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Review Article

ADVANCEMENTS IN SGLT2 INHIBITORS: PHARMACOKINETICS, PHARMACODYNAMICS, AND CLINICAL EFFICACY WITH A FOCUS ON PHARMACOGENOMICS

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ABSTRACT

Sodium-glucose co-transporter 2 (SGLT2) inhibitors represent a pivotal advancement in the treatment of type 2 diabetes mellitus (T2DM), offering substantial improvements in glycemic control, cardiovascular protection, and renal outcomes. This review explores the pharmacokinetics, pharmacodynamics, and clinical efficacy of SGLT2 inhibitors, with a particular focus on pharmacogenomics and its impact on individual patient response. Bexagliflozin, a potent SGLT2 inhibitor, exhibits robust glycemic control through selective SGLT2 inhibition, while studies on luseogliflozin, ertugliflozin, tofogliflozin, and remogliflozin have further demonstrated the versatility and safety of this drug class. These inhibitors not only reduce HbA1c but also lower blood pressure, improve renal outcomes, and reduce the risk of major adverse cardiovascular events. Pharmacogenomics has revealed genetic polymorphisms that affect the metabolism and efficacy of SGLT2 inhibitors, guiding more precise therapeutic decisions. Variants in genes like SLC5A2 and CYP enzymes influence drug transport, metabolism, and response, paving the way for personalized treatment approaches. This growing understanding underscores the potential for pharmacogenomics to refine the selection of SGLT2 inhibitors for optimal efficacy and minimal side effects. Despite promising results, further research is needed to fully integrate pharmacogenomics into clinical practice. As personalized medicine continues to evolve, SGLT2 inhibitors, bolstered by pharmacogenomic insights, offer a compelling avenue for enhancing the management of T2DM, ultimately transforming patient care with a more tailored and effective approach.

KEYWORDS: Diabetes Mellitus, SGLT2 Inhibitors, Pharmacogenomics, Pharmacology, Clinical Practice

1. Introduction

Diabetes mellitus, a metabolic disorder marked by chronic hyperglycemia, has reached alarming levels worldwide, representing a significant global health burden. The International Diabetes Federation estimates that in 2021, approximately 537 million individuals lived with diabetes, with around 90-95% of these cases attributed to type 2 diabetes mellitus (T2DM) [1]. This disorder has not only infiltrated developed nations but has also become a rising concern in developing countries, reflecting its vast impact on diverse populations. The increasing prevalence of diabetes has been driven by factors such as sedentary lifestyles, poor dietary habits, and the global rise in obesity. In this context, the necessity for effective management and prevention strategies cannot be overstated. The complications associated with diabetes mellitus further amplify the urgency of addressing the condition. Chronic hyperglycemia can lead to a host of life-threatening complications, including chronic kidney disease (CKD), diabetic retinopathy, and cardiovascular disease, all of which significantly impair quality of life and increase mortality risk. CKD, often progressing to end-stage renal disease (ESRD), necessitates either dialysis or a kidney transplant, adding substantial physical, emotional, and financial strain on affected individuals [2].

Diabetic retinopathy, one of the leading causes of blindness in working-age adults, can progressively worsen without timely intervention, leading to vision loss due to

damage to the blood vessels of the retina [3]. Moreover, cardiovascular disease (CVD) remains the primary cause of mortality among individuals with diabetes. Prolonged exposure to high blood sugar levels can cause extensive damage to blood vessels and nerves, leading to a heightened risk of coronary artery disease, myocardial infarction, stroke, and peripheral artery disease [2]. Alarmingly, in 2022, cardiac failure affected approximately 64 million people globally, with a notable rise in prevalence among older adults—over 10% of those aged 75 years and above [4]. Among the subtypes of heart failure, heart failure with preserved ejection fraction (HFpEF) has emerged as a critical concern, especially in individuals with T2DM, which is a significant risk factor for this condition [5].

While the burden of diabetes is immense, it is not insurmountable. Advances in medical research have led to the development of more effective diagnostic tools and therapeutic strategies. One key development is the adoption of the glycated hemoglobin (HbA1c) test, which has been recommended by the American Diabetes Association as a viable alternative to fasting blood glucose for diagnosing diabetes [6]. HbA1c provides a comprehensive picture of a patient's average blood glucose levels over the past three months, correlating well with other metabolic parameters, such as 24-hour urinary glucose concentration and mean plasma glucose levels [7]. This assay has become a cornerstone of diabetes management, offering a more practical and informative approach to disease monitoring.

In addition to diagnostic innovations, the therapeutic landscape for diabetes has undergone significant transformation, particularly with the introduction of sodium-glucose co-transporter 2 (SGLT2) inhibitors. These inhibitors have revolutionized the treatment of T2DM by offering a novel mechanism of action that works independently of β-cell function or insulin resistance [8-9]. SGLT2 inhibitors prevent the reabsorption of glucose in the kidneys, resulting in increased urinary glucose excretion and consequently, a reduction in plasma glucose levels. Unlike other glucose-lowering agents, SGLT2 inhibitors do not rely on insulin pathways, making them particularly advantageous for individuals with insulin resistance — a hallmark of T2DM. Furthermore, these inhibitors also provide secondary benefits, such as modest weight loss and blood pressure reduction, contributing to an overall improvement in metabolic health [10].

Beyond glycemic control, SGLT2 inhibitors have garnered attention for their profound cardiovascular benefits. Cardiovascular disease remains one of the most devastating complications of diabetes, and traditional glucose-lowering therapies often fall short in addressing the elevated cardiovascular risk in diabetic patients. However, SGLT2 inhibitors have been shown to reduce the risk of hospitalization for heart failure, a critical advancement in the management of both diabetic and non-diabetic patients with heart failure [11]. This class of drugs has also demonstrated efficacy in lowering the incidence of major cardiovascular events, such as heart attacks and strokes, providing a dual benefit in glucose and cardiovascular risk management [12].

As the medical community continues to explore the full potential of SGLT2 inhibitors, newer-generation molecules, such as bexagliflozin, have emerged as promising therapeutic options. Bexagliflozin retains the core benefits of its predecessors but may offer enhanced efficacy and safety profiles, making it a valuable addition to the therapeutic toolkit for diabetes management [13]. By addressing both glycemic control and cardiovascular protection, bexagliflozin exemplifies the evolving nature of diabetes care, where the focus extends beyond mere symptom management to encompass broader patient outcomes.

2. Complications of Diabetes Mellitus

Diabetes mellitus is associated with several chronic complications, each contributing significantly to patient morbidity and mortality. Among these, CKD, diabetic retinopathy, and cardiovascular complications are the most prevalent and severe.

2.1. Chronic Kidney Disease and Diabetic Retinopathy

CKD, a common complication of long-standing diabetes, results from damage to the kidneys' filtering units, leading to the gradual loss of renal function. As CKD progresses, patients may eventually reach ESRD, which requires either dialysis or a kidney transplant [14]. The pathophysiology of CKD in diabetes is primarily driven by hyperglycemia-induced damage to renal blood vessels, oxidative stress, and inflammation. The prognosis of CKD is poor, with a high risk of cardiovascular events and mortality.

Similarly, diabetic retinopathy is a microvascular complication that arises from chronic hyperglycemia. It is characterized by damage to the retinal blood vessels, leading to visual impairment and, in severe cases, blindness [15]. Early detection and management are crucial, as timely intervention can slow the progression of retinopathy and prevent vision loss.

2.2. Cardiovascular Complications

Cardiovascular disease remains the leading cause of death among diabetic patients, with coronary artery disease, myocardial infarction, and stroke being the most common manifestations. The detrimental effects of prolonged hyperglycemia on blood vessels and nerves, compounded by other risk factors such as hypertension and dyslipidemia, contribute to the increased cardiovascular risk in diabetes [16]. In particular, T2DM is a well-established risk factor for heart failure, including HFpEF, which is characterized by preserved ejection fraction but impaired diastolic function. The prevalence of heart failure in diabetic patients underscores the need for therapies that address both glycemic control and cardiovascular protection [17].

3. SGLT2 Inhibitors in Diabetes Management

SGLT2 inhibitors have emerged as a key therapeutic option in the management of T2DM. These agents work by inhibiting the reabsorption of glucose in the kidneys, leading to increased urinary glucose excretion and reduced plasma glucose levels. Unlike traditional glucose-lowering medications, SGLT2 inhibitors do not target insulin pathways, making them particularly beneficial for patients with insulin resistance, a common feature of T2DM [8-10]. In addition to improving glycemic control, SGLT2 inhibitors have been associated with modest weight loss and

reductions in systolic blood pressure, making them a well-rounded option for managing metabolic health.

3.1. SGLT2 Structure and Functional Insights

Sodium-glucose co-transporter 2 (SGLT2) is a 14-transmembrane helical protein, predominantly located at the junction between the S1 and S2 segments of the proximal convoluted tubule in the kidney. This protein plays a vital role in glucose reabsorption by transporting glucose molecules from the renal tubules back into the bloodstream. Structurally, SGLT2 consists of transmembrane segments (TM1 to TM14) that exhibit an inverted repeat topology, with TM2 to TM6 and TM7 to TM11 aligned by a 153-degree rotation parallel to the membrane plane [18]. This distinct arrangement is crucial for SGLT2's glucose transport function, which reabsorbs around 90% of filtered glucose, preventing its loss through urine.

3.2. Molecular Characteristics of the SGLT2 Active Site

Recent studies by Nakka and Guruprasad have shed light on the molecular characteristics of SGLT2's active site, emphasizing its composition of both polar and non-polar amino acid residues. The polar residues (Ser74, Asn75, His80, Glu99, Lys154, Ser287, Lys321, Ser393, Ser396, and Gln457) are essential for forming hydrogen bonds with the hydroxyl groups of inhibitors, thereby enhancing binding specificity and stability. On the other hand, non-polar residues (Phe98, Ala102, Val286, Trp289, Tyr290, Trp293, Ile397, Phe453, and Ile456) facilitate hydrophobic interactions, helping anchor inhibitors within the active site. This interplay of polar and non-polar interactions is key in the design of potent SGLT2 inhibitors, which effectively block glucose reabsorption in the kidneys and serve as critical therapeutic tools in managing hyperglycemia [19].

3.3. Therapeutic Targeting of SGLT2 in Diabetes Management

SGLT2 has emerged as a pivotal therapeutic target for treating type 2 diabetes mellitus (T2DM) due to its high glucose reabsorption capacity. Inhibition of SGLT2 decreases glucose reabsorption in the kidneys, leading to enhanced urinary glucose excretion, thus lowering blood glucose levels. This process occurs independently of insulin action or secretion, making SGLT2 inhibitors particularly advantageous for patients with insulin resistance. Most marketed SGLT2 inhibitors, such as dapagliflozin, are structurally characterized by a glucose moiety, two benzene rings, and a methylene bridge [18,20].

3.4. Bexagliflozin: A Next-Generation SGLT2 Inhibitor

Bexagliflozin, a newer-generation SGLT2 inhibitor, represents a promising advancement in the treatment of T2DM. Like its predecessors, bexagliflozin reduces plasma glucose levels by increasing urinary glucose excretion but may offer improved efficacy and tolerability. Early clinical data suggest that bexagliflozin not only lowers blood glucose levels but also provides cardiovascular protection, further solidifying the role of SGLT2 inhibitors in the comprehensive management of diabetes [13-21]. Bexagliflozin represents a newer generation of SGLT2 inhibitors, designed to provide enhanced glucose-lowering efficacy. Structurally, it is a C-glycosyl compound derived from beta-D-glucose, where the anomeric hydroxyl group is substituted with a 4-chloro-3-({4-[2-(cyclopropyloxy)ethoxy]phenyl}methyl)phenyl group. This compound is classified under several chemical categories, including aromatic ethers, monochlorobenzenes, diethers, and cyclopropanes [22]. Its chemical formula is $C_{24}H_{29}ClO_7$, with a molar mass of 464.94 g/mol [18].

Bexagliflozin's unique molecular structure, featuring both polar and non-polar groups, allows for stronger binding within the SGLT2 active site, thus improving its ability to inhibit glucose reabsorption. Developed by TheracosBio, bexagliflozin received its initial approval from the U.S. Food and Drug Administration in December 2022, adding to the growing arsenal of SGLT2 inhibitors. The drug offers benefits beyond glycemic control, such as reducing body weight and improving cardiovascular outcomes, making it a promising option for treating T2DM and its complications. With bexagliflozin, healthcare providers can address not only the metabolic aspects of diabetes but also the associated cardiovascular risks, offering a comprehensive therapeutic approach [23].

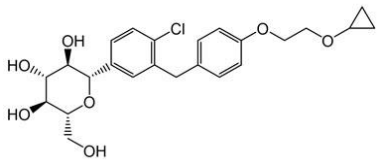
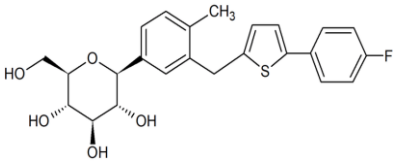
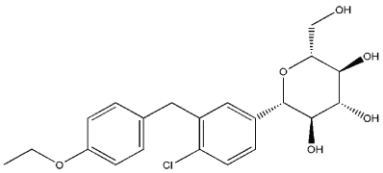
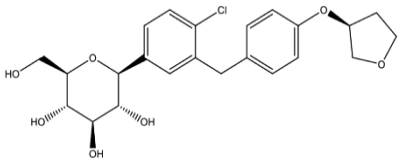
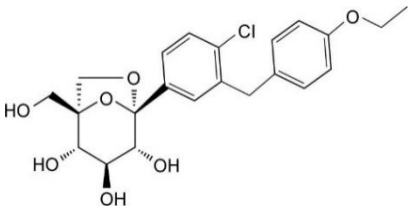
3.5. FDA-Approved Indications for SGLT-2 Inhibitors

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are FDA-approved for several critical indications. Primarily, they are prescribed to improve glycemic control in patients with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise. Beyond glycemic management, SGLT-2 inhibitors play a significant role in reducing the risk of major adverse cardiovascular events (MACE), including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death, in patients with T2DM who have established cardiovascular disease. Additionally, these inhibitors help reduce the risk of hospitalization and death in patients with heart failure with reduced ejection fraction (HFrEF), particularly those classified as New York Heart Association (NYHA) class II-IV. For patients at risk of chronic kidney disease (CKD), SGLT-2 inhibitors help mitigate the progression of CKD by reducing the risk of eGFR decline and hospitalization. Furthermore, they improve cardiovascular outcomes in patients with heart failure with preserved ejection fraction (HFpEF). Dapagliflozin, specifically, has received expanded FDA approval for treating heart failure across the entire spectrum of left-ventricular ejection fraction (LVEF), including HFrEF, HFpEF, and heart failure with mildly reduced ejection fraction (HFmrEF) [28].

3.6. Glycemic and Non-Glycemic Effects of SGLT-2 Inhibitors

SGLT-2 inhibitors have become a preferred treatment option for patients with T2DM, especially those with high cardiovascular risk. The SGLT-2 transporter, located in the proximal tubule of the kidney, is responsible for the majority of glucose reabsorption. By inhibiting this transporter, SGLT-2 inhibitors increase renal glucose excretion, leading to a daily loss of 60–80 grams of glucose, equivalent to 240–320 calories, in individuals with normal

Table 1: Comparison of SGLT2 inhibitors – chemical structures, mechanism and clinical indications [22,24-27]

Drug	Chemical Structure	Molecular Weight	FDA Approval Year	Indication
Bexagliflozin		464.94 g/mol	2022	Type 2 Diabetes
Canagliflozin		453.53 g/mol	2013	Type 2 Diabetes, Cardiovascular Risk
Dapagliflozin		408.87 g/mol	2014	Type 2 Diabetes, Heart Failure
Empagliflozin		450.91 g/mol	2014	Type 2 Diabetes, Cardiovascular Risk
Ertugliflozin		436.89 g/mol	2017	Type 2 Diabetes

renal function. This results in a decrease in plasma glucose concentrations [29-30]. These inhibitors have been shown to reduce HbA1c by 0.4% to 1.1% in a dose-dependent manner, depending on baseline hyperglycemia. For instance, in a 24-week trial, dapagliflozin 10 mg reduced HbA1c by -0.57% as compared to placebo. Similarly, empagliflozin achieved a reduction in HbA1c of -0.41% compared to placebo [31-32].

3.7. Effects on Body Weight

SGLT-2 inhibitors are also associated with weight loss, primarily by increasing urinary glucose excretion and thus promoting calorie loss. On average, patients lose 60–80 grams of glucose per day, resulting in a caloric deficit of 240–320 calories daily. Over two weeks, this equates to an approximate weight loss of 450 grams [33-34]. While SGLT-2 inhibitors contribute to sustained weight loss, this effect tends to attenuate over time due to as-yet-unidentified mechanisms. In clinical comparisons, dapagliflozin plus metformin resulted in a weight loss of -3.2 kg, whereas glipizide was associated with a weight gain of 1.44 kg [35]. A systematic review and network meta-analysis, which included 424 trials involving over 276,000 patients, revealed that SGLT-2 inhibitors such as empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin were among the most effective in promoting weight loss after subcutaneous semaglutide, exenatide, and liraglutide [36].

3.8. Effects on Blood Pressure

Hypertension is a common comorbidity in individuals with type 2 diabetes, significantly increasing the risk of cardiovascular complications. Several clinical trials have demonstrated the positive impact of sodium-glucose co-transporter 2 (SGLT-2) inhibitors on blood pressure regulation. For instance, a randomized controlled trial utilizing both ambulatory blood pressure monitoring (ABPM) and office BP measurements with empagliflozin revealed that reducing systolic blood pressure (SBP) to less than 150 mmHg and diastolic blood pressure (DBP) to at least 85 mmHg was associated with a decrease in major cardiovascular events [37].

Additionally, clinical trials have highlighted the efficacy of dapagliflozin in lowering blood pressure. In one such study, a significant reduction in mean seated SBP was observed after 24 weeks of treatment with dapagliflozin compared to placebo. However, the difference in the proportion of patients achieving a seated SBP of <130 mmHg by week 24 was less pronounced between the dapagliflozin and placebo groups. The overall reduction in SBP ranged from 2.3 to 7.2 mmHg, while reductions in DBP ranged from 1.0 to 2.8 mmHg [38]. Although primarily

prescribed for glycemic control, SGLT-2 inhibitors also provide considerable benefits in managing weight and blood pressure, particularly in patients with chronic kidney disease (CKD) [39]. Moreover, these drugs seem to improve cardiovascular markers such as arterial stiffness, a known risk factor for cardiovascular events and mortality [40]. One additional mechanism by which SGLT-2 inhibitors help lower blood pressure is through the modulation of sympathetic nervous system activity. For example, dapagliflozin has been shown to reduce renal sympathetic activity, indicated by decreased innervation of tyrosine hydroxylase-positive nerves and reduced norepinephrine content. This reduction in sympathetic activity was observed in neurogenic hypertensive Schlager (BPH/2J) mice fed a high-fat diet, further contributing to blood pressure reduction [41].

3.9. Cardiovascular Outcomes

SGLT2 inhibitors have been recognized for their significant impact on cardiovascular outcomes, though their effects vary among different drugs within this class.

3.9.1 Empagliflozin: Cardiovascular Death and Heart Failure Benefits

The EMPA-REG OUTCOME trial has provided compelling evidence regarding the cardiovascular benefits of empagliflozin. This study revealed that empagliflozin significantly reduces the risk of cardiovascular death and hospitalization for heart failure. Specifically, patients receiving empagliflozin had a 38% relative risk reduction in cardiovascular death and a 35% relative risk reduction in hospitalization for heart failure compared to those receiving a placebo [42-43]. This trial included 7,020 patients with type 2 diabetes and a history of cardiovascular disease, who were followed for a median of 3.1 years. The significant benefits observed in this trial underscore empagliflozin's effectiveness in improving cardiovascular outcomes.

3.9.2. Canagliflozin: Efficacy and Safety in Heart Failure Management

The CANVAS Program highlighted canagliflozin's cardiovascular benefits, particularly its role in reducing hospitalization for heart failure. In this program, which involved patients with type 2 diabetes and a history of cardiovascular disease, canagliflozin was associated with a 14% reduction in the combined primary outcome of cardiovascular death and hospitalization for heart failure. Although the impact on cardiovascular death was less pronounced than with empagliflozin, canagliflozin still demonstrated notable efficacy in reducing heart failure hospitalization [44-46]. However, it is important to note that the CANVAS Program also reported a higher incidence of lower limb amputations among patients treated with canagliflozin, an adverse effect that warrants attention.

3.9.3. Dapagliflozin: Focus on Heart Failure Hospitalizations

The DECLARE-TIMI 58 study assessed dapagliflozin's impact on cardiovascular outcomes, focusing on its effectiveness in reducing hospitalization for heart failure. The study demonstrated that dapagliflozin led to a significant reduction in cardiovascular death or hospitalization for heart failure. While dapagliflozin did not show a significant reduction in the overall rate of major adverse cardiovascular events compared to placebo, it was associated with a decrease in heart failure hospitalizations and a reduction in cardiovascular death or hospitalization for heart failure [45]. This highlights dapagliflozin's role in managing heart failure, though its impact on broader cardiovascular outcomes was more modest.

3.10. Renal Outcomes

Type 2 diabetes mellitus is a leading cause of kidney failure globally, and while effective long-term treatments are scarce, sodium-glucose co-transporter 2 (SGLT2) inhibitors offer promising improvements in renal outcomes. These medications function by inhibiting glucose reabsorption in the kidneys, which not only lowers blood glucose levels but also reduces the workload on the kidneys. This mechanism is associated with several beneficial effects on kidney health, including reduced albuminuria, slowed progression of kidney disease, and lower risk of advancing to end-stage kidney disease [46].

SGLT2 inhibitors operate by blocking SGLT2 proteins on the luminal surface of proximal tubular cells in the kidneys. This action enhances the excretion of glucose and sodium in the urine. However, the glucose-lowering effect of these inhibitors diminishes as the estimated glomerular filtration rate (eGFR) decreases, which led to initial regulatory guidelines limiting their use to patients with an eGFR of at least 45 or 60 mL/min per 1.73 m^2 [47].

3.10.1. Ertugliflozin: Glucose Control and Renal Protection

In clinical studies, ertugliflozin has shown efficacy in both glucose control and renal protection. In a trial involving patients with type 2 diabetes and established atherosclerotic cardiovascular disease, ertugliflozin demonstrated benefits by preserving eGFR and reducing urinary albumin-to-creatinine ratio (UACR) [48]. These findings underscore its role not only in managing glucose levels but also in improving renal function.

3.10.2. Bexagliflozin: Efficacy in Chronic Kidney Disease

Bexagliflozin has been evaluated in patients with chronic kidney disease (CKD) in a study involving those with CKD stages 3a and 3b. The treatment led to significant reductions in HbA1c levels, body weight, fasting plasma glucose levels, and albuminuria. Specifically, bexagliflozin resulted in a 20.1% reduction in albuminuria, demonstrating its efficacy in managing type 2 diabetes and CKD [49].

3.10.3. Empagliflozin: Renal and Metabolic Benefits in CKD

Empagliflozin has also been studied for its effects on renal outcomes. It was found to significantly increase 24-hour urine volume without raising urinary sodium levels when used alongside a loop diuretic in patients with stage 3a or 3b CKD. This treatment not only improved renal function but was also well tolerated, contributing to reductions in body weight and serum urate levels [50].

3.11. Bexagliflozin Overview

Bexagliflozin is a potent and selective inhibitor of sodium-glucose cotransporter 2 (SGLT2), notable for its significant efficacy in lowering blood sugar levels. It achieves this through its high potency, demonstrated by an in vitro IC50 of 2 nanomolar, and a remarkable 2435-fold selectivity for SGLT2 over SGLT1 [51]. This selective action helps to ensure effective glucosuria, as shown in experimental animal models [52-53].

3.11.1. Pharmacokinetics and Pharmacodynamics

Bexagliflozin is metabolized primarily through oxidation and glucuronidation, resulting in six major metabolites. The most significant circulating metabolite is the 3′-O-glucuronide, mainly formed by the enzyme UGT1A9. Major oxidative metabolites arise from the cleavage of the cyclopropyl ether, with subsequent oxidation to a carboxylic acid, or direct formation of the carboxylic acid. The contribution of these metabolites to the pharmacodynamic effects of bexagliflozin is estimated to be less than 1% [54].

In terms of pharmacokinetics, bexagliflozin exhibits similar profiles in both healthy individuals and adults with type 2 diabetes mellitus. When fasted, the mean peak plasma concentration (Cmax) is 134 ng/mL, and the area under the curve (AUC0-∞) is 1,162 ng·h/mL. Peak concentration typically occurs between 2 and 4 hours post-administration, though this can be delayed by food or medications. The drug has a volume of distribution of 262 L, an oral clearance of 19.1 L/h, and is metabolized mainly by UGT1A9 and CYP3A (Fig. 1), with the 3'-O-glucuronide being the primary metabolite. Approximately 91.6% of the drug is recovered in feces and urine, with a terminal half-life of about 12 hours [22].

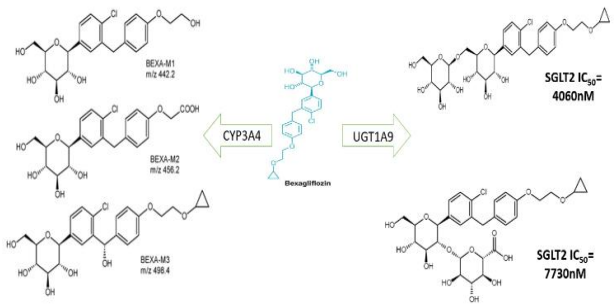


Fig. 1. Metabolism of bexagliflozin by UGT1A9 and CYP3A4 [55,56,23]

3.11.2. Contraindications

Bexagliflozin is contraindicated in individuals with hypersensitivity to the drug or any of its excipients, as well as in patients undergoing dialysis or those with end-stage renal disease with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2 [57]. Common adverse effects include diabetic ketoacidosis, lower limb amputation, urosepsis, pyelonephritis, hypoglycemia (especially with insulin), necrotizing fasciitis (Fournier's gangrene), and genital mycotic infections [58].

3.11.3. Safety Data

Safety data from clinical trials indicate that SGLT2 inhibitors, including bexagliflozin, have been associated with an increased risk of urinary and genital infections. However, no renal impairment was observed compared to placebo [59-61]. Diuresis-related adverse events were noted in the bexagliflozin cohorts, consistent with the drug's mechanism of action. Mild to moderate genital mycotic infections were reported in 2.3% of bexagliflozin participants, with no severe hypoglycemic events observed. The incidence of hypoglycemia was 0.5% in bexagliflozin-treated patients compared to 2.1% in those receiving sitagliptin. Bexagliflozin was also associated with increases in hemoglobin, hematocrit, and erythrocytes, and changes in cholesterol, whereas sitagliptin was linked to decreased bilirubin levels. Both drugs led to reduced alkaline phosphatase activity [62].

3.11.4. Efficacy Data

In a meta-analysis involving six studies with 3,111 patients, bexagliflozin significantly reduced HbA1c by 0.53%, fasting plasma glucose by 1.45 mmol/L, blood pressure, and body weight. It also increased the likelihood of achieving HbA1c <7% (OR 1.94) [63]. A comparative study of bexagliflozin and dapagliflozin showed that both drugs had similar effects on HbA1c, fasting plasma glucose, body weight, and systolic blood pressure, with comparable adverse event rates. Specifically, bexagliflozin's model-adjusted mean change in HbA1c at 24 weeks was -1.08% compared to -1.10% for dapagliflozin, indicating noninferiority [64]. Additionally, in high-risk type 2 diabetes patients, bexagliflozin improved HbA1c by 0.48%, reduced systolic blood pressure by 3.0 mmHg, and decreased weight by 2.7 kg, demonstrating non-inferiority for major adverse cardiovascular events (HR 0.79, 95% CI 0.56, 1.09) [65].

3.12. Other SGLT2 Inhibitors

Several SGLT2 inhibitors, primarily developed by Japanese pharmaceutical companies, have been introduced for managing type 2 diabetes mellitus (T2DM). Here are details on some notable SGLT2 inhibitors:

3.12.1. Luseogliflozin: Pharmacokinetics and Clinical Applications

It was developed by Taisho Pharmaceutical, and is an oral SGLT2 inhibitor used for T2DM management. It is available in Japan in 2.5 mg and 5 mg tablets, suitable for both monotherapy and combination therapy [66]. Clinical trials with healthy Japanese males tested luseogliflozin in single doses ranging from 1 to 25 mg and multiple doses of 5 or 10 mg/day for 7 days. The results demonstrated a dose-dependent increase in peak plasma concentration (C_{max}) and area under the curve (AUC), with peak plasma concentrations (t_{max}) occurring between 0.667 and 2.25 hours. Following multiple doses, the mean plasma half-life was between 9.14 and 10.7 hours, with no drug accumulation observed. Luseogliflozin increased urinary glucose excretion dose-dependently, from 18.9 to 70.9 grams in single-dose studies, with no significant food effects on its pharmacokinetics [67]. When added to insulin therapy, luseogliflozin significantly improved glycemic control and reduced body weight in Japanese patients with type 2 diabetes. Its efficacy was slightly reduced with moderate renal impairment, but it was generally well tolerated and safe across different eGFR levels [68,69].

3.12.2. Ertugliflozin: Cardiovascular Safety and Glycemic Control

It is the fourth SGLT2 inhibitor to be approved by the US Food and Drug Administration, receiving approval in December 2017 for use in patients with T2DM [70]. A study involving a single 25 mg oral dose of [(14)C]-ertugliflozin assessed its disposition in healthy subjects [71]. In a large-scale trial with 8,246 patients followed for an average of 3.5 years, ertugliflozin demonstrated noninferiority to placebo concerning major cardiovascular events and had similar rates of amputations. In patients with T2DM and atherosclerotic cardiovascular disease, ertugliflozin was found to be noninferior to placebo for major adverse cardiovascular events [72].

3.12.3. Tofogliflozin: Improved Quality of Life and Glycemic Outcomes

It is an SGLT2 inhibitor developed by Chugai Pharmaceutical and was first approved in Japan in 2013 for T2DM, either as monotherapy or in combination with other agents [73]. Tofogliflozin has been shown to improve quality of life and glycemic control, with associated body weight loss compared to conventional treatments in Japanese patients with T2DM. In comparison to conventional treatment, tofogliflozin users had reduced use of antihypertensive and lipid-lowering medications. It improved the DTR-QOL7 score and showed significant changes in HbA1c, fasting glucose, BMI, and waist circumference, which were negatively correlated with changes in QOL7 scores. Tofogliflozin was well-tolerated and effectively reduced MRI-PDFF levels, contributing to body weight reduction in NAFLD patients with T2DM [74,75].

3.12.4. Remogliflozin Etabonate[RE]: A Newer Option for T2DM Management

RE is a newer SGLT2 inhibitor approved in India for T2DM. It functions as a prodrug with active metabolites, requiring twice-daily dosing due to its short half-life [76]. A study involving 612 patients found that remogliflozin etabonate at doses of 100 mg and 250 mg demonstrated noninferiority to dapagliflozin in lowering HbA1c levels in T2DM patients. Both remogliflozin etabonate and dapagliflozin had similar safety profiles, with no significant differences in adverse events. This makes remogliflozin etabonate a viable alternative for glycemic control [77].

4. Pharmacogenomics and Pharmacogenetics of SGLT2 Inhibitors

SGLT2 inhibitors have become a cornerstone in the management of type 2 diabetes mellitus (T2DM). These agents reduce blood glucose levels by preventing glucose reabsorption in the kidneys, thereby increasing glucosuria. Although they have demonstrated significant efficacy and additional benefits such as weight loss and cardiovascular protection, individual responses to SGLT2 inhibitors can vary due to genetic factors. Pharmacogenomics and pharmacogenetics study these genetic variations and their impact on drug efficacy, safety, and metabolism. This section delves into the genetic factors influencing the pharmacokinetics, pharmacodynamics, and adverse effects of SGLT2 inhibitors.

4.1. Genetic variants influencing efficacy

4.1.1. SGLT2 Gene Variations: Impact on Drug Response

Genetic variants in the SGLT2 gene, which encodes the sodium–glucose cotransporter 2, play a critical role in the variability of drug response. Polymorphisms in this gene can affect the transporter's function, impacting the effectiveness of SGLT2 inhibitors [78]. For example, variants like rs10811661 and rs13266634 have been associated with altered glucose reabsorption efficiency, which can influence the extent to which these drugs lower blood glucose levels [79,80]. Research indicates that carriers of specific alleles may experience either enhanced or reduced efficacy of SGLT2 inhibitors, underscoring the need for personalized treatment approaches [81-82].

4.1.2. Pharmacokinetic Variations: Role of Metabolizing Enzymes

Variations in drug-metabolizing enzymes also affect the pharmacokinetics of SGLT2 inhibitors, which can lead to differences in drug exposure and therapeutic outcomes. Key enzymes involved include UDP-glucuronosyltransferase 1A9 (UGT1A9) and cytochrome P450 3A (CYP3A) [83-84]. For instance, bexagliflozin is primarily metabolized by UGT1A9, and genetic variations in this enzyme can influence its metabolism and clearance [85-86]. Variants such as UGT1A9*3 and UGT1A9*6 have been shown to affect the drug's pharmacokinetic profile, potentially leading to variations in efficacy and risk of adverse effects [87]. CYP3A enzymes also play a role in the metabolism of other SGLT2 inhibitors like dapagliflozin and empagliflozin, with genetic variations impacting drug metabolism and patient response [88-89].

4.2. Impact of Genetic Variants on Adverse Effects

4.2.1. Transporter Proteins: Influence on Drug Clearance

Genetic variants in drug transporters, such as organic anion transporter 3 (OAT3) and organic cation transporter 2 (OCT2), can affect the renal excretion of SGLT2 inhibitors [90]. These transporters are crucial for the elimination of the drugs from the body, and variations can lead to altered drug exposure and potential adverse effects. For example, certain variants in OAT3 may result in decreased drug clearance, increasing the risk of side effects like urinary tract infections or genital mycotic infections [91].

4.2.2. Genetic Risk of Adverse Events

Genetic predispositions can also influence the likelihood of adverse events associated with SGLT2 inhibitors [92]. Diabetic ketoacidosis (DKA) is a serious adverse effect linked to these drugs, and genetic factors related to renal function and glucose metabolism may affect the risk [93]. Studies have identified genetic variants that increase susceptibility to DKA, highlighting the importance of genetic screening to predict and manage this risk [94]. Additionally, genetic factors may influence the risk of other adverse events, such as lower limb amputations and urosepsis, though the relationship between specific genetic variants and these outcomes remains an area of ongoing research.

4.3. Pharmacogenomics and Drug Response

4.3.1. Clinical Implications of Genetic Variations

Pharmacogenomic studies offer valuable insights into how genetic variations influence individual responses to SGLT2 inhibitors. Identifying genetic markers associated with drug metabolism and efficacy can guide personalized treatment strategies. For example, patients with specific genetic profiles may benefit from dose adjustments or alternative medications based on their predicted response to SGLT2 inhibitors [95-96]. Personalized medicine approaches, informed by pharmacogenomic data, aim to optimize treatment efficacy and minimize adverse effects by tailoring therapy to individual genetic characteristics.

4.3.2. Personalized Treatment Strategies for T2DM

Incorporating pharmacogenomic testing into clinical practice can enhance the personalization of diabetes management. Genetic testing for variants affecting SGLT2 inhibitor metabolism and efficacy can help healthcare providers choose the most appropriate therapy for each patient. Personalized treatment strategies can address the variability in drug response observed among patients, improving therapeutic outcomes and reducing the incidence of adverse effects [97]. Implementing pharmacogenomic data into routine clinical decision-making is a promising approach to achieving more effective and safer management of T2DM.

5. Drug-Specific Genetic Interactions

5.1. Empagliflozin: Role of UGT Enzymes and Transporters

Empagliflozin is metabolized primarily by UGT2B7 and UGT2B4. Genetic variations in these UGT enzymes can influence the drug's pharmacokinetics and patient response [98-99]. For instance, UGT2B7 polymorphisms may affect the drug's clearance and efficacy. Additionally, genetic variations in SGLT2, as well as in transporters like OAT3, can impact the therapeutic outcomes and safety profile of empagliflozin

5.2. Dapagliflozin: Genetic Variants in CYP3A4 and UGT1A9

Dapagliflozin's pharmacokinetics are influenced by CYP3A4 and UGT1A9. Variants in these enzymes can lead to differences in drug metabolism and exposure. For example, CYP3A4*22 and UGT1A9*28 variants may alter the drug's clearance and efficacy [100]. Genetic variations in transporters like OAT1 and OAT3 can also affect the renal elimination of dapagliflozin, influencing its safety profile.

5.3. Canagliflozin: Influence of UGT Variants and Renal Transporters

Canagliflozin is predominantly metabolized by UGT2B4 and UGT2B7. Genetic variants in these enzymes, such as UGT2B4*3 and UGT2B7*2, can affect the drug's metabolism and patient response. Variations in SGLT2, as well as in renal transporters like OAT3, can also influence the drug's pharmacokinetics and the risk of adverse effects [101].

6. Future Directions in Pharmacogenomics of SGLT2 Inhibitors

6.1. Integration of Pharmacogenomics into Clinical Practice

The integration of pharmacogenomic data into clinical practice represents a significant advancement in the management of T2DM. Future research should focus on validating genetic biomarkers associated with SGLT2 inhibitor response and developing guidelines for their use in clinical settings. Establishing standardized protocols for pharmacogenomic testing can enable widespread implementation and enhance patient outcomes.

6.2. Advancing Genetic Research for Personalized Therapy

Ongoing research is needed to identify additional genetic variants that may influence SGLT2 inhibitor response and safety. Large-scale genome-wide association studies (GWAS) and pharmacogenomic studies can provide valuable insights into the genetic factors affecting drug efficacy and adverse events. Expanding genetic research will improve our understanding of individual variability in drug response and contribute to the development of personalized treatment strategies for T2DM.

7. Conclusion

In conclusion, the evolution of SGLT2 inhibitors has revolutionized the management of type 2 diabetes mellitus, offering significant benefits in glycemic control, cardiovascular protection, and weight management. The integration of pharmacogenomic insights has further enhanced their clinical utility by revealing how genetic variations impact drug metabolism and efficacy. While current research underscores the potential for personalized medicine to optimize treatment outcomes, ongoing studies are essential to fully understand these genetic influences and refine therapeutic strategies. Embracing pharmacogenomics in clinical practice will enable a more tailored approach to diabetes care, improving patient outcomes and advancing the field towards truly personalized treatment paradigms.

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