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PRACTICAL APPROACH/CME ARTICLE

Practical Approach to Initiating SGLT2 Inhibitors in Type 2 Diabetes

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ABSTRACT

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are an attractive novel therapeutic option for the treatment of type 2 diabetes. They block the reabsorption of filtered glucose in kidneys, mainly in proximal renal tubules, resulting in increased urinary glucose excretion and correction of the diabetes-related hyperglycemia. Beyond improving glucose control, SGLT2 inhibitors offer potential benefits by reducing body weight and blood pressure. On the basis of the efficacy demonstrated in clinical trials, SGLT2 inhibitors are recommended as second- or third-line agents for the management of patients with type 2 diabetes. Beneficial effects on kidney disease progression, cardiovascular and all-cause mortality, and hospitalization for heart failure have also been demonstrated with one SGLT2 inhibitor (empagliflozin). Potential adverse events resulting from their mechanism of action or related to concomitant therapies are reviewed. A treatment algorithm for the adjustment of

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concomitant therapies after initiating SGLT2 inhibitors is also proposed.

Keywords: Concomitant; Initiation; Management; SGLT2 inhibitors; Type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition characterized by a hyperglycemic state due to impaired insulin secretion and diminished insulin action in peripheral tissues [1]. Diabetes is the leading cause of blindness, non-traumatic limb amputations, and chronic kidney disease. It is strongly associated with an increased risk of life-threatening cardiovascular complications, such as myocardial infarction or stroke. Achieving optimal glycemic control remains a challenge due to several obstacles: the pathophysiology of diabetes, involving multiple deficiencies and/or resistances; low treatment adherence; clinical inertia; and resistance to implementing behavioral and lifestyle changes [2]. Adverse events (AEs), such as hypoglycemia or weight gain, also contribute to the challenge [3]. Traditional therapeutic approaches have been characterized by stimulating insulin secretion and/or improving peripheral insulin resistance. Sodium-glucose co-transporter 2 (SGLT2) inhibitors (dapagliflozin, canagliflozin, and empagliflozin in the USA and Europe, and ipragliflozin, luseogliflozin, and tofogliflozin in Japan) are a novel and attractive therapeutic approach for the treatment of T2DM [4].

PHYSIOLOGICAL ACTION OF SGLT2 INHIBITORS

SGLT2 inhibitors treat T2DM by selectively blocking SGLT2, a high capacity and low affinity glucose transporter expressed mainly in the S1 and S2 segments of the proximal tubule, inhibiting glucose reabsorption, lowering the renal glucose threshold, and inducing urinary glucose elimination (Fig. 1) [5]. SGLT2 activity seems to be upregulated in patients with T2DM, thereby increasing the renal glucose threshold and exacerbating the tendency to hyperglycemia. Inhibiting SGLT2 activity is accompanied by glycosuria and osmotic diuresis. Despite the fact that SGLT2 activity accounts for up to 90% of renal glucose reabsorption, in clinical practice SGLT2 inhibitors only block 30–50% of the filtered glucose load, even at higher doses [6]. An excess of 40–80 g of glucose and 200–600 mL urine per day are reported with the chronic administration of SGLT2 inhibitors [6]. Dosing and glomerular filtration rate cutoffs for SGLT2 inhibitors are shown in Table 1. The therapeutically induced glycosuria and osmotic diuresis lead to reductions in plasma glucose, body weight, and systolic and diastolic blood pressure [7]. These collateral effects are potentially beneficial because they may reduce the development of microvascular and macrovascular complications. On the basis of the efficacy demonstrated in clinical trials, SGLT2 inhibitors are recommended as second- or third-line agents for the management of patients with T2DM [8]. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

CLINICAL EFFICACY

In randomized phase 2 and 3 clinical trials, the use of SGLT2 inhibitors as monotherapy (only indicated when intolerance to metformin or side effects exist) has been shown to significantly improve glycemic control in patients with T2DM. A systematic review of 45 randomized clinical studies comparing SGLT2 inhibitors to placebo (11,232 patients implicated) and 13 studies comparing SGLT2 inhibitors to active comparators (5175 patients using metformin, sitagliptin, or sulfonylurea) reported a reduction in HbA1c of −0.66% (95% confidence interval (CI) −0.73% to −0.58%) compared with placebo and −0.06% (95% CI −0.18% to 0.05%) with respect to active comparators [7]. Greater HbA1c reductions (0.44%, 0.54%, and 1.01%) have been observed in patients with high baseline HbA1c levels, i.e., HbA1c less than 8.0% (64 mmol/mol),

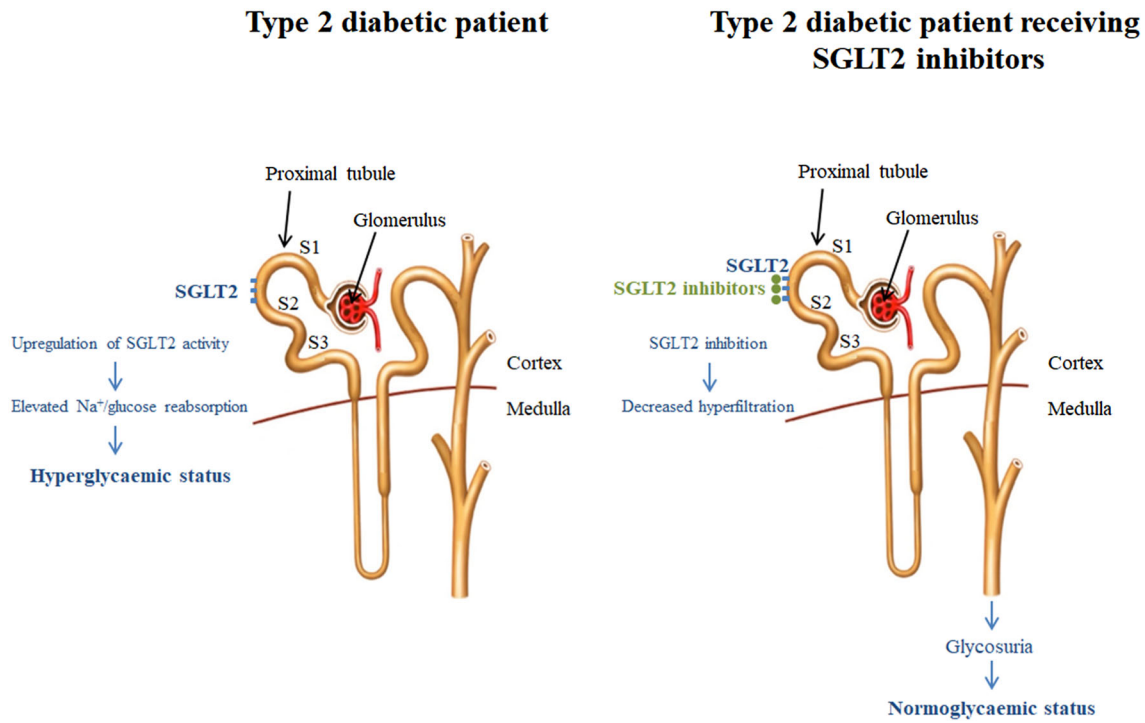


Fig. 1 Renal hyperfiltration in type 2 diabetes patients and the impact of receiving SGLT2 inhibitors. Modified from Fioretto et al. [5]. *SGLT2* sodium-glucose co-transporter 2

HbA1c = 8.0–9.0% (64–75 mmol/mol), and HbA1c greater than 9.0% (75 mmol/mol), respectively [9]. In addition, SGLT2 inhibitor therapy as monotherapy or in combination with metformin has been described to induce stable weight loss [10, 11]. In a systematic review, in comparison with other agents, SGLT2 inhibitors reduced mean body weight by −1.80 kg (95% CI −3.50 to −0.11 kg) [7]. In this vein, SGLT2 inhibitors have also been associated with a reduced systolic blood pressure of −4.45 mmHg (95% CI −5.73 to −3.18 mmHg) from baseline. A meta-analysis involving 27 randomized clinical trials and 12,960 individuals (follow-up period ranging from 4 to 52 weeks) recently demonstrated that SGLT2 inhibitors achieve a reduction of systolic and diastolic blood pressure of −4.0 and −1.6 mmHg, respectively [12]. Finally, the EMPA-REG OUTCOME trial, which aimed to evaluate long-term effects of empagliflozin on renal and cardiovascular outcomes in T2DM patients (3.1 years of median follow-up period), has demonstrated that, in addition to standard care, empagliflozin reduced the rate of incident or worsening nephropathy (approximately 39% reduction), serum creatinine doubling (44%), initiation of renal replacement therapy (55%), the risk of death from cardiovascular disease (38%), hospitalization for heart failure (35%), and all-cause death (32%) in patients with T2DM and high cardiovascular risk [13, 14]. Separation of event curves started very early in the study and is a matter of debate. The mechanisms involved in cardiovascular and renal benefits of empagliflozin are multifactorial. Hemodynamic effects, specifically reduced blood pressure and extracellular volume, driven by the direct drug class mechanism of action (osmotic diuresis), seems to be the main explanation for such a rapid effect, especially applied to the reduction in cardiovascular mortality and heart failure-related events. Many other factors including changes in weight, cardiac function, and metabolic actions could also be implied. A possible class effect should be confirmed in upcoming cardiovascular outcomes trials using other SGLT2 inhibitors.

Table 1 Dosing and glomerular filtration rate cutoffs for SGLT2 inhibitors

SGLT2 inhibitor	Dose (mg)	Glomerular filtration rate cutoffs (mL/min/1.73 m^2)	Recommendation
Dapagliflozin	5	>60	No dose adjustment
	10[a]	<60	Initial use is not recommended
			Discontinue in patients already on treatment
		<30	Contraindicated
Canagliflozin	100	<30	Avoid
	300	45–60	Use 100 mg dosing
		<45	Discontinue in patients already on treatment
		30–45	Initial use is not recommended
Empagliflozin	10	≥45	No dose adjustment
	25	<45	Initial use is not recommended
			Discontinue in patients already on treatment
		<30	Contraindicated

[a] In Europe dapagliflozin has only been commercialized as a dose of 10 mg

ADVERSE EVENTS ASSOCIATED WITH SGLT2 AND CONCOMITANT THERAPIES

The overall incidence of AEs using dapagliflozin, canagliflozin, or empagliflozin varies between 57.3% and 83.0% in different clinical trials, which is similar to other antidiabetic drugs (e.g., with metformin it ranges between 36.6% and 81.0%) [15]. Most frequent AEs are infections of the genitourinary tract (including vulvovaginitis in women or balanitis in men), with a frequency between 3.6% and 9.0%. Patients usually experience only a single episode, mild in intensity, and that responds to standard treatment [4].

SGLT2 inhibitors, when used in monotherapy, are associated with a low risk of hypoglycemia owing to their insulin-independent mechanism of action [7]. Additionally, long-term use of SGLT2 inhibitors has been associated with a rise in plasma glucagon levels and increased hepatic glucose production [16]. Interestingly, SGLT2-induced glucagon secretion is prevented by administering sulfonylureas concomitantly, thus explaining the risk of hypoglycemia with the use of these agents [11, 17–19]. The frequency of hypoglycemia increases significantly when SGLT2 inhibitors are used with a background therapy that includes sulfonylureas [11, 17–19] or insulin [20–23], compared to placebo. Reported frequencies of hypoglycemia using SGLT2 inhibitors vary greatly, from 6.9% [11] to 43.2% [12] with sulfonylureas, and from 29.2% [20] to 60.4% [21] with insulin. AEs are more likely to occur during the first few days or weeks of treatment [24].

Reducing the insulin dose has also been associated with euglycemic diabetic ketoacidosis [25]. The US Food and Drug Administration (FDA) issued a warning in May 2015 about the potential risk of diabetic ketoacidosis in patients receiving SGLT2 inhibitors and, in February 2016, the European Medicines Agency (EMA) established recommendations to reduce the risk of diabetic ketoacidosis reported in these patients [26, 27]. Nevertheless, the warning and recommendations come from case series with few patients, mainly those with type 1 diabetes who are insulin deficient [28]. To date, the cause of the higher frequency of diabetic ketoacidosis

in patients with T2DM is unclear and requires further investigation. Recent studies have reported that SGLT2 inhibitors in pancreatic alpha cells trigger glucagon secretion [16]. The resulting hyperglucagonemia might contribute to ketogenesis under conditions of low insulin concentration. The osmotic diuresis induced by SGLT2 inhibitors can lead to dehydration, reduction in intravascular volume, and orthostatic hypotension.

The reported frequency of volume depletion-related events ranges between 1.2% and 1.5% [24, 29]. The risk of postural hypotension and dehydration is higher among patients receiving diuretics (2.2–2.7%) than those who do not (0.9–1.0%) [4, 30]. This risk is particularly increased when combined with thiazides and loop diuretics as a result of their mechanism of action, enhancing the removal of sodium and water. Patients over the age of 75 years have shown an up to 4.4% increased frequency of postural hypotension [20, 21, 31]. Gastrointestinal AEs, such as nausea, vomiting, and diarrhea, are main AEs of incretin drugs (DPP4 inhibitors and GLP-1 receptor agonists, GLP1ra), and metformin [32–34]. While in most cases these symptoms are intermittent and insidious, in some cases they can lead to dehydration and an added risk of SGLT2 therapy-associated volume depletion.

SGLT2 inhibitors might also affect bone metabolism given the increased number of bone fractures reported in some clinical trials [35]. Indeed, the FDA released a warning for the use of canagliflozin for this regard in 2005 [36, 37]. Nevertheless, a recent meta-analysis of 38 randomized controlled trials (involving 30,384 patients, and a follow-up period between 24 and 160 weeks) has questioned the harmful effect of SGLT2 inhibitors on bone fractures [38]. A pooled analysis of 10 randomized trials has also suggested that the risk of fractures with canagliflozin might be caused by falls, potentially related to volume depletion-related AEs [39].

Furthermore, the FDA and EMA recently warned about a potential increased risk of lower limb amputation, mainly toes, in patients receiving canagliflozin [40, 41]. This warning is based on the interim analysis of the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial, in which the incidence of lower limb amputation was 7, 5, and 3 cases every 1000 patients with 100, 300 mg canagliflozin, and placebo, respectively. Further studies are required to corroborate the implication of SGLT2 inhibitors in bone fractures and lower limb amputations.

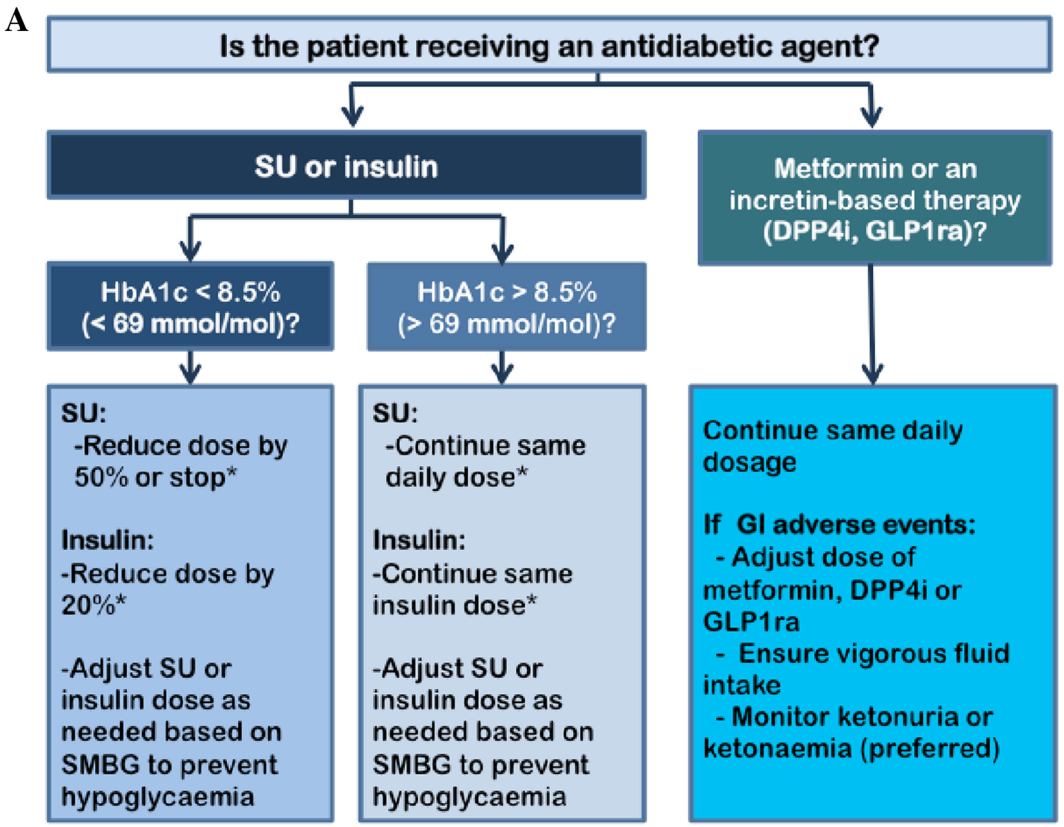
MANAGEMENT WHEN INITIATING SGLT2 INHIBITORS

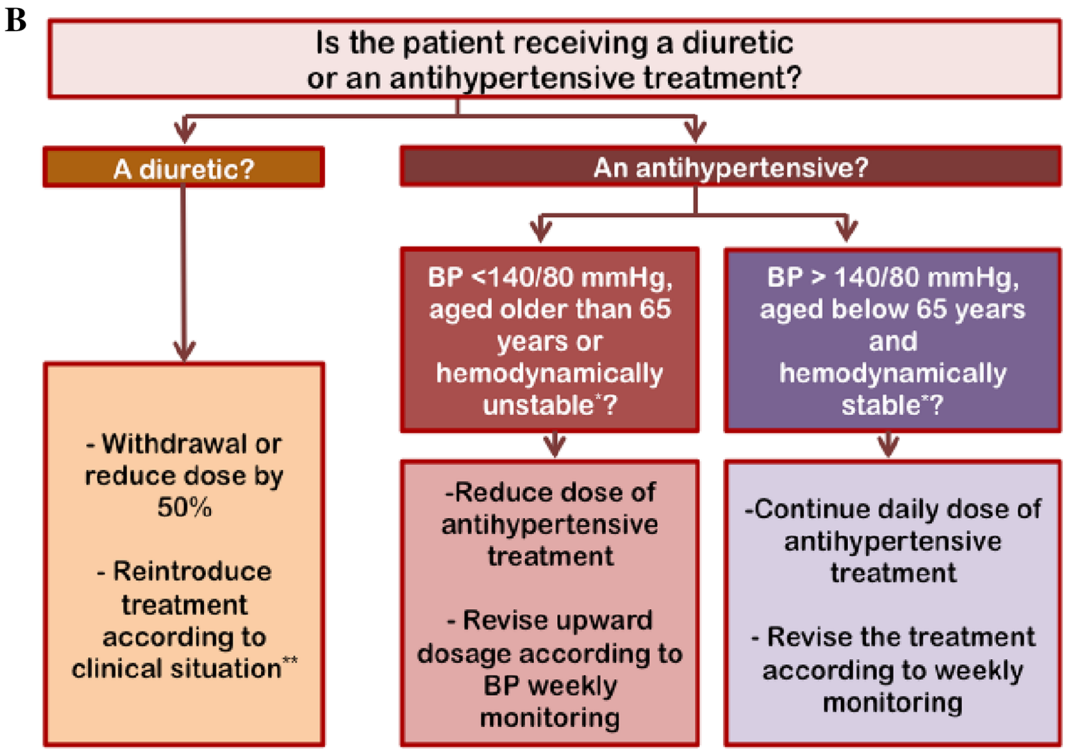
Suitable Patients

SGLT2 inhibitors are effective at any stage of the natural history of T2DM owing to their insulin-independent mechanism of action. This fact supports their use as add-on therapy to any other antidiabetic agent, and as monotherapy in patients who are intolerant to metformin. However, the requirement of an adequate renal function and the development of AEs may limit their use. The patient profile that can most advantageously benefit from the properties of these drugs includes younger ages; estimated glomerular filtration rate at least 60 mL/min/1.73 m^2 (renal function not impaired); established cardiovascular disease, no frequent genitourinary tract infections, overweight or obese; or hypertension (moderate to high blood pressure).

Adjustment of Concomitant Therapies

Lower doses of SGLT2 inhibitors are recommended when initiating treatment. It is also important to review concomitant therapies in order to minimize the risk of AEs. In the case of glucose-lowering therapies (insulin, sulfonylureas), the recommendation for patients with HbA1c less than 8.5% (less than 69 mmol/mol) is to reduce their daily insulin dose by 20%, with special caution to avoid insulin withdrawal to minimize the risk of euglycemic diabetic ketoacidosis (Fig. 2) [28, 31, 37, 42, 43]. Sulfonylureas should be reduced or stopped when initiating SGLT2 inhibitors. In contrast, maintaining the insulin dose is recommended for


A
Is the patient receiving an antidiabetic agent?
SU or insulin
Metformin or an incretin-based therapy (DPP4i, GLP1ra)?
HbA1c < 8.5% (< 69 mmol/mol)?
HbA1c > 8.5% (> 69 mmol/mol)?
SU:
-Reduce dose by 50% or stop*
Insulin:
-Reduce dose by 20%*
-Adjust SU or insulin dose as needed based on SMBG to prevent hypoglycaemia
SU:
-Continue same daily dose*
Insulin:
-Continue same insulin dose*
-Adjust SU or insulin dose as needed based on SMBG to prevent hypoglycaemia
Continue same daily dosage
If GI adverse events:
- Adjust dose of metformin, DPP4i or GLP1ra
- Ensure vigorous fluid intake
- Monitor ketonuria or ketonaemia (preferred)


B
Is the patient receiving a diuretic or an antihypertensive treatment?
A diuretic?
An antihypertensive?
- Withdrawal or reduce dose by 50%
- Reintroduce treatment according to clinical situation**
BP <140/80 mmHg, aged older than 65 years or hemodynamically unstable*?
BP > 140/80 mmHg, aged below 65 years and hemodynamically stable*?
-Reduce dose of antihypertensive treatment
- Revise upward dosage according to BP weekly monitoring
-Continue daily dose of antihypertensive treatment
- Revise the treatment according to weekly monitoring

◀**Fig. 2** Proposed algorithm for adjusting antidiabetic agents (**a**) and diuretic/antihypertensive therapy (**b**) when initiating SGLT2 inhibitors in patients with type 2 diabetes. *DPP4i* DPP4 inhibitors, *GI* gastrointestinal, *GLP1ra* GLP-1 receptor agonists, *SU* sulfonylureas, *SMBG* self-monitoring of blood glucose, *BP* blood pressure. *Avoid insulin withdrawal to minimize the risk of euglycemic diabetic ketoacidosis. **Hemodynamically unstable defined as atrial fibrillation, orthostatic hypotension or blood pressure lability, prior syncope, etc. ***Clinical situation defined by congestive heart failure, edema, renal function

patients with HbA1c greater than 8.5% (greater than 69 mmol/mol). In both cases, it is recommended that the patients self-monitor their blood glucose and adjust their insulin dose according to their glycemic control. Patients receiving metformin or an incretin-based therapy (DPP4 inhibitors, GLP1ra) should be especially monitored for the occurrence of gastrointestinal AEs. In the presence of vomiting or diarrhea, lowering the dose of metformin, DPP4 inhibitors/GLP1ra should be considered and vigorous fluid intake ensured. Ketonuria and/or ketonemia (preferred) monitoring is indicated in patients taking an SGLT2 inhibitor who present with symptoms suggestive of diabetic ketoacidosis, such as abdominal pain, nausea, vomiting, fatigue, and dyspnea [28]. When the concomitant therapy is a diuretic, recommendations include withdrawing the agent, and reconsidering the treatment according to the clinical situation, such as congestive heart failure, peripheral edema, or impaired renal function. In patients who are elderly and hemodynamically unstable (defined as the presence of atrial fibrillation, blood pressure lability, prior syncope), or with blood pressure under 140/80 mmHg, the recommendation is to decrease the antihypertensive treatment, and to review the treatment according to weekly monitoring. In contrast, in patients receiving antihypertensive treatment with high blood pressure who are hemodynamically stable, the recommendation is to maintain the antihypertensive treatment, and to review the treatment according to weekly monitoring.

CONCLUSIONS

SGLT2 inhibitors are an attractive novel therapeutic option for the treatment of T2DM. They block the reabsorption of filtered glucose, mainly in proximal renal tubules, resulting in increased urinary glucose excretion and correction of diabetes-related hyperglycemia. Beyond improving glucose control, SGLT2 inhibitors offer potential benefits by reducing body weight and blood pressure. On the basis of the efficacy demonstrated in clinical trials, SGLT2 inhibitors are recommended as second- or third-line agents for the management of patients with T2DM. Beneficial effects on kidney disease progression, cardiovascular and all-cause mortality, and hospitalization for heart failure have also been demonstrated with one SGLT2 inhibitor (empagliflozin). Potential AEs resulting from their mechanism of action (hypoglycemia and volume depletion-related events) make it advisable to review concomitant therapies when initiating with SGLT2 inhibitors. Although the overall frequency of AEs is relatively low among these patients, some individual characteristics (elderly, patients receiving diuretics, previous orthostatic hypotension, blood pressure lability, or prior syncope) may increase the risk of developing them.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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