SGLT2 inhibitors in type 2 diabetes mellitus: a pharmacist's guide to optimised care

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Abstract

Objectives: To review current evidence on sodium–glucose co-transporter-2 (SGLT2) inhibitors in the management of type 2 diabetes mellitus (T2DM), highlighting their mechanisms, efficacy, safety, and relevance to the growing burden of diabetes mellitus within the South African healthcare context, where high rates of undiagnosed disease and limited specialist access amplify the importance of pharmacist-led interventions. This review underscores the vital role of pharmacists as frontline diabetes care providers – facilitating optimal use of SGLT2 inhibitors such as empagliflozin and dapagliflozin through patient counselling, safety monitoring, and therapeutic guidance.

Methods: A narrative literature review was conducted by searching PubMed, Google Scholar, and local databases. Key articles on SGLT2 inhibitors, their effects on cardiovascular and renal outcomes, and prevalence data on T2DM in South Africa were included. Relevant clinical trials and meta-analyses published in English were appraised, with a focus on recent developments and guidelines.

Results: *Burden of diabetes in South Africa:* T2DM prevalence can reach 12.9% or higher in certain urban black populations, exceeding the overall International Diabetes Federation (IDF) estimate of 10.8%. Nearly half (45.4%) of those affected remain undiagnosed.
Mechanism and benefits: SGLT2 inhibitors lower blood glucose by enhancing urinary excretion of glucose, providing insulin-independent glycaemic control. They induce weight loss and mild blood pressure reductions.
Cardiorenal protection: Large-scale trials conducted in T2DM patients with either established chronic kidney disease or cardiovascular disease or high cardiovascular risk demonstrate meaningful reductions in cardiovascular events, hospitalisation for heart failure, and progression of chronic kidney disease.
Safety profile: While generally well tolerated, key adverse effects include genitourinary infections and rare euglycaemic ketoacidosis, especially during acute illness or low-carbohydrate intake.

Conclusion: SGLT2 inhibitors address both the escalating rates of T2DM in South Africa and its serious complications. Their robust cardiorenal benefits, combined with modest weight loss and minimal hypoglycaemia risk, make them an essential component of contemporary diabetes pharmacotherapy. Pharmacists play a central role in identifying appropriate candidates, advising on safety precautions, and improving patient outcomes in an increasingly burdened healthcare landscape.

Keywords: Sodium-glucose co-transporter-2 (SGLT2) inhibitors, canagliflozin, dapagliflozin, empagliflozin, efficacy, safety

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Introduction

Diabetes Mellitus (DM) is a significant and escalating health concern, both globally and in South Africa, driven by urbanisation and lifestyle changes.[1] Recent estimates place the local prevalence as high as 12.9% in some urban black populations – surpassing the country's overall IDF rate of 10.8% – with nearly half (45.4%) of all individuals remaining undiagnosed.[2,3]

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a revolutionary class of medications for the management of type 2 diabetes mellitus (T2DM). Beyond their primary glycaemic-lowering effects, SGLT2 inhibitors confer substantial cardiovascular and renal benefits, positioning them as essential medicines in diabetes care. The versatility of these agents is demonstrated by their FDA-approved indications, which include: enhancing glycaemic control in type 2 diabetes mellitus (T2DM) when used alongside diet and exercise; lowering the risk of major adverse cardiovascular events (such as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) in individuals with T2DM and established cardiovascular disease; reducing the likelihood of cardiovascular-related hospitalisation and mortality in patients with heart failure with reduced ejection fraction (NYHA class II-IV); slowing the progression of chronic kidney disease (CKD) by mitigating eGFR decline and reducing hospitalisation risk in at-risk patients; and improving cardiovascular outcomes in individuals with heart failure with preserved ejection fraction. Notably, dapagliflozin has received FDA approval for the treatment of heart failure across the entire spectrum of left-ventricular ejection fraction (LVEF).

This review provides pharmacists with a comprehensive overview of SGLT2 inhibitors in T2DM, focusing on their mechanisms, differences, side effect profiles, interactions, metabolism, safety considerations, and indications in special populations.

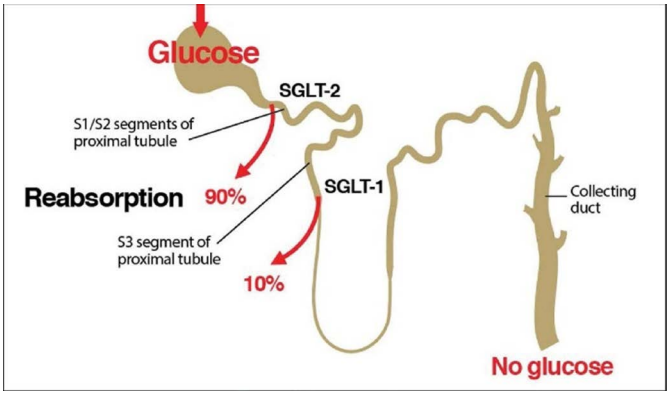

Figure 1: Mechanism of action of SGLT2 inhibitors

Adapted from[4]

Mechanism of action

Kidney glucose regulation

In individuals with normal health, most of the glucose (90%) that passes through the kidneys' filtration systems is reabsorbed by SGLT2 within the initial and middle sections of the proximal tubule (S1 and S2). The small amount of glucose that remains (10%) is then taken up by SGLT1 in the final portion (S3) of the same tubule (Figure 1).[4] Inhibiting SGLT2-mediated glucose reabsorption in the proximal tubule, thus enhances urinary glucose excretion and therefore reduces plasma glucose concentrations. This insulin-independent mechanism contributes to glucose control while also inducing osmotic diuresis, which leads to weight loss and a reduction in blood pressure. The unique insulin-independent nature of SGLT2 inhibitors results in a minimal risk of hypoglycaemia when used as monotherapy.[5-7]

Pharmacokinetics, metabolism and interactions

SGLT2 inhibitors, which are taken orally with a bioavailability in excess of 60%, exhibit variable protein binding and are primarily metabolised by hepatic glucuronidation via uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes, with renal and faecal excretion of metabolites (Table I).[5]

It is important to note that drugs influencing UGT enzyme activity may alter the metabolism of SGLT2 inhibitors. For example, inducers like rifampicin may decrease the plasma concentration of SGLT2 inhibitors, potentially reducing their efficacy (Table II).[8]

Pharmacists need to be vigilant particularly for patients with impaired hepatic or kidney function or those taking multiple medications such as concomitant use of UGT inducers (e.g. rifampicin, phenytoin, phenobarbital) as they can potentially reduce SGLT2 effectiveness, and inhibitors (e.g. kinase inhibitors, deferasirox, quercetin) which may cause elevated plasma levels and toxicity. Thus, potential interactions with UGT inducers/inhibitors should be monitored to mitigate these potential issues.

Interactions with other drugs and food

Because SGLT2 inhibitors are widely used for managing T2DM, they are often used in combination with other medications due

Table I: Comparative overview of SGLT2 inhibitors

Feature	Empagliflozin	Dapagliflozin	Canagliflozin (Canagliflozin (not registered in SA)
Selectivity for SGLT2	High	Moderate	Moderate
Half-life	12.4 h	12.2 h	11h–13 h
Dosing	10–25 mg OD	5–10 mg OD	100–300 mg OD
Oral bioavailability	> 60 %	78%	~ 65%
Plasma protein binding	86%	91%	98%
Hepatic metabolism	Extensive	Extensive	Extensive
Urinary elimination	28.6%	< 2%	< 1%
Cardiovascular benefits	Strongest evidence	Moderate evidence	Moderate evidence
Renal benefits	Yes (renal protection in chronic kidney disease [CKD])	Yes	Yes
Risk of genital infections	Moderate	Moderate	Higher
Bone fracture risk	No significant risk	No significant risk	Increased risk
Administration (with/without food)	With or without food	With or without food	Preferably before first meal.[4,5]
Trade name (numerous generics available in SA)	Jardiance 10 mg, Jardiance 25 mg (SA, US, EU)	Forxiga 5, Forxiga 10 (SA, US, EU)	Invokana 100, Invokana 300 (US, EU)

Abbreviations: US, United States of America; EU, Europe; SA, South Africa

Table II: Metabolism and UGT enzyme interactions of SGLT2 inhibitors[8]

SGLT2 inhibitor	Primary UGT enzymes involved	Effect of UGT inducers (e.g. rifampicin)	Clinical implication
Dapagliflozin	UGT1A9	↓ Plasma concentration	May reduce efficacy – monitor glycaemic control
Canagliflozin	UGT1A9, UGT2B4	↓ Plasma concentration	Dose adjustment may be necessary
Empagliflozin	UGT1A3, UGT1A8, UGT1A9, UGT2B7	↓ Plasma concentration	Monitor response; limited data on dose adjustment necessity

Table III: Drug and food interactions of SGLT2 inhibitors

Interaction	Potential effect
Diuretics	Enhanced diuresis and increased risk of dehydration and hypotension, especially in elderly patients.[9]
Insulin and sulfonylureas	The risk of SGLT2 inhibitors as monotherapy is low, however, increased risk of hypoglycaemia when used together, as both drugs lower blood glucose.[9,10]
NSAIDs (e.g. mefenamic acid)	Potential for reduced renal function, especially in elderly or volume-depleted patients. Mefenamic acid inhibits UGT1A9, increasing dapagliflozin plasma exposure.[8]
Probenecid	Increases plasma exposure of canagliflozin due to UGT enzyme inhibition, but the interaction is not clinically significant.[8]
Rifampicin	Reduces plasma levels of dapagliflozin and canagliflozin due to UGT enzyme induction, which may reduce effectiveness. Canagliflozin dose adjustment may be required.[9]
Other UGT inducers (phenytoin, phenobarbital, ritonavir)	Can reduce plasma levels of canagliflozin, requiring dose adjustment to 300 mg if tolerated.[8]
Paracetamol	No clinically relevant interaction observed.[8]
Warfarin	No significant effect on warfarin pharmacokinetics, no dose adjustment required.8
Digoxin	Canagliflozin may slightly increase digoxin levels, requiring monitoring of plasma digoxin concentrations.[9]
Simvastatin	Slight increase in simvastatin levels, but not clinically significant.[9]
Valsartan	Minor increase in valsartan exposure, but no clinical significance.[9]
Oral contraceptives	Canagliflozin may slightly increase ethinyl oestradiol and levonorgestrel exposure, though the effect is not significant.[9]
Thiazide diuretics	No significant pharmacokinetic interactions with hydrochlorothiazide.[9]
Food	SGLT2 inhibitors can be taken with or without food. However, canagliflozin is recommended to be taken before the first meal of the day for optimal absorption.[9]

to numerous comorbidities of lifestyle diseases. While SGLT2 inhibitors may interact with drugs that inhibit or induce UGT enzymes, their additional effects on renal glucose excretion and osmotic diuresis necessitate caution when used with diuretics, antihypertensives, and insulinotropic agents to prevent adverse outcomes such as dehydration, hypotension, or hypoglycaemia.[8,9] Table III outlines key drug and food interactions associated with SGLT2 inhibitors.

Clinical efficacy of SGLT2 inhibitors

SGLT2 inhibitors reduce HbA1c levels by approximately 0.6%–1.0%.[11,12]

A systematic review and meta-analysis evaluated SGLT2 inhibitors in 45 placebo-controlled studies involving 11 232 participants, and 13 studies with active comparators including 5 175 participants.[13] This systematic review indicated that SGLT2 inhibitors, when compared with other antidiabetic agents, promote weight reduction and lower systolic blood pressure. Specifically, a meta-analysis demonstrated that SGLT2 inhibitors are associated with a mean weight loss of 1.8 kg (95% CI: 0.11–3.50 kg). Additionally, they contribute to a reduction in systolic blood pressure by an average of 4.45 mmHg (95% CI: 3.18–5.73 mmHg).

Beyond glycaemic control, recent data have shown that SGLT2 inhibitors provide significant cardiovascular and renal benefits.

Cardiovascular and renal protection

Cardiovascular disease is the foremost contributor to mortality in South Africa, second only to HIV/AIDS.[14]

Large-scale clinical trials have demonstrated SGLT2 inhibitors' ability to reduce major adverse cardiovascular events (MACE), lower cardiovascular mortality, and decrease hospitalisation for heart failure (HF) (Table IV). The EMPA-REG trial highlighted a 38% reduction in cardiovascular mortality with empagliflozin in patients with T2DM and high cardiovascular risk.[15] These findings were further supported by DAPA-HF and DECLARE-TIMI 58, which confirmed the benefit of dapagliflozin in reducing heart failure-related hospitalisations.[16,17]

Exact nationwide incidence data on CKD in South Africa are limited, but are estimated at more than 10% of adults, primarily due to poorly controlled hypertension and T2DM. Local renal registry reports show a rising number of patients progressing to end-stage kidney disease (ESRD), with both hypertension and T2DM frequently implicated.[18]

In addition to cardiovascular protection, SGLT2 inhibitors have been shown to preserve renal function and slow the progression of chronic kidney disease (CKD). The CREDENCE[19] and DAPA-CKD[20] trials demonstrated a significant reduction in CKD progression, even in patients without diabetes. These findings have led to their widespread recommendation in guidelines for patients with established cardiovascular disease (CVD), heart failure with reduced ejection fraction (HFrEF), and CKD, regardless of diabetes status.[21] As a result, SGLT2 inhibitors are now a cornerstone therapy for improving outcomes in these high-risk populations and current guidelines (consensus report of the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and European Society of Cardiology (ESC) recommend the inclusion of SGLT2 inhibitors in the management of these conditions to improve patient outcomes.[22]

Table IV: Cardiovascular and renal protection data

Study	Drug	Population	Primary outcome	Key findings
EMPA-REG OUTCOME[15]	Empagliflozin	T2DM patients with high CV risk	Cardiovascular mortality	**38% reduction in CV death.** ↓ MACE, 0.86 (0.74–0.99) ↓ HHF ($p = 0.04$)
DAPA-HF[16]	Dapagliflozin	Patients with HFrEF (with/without T2DM)	Heart failure outcomes	**26% reduction in hospitalisation for heart failure.** At ($p < 0.001$) ↓ reduction of CV death and HF 0.74 (0.65–0.85)
CREDENCE[19]	Canagliflozin	T2DM patients with CKD	CKD progression	**30% reduction in CKD progression.** ↓ ESRD, doubling of sCr, renal death, or CV death at ($p = 0.00001$) 0.70 (0.59–0.82)
DAPA-CKD[20]	Dapagliflozin	CKD patients (with/ without T2DM)	CKD progression, mortality	**39% reduction in CKD progression, 31% reduction in all-cause mortality.** At ($p < 0.001$) ↓ Decline in eGFR, new ESRD, CV death or renal death, 0.61 (0.51–0.72)
DECLARE-TIMI 58[17]	Dapagliflozin	T2DM patients with or at risk for CV disease	Cardiovascular safety	**27% reduction in hospitalisation for heart failure.** At ($p = 0.005$) ↓ CV death or HHF 0.83 (0.73–0.95)

Abbreviations: CV, Cardiovascular; MACE, Major Adverse Cardiovascular Events; HHF, Hospitalisation for Heart Failure; HFrEF, Heart Failure with reduced Ejection Fraction; T2DM, Type 2 Diabetes Mellitus; CKD, Chronic Kidney Disease; ESRD, End Stage Renal Disease; sCR, serum Creatinine.

These findings underscore the multifaceted benefits of SGLT2 inhibitors, extending beyond glucose lowering to include significant cardiovascular and renal protection.[6]

Safety considerations

Potential adverse effects linked to SGLT2 inhibitors encompass urinary tract infections, genital fungal infections, Fournier gangrene, hypovolaemia and low blood pressure, acute kidney injury, diabetic ketoacidosis, as well as a heightened likelihood of osteoporosis and fractures (Table I).[23]

Genitourinary infections

Although SGLT2 inhibitors are generally well tolerated, they are associated with some important safety concerns. One of the most common adverse effects is an increased risk of genitourinary infections, including fungal infections and urinary tract infections, due to elevated glucose levels in the urine.[24]

Ketoacidosis

A rare but serious complication is euglycaemic ketoacidosis, which can occur even with normal blood glucose levels, particularly in cases of dehydration, reduced carbohydrate intake, or acute illness. During these states, the body may increase ketone production despite normal glucose levels, leading to ketoacidosis. It is thus essential for healthcare providers to be aware of this potential adverse effect to ensure prompt recognition and appropriate management.[25]

Hypotension

Furthermore, the osmotic diuresis induced by SGLT2 inhibitors may result in hypovolaemia and hypotension, necessitating caution in patients taking diuretics or those with a low baseline blood pressure.[26]

Fractures and lower limb amputations

Another significant concern is the potential for fractures and lower limb amputations, particularly with canagliflozin, which has been linked to an increased risk of these events.[27] As a result, careful patient selection and monitoring are necessary, especially for individuals at high risk for falls, fractures, or peripheral vascular disease.

Special populations

Renal impairment

Chronic kidney disease (CKD) is anticipated to rank as the fifth leading cause of death worldwide by 2040, with diabetic kidney disease (DKD) being the primary driver of this alarming trend.[28] Encouragingly, recent evidence has shown that SGLT2 inhibitors offer substantial renal and cardiovascular protection.[19,20] As a result, current clinical guidelines now recommend these therapies for individuals living with both CKD and DM to slow disease progression and improve outcomes.[22]

The efficacy of SGLT2 inhibitors diminishes as renal function declines, necessitating careful consideration in patients with renal impairment. Specifically, their glucose-lowering effect is reduced in individuals with an estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m^2, and they are generally not recommended for use when eGFR falls below this threshold (Table V).[29]

However, certain SGLT2 inhibitors have demonstrated renal protective benefits even in patients with eGFR as low as 30 mL/min/1.73 m^2, suggesting potential use in this population under specialist guidance.[30-32]

Over time, a variety of clinical trials evaluating different SGLT2 inhibitors across diverse patient groups and focusing on varied primary and secondary outcomes – including several post hoc analyses – have deepened our understanding of how these agents

Table V: SGLT2 inhibitors dose adjustment in renal and hepatic impairment

	CKD Stage 3b (eGFR 30–44 mL/min/1,73 m²)	CKD Stage 4 (eGFR 15–29 mL/min/1,73 m²)	CKD Stage 5 (eGFR < 15 mL/min/1,73 m²)	Hepatic dysfunction
Canagliflozin	100 mg	Do not initiate if eGFR < 45.[29]		Avoid in severe impairment (Child-Pugh class C)[30]
Dapagliflozin	10 mg	Do not initiate if eGFR < 25. If previously taking, may continue until dialysis.[29] Initiation is not recommended if eGFR < 25; however, patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death, and heart failure.[23]		No dosage adjustment; use with caution if initiating in severe impairment[30]
Empagliflozin[33]	10 mg, 25 mg	No dosage adjustment necessary for eGFR ≥ 30 (SA PI), eGFR ≥ 20.[29,34] Empagliflozin is not advised in patients with an eGFR < 30 and is contraindicated in those receiving dialysis**.** Due to limited evidence, no dosing guidance is available for individuals with T2DM and cardiovascular disease if eGFR is < 30, or for those with heart failure with reduced ejection fraction and eGFR < 20.[23]		No dosage adjustment necessary[29]

Adapted from[23,30]

may help prevent and manage CKD.[19,20] To fully grasp the impact of SGLT2 inhibitors on renal protection**,** it is essential to consider the combined findings from the CREDENCE[19] and DAPA-CKD[20] studies, which together paint a more comprehensive picture of their therapeutic value in CKD care.[32]

Hepatic impairment

In hepatic impairment, while specific dose adjustments may not be universally required, caution is advised, particularly in severe cases, due to limited data on safety and efficacy (Table V).

Pregnancy and lactation

The use of SGLT2 inhibitors during pregnancy and lactation is not recommended due to potential risks to foetal and neonatal development.[34] Human data are limited, but the few that are available suggest an increased incidence of miscarriages and congenital anomalies associated with SGLT2 inhibitor use during pregnancy.[34] Furthermore, these agents are excreted in animal milk, and their effects on the breastfed infant are unknown; therefore, breastfeeding is not advised during SGLT2 inhibitor therapy.[34] Healthcare providers should counsel women of childbearing potential on these risks and consider alternative glucose-lowering therapies during pregnancy and lactation.[34]

Take home messages for pharmacists

Pharmacists should be aware that SGLT2 inhibitors induce osmotic diuresis, which can lead to increased urination, volume depletion, and hypotension.[35] It is important to counsel patients to maintain adequate hydration (preferably water) and electrolyte balance to prevent dehydration and dizziness.[36]

Similarly, caution is advised if the patient is on diuretics, as concomitant loop or thiazide diuretics can exacerbate fluid loss – dose adjustments may be needed to avoid hypotension.[37]

Educate patients about the rare risk of euglycaemic diabetic ketoacidosis (DKA): this can occur even with normal blood glucose, so advise them to be vigilant for warning signs (e.g. nausea, vomiting, abdominal pain, or a fruity breath odour) and seek immediate medical attention if these occur.[38,39]

In addition, pharmacists should advise withholding the SGLT2 inhibitor during any acute serious illness (such as vomiting, severe infection, or dehydration) or prior to major surgery, and restarting only once the patient's condition stabilises.[36] This "sick day" precaution helps reduce the risk of DKA in stressful conditions.

Pharmacists also play a key role in preventing and managing infections associated with SGLT2 inhibitors. Because these drugs cause persistent glucosuria, they increase the risk of genital fungal infections (e.g. candidal vulvovaginitis or balanitis).[39] Emphasise good perineal hygiene – keeping the genital area clean, dry, and following proper daily washing – to reduce this risk. Patients should be counselled to report any signs of genital infection or urinary tract infection promptly so that treatment can be initiated.

Another important point is managing drug interactions: SGLT2 inhibitors alone have a low hypoglycaemia risk, but when combined with insulin or sulfonylureas, there is an increased risk of hypoglycaemia.[35] Therefore, the doses of insulin or secretagogues may need to be reduced to prevent hypoglycaemic episodes.

Similarly, blood pressure and volume status should be monitored if patients are on antihypertensives or diuretics, given the additive hypotensive effect.[15]

Renal function monitoring is advisable as well – check baseline and periodic kidney function – since these agents rely on glomerular filtration to exert their effect. Efficacy diminishes in advanced kidney disease, and most SGLT2 inhibitors are not recommended for glycaemic control in patients with significantly reduced eGFR (generally < 45 mL/min/1.73 m²). Refer to Table V.[29]

By staying vigilant about hydration status, infection prevention, potential interactions, and appropriate monitoring, pharmacists can ensure safe dispensing of SGLT2 inhibitors and provide valuable counselling to optimise patient outcomes.

Pharmacist Quick Tips

- Counsel on DKA symptoms and hydration
- Withhold during acute illness/surgery
- Monitor renal function regularly

- Adjust insulin/sulfonylurea doses to prevent hypoglycaemia
- Watch for genital infections – advise on hygiene
- Be alert to UGT-related drug interactions

Conclusion

SGLT2 inhibitors have revolutionised the management of T2DM by offering glycaemic control alongside significant cardiovascular and renal benefits. Their role in reducing heart failure hospitalisations and slowing CKD progression makes them a valuable addition to diabetes care. However, optimising their use requires pharmacist-led interventions, including patient education, monitoring for adverse effects, and ensuring appropriate therapy selection. By integrating SGLT2 inhibitors effectively into individualised treatment plans, pharmacists can enhance patient outcomes and contribute to a holistic approach to diabetes management.

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