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Review Article

Adverse Drug Reactions Associated With Sodium-Glucose Cotransporter-2 Inhibitors: A Comprehensive Review

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ABSTRACT

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are an important class of antihyperglycemic agents used in the management of type 2 diabetes mellitus (T2DM). In addition to improving glycemic control, these agents provide significant cardiovascular and renal benefits and are increasingly used in patients with heart failure and chronic kidney disease. However, SGLT2 inhibitors are associated with several adverse drug reactions (ADRs), ranging from common genital mycotic infections and volume depletion to rare but serious events such as diabetic ketoacidosis, euglycemic diabetic ketoacidosis, acute kidney injury, Fournier's gangrene, and lower-limb complications. This review summarizes the classification, mechanism of action, clinical benefits, and adverse effects of SGLT2 inhibitors, with particular emphasis on their safety profile. The review also discusses selected risk factors and considerations for preventing and managing adverse reactions. Appropriate patient selection, monitoring, patient education, and early recognition of ADRs are essential to maximize therapeutic benefits and promote safe long-term use. Continued pharmacovigilance and long-term safety studies remain important for optimizing their clinical use.

INTRODUCTION

Type 2 Diabetes Mellitus is a significant global health concern affecting approximately 463 million individuals worldwide. Its prevalence is increasing, leading to various clinical and pathological challenges associated with treatment and complications (1). Diabetes mellitus is linked to cardiovascular disease through various mechanisms. Key contributing factors include

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hyperglycemia, insulin resistance, chronic inflammation, hypertension, dyslipidemia, and obesity. Each of these elements plays a significant role in exacerbating the risk of developing cardiovascular complications in individuals with diabetes(2). Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a newer class of oral hypoglycemic agents developed following the discovery of phlorizin, a natural SGLT inhibitor isolated from apple tree bark in 1835. Subsequent advances in understanding glucose transport mechanisms and the identification of SGLTs during the 1980s and 1990s facilitated the development of this therapeutic class(3). Sodium-glucose co-transporter 2 inhibitors (SGLT2i) were initially created to lower glucose levels in patients with type 2 diabetes mellitus (T2DM). However, subsequent research revealed that these agents also provide significant life-saving benefits for individuals with heart failure (HF) and chronic kidney disease (CKD), regardless of whether they have diabetes. Large randomized controlled trials (RCTs) have demonstrated these cardiometabolic advantages, leading to an increased interest in exploring the potential use of SGLT2i in the prevention and treatment of atherosclerosis(4). Beyond their primary function of lowering glucose levels, Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) exhibit additional pleiotropic effects in animal studies. These effects include mitigating inflammation, facilitating vascular remodeling, slowing down vascular aging, and providing systemic benefits related to cardiometabolic health(5). SGLT2 is mainly found in the proximal convoluted tubules of the kidney. It is a low-affinity ,high capacity transporter located in the S1 and S2 segments and is responsible for reabsorbing about 80-90 % of filtered glucose(6,7). SGLT2 inhibitors are well absorbed from the gastrointestinal tract and have high plasma protein binding ,allowing extensive distribution throughout the body. Their plasma protein binding is approximately 91% for dapagliflozin,86% for empagliflozin,93% for ertugliflozin and 99% for canagliflozin (8).SGLT2 inhibitors are mainly metabolized by UDP-glucuronosyltransferases (UGTs) through glucuronidation , undergo minimal metabolism by the cytochrome P450 system, and are primarily excreted in the urine (9,10). Four SGLT2 inhibitors – canagliflozin, dapagliflozin, empagliflozin and ertugliflozin are approved for use in adults in the United States. Canagliflozin the first SGLT 2 inhibitor, was approved in March 2013, followed by dapagliflozin in 2014, empagliflozin in August 2014 and ertugliflozin in 2017 (11). Empagliflozin is the most selective for SGLT2 compared to SGLT1 among the four FDA-approved drugs, while canagliflozin is the least selective (12). SGLT2 inhibitors include canagliflozin, dapagliflozin, ertugliflozin, bexagliflozin, ipragliflozin and sotagliflozin(13). The benefits of SGLT2 inhibitors include preventing complications from uncontrolled diabetes, reducing microalbuminuria, providing nephroprotective effects, promoting weight loss, and improving heart failure outcomes (14,15).

CLASSIFICATION

1. Canagliflozin
2. Dapagliflozin
3. Empagliflozin
4. Ertugliflozin
5. Bexagliflozin
6. Sotagliflozin

1. Canagliflozin

Canagliflozin is prescribed alongside diet and exercise to enhance glycemic control in adults and children aged 10 and older with Type2 Diabetes Mellitus(T2DM). It is also FDA-approved for reducing major adverse cardiovascular events (MACE) in adults with T2DM and cardiovascular disease, and for providing renal and cardiovascular protection in those with diabetic nephropathy, which is characterized by

high albuminuria(16). The CREDENCE trial demonstrated that canagliflozin offers renal protection in patients with T2DM and CKD with albuminuria, significantly reducing the risk of major renal endpoints ESKD, serum creatinine doubling, or renal/cardiovascular death-by 30% compared to placebo(17).

2. Dapagliflozin

Dapagliflozin is approved for use alongside diet and exercise to enhance glycemic control in both adults and pediatric patients ages10 and older with type 2 diabetes mellitus (T2DM). Additionally, it has received FDA approval for several other indications in adults: it helps reduce the risk of cardiovascular death, hospitalization for heart failure visits in those with heart failure, regardless of ejection fraction status. For patients with chronic kidney disease (CKD) at risk of progression, dapagliflozin lowers the livelihood of a decline in kidney function, progression to end-stage kidney disease (ESKD), cardiovascular death, and HHF in adults with T2DM who have established cardiovascular disease (CVD) or multiple risk factors (18).

3. Empagliflozin

Empagliflozin is used alongside diet and exercise to help control blood sugar in adults and children aged 10 and older with Type 2 diabetes (T2DM). It has FDA approval for several conditions. First, it reduces the risk of cardiovascular death and hospitalizations for hearth failure, regardless of heart function. Second, it protects the kidneys and heart in adults with chronic kidney disease (CKD), lowering the chances of kidney decline and cardiovascular issues. Third, it helps lower the risk of death in T2DM patients who have established atherosclerotic cardiovascular disease (ASCVD). Empagliflozin has shown effectiveness in various types of heart failure and can be started in patients hospitalized for acute heart failure to improve outcomes (19).

4. Ertugliflozin

Ertugliflozin is approved as an adjunct to diet and exercise for managing glycemic control in adults with Type 2 Diabetes Mellitus (T2DM) but is not approved for pediatric use. Its FDA-approved indications are focused solely on glycemic management, lacking claims for cardiovascular or renal risk reduction compared to other SGLT2 inhibitors (20).

5. Bexagliflozin

Bexagliflozin is indicated for adults with Type 2 Diabetes Mellitus (T2DM) as an adjunct to diet and exercise for glycemic control, but it is not approved for pediatric use. Its indications are limited to glycemic management without claims for cardiovascular or renal risk reduction. A cardiovascular outcomes trial showed that bexagliflozin does not increase cardiovascular risk compared to placebo, although it did not show statistical significance for certain favorable outcomes. Overall, it has favorable safety profile with modest benefits in glycemic control, blood pressure and body weight, nut remains approved only for glycemic management in adults with T2DM (21).

6. Sotagliflozin

Sotagliflozin is an oral small-molecule that dual inhibits SGLT1 and SGLT2 aimed at reducing glucose absorption in the gastrointestinal tract and renal glucose reabsorption (22). The SOLOIST-WHF trial showed that sotagliflozin significantly reduced cardiovascular death and heart failure-related events in type 2 diabetes patients post-hospitalization for worsening heart failure. The SCORED trial demonstrated its efficacy in decreasing cardiovascular events in T2DM patients with chronic kidney disease. Sotagliflozin dual action on SGLT1 and SGLT2 contributes to its distinct clinical benefits, solidifying SGLT2 inhibitors as essential in heart failure management. (23,24).

MECHANISM OF ACTION

BLOOD GLUCOSE MANAGEMENT

SGLT2 inhibitors, such as canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and bexagliflozin, primarily act on the SGLT2 proteins located in the proximal convoluted tubules of the kidneys, which are responsible for the reabsorption of glucose and sodium. These medications competitively inhibit SGLT2 activity, resulting in a significant reduction in glucose reabsorption—by 30% to 60%. This mechanism also lowers the renal threshold for glucose, promoting increased urinary glucose excretion. Consequently, patients with type 2 diabetes mellitus (T2DM) experience an average decrease in hemoglobin A1c (HbA1c) levels ranging from 0.5% to 1.0%. This effect contributes to improved glycemic control in individuals managing T2DM(25).

CARDIOPROTECTIVE EFFECTS

SGLT2 inhibitors provide cardioprotection mainly by blocking glucose and sodium reabsorption in the kidneys, leading to enhanced sodium delivery in distal tubules and suppression of the renin-angiotensin-aldosterone system(26). The resultant reduction in preload, due to natriuresis and diuresis, along with a decrease in afterload through arterial vasodilation, leads to enhanced cardiac hemodynamics. Both clinical and preclinical evidence validate the hemodynamic advantages of SGLT2 inhibitors, with empagliflozin demonstrating reductions in mean arterial pressure and ambulatory arterial stiffness index in clinical studies(27). Dapagliflozin promotes vascular health by enhancing vasodilation, improving endothelial function, and mitigating oxidative stress, as shown in preclinical models and clinical trials(28,29). In patients with Type 2 Diabetes Mellitus (T2DM), canagliflozin has been shown to reduce the increase in N-terminal pro–B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin I, both of which are indicators of cardiac stress, as indicated by the CANVAS trial. Additionally, these medications alter cardiac energy metabolism, promoting a shift from glucose and fatty acid oxidation to ketogenesis. This mild hyperketonemia encourages the use of β-hydroxybutyrate as a more efficient myocardial fuel source, which may enhance cardiac efficiency and provide antiarrhythmic benefits by stabilizing membrane potential. The clinical implications of these mechanisms are supported by large-scale randomized controlled trials (RCTs). Specifically, the DAPA-HF and EMPEROR-Reduced trials found that dapagliflozin and empagliflozin significantly lower hospitalization for heart failure (HHF) and cardiovascular mortality in patients with heart failure with reduced ejection fraction (HFrEF), regardless of T2DM status(30,31).

NEPHROPROTECTIVE EFFECTS

SGLT2 inhibitors provide nephroprotective effects primarily by enhancing distal sodium delivery and inhibiting tubuloglomerular feedback. This leads to afferent vasoconstriction, decreased intraglomerular pressure, reduced albuminuria, and slowed progression of chronic kidney disease (CKD), as evidenced by trials such as CREDENCE, DAPA-CKD, and EMPA-KIDNEY. The inhibition of proximal glucose and sodium reabsorption further promotes natriuresis. Additionally, SGLT2 inhibitors decrease effective circulating volume, lower blood pressure, and induce modest weight loss. Beyond these hemodynamic benefits, they also address inflammatory and fibrotic pathways, reduce kidney hypoxia, and affect mitochondrial metabolism in renal tissue(32,33).

ADVERSE EFFECTS

GENITAL MYCOTIC INFECTIONS

Genital mycotic infections, which include vulvovaginal candidiasis , vulvovaginitis, vulval abscess, and bacterial vaginitis, are notably associated with certain risk factor. The most significant of these is the female sex, alongside a history of recurrent infections, defined as three or more episodes per year.

Preventative measures focus in optimizing glycemic control and ensuring good personal hygiene. Generally, these infections are mild in nature and tend to resolve quickly once appropriate treatment is administered. It is also rare for healthcare providers to require the discontinuation of SGLT2 inhibitors in affected patients. The management of these infections typically involves the use of oral anti-fungal medications, such as fluconazole, or a short-course of topical anti-fungal treatments, including miconazole or clotrimazole, applied over a duration of one to three days(34).

UROSEPSIS AND PYELONEPHIRITIS

SGLT2 inhibitors have been associated with serious urinary tract infections (UTIs), including urosepsis and pyelonephritis, by inhibiting glucose reabsorption in the proximal tubule, these drugs cause glucosuria, creating an environment that may promote bacterial growth and increase the risk of UTIs. A meta-analysis of 52 randomized controlled trials (RCTs) found a dose-dependent increase in UTI risk with dapagliflozin use(35).

The available evidence about the link between SGLT2 inhibitors and a higher chance of developing urinary tract infections (UTIs) is not clear and varies. This might be because these medications can increase the amount of urine passed, a process known as osmotic diuresis and natriuresis, which may help prevent bacteria from growing in the urinary tract. However, doctors should be careful when giving these drugs to patients who have problems with urine flow or blockage in the bladder outlet, as there have been rare reports of serious UTIs, including cases of acute pyelonephritis linked to dapagliflozin. It is important to recognize these issues early and provide proper treatment(36).

LOWER LIMB AMPULATION

Patients with peripheral vascular disease neuropathy, previous diabetic foot ulcer, or a history of lower-limb amputation are at greater risk of amputation. SGLT2 inhibitors should be discontinued in patients who develop active lower-limb ulcers or infections. Among this drug class, canagliflozin has shown the strongest association with an increased risk of lower-limb amputation, whereas dapagliflozin has been associated with a higher risk of toe amputation(37).

A pooled analysis of phase 3 randomized controlled trials (RCTs) reported a slight increase in toe amputations with ertugliflozin. However, all affected patients had pre-existing peripheral neuropathy and peripheral artery disease, suggesting that underlying risk factors may have contributed to the observed events(38).

DIABETIC KETOACIDOSIS

SGLT2 inhibitors are associated with an approximately threefold risk of diabetic ketoacidosis (DKA). Patients with suspected DKA should undergo immediate clinical avaluation, and SGLT2 inhibitors therapy should be discontinued. Before initiating treatment, clinicians should assess individual risk factors and consider temporarily withholding these agents during conditions that increase the likelihood of ketoacidosis. Among the available SGLT2 inhibitors, canagliflozin appears to have the highest risk of DKA, followed by empagliflozin and dapagliflozin(39).

EUGLYCEMIC DIABETIC KETOACIDOSIS

Euglycemic diabetic ketoacidosis (euDKA) is characterised by high anion gap metabolic acidosis, ketosis,and blood glucose levels below 250 mg/dl. SGLT2 inhibitors may contribute to this condition through mechanism such as increased non-insulin-dependent glucose excretion, elevated glucagon levels, and volume depletion. Although ertugliflozin and canagliflozin have been most commonly associated with euDKA, this adverse effect has been reported has been most commonly associated with euDKA, this adverse effect has been reported with other SGLT2 inhibitors as well.(40,41)

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) may occur during the inhibitors therapy as a result of intravascular volume depletion. Therefore, volume status should be assessed and corrected before starting treatment, particularly in older adults, patients receiving diuretics, and those with impaired renal function. Pharmacovigilance data from the FDA Adverse Event Reporting System (FAERS) have shown a significant associated between canagliflozin,other SGLT2 inhibitors, and AKI, with individuals over 65 years of age being at greater risk(42).

HYPOGLYCEMIA

The risk of hypoglycemia increases when SGLT2 inhibitors are used in combination with insulin or insulin secretagoguses, such as sulfonylureas. To minimize this risk, does adjustments of insulin or sulfonylureas may be necessary. Older adults are particularly susceptible to hypoglycemia during combination therapy and should be monitored closely.(43)

FOURNIER GANGRENE

Fournier gangrene is a rare but life-threatening necrotizing infection of the perineal and genital regions that requires immediate surgical intervention. It can affect both men and women and typically presents with fever, sever pain, tenderness, and swelling in the affected area. Risk factors include diabetes mellitus, advanced age, obesity, hypertension, smoking, alcohol use, immunocompromised states, liver disease,end-stage renal disease, previous radiotherapy, and genital trauma or invasive procedures. The infection is usually polymicrobial; therefore, prompt treatment with broad-spectrum antibiotics, aggressive surgical debridement, and supportive care, including intravenous fluids and vasopressors when indicated, is essential. Antifungal therapy should be considered in cases of fungal superinfection.(44)

HYPERSENSITIVITY REACTIONS

SGLT2 inhibitor therapy has been associated with hypersensitivity reactions,including erythema , rash, pruitus and angioedema . In such cases, the medication should be discontinued and patients should be monitored until the symptoms have completely resolved (45).

BONE FRACTURE

SGLT2 inhinitors , especially Canagliflozin are associated with an increased risk of bone fractures with events noted as early as 12 weeks after starting treatment (46).Although some studies have not demonstrated an increased fracture risk with Canagliflozin compared with glucagon like peptide (GLP-1) receptor agonists, the findings may be influenced by cofounding factors and measurement bias.Proposed mechanisms for SGLT2 inhibitor-associated fractures include volume depletion leading to dizziness and falls , as well as disturbances in calcium,phosphate and vitamin D metabolism that may reduce bone mineral density(47).

BLADDER CANCER

Dapagliflozin may be associated with bladder cancer based on pooled analysis of 22 RCTs, suggesting it should be avoided in patients with active bladder cancer. However,SGLT2 inhibitors overall do not significantly increase cancer risk compared to other glucose-lowering therapies(48).Clinical guidance recommends against dapagliflozin for patient with hematuria or a history of bladder cancer due to potential tumor promotion risks(49).

HYPERKALEMIA

Canagliflozin has been associated with an increased risk of hyperkalemia particularly when used concurrently with angiotensin-converting enzyme(ACE) inhibitors or angiotensin receptor blockers(ARBs).This risk is greater in patient with

renal impairment , making regular monitoring of serum potassium levels important during the initiation and adjustment of therapy(50,51).

DYSLIPIDEMIA

SGLT2 inhibitors may lead to minor modifications in lipid metabolism,notably slight increases in low-density lipoprotein and high-density lipoprotein cholesterol levels.Monitoring lipid profiles regularly is advised to detect significant changes and inform subsequent management if needed(52).

CLINICAL BENEFIT

HEMODYNAMIC EFFECT

The combined natriuretic and osmotic effects of SGLT2 inhibitors balanced reduction in both intracellular and extracellular fluid volumes(53,54).The sustained reduction in intravascular volume and blood pressure produced by by SGLT2 inhibitors decreases cardiac preload and afterload thereby reducing cardiac workload and improving left ventricular function(55-58).SGLT2 inhibitors reduce reflex sympathethetic nervous system activity and modulate neurohormonal pathways involved in cardiovascular regulation by improving intravascular volume and blood pressure dynamics.Despite these hemodynamic effects they do not cause a compensatory increase in heart rate(59,60).Several clinical studies have demonstrated that treatment with SGLT2 inhibitors is associated with significant reductions in body weight among patients(61,62).

DIURESIS AND NATRIURESIS

SGLT2 inhibitors promote natriuresis and glucosuria, leading to osmotic diuresis that may contribute to improved outcomes in patients with heart failure. Mediation analyses from the EMPA-REG OUTCOME trial indicated that hemoconcentration, likely resulting from volume contraction, may account for approximately 50% of the observed cardiovascular benefits(63). The cardiovascular benefits of SGLT2 inhibitors cannot be explained solely by their diuretic effects, as conventional diuretics have not consistently demonstrated similar reductions in heart failure events. Evidence suggests that SGLT2 inhibitors differ from traditional diuretics. For instance, a comparative study showed that dapagliflozin reduced plasma volume and increased erythrocyte mass, effects that were not observed with hydrochlorothiazide(64).Compared with the loop diuretic bumetanide, dapagliflozin produced a greater reduction in interstitial fluid volume while preserving intravascular volume to a greater extent, suggesting a distinct pattern of fluid redistribution(65).

REDUCTION IN INFLAMMATION

Inflammation plays a significant role in the progression of heart failure, and elevated levels of proinflammatory biomarkers have been associated with increased disease severity(66,67).The association between heart failure and elevated inflammatory biomarkers has been observed in patients with both reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), indicating that inflammation contributes to disease progression across both forms of heart failure(68).Proinflammatory cytokines contribute to endothelial dysfunction, extracellular matrix remodeling, and cardiac fibrosis in heart failure. SGLT2 inhibitors, including empagliflozin, canagliflozin, and dapagliflozin, have demonstrated anti-inflammatory effects in patients with diabetes, which may help reduce extracellular matrix turnover and fibrosis, thereby contributing to improved cardiovascular outcomes(69,70,71,72). Experimental studies have shown that dapagliflozin exerts significant antifibrotic effects in post-infarction rat hearts by inhibiting collagen synthesis, suggesting a potential role in reducing cardiac fibrosis(72).Empagliflozin has also been shown to significantly reduce cell-mediated extracellular matrix collagen remodeling, suggesting a

potential role in limiting cardiac fibrosis and improving myocardial structural integrity(73).

BLOOD PRESSURE LOWERING

Hypertension is a common modifiable risk factor contributing to the onset of heart failure. SGLT2 inhibitors play a role in managing this condition by effectively lowering blood pressure(74).SGLT2 inhibitors improve blood pressure and cardiac energetics in heart failure, likely through osmotic and diuretic actions from sodium reabsorption inhibition, resulting in a 30% to 60% increase in urinary sodium excretion(75).The statement indicates that SGLT2 inhibition has a more significant antihypertensive effect compared to thiazide diuretics, especially when combined with ß-blockers or calcium antagonists. This suggests a favorable role for SGLT2 inhibitors in managing hypertension in certain patient populations(76,77).By reducing blood pressure, SGLT2 inhibitors may contribute to decreased cardiac afterload, leading to improved ventricular arterial coupling and enhanced cardiac efficiency. This mechanism is presumed to be advantageous for patients with heart failure. Nonetheless, the reduction in blood pressure associated with SGLT2 inhibition is relatively modest and is unlikely to fully account for the observed cardiovascular and renal benefits offered by these medications. Furthermore, while such blood pressure reductions are generally expected to more significantly impact stroke rates compared to other cardiovascular outcomes, this correlation was not demonstrated in the EMPA-REG OUTCOME trial(78).

WEIGHT LOSS

The use of SGLT2 inhibitors leads to glucose excretion by the kidneys, resulting in calorie loss and a reduction in body weight. This weight loss occurs as fatty acids are mobilized from adipose tissue. Clinical studies have consistently demonstrated a decrease in body weight among patients undergoing SGLT2 inhibitor treatment(79).Whereas weight loss may play a role in the beneficial effects of SGLT2 inhibition, it is not the primary mechanism behind the observed reductions in heart failure severity. This assertion is supported by the findings of the DAPA-HF trial, which indicated only a modest numeric reduction in weight, particularly in diabetic patients. Importantly, the impact of weight loss strategies on heart failure severity is significantly less pronounced compared to the effects of SGLT2 inhibition, suggesting that other mechanisms are likely contributing to the heart failure benefits seen in patients receiving this therapy(80). Additionally, the impact of SGLT2 inhibition on weight reduction is considered moderate and tends to decrease over time. This decline can be attributed to various counter-regulatory mechanisms, such as an increase in energy intake, which are triggered to help maintain weight(81).

IMPROVING GLUCOSE CONTROL

Inhibitors of SGLT2 are recognized as effective agents for lowering glucose levels; however, their impact on heart failure is unlikely to stem from improvements in glucose control. Research indicates that hyperglycemia is a weak risk factor for cardiovascular disease.In examining the rapid efficacy observed within days of treatment initiation, it appears challenging to align this with a glucose-lowering effect. Additionally, the minimal differences in glycemic control seen in cardiovascular outcome trials were intended to maintain the glycemic equipoise principle. Post hoc analyses from these trials indicated that neither baseline A1c levels nor changes in A1c were linked to any treatment adjustments when using SGLT2 inhibitors(82). Definitive evidence from the DAPA-HF trial demonstrated that dapagliflozin's efficacy in reducing heart failure and mortality is consistent across individuals with and without diabetes. Notably, those with pre-diabetes or impaired glucose tolerance exhibited similar benefits to those with normal glucose levels. Continuous studies using fractional polynomial analyses showed no correlation between baseline A1c

levels and dapagliflozin's effectiveness. Furthermore, experimental models of heart failure revealed that the advantages of SGLT2 inhibition occur independently of diabetes or hyperglycemia(83,84,85).

CONCLUSION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have become an important class of medications in the management of type 2 diabetes mellitus, with additional benefits in patients with heart failure and chronic kidney disease. Despite their established clinical benefits, these agents are associated with several adverse drug reactions, ranging from common genital mycotic infections, urinary tract infections, and volume depletion to rare but potentially serious events such as euglycemic diabetic ketoacidosis, acute kidney injury, Fournier's gangrene, and lower-limb complications. The occurrence and severity of these adverse effects may vary among individual SGLT2 inhibitors and can be influenced by patient-related factors, concomitant medications, and underlying diseases. Therefore, appropriate patient selection, dose adjustment, monitoring, patient education, and early recognition of adverse reactions are essential for ensuring safe and effective therapy. Overall, the benefits of SGLT2 inhibitors generally outweigh their potential risks when used appropriately. Continued pharmacovigilance and well-designed long-term studies are required to further clarify the safety profile of individual SGLT2 inhibitors and support their optimal use in clinical practice.

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