SGLT1," Kidney and Dialysis, vol. 2, no. 2, pp. 349–368, Jun. 2022, doi: 10.3390/kidneydial2020032.

19 K. Chatzianagnostou, M. Gaggini, A. Suman Florentin, L. Simonini, and C. Vassalle, "New Molecules in Type 2 Diabetes: Advancements, Challenges and Future Directions," Int J Mol Sci, vol. 25, no. 11, p. 6218, Jun. 2024, doi: 10.3390/ijms25116218.

20 T. Salvatore et al., "An Overview of the Cardiorenal Protective Mechanisms of SGLT2 Inhibitors," Int J Mol Sci, vol. 23, no. 7, p. 3651, Mar. 2022, doi: 10.3390/ijms23073651.

21 N. Komaniecka, S. Maroszek, M. Drozdzik, S. Oswald, and M. Drozdzik, "Transporter Proteins as Therapeutic Drug Targets—With a Focus on SGLT2 Inhibitors," Int J Mol Sci, vol. 25, no. 13, p. 6926, Jun. 2024, doi: 10.3390/ijms25136926.

22 L. V. Gromova, S. O. Fetissov, and A. A. Gruzdkov, "Mechanisms of Glucose Absorption in the Small Intestine in Health and Metabolic Diseases and Their Role in Appetite Regulation," Nutrients, vol. 13, no. 7, p. 2474, Jul. 2021, doi: 10.3390/nu13072474.

23 C. M. A. Cefalo et al., "Sotagliflozin, the first dual SGLT inhibitor: current outlook and perspectives," Cardiovasc Diabetol, vol. 18, no. 1, p. 20, Dec. 2019, doi: 10.1186/s12933-019-0828-y.

24 X. Lingli and X. Wenfang, "Characteristics and molecular mechanisms through which SGLT2 inhibitors improve metabolic diseases: A mechanism review," Life Sci, vol. 300, p. 120543, Jul. 2022, doi: 10.1016/j.lfs.2022.120543.

25 N. J. Deshmukh, M. S. Kalshetti, M. Patil, P. Autade, and G. V. Sangle, "Exploring the modulatory effects of sotagliflozin on dyslipidemia in mice: The role of glucagon, fibroblast growth factor 21 and glucagon-like peptide 1," Clin Exp Pharmacol Physiol, vol. 51, no. 5, May 2024, doi: 10.1111/1440-1681.13854.

26 Z. Siddiqui, N. Rasouli, E. Felder, and W. H. Frishman, "A Review of Sotagliflozin: The First Dual SGLT-1/2 Inhibitor," Cardiol Rev, Jul. 2024, doi: 10.1097/CRD.0000000000000760.

27 K. Seni and P. A. Chawla, "Managing heart failure in diabetics with dual acting sotagliflozin—A review," Health Sciences Review, vol. 9, p. 100130, Dec. 2023, doi: 10.1016/j.hsr.2023.100130.

28 R. B. Singh et al., "Sodium Glucose Transporters (SGLT) Inhibitors with Reference to SGLT-1 Inhibitor," vol. 14, no. 4, 2022.

29 C. M. A. Cefalo et al., "Sotagliflozin, the first dual SGLT inhibitor: current outlook and perspectives," Cardiovasc Diabetol, vol. 18, no. 1, p. 20, Dec. 2019, doi: 10.1186/s12933-019-0828-y.

30 C. M. A. Cefalo et al., "Sotagliflozin, the first dual SGLT inhibitor: current outlook and perspectives," Cardiovasc Diabetol, vol. 18, no. 1, p. 20, Dec. 2019, doi: 10.1186/s12933-019-0828-y.

31 A. Sciacqua et al., "Pharmacological treatment of type 2 diabetes in elderly patients with heart failure: randomized trials and beyond," Heart Fail Rev, vol. 28, no. 3, pp. 667–681, Dec. 2021, doi: 10.1007/s10741-021-10182-x.

32 A. Long and M. Salvo, "Sotagliflozin: Efficacy, Safety, and Potential Therapeutic Applications in Heart Failure," Annals of Pharmacotherapy, vol. 58, no. 9, pp. 935–946, Sep. 2024, doi: 10.1177/10600280231211179.

33 Y. Gong, B. Kong, W. Shuai, T. Chen, J. Zhang, and H. Huang, "Effect of sotagliflozin on ventricular arrhythmias in mice with myocardial infraction," Eur J Pharmacol, vol. 936, p. 175357, Dec. 2022, doi: 10.1016/j.ejphar.2022.175357.

34 V. Elian, V. Popovici, O. Karampelas, G. G. Pircalabioru, G. Radulian, and M. Musat, "Risks and Benefits of SGLT-2 Inhibitors for Type 1 Diabetes Patients Using Automated Insulin Delivery Systems—A Literature Review," Int J Mol Sci, vol. 25, no. 4, p. 1972, Feb. 2024, doi: 10.3390/ijms25041972.

35 G. Gyimesi, J. Pujol-Giménez, Y. Kanai, and M. A. Hediger, "Sodium-coupled glucose transport, the SLC5 family, and therapeutically relevant inhibitors: from molecular discovery to clinical application," Pflugers Arch, vol. 472, no. 9, pp. 1177–1206, Sep. 2020, doi: 10.1007/s00424-020-02433-x.

36 Z. Szekeres, K. Toth, and E. Szabados, "The Effects of SGLT2 Inhibitors on Lipid Metabolism," Metabolites,

vol. 11, no. 2, p. 87, Feb. 2021, doi: 10.3390/metabo11020087.
37 A. Gupta, S. Mittal, Monika, R. Dhingra, and N. Dhingra, "Turning Foes to Friends: Knocking Down Diabetes Associated SGLT2 Transporters and Sustaining Life," Curr Diabetes Rev, vol. 16, no. 7, pp. 716–732, Jul. 2020, doi: 10.2174/1573399816666200117155016.
38 M. Szarek et al., "Effect of Sotagliflozin on Total Hospitalizations in Patients With Type 2 Diabetes and Worsening Heart Failure," Ann Intern Med, vol. 174, no. 8, pp. 1065–1072, Aug. 2021, doi: 10.7326/M21-0651.
39 A. Caturano et al., "Modern Challenges in Type 2 Diabetes: Balancing New Medications with Multifactorial Care," Biomedicines, vol. 12, no. 9, p. 2039, Sep. 2024, doi: 10.3390/biomedicines12092039.
40 C. M. A. Cefalo et al., "Sotagliflozin, the first dual SGLT inhibitor: current outlook and perspectives," Cardiovasc Diabetol, vol. 18, no. 1, p. 20, Dec. 2019, doi: 10.1186/s12933-019-0828-y.
41 I.-A. Minciună et al., "Recent Advances in Understanding the Molecular Mechanisms of SGLT2 Inhibitors in Atrial Remodeling," Curr Issues Mol Biol, vol. 46, no. 9, pp. 9607–9623, Aug. 2024, doi: 10.3390/cimb46090571.
42 "The Effect of SGLT2 Inhibition on Biomarkers of Diabetic Kidney Disease and Cardiovascular Disease - ProQuest." Accessed: Jan. 26, 2025. [Online]. Available: https://www.proquest.com/openview/45ba22b653857c6513aa2ae5b087cce2/1?pq-origsite=gscholar&cbl=18750&diss=y
43 A. Saleem, S. M. Khan, I. Ullah, S. S. Nasim, S. Rahman, and A. Tayyab, "Investigating the Role of Sodium-glucose Cotransporter-2 Inhibitors in Slowing Down the Diabetic Kidney Disease Progression: A Meta-analysis of Randomized Control Trials," J Adv Med Med Res, vol. 36, no. 5, pp. 343–360, May 2024, doi: 10.9734/jammr/2024/v36i55443.
44 T. Salvatore et al., "An Overview of the Cardiorenal Protective Mechanisms of SGLT2 Inhibitors," Int J Mol Sci, vol. 23, no. 7, p. 3651, Mar. 2022, doi: 10.3390/ijms23073651.
45 D. Z. I. Cherney et al., "Effect of sotagliflozin on albuminuria in patients with type 2 diabetes and chronic kidney disease," Diabetes Obes Metab, vol. 25, no. 11, pp. 3410–3414, Nov. 2023, doi: 10.1111/dom.15203.
46 M. A. Bantounou et al., "Effect of the dual sodium-glucose co-transporter-1 and -2 inhibitor sotagliflozin on renal outcomes in type 1 diabetes and type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials," Diabetes Obes Metab, vol. 26, no. 2, pp. 710–720, Feb. 2024, doi: 10.1111/dom.15364.
47 G. Miceli et al., "The Potential Impact of SGLT2-I in Diabetic Foot Prevention: Promising Pathophysiologic Implications, State of the Art, and Future Perspectives—A Narrative Review," Medicina (B Aires), vol. 60, no. 11, p. 1796, Nov. 2024, doi: 10.3390/medicina60111796.
48 T. Salvatore et al., "An Overview of the Cardiorenal Protective Mechanisms of SGLT2 Inhibitors," Int J Mol Sci, vol. 23, no. 7, p. 3651, Mar. 2022, doi: 10.3390/ijms23073651.
49 G. Miceli et al., "The Potential Impact of SGLT2-I in Diabetic Foot Prevention: Promising Pathophysiologic Implications, State of the Art, and Future Perspectives—A Narrative Review," Medicina (B Aires), vol. 60, no. 11, p. 1796, Nov. 2024, doi: 10.3390/medicina60111796.
50 B. Liu, Y. Wang, Y. Zhang, and B. Yan, "Mechanisms of Protective Effects of SGLT2 Inhibitors in Cardiovascular Disease and Renal Dysfunction," Curr Top Med Chem, vol. 19, no. 20, pp. 1818–1849, Oct. 2019, doi: 10.2174/1568026619666190828161409.
51 A. Alblooshi, "THE EFFECT OF LICOGLIFLOZIN (SGLT1/2 INHIBITOR) ON DIABETES AND CARDIAC COMPLICATIONS," Theses, Nov. 2022, Accessed: Jan. 26, 2025. [Online]. Available: https://scholarworks.uaeu.ac.ae/all_theses/1052
52 "The Effects of Sodium-Glucose Co-Transporter 2 Inhibition on Plasma and Urine Ketones in Type 1 Diabetes - ProQuest." Accessed: Jan. 26, 2025. [Online]. Available: https://www.proquest.com/openview/58d0cba3836fbaaed1a3eb581f6f57f0/1?pq-origsite=gscholar&cbl=18750&diss=y
53 A. Azizogli, M. R. Vitti, R. Mishra, L. Osorno, C. Heffernan, and V. A. Kumar, "Comparison of SGLT1, SGLT2, and Dual Inhibitor Biological Activity in Treating Type 2 Diabetes Mellitus," Adv Ther (Weinh), vol. 6, no. 12, Dec. 2023, doi: 10.1002/adtp.202300143.
54 "Exploring Metabolically Compromised Secretome and Bioactives on Islet Differentiation and Function for Effective Diabetic Therapy - ProQuest." Accessed: Jan. 26, 2025. [Online]. Available: https://www.proquest.com/openview/40dc2c0299956c873fb535077ce5edb7/1?pq-origsite=gscholar&cbl=2026366&diss=y
55 R. Lajara, "The potential role of sodium glucose co-transporter 2 inhibitors in combination therapy for type 2 diabetes mellitus," Expert Opin Pharmacother, vol. 15, no. 17, pp. 2565–2585, Dec. 2014, doi: 10.1517/14656566.2014.968551.
56 K. Abdullah et al., "Sodium-Glucose Cotransporter-2 Inhibitors: Who, When & How? Guidance for Use from a Multidisciplinary Practical Approach," Int J Clin Med, vol. 15, no. 09, pp. 413–435, 2024, doi: 10.4236/ijcm.2024.159026.
57 P. Maffei, S. Bettini, L. Busetto, and F. Dassie, "SGLT2 Inhibitors in the Management of Type 1 Diabetes (T1D): An Update on Current Evidence and Recommendations," Diabetes, Metabolic Syndrome and Obesity, vol. 16, pp. 3579–3598, 2023, doi: 10.2147/DMSO.S240903.
58 K. Seni and P. A. Chawla, "Managing heart failure in diabetics with dual acting sotagliflozin—A review," Health Sciences Review, vol. 9, p. 100130, Dec. 2023, doi: 10.1016/j.hsr.2023.100130.
59 C. M. A. Cefalo et al., "Sotagliflozin, the first dual SGLT inhibitor: current outlook and perspectives," Cardiovasc Diabetol, vol. 18, no. 1, p. 20, Dec. 2019, doi: 10.1186/s12933-019-0828-y.

60 J. Lin, S. Wang, T. Wen, and X. Zhang, "Renal protective effect and safety of sodium-glucose cotransporter-2 inhibitors in patients with chronic kidney disease and type 2 diabetes mellitus: a network meta-analysis and systematic review," Int Urol Nephrol, vol. 54, no. 9, pp. 2305–2316, Feb. 2022, doi: 10.1007/s11255-022-03117-4.

61 Z. Siddiqui, N. Rasouli, E. Felder, and W. H. Frishman, "A Review of Sotagliflozin: The First Dual SGLT-1/2 Inhibitor," Cardiol Rev, Jul. 2024, doi: 10.1097/CRD.0000000000000760.

62 D. L. Bhatt et al., "Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease," New England Journal of Medicine, vol. 384, no. 2, pp. 129–139, Jan. 2021, doi: 10.1056/NEJMoa2030186.

63 T. Rieg and V. Vallon, "Development of SGLT1 and SGLT2 inhibitors," Diabetologia, vol. 61, no. 10, pp. 2079–2086, Oct. 2018, doi: 10.1007/s00125-018-4654-7.

64 D. H. van Raalte et al., "The Impact of Sotagliflozin on Renal Function, Albuminuria, Blood Pressure, and Hematocrit in Adults With Type 1 Diabetes," Diabetes Care, vol. 42, no. 10, pp. 1921–1929, Oct. 2019, doi: 10.2337/dc19-0937.

65 M. Rendell, "Lessons learned from early-stage clinical trials for diabetic nephropathy," Expert Opin Investig Drugs, vol. 33, no. 4, pp. 287–301, Apr. 2024, doi: 10.1080/13543784.2024.2326025.

66 G. Santulli et al., "Functional and Clinical Importance of SGLT2-inhibitors in Frailty: From the Kidney to the Heart," Hypertension, vol. 80, no. 9, pp. 1800–1809, Sep. 2023, doi: 10.1161/HYPERTENSIONAHA.123.20598.

67 D. H. van Raalte et al., "The Impact of Sotagliflozin on Renal Function, Albuminuria, Blood Pressure, and Hematocrit in Adults With Type 1 Diabetes," Diabetes Care, vol. 42, no. 10, pp. 1921–1929, Oct. 2019, doi: 10.2337/dc19-0937.

68 K. Seni and P. A. Chawla, "Managing heart failure in diabetics with dual acting sotagliflozin—A review," Health Sciences Review, vol. 9, p. 100130, Dec. 2023, doi: 10.1016/j.hsr.2023.100130.

69 "Ofloxacin and sotagliflozin Interactions - Drugs.com." Accessed: Jan. 26, 2025. [Online]. Available: https://www.drugs.com/drug-interactions/ofloxacin-with-sotagliflozin-1741-0-4492-0.html?professional=1

70 S. Z. Khan and A. Salman, "Acute emergencies in diabetes," in BIDE' s Diabetes Desk Book, Elsevier, 2024, pp. 103–139. doi: 10.1016/B978-0-443-22106-4.00017-6.

71 C. Ghezzi, B. A. Hirayama, E. Gorraitz, D. D. F. Loo, Y. Liang, and E. M. Wright, "SGLT2 inhibitors act from the extracellular surface of the cell membrane," Physiol Rep, vol. 2, no. 6, 2014, doi: 10.14814/phy2.12058.

72 D. M. Keller et al., "SGLT2 Inhibitors in Type 2 Diabetes Mellitus and Heart Failure—A Concise Review," J Clin Med, vol. 11, no. 6, p. 1470, Mar. 2022, doi: 10.3390/jcm11061470.

73 R. J. Riello, "Heart Failure with Reduced Ejection Fraction," PSAP 2022 Book 1 • Cardiology, vol. 7.

74 R. B. Singh et al., "Sodium Glucose Transporters (SGLT) Inhibitors with Reference to SGLT-1 Inhibitor," vol. 14, no. 4, 2022.