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Elements for Success in Managing Type 2 Diabetes With SGLT-2 Inhibitors

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Elements for Success in Managing Type 2 Diabetes With SGLT-2 Inhibitors



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LEARNING OBJECTIVES

- Describe the role of the kidney in glucose homeostasis.
- Describe the mechanism of action of SGLT-2 inhibitors in the treatment of type 2 diabetes mellitus.
- Describe the glycemic effects of SGLT-2 inhibitors.
- List the most clinically important adverse events associated with SGLT-2 inhibitors.
- Differentiate key characteristics of SGLT-2 inhibitors from other antihyperglycemic medications.
- Select SGLT-2 inhibitor therapy to meet the needs, interests, and capabilities of patients with type 2 diabetes mellitus.
- Initiate strategies to minimize the risk of adverse events associated with SGLT-2 inhibitors.

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DISCLOSURE

Eden M. Miller, DO discloses that she is on the advisory boards and speakers' bureaus for AstraZeneca, Eli Lilly and Company, and Janssen Pharmaceuticals, Inc.

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Role of the Kidney in Glucose Homeostasis: Implications for SGLT-2 Inhibition in the Treatment of Type 2 Diabetes Mellitus

Eden M. Miller, DO

INTRODUCTION

In the context of diabetes, the kidney has been considered primarily in terms of the nephrotoxic consequences of hyperglycemia.¹ However, in the last decade or two, there has been renewed interest in the role of the kidney in glucose homeostasis and in the development of hyperglycemia in type 2 diabetes mellitus (T2DM).² Similarly, glucosuria and its attendant classical symptoms of polyuria and polydipsia that characterize uncontrolled hyperglycemia historically have been considered markers of disease.^{2,3} An alternative view is to consider glucosuria as an attempt by the kidney to mitigate the endothelial damage and associated complications caused by hyperglycemia by preventing an excessive elevation in blood glucose.³ This view suggests that agents promoting glucosuria might help reduce hyperglycemia, control diabetes, and reduce long-term complications.³ This focus on the kidney as a therapeutic target for the treatment of T2DM has led to the development of the sodium-glucose cotransporter-2 (SGLT-2) inhibitors, of which 3 are available in the United States (canagliflozin, dapagliflozin, and empagliflozin).

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ROLE OF THE KIDNEY IN NORMAL GLUCOSE HOMEOSTASIS AND TYPE 2 DIABETES MELLITUS

In healthy, nondiabetic individuals, virtually all of the glucose filtered from the plasma by the kidneys is reabsorbed in the proximal tubule, with little to no glucose appearing in the urine.¹ However, plasma glucose concentrations above the renal threshold for glucose (~180 mg/dL in healthy individuals) exceed the maximum glucose transport capacity (T_m glucose) of the proximal tubule.^{4,5} Consequently, excess glucose that cannot be reabsorbed is excreted, resulting in glucosuria.

In patients with T2DM, hyperglycemia increases the glucose load presented to the kidney.⁶ However, the level of glucosuria does not typically rise in tandem because the capacity of the kidney to reabsorb glucose (ie, T_m glucose) is increased in diabetes, resulting in an increased renal threshold for glucose excretion (~200 to 250 mg/dL). As a consequence, hyperglycemia is exacerbated.^{6,7} To make matters worse, the kidney may further contribute to hyperglycemia in T2DM through increased gluconeogenesis.⁸ An increased understanding of the role of renal glucose handling in the pathophysiology of diabetes mellitus has prompted targeting of the kidney for therapeutic intervention.

SGLTs in normal glucose homeostasis and type 2 diabetes mellitus

Glucose transport across cell membranes is mediated primarily by 2 types of active sodium-glucose cotransporters: SGLT-1 and SGLT-2. The SGLT-2 is a high-capacity, low-affinity glucose transporter located primarily in the brush border membrane of the convoluted (S1) segment of the proximal

renal tubule. SGLT-2 is responsible for reabsorbing approximately 90% of filtered glucose in the kidney.⁵ SGLT-1 is a high-affinity, low-capacity glucose transporter that reabsorbs the remaining 10% of filtered glucose in the distal straight segment (S3) of the proximal tubule.⁶ As glucose that is reabsorbed via SGLT-2 and SGLT-1 accumulates inside the proximal tubular cells, glucose transporter 2 (GLUT2) facilitates passive transport back into the surrounding interstitial fluid.⁹

In addition to its expression in the proximal renal tubule, SGLT-1 is abundant in intestinal mucosa enterocytes, where it facilitates the absorption of dietary glucose.^{9,10} SGLT-2 is found primarily in the luminal membrane of the S1 and S2 early segments of the proximal renal tubule, with possible limited expression in brain, liver, thyroid, muscle, and heart tissue.¹⁰

The increased capacity of the kidney to reabsorb glucose from glomerular filtrate in individuals with T2DM is due in large part to upregulation of SGLT-2 and GLUT2 expression and activity in uncontrolled diabetes.¹¹ This maladaptive response to hyperglycemia results in reduced urinary glucose excretion (UGE) and further worsening of the hyperglycemic condition.⁵ It also provides a rationale for inhibition of SGLT-2 as a therapeutic approach to control glucose levels in diabetes by suppressing glucose reabsorption and increasing glucosuria.^{2,12}

Inhibition of SGLT-2 in the treatment of type 2 diabetes mellitus

Selective SGLT-2 inhibitors reduce renal glucose reabsorption by inhibiting SGLT-2 in the kidney, thus reducing the maximum glucose transport capacity in the proximal renal tubule and increasing renal glucose excretion.¹³ This results in a lower renal threshold for glucose, so UGE occurs at a lower plasma glucose concentration. The overall result is increased UGE and decreased plasma glucose.⁹ The magnitude of UGE achieved with available SGLT-2 inhibitors in patients with T2DM is 100 g/day for canagliflozin 100 mg or 300 mg, 70 g/day for dapagliflozin 5 mg or 10 mg, and 64 g/day or 78 g/day for empagliflozin 10 mg and 25 mg, respectively.¹⁴⁻¹⁶

Because the action of selective SGLT-2 inhibitors is dependent on blood glucose levels and independent of the action of insulin, these agents have minimal potential for hypoglycemia.³ Since the mode of

action of SGLT-2 inhibitors relies on renal glomerular-tubular function, their effectiveness may be reduced in individuals with renal impairment.³

Increased UGE caused by SGLT-2 inhibitors is associated with osmotic diuresis as a result of a transient increase in urinary volume.¹⁴⁻¹⁶ SGLT-2 inhibitors are associated with an increased risk of adverse events related to osmotic diuresis (eg, polyuria, urinary frequency). Therefore, proactive consideration of intravascular volume and fluid balance issues is important with the use of these agents to monitor for and prevent possible adverse events such as dehydration and orthostatic hypotension.¹⁴⁻¹⁶ The increased glucose concentrations in the urine caused by SGLT-2 inhibitors may also predispose patients to genitourinary infections (predominantly vulvovaginal candidiasis among women).¹⁷

SUMMARY

The elevated renal threshold for glucose in patients with type 2 diabetes mellitus became a key therapeutic target upon discovery of the sodium glucose cotransporter system. The SGLT-2 inhibitors reduce renal glucose reabsorption, leading to a lower plasma glucose concentration. As a consequence of their mechanism of glucose lowering, the SGLT-2 inhibitors have minimal potential for hypoglycemia but are associated with adverse events consistent with their mechanism of action, ie, genital mycotic infections and increased volume or frequency of urination. ●

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Overview of the Efficacy and Safety of SGLT-2 Inhibitors in Type 2 Diabetes Mellitus

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ROLE OF SGLT-2 INHIBITORS ACROSS THE SPECTRUM OF TYPE 2 DIABETES MANAGEMENT

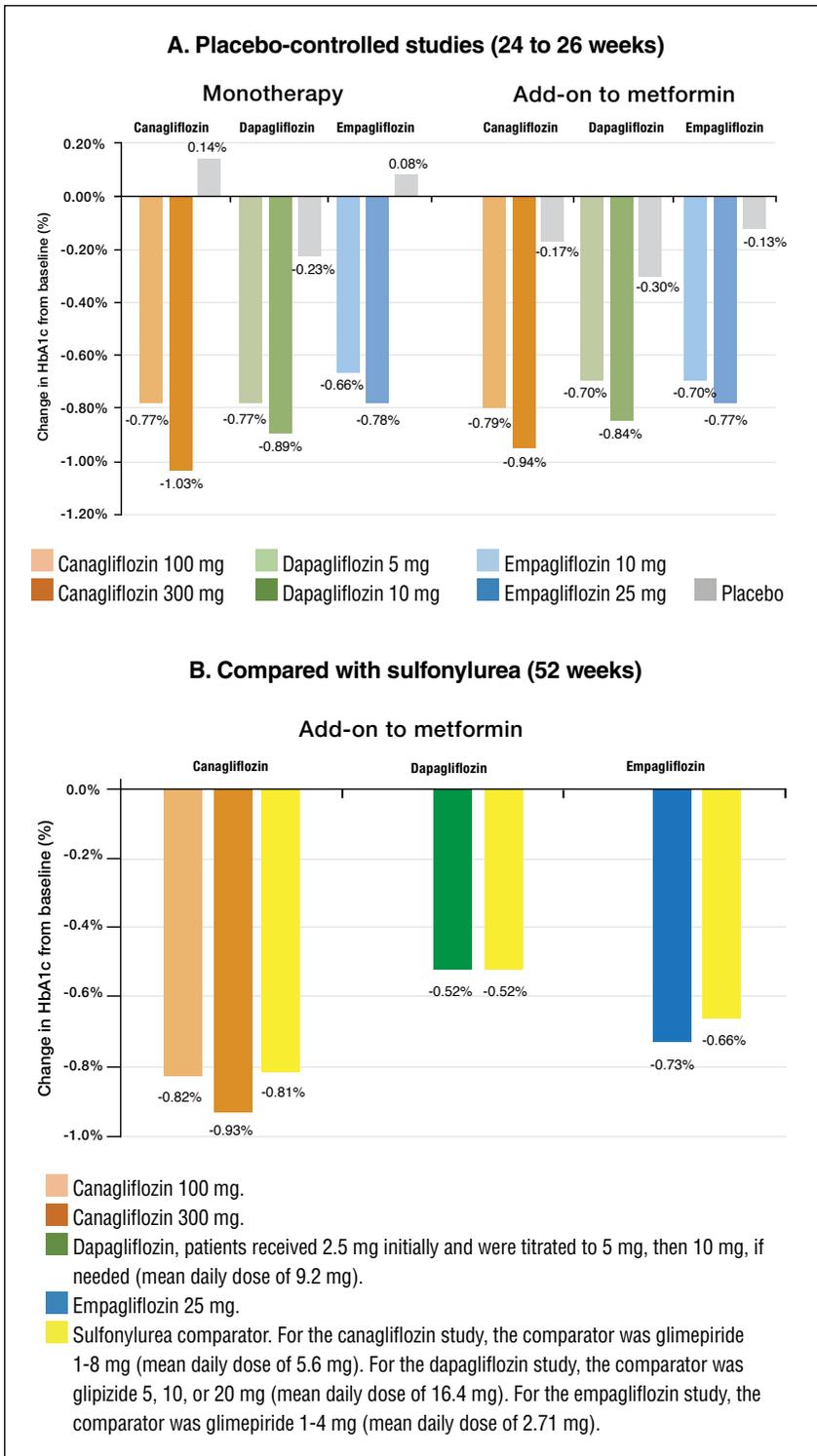
Since the approval of the first sodium-glucose cotransporter-2 (SGLT-2) inhibitor by the US Food and Drug Administration (FDA) in 2013, the SGLT-2 inhibitors have assumed key roles in the management of patients with type 2 diabetes mellitus (T2DM). Because their mechanism of action is in the kidney and independent of beta cell function, SGLT-2 inhibitors may be used at any stage of T2DM, even after insulin secretion has declined significantly.¹ All 3 SGLT-2 inhibitors, canagliflozin, dapagliflozin, and empagliflozin, have been approved by the FDA for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.²⁻⁴ Empagliflozin was recently approved to reduce the risk of cardiovascular (CV) death in adults with T2DM and established CV disease.⁴ Current guidelines suggest SGLT-2 inhibitors could be used as monotherapy in patients who do not tolerate or have a contraindication to metformin.^{1,5} In addition, SGLT-2 inhibitors are recommended as an option for dual and triple combination therapy with any antihyperglycemic medications, including insulin.^{1,5}

CLINICAL EXPERIENCE WITH SGLT-2 INHIBITORS

Glycemic and non-glycemic effects

The use of SGLT-2 inhibitor therapy across the spectrum of managing patients with T2DM is based on extensive experience from randomized, double-blind, clinical trials. As monotherapy or in combination with metformin, SGLT-2 inhibitor therapy significantly reduced the hemoglobin A1c (HbA1c) compared with placebo (**FIGURE 1A**).⁶⁻¹¹ In head-to-head studies versus a sulfonylurea, SGLT-2 inhibitor therapy provides similar reductions of HbA1c at 52 weeks, except for canagliflozin 300 mg, which resulted in a significantly greater reduction in HbA1c compared with glimepiride (**FIGURE 1B**).¹²⁻¹⁴ Greater reduction in HbA1c was also noted with canagliflozin 300 mg compared with sitagliptin 100 mg when added to metformin in patients with T2DM.⁹ As noted with other antihyperglycemic medications, larger reductions in HbA1c are observed in patients with higher baseline HbA1c. Smaller reductions in HbA1c are generally observed with older vs younger adults, ie, age ≥ 65 years vs < 65 years, likely because of declining renal function with advancing age.^{2-4,15} As monotherapy or as part of

FIGURE 1 Effects of SGLT-2 inhibitors on HbA1c as monotherapy and in combination with metformin⁶⁻¹⁴



dual or triple therapy, SGLT-2 inhibitors reduce HbA1c and fasting and 2-hour postprandial plasma glucose in patients with T2DM (TABLE 1).^{6-10,12-14,16-39} In addition, canagliflozin 300 mg given before a mixed meal has been shown to delay intestinal glucose absorption and reduce postprandial glucose excursions.^{37,38,40} The addition of an SGLT-2 inhibitor to basal, bolus, or basal-bolus insulin therapy provides further HbA1c reduction.⁴¹⁻⁴⁵ The amount of insulin required also may be reduced, particularly in patients requiring high doses of insulin.¹ Other benefits of SGLT-2 inhibitor therapy include weight loss of 2 kg to 4 kg, reduction of systolic blood pressure of 2 to 5 mm Hg, and reduction of serum uric acid of 13% to 15%.^{11,30,46}

Safety and tolerability

Pooled analyses of each of the 3 SGLT-2 inhibitors show that they are generally well tolerated, with a small increase overall in the incidence of treatment-related adverse events (AEs) compared with placebo.⁴⁷⁻⁴⁹ While it is not possible to compare rates of AEs among the SGLT-2 inhibitors because of a lack of head-to-head trials of similar design, discontinuation rates due to an AE are low and equally likely with an SGLT-2 inhibitor and a placebo.

The incidence and severity of hypoglycemia with SGLT-2 inhibitor therapy generally is similar to placebo.^{6,7,12,14,16-36} Severe hypoglycemia is infrequent. The exception is when an SGLT-2 inhibitor is added to

Abbreviations: HbA1c, glycated hemoglobin; SGLT-2, sodium glucose cotransporter-2.

The values shown at the end of each bar represent the change in HbA1c (%) from baseline to study end.

TABLE 1 Glycemic and non-glycemic effects of SGLT-2 inhibitors in type 2 diabetes mellitus^{6-10,16,18}

Endpoint	Effect of SGLT-2 inhibitor (compared with placebo)
HbA1c	0.3%-1.2% reduction
Fasting plasma glucose	12 mg/dL-36 mg/dL reduction
Postprandial glucose	36 mg/dL-59 mg/dL reduction
Weight	1.9 kg-4 kg (4.2 lb-8.8 lb) reduction
Systolic blood pressure	2.1 mm Hg-5.2 mm Hg reduction
Lipids	HDL: up to 13% increase LDL: up to 8% increase Triglycerides: up to 10% reduction

Abbreviations: HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; lb, pounds; LDL, low-density lipoprotein cholesterol; SGLT-2, sodium glucose cotransporter-2.

These data are from multiple studies with different designs and patient populations that compared an SGLT-2 inhibitor with placebo or a variety of other glucose-lowering medications.

insulin or sulfonylurea therapy, in which case the incidence of hypoglycemia is increased. Consequently, the dose of insulin or sulfonylurea should be decreased when an SGLT-2 inhibitor is added.⁴⁷⁻⁵⁰

The unique mechanism of glucose-lowering of SGLT-2 inhibitors via increased urinary glucose excretion is associated with specific AEs, including genital

mycotic infection and urinary tract infection, as well as several AEs related to osmotic diuresis (pollakiuria, polyuria) and volume depletion (postural dizziness, orthostatic hypotension) (TABLE 2).⁴⁷⁻⁵⁰ The most prominent difference is seen in the rate of genital mycotic infections in women, which is approximately 3 to 4 times higher with SGLT-2 inhibitor treatment

TABLE 2 Selected adverse events⁴⁷⁻⁴⁹

	Canagliflozin (N=2313) ⁴⁷			Dapagliflozin (N=3731) ⁴⁸			Empagliflozin (N=12,283) ⁴⁹		
	Placebo (%)	CAN 100 mg (%)	CAN 300 mg (%)	Placebo (%)	DAP 5 mg (%)	DAP 10 mg (%)	Placebo (%)	EMP 10 mg (%)	EMP 25 mg (%)
Genital mycotic infection^a									
Female	3.2	10.4	11.4	1.5	8.4	6.9	1.6	6.8	8.7
Male	0.6	4.2	3.7	0.3	2.8	2.7	0.8	3.4	3.7
Urinary tract infection^b									
Female	4	5.9	4.3	6.6	9.6	7.7	19.3	20.2	20.1
Male				1	1.6	0.8	3.3	3.8	4.6
Volume depletion^c	1.1	1.2	1.3	0.4	0.6	0.8	1.4	1.5	1.5

Abbreviations: CAN, canagliflozin; DAP, dapagliflozin; EMP, empagliflozin; N, number.

^aFor canagliflozin, includes vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, vaginal infection, vulvitis, and genital infection (fungal). For dapagliflozin, includes vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis *Candida*, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, balanoposthitis, balanoposthitis infective, genitourinary tract infection, posthitis, vaginitis bacterial, and vulval abscess. For empagliflozin, vulvovaginal mycotic infection, balanitis, and vulvovaginal candidiasis were the most common.

^bFor canagliflozin, includes urinary tract infection, cystitis, kidney infection, and urosepsis. For dapagliflozin, includes urinary tract infection, cystitis, *Escherichia* urinary tract infection, trigonitis, genitourinary tract infection, prostatitis, pyelonephritis, urethritis, and urinary tract infection fungal. For empagliflozin, urinary tract infection, cystitis, and asymptomatic bacteriuria were the most common.

^cFor canagliflozin, hypotension, dizziness postural, and orthostatic hypotension were the most common. For dapagliflozin, includes hypotension, syncope, dehydration, urine flow decrease, blood pressure decrease, orthostatic hypotension, and urine output decreased. For empagliflozin, hypotension, syncope, and orthostatic hypotension were the most common.

compared with placebo, averaging 8.3% vs 1.8%, respectively, across agents and studies.

Cardiovascular risk

The SGLT-2 inhibitors affect several risk factors for CV disease, including reductions in systolic and diastolic blood pressure, a small increase in low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol, and a small reduction to no change in triglycerides (**TABLE 1**).^{6-10,16,18} The clinical relevance of the increase in LDL-cholesterol is uncertain based on the results of the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial, completed in 2015. EMPA-REG OUTCOME was a CV safety study required by the FDA of all new antihyperglycemic medications to demonstrate that the new medication is not associated with an unacceptable increase in CV risk compared with placebo as part of standard care.⁵¹ The required clinical trial must assess major adverse CV events (MACE), which is a composite of CV death, nonfatal myocardial infarction, and nonfatal stroke compared with placebo.⁵¹ Similar studies are being conducted for canagliflozin (the CANVAS [Canagliflozin Cardiovascular Assessment Study] and CANVAS-R [Canagliflozin Cardiovascular Assessment Study-Renal] and dapagliflozin (the DECLARE-TIMI58 [Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events]).⁵²⁻⁵⁴

Results of the EMPA-REG OUTCOME trial showed that empagliflozin not only posed no increased risk of MACE but also was superior to placebo by significantly reducing the incidence of MACE (hazard ratio 0.86, 95% confidence interval 0.74-0.99).⁵⁵ The benefit was primarily due to a significant reduction in CV and all-cause death. These results led to the recent approval of empagliflozin to reduce the risk of CV death in adults with T2DM and established CV disease.⁴ Other benefits of empagliflozin observed in the EMPA-REG OUTCOME trial included significant reductions in risk of hospitalization for heart failure and kidney-related outcomes.^{55,56} The CV benefits of empagliflozin may stem not only from metabolic effects but also from favorable hemodynamic effects.^{57,58}

A pooled analysis of 21 studies suggests no increased risk with dapagliflozin for the composite of CV death, myocardial infarction, stroke, and hospital-

ization for unstable angina for up to 4 years.⁵⁹ A comprehensive systematic review and meta-analysis of regulatory submissions and published clinical trials involving more than 33,000 patients showed no clear evidence of differences among the SGLT-2 inhibitors with respect to CV outcomes.⁶⁰

Older adults

The safety and tolerability of SGLT-2 inhibitors in older adults has been assessed in pooled analyses of phase 3 clinical trials. For canagliflozin, a higher incidence of AEs leading to discontinuation occurred in adults aged ≥ 65 years compared with those aged < 65 years at doses of 100 mg (8.8% vs 3.3%) and 300 mg (5.4% vs 3.2%), respectively.⁶¹ While there was no difference in the risk of urinary tract infection, genital mycotic infection, or osmotic diuresis-related AEs, there were more volume depletion-related AEs (eg, dizziness and hypotension) in adults aged ≥ 65 years than aged < 65 years at doses of 100 mg (2.5% vs 0.9%) and 300 mg (2.0% vs 1.2%). The incidence of AEs, including those related to volume depletion, was highest in adults aged ≥ 75 years.¹⁵ In adults not on sulfonylurea therapy, the incidence of hypoglycemia did not vary in those aged ≥ 65 years compared with those aged < 65 years, with either the 100 mg (4.1% vs 3.8%) or 300 mg (4.0% vs 4.3%) dose of canagliflozin. Although the incidence of hypoglycemia was higher in adults who were on sulfonylurea therapy, the incidence was similar between age groups at both doses.

A higher incidence of AEs leading to discontinuation with increasing age was found in a pooled analysis of 30 studies of dapagliflozin 10 mg (age < 65 years, 5.9%; age ≥ 65 years, 14.4%; age ≥ 75 years, 26.8%).⁵⁹ Urinary tract infection was nearly twice as common in males aged ≥ 75 years than in males aged < 65 years (7.4% vs 4.0%, respectively). Volume-depletion AEs were more common with increasing age (age < 65 years, 1.7%; age ≥ 65 years, 2.3%; age ≥ 75 years, 3.1%). There was no increased risk of falls with increasing age associated with dapagliflozin. AEs related to kidney function, primarily transient increases in serum creatinine, were more common with increasing age (age < 65 years, 3.5%; age ≥ 65 years, 14.0%; age ≥ 75 years, 29.9%). The incidence of hypoglycemia was similar among the 3 age groups.

A pooled analysis of clinical trials involving empagliflozin showed a progressive increase in the

frequency of volume depletion-related AEs with both the 10 mg and 25 mg doses.⁴⁹ At the 25 mg dose, a volume depletion-related AE was observed in 1.2% of patients aged <50 years, 1.0% of patients aged 50 to <65 years, 2.2% of patients aged 65 to <75 years, and 4.3% of patients aged ≥75 years.

Bone and fractures

An interim analysis of results from the ongoing CANVAS study reported that the incidence of fractures was 4.0% with canagliflozin and 2.6% with placebo.⁶² The fracture rates in patients treated with canagliflozin were independent of sex, age (<65 years vs ≥65 years), and renal function (estimated glomerular filtration rate <60 mL/min/1.73 m² vs ≥60 mL/min/1.73 m²). Fractures primarily involved the upper and lower limbs.⁶² This led the FDA to issue a drug safety warning and revise the labeling for canagliflozin to encourage consideration of factors that contribute to fracture risk before initiating canagliflozin therapy.⁶³ Factors contributing to the increased fracture risk with canagliflozin are unclear but could be related to the higher risk population in CANVAS, which consisted of patients with a history of or at high risk of a CV event. A separate prospective trial in older patients with T2DM showed a small (1%) but statistically significant reduction with canagliflozin after 2 years in total hip bone mineral density compared with placebo, as well as weight loss-related increases in both bone formation and resorption biomarkers with canagliflozin.⁶⁴ In contrast, no changes were observed after 2 years with canagliflozin treatment relative to placebo at other skeletal sites (femoral neck, lumbar spine, and distal forearm).

The pooled analyses of dapagliflozin and empagliflozin indicated no statistically significant increased risk of fracture compared with placebo.^{49,59} However, an increased incidence of bone fractures was observed with dapagliflozin in a clinical trial involving patients with impaired renal function.³ In the EMPA-REG OUTCOME trial, a numerically higher rate of upper-extremity fractures was observed with empagliflozin compared with placebo.⁶⁵

Other concerns

Since the introduction of SGLT-2 inhibitor therapy in 2013, the FDA has issued drug safety communications regarding one or more SGLT-2 inhibitor medications based on postmarketing reports. These concern

an increased risk of: 1) diabetic ketoacidosis (DKA) and severe urinary tract infection (eg, pyelonephritis) with canagliflozin, dapagliflozin, and empagliflozin⁶⁶; 2) acute kidney injury with canagliflozin, dapagliflozin, and empagliflozin, with many of the postmarketing reports occurring within 1 month of starting the drug and with most patients improved after stopping it^{4,67}; and 3) leg and foot amputations, primarily of the toes, with canagliflozin, although an association with canagliflozin has yet to be confirmed.⁶⁸ In clinical studies, the incidence of DKA was less than 0.1% and similar to placebo.^{55,69} The completed and ongoing large CV safety studies will further define the efficacy and safety profile of SGLT-2 inhibitors.

Monitoring

During treatment with an SGLT-2 inhibitor, patients should be monitored for hypotension, acute kidney injury, impairment in renal function, hyperkalemia, urosepsis, pyelonephritis, hypoglycemia, genital mycotic infections, increased LDL-C, ketoacidosis, and hypersensitivity reactions (angioedema, urticaria).

Cost-effectiveness

Several analyses have been conducted in a variety of settings to determine the cost-effectiveness of SGLT-2 inhibitor therapy compared with other classes of medications, as well as among the SGLT-2 inhibitors. These analyses show SGLT-2 inhibitor therapy to be cost-effective compared with sulfonylureas or dipeptidyl peptidase-4 inhibitors as second- and third-line therapy in patients with T2DM, with an incremental cost-effectiveness ratio below accepted thresholds.⁷⁰⁻⁷⁸ Cost-effectiveness analyses have also shown that, when added to dual oral therapy, canagliflozin was found to be cost-effective compared with the addition of neutral protamine Hagedorn (NPH) insulin.⁷⁹

SUMMARY

SGLT-2 inhibitors have been shown to be effective and well tolerated as monotherapy and in combination with other antihyperglycemic medications, including metformin, in patients with T2DM. Similar reductions in HbA1c at 52 weeks have been observed with SGLT-2 inhibitors compared with sulfonylureas, except that canagliflozin 300 mg has been shown to result in greater HbA1c reduction

compared with sitagliptin and glimepiride. Available evidence indicates CV benefit with empagliflozin, leading to its recent approval to reduce the risk of CV death in adults with T2DM and established CV disease. CV trials involving canagliflozin and dapagliflozin are ongoing. The incidence of hypoglycemia is generally similar to placebo. Genital mycotic infection, urinary tract infection, and those related to osmotic diuresis and volume depletion are observed with SGLT-2 inhibitors. Those related to volume depletion are more common in older patients (ages >65 years) than younger patients. Investigation into other safety signals based on clinical studies and postmarketing reports is ongoing. ●

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Individualizing Treatment With SGLT-2 Inhibitor Therapy in Type 2 Diabetes Mellitus

Eden M. Miller, DO

GENERAL PRINCIPLES

The largely self-managed nature of type 2 diabetes mellitus (T2DM) underscores the importance of a collaborative decision-making process between patient and provider that best aligns the medication characteristics with the needs, interests, and abilities of the patient and with the treatment goals.^{1,2} The treatment regimen should be kept as simple as possible. Medication characteristics include efficacy in lowering the fasting and postprandial blood glucose levels and, consequently, the glycated hemoglobin A1c (HbA1c) mechanism of action; glycemic durability (time from initiation of treatment until maximal dose no longer achieves the glycemic target); risk of inducing hypoglycemia; effect on weight; patient tolerability; other adverse events; effects on nonglycemic endpoints such as blood pressure and blood lipids; ease of use; and cost-effectiveness. Patient characteristics include lifestyle; comorbidities such as cardiovascular (CV), kidney, or liver disease; potential for adherence; weight; hypoglycemia awareness; and ability and willingness to self-manage.²

CONSIDERATIONS WHEN USING SGLT-2 INHIBITOR THERAPY

This article applies these general principles to the use of sodium glucose cotransporter-2 inhibitor (SGLT-2) inhibitor therapy based on evidence from published studies and clinical experience of the author.

CASE SCENARIO #1

OT is a 53-year-old female diagnosed with T2DM 3 months ago. At diagnosis, her HbA1c was 8.7%, blood pressure (BP) 136/86 mm Hg, body weight 179 lb (body mass index 30.8 kg/m²) with a normal lipid profile; and estimated glomerular filtration rate (eGFR) 74 mL/minute/1.73 m². She had no evidence of retinopathy. She was started on

metformin twice daily, titrating up to 1000 mg over 2 weeks. OT and her primary care provider (PCP) discussed her lifestyle habits and agreed upon a plan to modify her diet and increase her physical activity.

She was seen 1 and 3 months after initiating metformin and lifestyle intervention. At the 3-month visit, her HbA1c was 7.7%, while her fasting plasma glucose (FPG) ranged from 102 mg/dL to 146 mg/dL over the previous 2 weeks and her postprandial glucose (PPG) from 194 mg/dL to 238 mg/dL.

Discussion: OT and her PCP discuss the options for use in combination with metformin (TABLE).²⁻³² The dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 receptor agonist (GLP-1RA), SGLT-2 inhibitor, sulfonylurea, and thiazolidinedione classes of medications all have a mechanism of action that is complementary to metformin. OT states that her primary concern is avoiding hypoglycemia; in addition, she would like to lose weight. For these reasons, they focus their discussion on GLP-1RAs and SGLT-2 inhibitors. Her PCP also notes that both GLP-1RAs and SGLT-2 inhibitors are associated with small to modest reductions in systolic BP (1.7 mm Hg to 6.8 mm Hg and 2.4 mm Hg to 8.5 mm Hg, respectively), which may be desirable in her case.⁴ They also talk about key safety and tolerability issues.

CASE SCENARIO #2

RH is a 67-year-old male who presents to the emergency department complaining of nausea and vomiting. He had checked his blood sugar a half-hour before and found it to be 286 mg/dL. He states he had been driving to the local area over the last 2 days and was not drinking much fluids because he did not want to stop driving to urinate; he had also stopped taking his diuretic. His vital signs are BP 114/62 mm Hg, pulse 88 beats per minute, respiratory rate 18 breaths per minute, tempera-

TABLE Key characteristics of selected antihyperglycemic medications²⁻³²

	Glycemic durability	Effect on weight	Risk of hypoglycemia	Key safety and tolerability issues	Cost
DPP-4 inhibitor	++	↔	Low	Acute pancreatitis; acute renal failure (sita); allergic/hypersensitivity reactions; arthralgia; heart failure (saxa, alo); hepatic failure (alo); hypoglycemia with SU or insulin	High
GLP-1RA	++/+++	↓	Low	Medullary thyroid cancer (alb, dula, ex QW, lira); Multiple Endocrine Neoplasia syndrome (alb, dula, ex QW, lira); thyroid C-cell tumors (alb, dula, ex QW, lira); pancreatitis; renal impairment; gastroparesis (alb, dula, ex QW); hypersensitivity reactions; injection-site reactions (ex QW); hypoglycemia with SU or insulin; nausea, vomiting, diarrhea	High
SGLT-2 inhibitor	++/+++	↓	Low	Severe renal impairment, ESRD, dialysis; hypotension; ketoacidosis; acute kidney injury/renal impairment; hyperkalemia (cana); urosepsis/pyelonephritis; genital mycotic infection; ↑LDL-C; bladder cancer (dapa); bone fracture; hypoglycemia with SU or insulin	High
SU	+	↑	Moderate	Sulfonamide hypersensitivity (glim, glyb); hypoglycemia; hypersensitivity reactions; hemolytic anemia weight gain	Low
TZD	++	↑	Low	Heart failure; ischemic CV events (rosi); hepatic failure; bladder cancer (pio); edema/weight gain; fractures; macular edema; decreased hemoglobin/hematocrit; hypoglycemia with SU or insulin	Low

Abbreviations: alb, albiglutide; alo, alogliptin; cana, canagliflozin; CV, cardiovascular; dapa, dapagliflozin; DPP-4, dipeptidyl peptidase-4; dula, dulaglutide; ex QW, exenatide once-weekly; ESRD, end-stage renal disease; glim, glimepiride; GLP-1RA, glucagon-like peptide-1 receptor agonist; glyb, glyburide; LDL-C, low-density lipoprotein cholesterol; lira, liraglutide; pio, pioglitazone; rosi, rosiglitazone; saxa, saxagliptin; SGLT-2, sodium glucose cotransporter-2; sita, sitagliptin; SU, sulfonylurea, TZD, thiazolidinedione.

+ = limited; ++ = good; +++ = excellent.

↓ = decrease; ↔ = no change; ↑ = increase.

Note: Data are not based on head-to-head comparisons.

ture 37.2°C. Random blood glucose is 298 mg/dL. His serum creatinine is 2.8 mg/dL, with an eGFR of 35 mL/min/1.73 m². Urinalysis is positive for glucose; complete blood count is normal other than showing a slight hemoconcentration. RH is found to be dehydrated. Current medications include metformin, SGLT-2 inhibitor, hydrochlorothiazide, and a statin. He is admitted for hydration, and his SGLT-2 inhibitor and hydrochlorothiazide are held.

Discussion: The mechanism of action of SGLT-2 inhibitor therapy to increase urinary glucose excretion causes an osmotic diuresis that can result in urinary frequency, polyuria, and volume depletion-related adverse events

such as hypotension and dizziness.³³⁻³⁵ Although these adverse events are not dose-dependent, they appear to increase with advancing age. Concomitant use of a diuretic should be done only with close monitoring. In addition to inadequate fluid intake, other causes of dehydration, such as protracted vomiting or diarrhea, prolonged exercise in the heat, urinary tract infection, illness, and overdiuresis with diuretics, should be investigated. Patients should be instructed to hold the SGLT-2 inhibitor (and diuretic) during periods of dehydration, illness, or surgery. The importance of staying hydrated can be reinforced by writing “Take each dose with a glass of water” on the prescription for the SGLT-2 inhibitor. Lastly, the SGLT-2 inhibitor would not be restarted until

the eGFR is above 45 (canagliflozin, empagliflozin) or 60 (dapagliflozin) mL/min/1.73 m².

CASE SCENARIO #3

KM is a 62-year-old female with T2DM who was started on an SGLT-2 inhibitor 3 months ago because of frequent hypoglycemia with metformin and sulfonylurea; the sulfonylurea was discontinued. She called the office saying she had developed her second yeast infection (“It’s just like the last one”) since starting the SGLT-2 inhibitor. She was asked to come in for a brief appointment to culture and examine the perineum. Physical examination revealed a moderately irritated vulva with little discharge. Routine vaginal culture 2 days later revealed normal flora with no yeast growth. KM was advised to treat the vulvar dermatitis with a barrier method such as A+D Ointment or zinc oxide ointment and told to be mindful of her perineal care. At a follow-up visit 3 months later, she reports that she continues to use A+D Ointment every day and has not experienced any further symptoms of irritation.

Discussion: While genital mycotic infections in women are more common when SGLT-2 inhibitor treatment is used, localized irritation can occur in both women and men taking an SGLT-2 inhibitor and can easily be mistaken by patients for a fungal infection. Patients should be educated about this possibility and instructed to be sure the genital area is clear of urine after voiding. Patients who experience urinary leakage, eg, those with overactive bladder or men with benign prostatic hyper trophy, may need to clean the genital area more frequently. Patients should be instructed to use a barrier method such as A+D Ointment or zinc oxide ointment.

CASE SCENARIO #4

LV is a 72-year-old female with a history of T2DM and well-controlled hypertension. She was started on an SGLT-2 inhibitor 2 weeks ago as add-on therapy to metformin. At that time, her BP was 102/65 mm Hg, HbA1c 7.9%, and eGFR 72 mL/min/1.73 m². Since starting the SGLT-2 inhibitor, she has experienced numerous episodes of dizziness when standing; she denies any chest pain. Current medications are metformin XR 750 mg, lisinopril/hydrochlorothiazide 40/25 mg, and simvastatin 20 mg, all taken once daily in the morning. Vital signs during her appointment are BP 100/62 mm Hg and pulse 89 beats per minute and regular without a murmur. She exhibits no lower extremity edema or jugular venous distension; her

lungs are clear. The remainder of her physical examination is normal.

The patient is advised to continue the SGLT-2 inhibitor and discontinue the hydrochlorothiazide portion of her medication. A new prescription for lisinopril 40 mg is given. She is advised to monitor her BP over the next few weeks with a goal of achieving levels lower than 140/90 mm Hg but higher than 110/65 mm Hg.

Discussion: Orthostatic hypotension occurs in <1.5% of patients treated with an SGLT-2 inhibitor.³³⁻³⁵ Older age and concomitant use of antihypertensive medications, eg, dihydropyridine calcium channel blockers (amlodipine, nifedipine, nimodipine, etc), would be expected to increase the possibility of orthostatic hypotension. Patients should be advised to avoid bending at the waist and to rise slowly from the supine or sitting position.

CASE SCENARIO #5

SJ is a 62-year-old male diagnosed with T2DM 3.5 years ago shortly after being hospitalized for a myocardial infarction. Until 3 weeks ago, he had been treated with the combination of metformin and a sulfonylurea; at that time, his treatment was intensified due to inadequate glycemic control (HbA1c 7.9%). Because of his history of myocardial infarction, a DPP-4 inhibitor, GLP-1RA, and SGLT-2 inhibitor were considered (**TABLE**).²⁻³² A DPP-4 inhibitor was thought unlikely to provide the needed glycemic reduction. SJ refused to begin a GLP-1RA because of the need for injection and perceived treatment complexity. Because an SGLT-2 inhibitor was felt to more closely align with SJ’s needs, interests, and abilities, an SGLT-2 inhibitor was started.

SJ is being seen urgently in clinic today because he has experienced several episodes of hypoglycemia over the past 2 to 3 weeks. In addition to the SGLT-2 inhibitor, his other medications are metformin 1000 mg twice daily, lisinopril 10 mg once daily, atorvastatin 40 mg once daily, and aspirin 81 mg once daily. During the physical examination, SJ mentions that he needs a new prescription for his sulfonylurea because he is about to run out. Upon questioning, SJ states that he has continued to take his sulfonylurea since starting the SGLT-2 inhibitor and does not remember being told to stop taking it.

Discussion: The incidence of hypoglycemia with SGLT-2 inhibitor therapy remains low when added to metformin monotherapy. However, the risk of hypoglycemia is increased when an SGLT-2 inhibitor, or most other

antihyperglycemic agents, is used in combination with a sulfonylurea or insulin.³³⁻³⁵ Consequently, consideration should be given to reducing the dose of the sulfonylurea or insulin upon the addition of an SGLT-2 inhibitor.²⁰⁻²² Moreover, patients should be instructed to monitor blood glucose more frequently and how to recognize and respond to hypoglycemia.

SUMMARY

The diverse attributes of the SGLT-2 inhibitor class of medications provide opportunities to individualize treatment to meet the needs, interests, and capabilities of patients with T2DM. In addition to addressing an important pathophysiologic mechanism of T2DM, SGLT-2 inhibitor therapy may be particularly beneficial in patients who are overweight or hypertensive or where hypoglycemia is a key concern. As shown with empagliflozin, CV risk reduction is a key benefit. Working with patients to minimize the risk of adverse events such as genital mycotic infection and those related to osmotic diuresis, with appropriate monitoring of body weight, BP, and kidney function, will facilitate the optimal use of SGLT-2 inhibitor therapy. ●

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