May 2015; Volume 11, No. 2

CME REPORT

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibition in Type 2 Diabetes Management: A New Therapeutic Option in Primary Care

An Evidence-Based CME Consensus Recommendation from an Expert Panel

NJAFP
New Jersey Academy of Family Physicians

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ACKNOWLEDGMENTS

The New Jersey Academy of Family Physicians developed this program. The Academy wishes to thank medical writer Charles A. Goldthwaite, Jr., PhD; project manager Jack Douglass; and graphic designer Karl Benner for their efforts in producing this material.

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This Enduring Material activity, *CME Report: Sodium-Glucose Cotransporter 2 (SGLT2) Inhibition in Type 2 Diabetes Management: A New Therapeutic Option in Primary Care*, has been reviewed and is acceptable for up to 2.00 Prescribed credit(s) by the American Academy of Family Physicians. Term of approval begins 05/15/2015. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Everett Schlam, MD, the reviewer for this activity, has disclosed no relevant financial relationships.

ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT

This program is supported by an educational grant from Janssen Pharmaceuticals , Inc., administered by Janssen Scientific Affairs, LLC.

DATE OF RELEASE AND TERMINATION DATE

The Date of Release for this activity is: May 15, 2015
The Terminate Date for this activity is: May 14, 2016

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GENERAL OBJECTIVE

To enable primary care clinicians to use SGLT2 inhibitors in the management of type 2 diabetes.

SPECIFIC OBJECTIVES

At the end of this program, participants will be able to:

- *Explain the role of the kidney in glucose homeostasis.*
- *Assess the mechanisms of agents targeting kidney function.*
- *Describe the rationale, mechanisms, and clinical consequences of SGLT2 inhibition.*
- *Develop practice-based strategies for using SGLT2 inhibitors.*
- *Create individualized treatment plans for patients with type 2 diabetes, using the most appropriate pharmacotherapy available.*

AT A GLANCE

- *Type 2 diabetes is a progressive disorder that affects numerous organs and tissues.*
- *Achieving glycemic control is essential to manage diabetes and its complications.*
- *Many patients can reach and maintain glycemic goals by implementing lifestyle changes (e.g., diet, physical activity).*
- *When lifestyle intervention is insufficient to attain or maintain glycemic control, oral or parenteral antihyperglycemic agents should be initiated.*
- *The progressive nature of the disease often necessitates multiple agents with complementary mechanisms of action.*
- *SGLT2 inhibitors are a new class of oral agents that reduce renal glucose reabsorption independently of insulin.*
- *SGLT2 inhibitors are appropriate for implementation by primary care clinicians and are especially useful because their mechanism of action is complementary to essentially all other classes of antihyperglycemic agents.*
- *Since 2013, three SGLT2 inhibitors—canagliflozin, dapagliflozin, and empagliflozin--have been approved by the US FDA. These agents are indicated as adjuncts to diet and exercise to improve glycemic control in adults who have type 2 diabetes.*
- *SGLT2 inhibitors do not promote hypoglycemia and are associated with weight loss and reduction in blood pressure.*
- *Diabetes management strategies should treat-to-target and involve the patient in the process of his/her disease management.*
- *By identifying individuals who will benefit from SGLT2 inhibitors, the primary care clinician can help patients manage their type 2 diabetes, thereby reducing complications and enhancing quality of life.*

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INTRODUCTION

According to statistics released in 2014 by the Centers for Disease Control and Prevention (CDC),[1] more than 29 million US children and adults have diabetes, 8.1 million of whom are currently undiagnosed. Moreover, using data from fasting glucose and hemoglobin A_{1c} levels, the CDC estimates that an additional 86 million American adults have pre-diabetes, as defined by A_{1c} or fasting or post-load glucose levels that are higher than normal but not sufficiently elevated to be diagnosed as diabetes. A major cause of heart disease and stroke, diabetes is the seventh leading cause of death in the United States.[1] The American Diabetes Association (ADA) has estimated that diagnosed diabetes cost $245 billion dollars in the US in 2012 ($176 billion in direct medical costs plus $69 billion in reduced productivity), accounting for roughly one in five healthcare dollars spent.[2] When undiagnosed diabetes, gestational diabetes, and pre-diabetes are included, the burden exceeds $322 billion–more than $1,000 for each American.[3] Persons with diabetes incur, on average, annual medical expenditures of $13,700, of which nearly $8,000 is attributed to diabetes. Individuals with diagnosed diabetes incur medical expenses that are approximately 2.3 times higher than corresponding expenditures in the absence of diabetes.[2] Moreover, diabetes disproportionately affects minority populations in the US. Whereas 7.6% of non-Hispanic white US adults had diagnosed diabetes in 2012, the age-adjusted rates of diagnosed diabetes were higher for Asian-Americans (9.0%), Hispanics (12.8%), non-Hispanic blacks (13.2%), and American Indians/Alaska Natives (15.9%).[1] Projections by the International Diabetes Federation suggest that diabetes will exert an even greater global burden in the next two decades, with an estimated 242,000 new cases projected per year in the United States alone.[4]

Glycemic control is essential to manage diabetes and its complications. Many patients can achieve glycemic goals with lifestyle changes (e.g., diet, physical activity) and oral antihyperglycemic agents. However, the progressive nature of type 2 diabetes often necessitates multiple agents with complementary mechanisms of action. Although most currently-approved oral antihyperglycemic agents target insulin either directly or indirectly,[5] a new class of agents, the sodium-glucose cotransporter 2 (SGLT2) inhibitors, reduce renal glucose reabsorption independently of insulin. SGLT2 inhibitors can be used as a component of diabetes management in the primary care setting, thus providing primary care clinicians with an additional means to help their patients achieve and maintain glycemic control.

To address the use of SGLT2 inhibitors in type 2 diabetes management, the New Jersey Academy of Family Physicians (NJAFP) assembled a panel of experts in 2014 to inform and educate primary care clinicians about using SGLT2 inhibitors to control glycemia. To help clinicians identify candidates for pharmacotherapy and understand issues related to the safety and efficacy of SGLT2 inhibitors, this publication reviews the current American Diabetes Association (ADA) guidelines and provides recommendations for using SGLT2 inhibitors as part of a personalized type 2 diabetes management plan.

TYPE 2 DIABETES IMPACTS MULTIPLE ORGANS

Type 2 diabetes, which accounts for 90-95% of diabetes cases, is a metabolic disorder characterized by insulin resistance in the muscles, liver, and adipose tissue. Progressive decline in pancreatic β-cell function, while of uncertain origin, appears inexorable, thereby requiring progressive advancement of pharmacotherapy.[6] In the face of sustained insulin resistance, as the body's capacity to produce sufficient quantities of insulin decreases, blood glucose concentration rises, ultimately leading to uncontrolled hyperglycemia. Insulin resistance has also been associated with hypertension and hyperlipidemia, factors that contribute to cardiometabolic risk.[7] Because of its spectrum of comorbidities, type 2 diabetes has been designated as a coronary heart disease risk equivalent by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).[8]

The pathogenesis of type 2 diabetes involves molecular signaling pathways in muscle tissue, liver, pancreatic α- and β-cells, adipocytes, gut, brain, and kidney, a combination that has been dubbed the "ominous octet" for the various roles that these tissues play in the onset of glucose intolerance.[9] The complex and multifaceted interplay between these tissues has several implications for managing type 2 diabetes.[9] First, successful glycemic control may necessitate using combinations of agents that target different pathophysiologic defects. Second, while glycemic control remains an essential goal for diabetes management (see next section), treatment regimens should also aim to correct other known pathogenic abnormalities, such as dyslipidemia, hypertension, and adiposity. Finally, the progressive nature of β-cell decline suggests that therapy should commence as early as possible in individuals who demonstrate impaired glucose tolerance and be advanced promptly whenever glycemic control deteriorates.

ESTABLISHING GLYCEMIC CONTROL IS ESSENTIAL FOR DISEASE MANAGEMENT

Diabetes management aims to prevent microvascular and macrovascular complications and to improve quality of life. While no prospective randomized clinical trial in type 2 diabetes has been able to confirm the macrovascular benefits of glycemic control, epidemiologic studies, meta-analyses, and a recent ten-year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) suggest that macrovascular benefits are associated with good glycemic control.[10-17] Moreover, the UKPDS demonstrated that tight control of glucose meaningfully impacts microvascular complications in patients with newly-diagnosed type 2 diabetes.[10, 11] These microvascular benefits persisted, and new macrovascular benefits were identified, at a ten-year follow-up in subjects who were treated intensively even if their glycemic control subsequently relaxed over time to that of the control arm of the trial.[18] However, outcomes from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which compared the effect of intensive therapy (targeting an A_{1c} level below 6.0%) versus standard therapy (targeting an A_{1c} level between 7.0% and 7.9%) on cardiovascular events in persons with type 2 diabetes who had or were at risk for cardiovascular disease (CVD), showed that intensive therapy for 3.5 years increased mortality yet did not significantly reduce major cardiovascular events.[19] Moreover, the intensively-treated cohort had higher incidence of hypoglycemia that required assistance and weight gain of more than 10 kg ($P < 0.001$). This hypoglycemia may have contributed to the increased mortality in the intensive-therapy group, and clinicians would be wise to avoid hypoglycemia at whatever target glucose level is deemed appropriate for a given patient.

To this end, the ADA[20] and the International Diabetes Federation[21] recommend an A_{1c} goal of less than 7.0% for adults diagnosed with diabetes, with the caveat that this goal may need to be more or less stringent depending on the individual's comorbid medical conditions and risk of hypoglycemia.[20] However, data from the National Health and Nutrition Examination Surveys (NHANES) from 1988-2010 indicate that 47% of adults with diabetes are above this level.[22] Guidelines issued by the American Association of Clinical Endocrinologists suggest an A_{1c} goal of ≤ 6.5% for healthy individuals but also include discussion about the need to individualize therapy.[23]

In 2010, 47% of American adults with diabetes had not achieved the American Diabetes Association's management goal of $A_{1c} < 7.0\%$.[22]

2015 ADA GLYCEMIC RECOMMENDATIONS FOR NON-PREGNANT ADULTS WITH DIABETES:[20]

A_{1c}:	< 7.0*
Preprandial PG:	80-130 mg/dL*
Peak postprandial PG§:	< 180 mg/dL*

*Individualize based on age/life expectancy, duration of diabetes, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and patient preferences. More or less stringent goals may be appropriate for some patients.

§Postprandial glucose may be targeted if A_{1c} goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, when levels generally peak in patients with diabetes.

Since cardiometabolic risk factors tend to cluster, however, diabetes care extends beyond tight glycemic control. Managing type 2 diabetes should generally incorporate four areas:

1) Lifestyle interventions for overweight and obese individuals

that are geared toward an initial loss of 5-10% of baseline body weight through the combination of 150 or more minutes of physical activity per week and a low-fat, reduced-calorie diet.

2) *Management of cardiovascular risk factors (e.g., hypertension, dyslipidemia, and microalbuminuria) using aspirin, statins, and angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers.*
3) *Normalization of blood glucose levels, as monitored using A_{1c} level.*
4) *Patient preferences and individualized care goals.*

THE KIDNEY'S ROLE IN GLUCOSE HOMEOSTASIS

To appreciate the use of SGLT2 inhibitors in managing type 2 diabetes, it is important to understand how the kidney controls blood glucose levels and how diabetes impacts normal renal physiology. The liver and the kidneys are the primary organs that maintain glucose homeostasis, responding accordingly to temporal fluctuations in glucose supply and demand. To avoid hypoglycemia, the liver and the kidneys can generate glucose from various substrates (e.g., pyruvate, lactate, glycerol, and others) through the gluconeogenesis pathway. The liver can also produce glucose by breaking down glycogen stores (glycogenolysis), a function that cannot be carried out by the kidney.[5] Continued fasting depletes hepatic glycogen stores, thus increasing the kidneys' relative contribution to circulating blood glucose levels. After a meal, hepatic glucose production drops dramatically, and the majority of glucose produced by the liver is used to replenish glycogen stores.[24, 25] During this time, renal gluconeogenesis increases two-fold, possibly to facilitate the repletion of glycogen.[25]

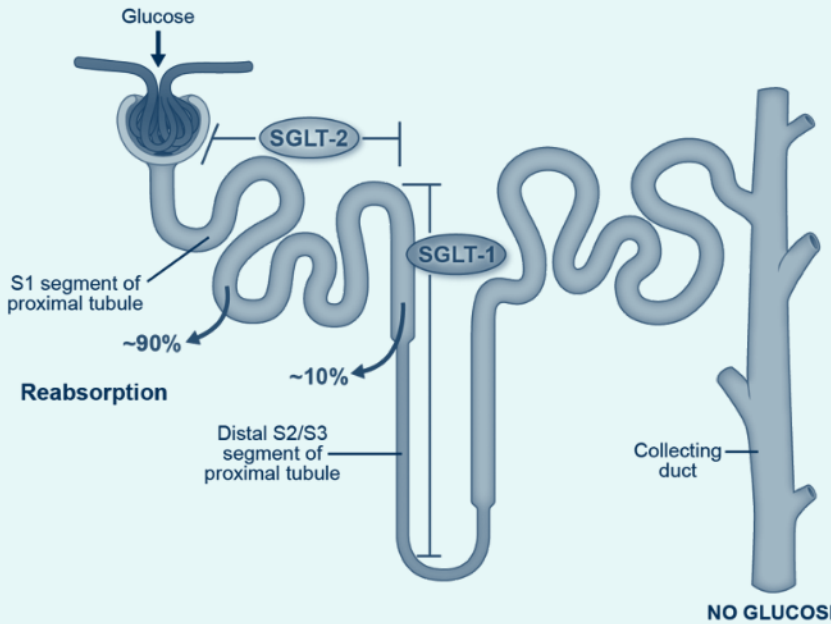
However, the kidneys predominantly affect circulating glucose concentration through renal glucose reabsorption.[24] Glucose in the blood is freely filtered by the glomerulus and thus must be reabsorbed through the kidneys. Nearly all of the approximately 180 g of glucose filtered daily in the glomeruli of a normal, healthy adult[26] is reabsorbed, mostly in the proximal renal tubules, with less than 1 percent being excreted in the urine **(Figure 1)**.[27] The transport of glucose from the tubule into the tubular epithelial cells is accomplished by sodium-glucose cotransporters (SGLTs), a family of membrane proteins that transport glucose, amino acids, vitamins, ions, and osmolytes across the brush-border membrane of proximal renal tubules.[26] The specific SGLT membrane proteins that are involved with glucose transport (but not the transport of amino acids, etc) are SGLT2 in the proximal segment of the renal proximal tubule and SGLT1 in the distal segment of the renal proximal tubule **(Figure 1)**. SGLT2 is often labeled as a "high-capacity, low-affinity" receptor, since it is responsible for approximately 90% of renal glucose reabsorption, in contrast to SGLT1, which is considered a "low-capacity, high-affinity" receptor that is responsible for capturing essentially all remaining glomerular filtrate glucose that was not reabsorbed by the SGLT2 receptor.[5] In healthy individuals, this highly efficient transport system becomes saturated at plasma glucose concentrations above 180 mg/dL, at which point any additional elevation of plasma glucose (and hence glomerular filtrate glucose) results in glucose spillage into the urine.[28]

Type 2 diabetes, which is characterized by persistent hyperglycemia, alters glucose homeostasis in several key ways. Compared to those of healthy individuals, the kidneys of individuals with type 2 diabetes increase gluconeogenesis following glucose induction and release glucose excessively after a meal is ingested.[29] Furthermore, the kidneys of individuals with type 2 diabetes demonstrate increased use of glucose during fasting and postprandially as compared to healthy individuals.[29] Individuals with type 2 diabetes also show increased expression of SGLT2 in proximal tubule cells.[5] As a consequence, the kidneys increase their capacity to reabsorb glucose, and glycosuria occurs at plasma concentrations above 220 mg/dL.[28]

SGLT2 INHIBITION: A NEW TREATMENT PARADIGM

SGLT2 inhibitors (see next section) reduce hyperglycemia by inhibiting renal glucose reabsorption, thereby increasing the amount of glucose excreted in the urine at a given plasma glucose concentration.[5] Small-scale studies suggest that inhibiting SGLT2 markedly lowers the threshold at which glucose begins to be excreted in the urine, typically to a glomerular filtrate glucose concentration of approximately 70 mg/dL.[30] These agents inhibit reabsorption of 30-50 percent of glucose filtered by the glomeruli

Figure 1. Schematic representation of glucose reabsorption along a nephron.



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in healthy individuals and can promote the urinary excretion of 50-90 grams of glucose daily.[31] However, elevated glycosuria has been traditionally viewed as cause for clinical concern; indeed, this phenomenon is the basis of the urine "dipstick" test for glycosuria/proteinuria often used to screen for diabetes in primary care offices or to evaluate blood sugar control.[32] For many clinicians, the concept that an oral antihyperglycemic agent can concomitantly lower A_{1c} level and elevate glycosuria may seem counterintuitive. Historically, clinicians have regarded the kidneys as the site of organ damage in diabetes, particularly for patients who develop clinically overt diabetic nephropathy.[33] To use SGLT2 inhibitors effectively, clinicians must reconsider this paradigm, envisioning the kidney as a potential treatment target to reduce hyperglycemia.

To use SGLT2 inhibitors effectively, clinicians must consider the kidney as a potential treatment target (rather than a site of organ damage) in type 2 diabetes.

Providers may be concerned about the clinical implications of promoting glycosuria. Research on patients with familial renal glucosuria (FRG), a rare genetic abnormality in which SGLT2 receptors are absent or non-functional (resulting in chronic glycosuria without diabetes), has provided reassurance about the potential physiologic consequences of SGLT2 inhibition. FRG has not been associated with any perceptible impact upon CVD or mortality and is not associated with typical diabetic complications, since plasma glucose concentration remains normal, and the genetic underpinnings of type 2 diabetes are not at play.[34, 35] For affected individuals, chronic glycosuria (10 to 120 g per day) is mostly asymptomatic and is rarely associated with adverse pathologic changes.[35-37] FRG is thereby considered a benign condition.[35] While it is recognized that type 2 diabetes alters normal renal physiology, long-term observation of normoglycemic individuals with FRG suggests that chronic glycosuria does not in itself cause negative clinical sequelae.[36]

SGLT2 INHIBITORS: PLEIOTROPIC EFFECTS

When individualizing a treatment regimen for patients with type 2 diabetes, clinicians may choose among various commonly-used classes of oral antihyperglycemic agents, including sulfonylureas, biguanides, thiazolidinediones, SGLT2 inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors **(Table 1)**. Tailoring a treatment plan to which a patient will adhere means that therapeutic efficacy must be considered in the context of other agent-specific effects, such as weight gain or hypoglycemia. To help providers determine how SGLT2 inhibitors can be integrated into a treatment regimen, this section will review the antihyperglycemic efficacy of SGLT2 inhibitors and the pleiotropic effects associated with this class of agents. The following section will provide specific guidance about the use and indications of the three SGLT2 inhibitors approved by the FDA as of January 2015. A review of clinical trials using these agents has recently been published.[28]

Table 1. Properties of Commonly-Used Classes of Oral Agents for the Treatment of Type 2 Diabetes.

Adapted from slide deck that accompanies Inzucchi, et.al.[38] Available at: ***http://care.diabetesjournals.org/content/38/1/140/suppl/DC2***

Oral Class	Mechanism	Advantages	Disadvantages	Cost
Biguanides	• Activates AMP-kinase (?other) • ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • Weight neutral • ? ↓ CVD	• Gastrointestinal • Lactic acidosis (rare) • B-12 deficiency • Contraindications	Low
Sulfonylureas	• Closes K_{ATP} channels • ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk	• Hypoglycemia • ↑ Weight • Low durability • ? Blunts ischemic preconditioning	Low
DPP-$ inhibitors	• Inhibits DPP-4 • Increases incretin (GLP-1, GIP) levels	• No hypoglycemia • Well tolerated	• Angioedema/ urticaria • ? Pancreatitis • ? ↑ Heart failure	High
TZDs	• PPAR-γ activator • ↑ Insulin sensivitity	• No hypoglycemia • Durability • ↓ TGs (pio) • ↑ HDL-C • ↓ CVD events (pio)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosi) • ? ↑ MI (rosi)	Low
SGLT2	• Inhibits SGLT2 in proximal nephron • Increases glucosuria	• ↓ Weight • No hypoglycemia • ↓ BP • Effective at all stages	• GU infections • Polyuria • Volume depletion • ↑ LDL-C	High

ANTIHYPERGLYCEMIC EFFICACY AND HYPOGLYCEMIA RISK. SGLT2 inhibitors cause blood glucose to be eliminated through the urine,[36, 39] promoting clinically significant reductions in fasting plasma glucose, postprandial plasma glucose, and A_{1c} level.[27, 40-42] A recent meta-analysis shows that SGLT2 inhibitors effectively reduce glycemia when used as monotherapy or in combination with other oral antihyperglycemic agents or insulin.[43] The individual agents appear to be comparably efficacious based on results from single-agent studies (although they have not been compared in head-to-head trials). When compared against placebo across 45 studies (n = 11,232), SGLT2 inhibitors reduced hemoglobin A_{1c} level by a mean difference of -0.66% [95% CI, -0.73% to -0.58%]. The insulin-independent mechanism of action (MOA) of SGLT2 inhibitors also suggests that the agents have a low intrinsic capacity to promote hypoglycemia,[28] an observation supported by meta-analysis of clinical trials.[43] A review of 45 randomized trials comparing SGLT2 inhibitors with placebo or other medication suggests that the hypoglycemic risk with SGLT2 inhibitors is slightly higher than with placebo (odds ratio: 1.28) but comparable to that observed with other antihyperglycemic agents (odds ratio: 1.01),[43] although the hypoglycemia risk will be affected by the specific combination of agents used.

WEIGHT LOSS. The use of an SGLT2 inhibitor has been associated with significant and potentially long-term weight loss in the majority of clinical trials to date.[28] A recent meta-analysis suggests that SGLT2 inhibitors reduce body weight by a mean difference of 1.80 kg [95% CI, -3.50 to -0.11 kg] compared to other agents.[43] This weight loss generally follows a pattern of initial rapid decline within the first few weeks that is supplanted by a more gradual decline that ultimately leads to a plateau. It has been hypothesized that the initial rapid loss reflects osmotic diuresis, with glycosuria-induced caloric loss (200-300 kcal/day) and subsequent loss of fat mass accounting for the gradual effect.

BLOOD PRESSURE. SGLT2 inhibitor-induced glycosuria is also associated with mild osmotic diuresis, which may be helpful in reducing elevated blood pressure.[44] A recent meta-analysis of 27 randomized controlled clinical trials (n = 12,960 participants) showed that SGLT2 inhibitors significantly reduced both systolic BP (weighted mean difference, -4.0 mm Hg; 95% CI, -4.4 to -3.5 mm Hg) and diastolic BP (weighted mean difference, -1.6 mm Hg; 95% CI, -1.9 to -1.3 mm Hg) from baseline, while demonstrating no significant effect on the incidence of orthostatic hypotension ($P > .05$).[45]

URINARY TRACT AND GENITAL INFECTIONS. SGLT2 inhibitors have been associated with an increased incidence of urinary and genital tract infections (odds ratios, 1.42 [CI, 1.06 to 1.90] and 5.06 [CI, 3.44 to 7.45], respectively),[43] most likely induced by glycosuria. These infections, which more frequently affect women (but may occur in men), are generally mild to moderate and usually respond to standard treatment.

LONG-TERM IMPLICATIONS. In different studies, SGLT2 inhibitors have been associated with small but significant changes in serum lipid concentrations, which could potentially negatively impact cardiovascular outcome.[28] However, SGLT2 inhibitors also have favorable effects on multiple cardiovascular risk factors, including glycemia, blood pressure, and weight, and meta-analyses have not identified an increase in cardiovascular events associated with the use of SGLT2 inhibitors.[28] All three SGLT2 inhibitors were approved by the US FDA with the provision that post-marketing studies be completed. Canagliflozin was approved in March 2013 with the provision that post-marketing studies monitor cardiovascular, bone, and pediatric safety as well as adverse events.[46] Dapagliflozin was approved in January 2014 with a requirement for post-marketing studies on cardiovascular outcomes, bladder cancer risks, pediatric patients, and adverse events.[47] Similarly, empagliflozin's August 2014 approval requires post-marketing studies to assess cardiovascular outcomes, pediatric safety and efficacy (including effects on bone health and development), and a non-clinical, animal-based juvenile toxicity study with particular focus on renal development, bone development, and growth.[48]

USE AND INDICATIONS OF APPROVED SGLT2 INHIBITORS

Since 2013, three oral SGLT2 inhibitors—canagliflozin, dapagliflozin, and empagliflozin--have been approved by the US FDA **(Table 2)**, with several other agents currently in Phase II and III clinical trials. These agents are indicated as adjuncts to diet and exercise to improve glycemic control in adults who have type 2 diabetes, but they are not indicated for the treatment of type 1 diabetes or for diabetic ketoacidosis.[49-51] In 2014, the FDA approved fixed-dose canagliflozin/metformin hydrochloride[52] and dapagliflozin/metformin hydrochloride tablets,[53] both indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes who are not adequately controlled on regimens containing the individual agents. All agents are contraindicated in patients with severe renal impairment **(see page 8)**, end-stage renal disease (ESRD), dialysis, or a history of serious hypersensitivity to the given agent. All agents are FDA Pregnancy Category C. Patients who take SGLT2 inhibitors in combination with insulin or an insulin secretagogue are at an increased risk for hypoglycemia relative to these agents alone and may require dose adjustments accordingly.

Footnote

On May 15, 2015, the US FDA issued a safety warning stating that SGLT2 inhibitors may lead to ketoacidosis, although no changes to the prescribing information were made with this announcement (***http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery***). The FDA recommends that patients pay close attention for signs of ketoacidosis (e.g., difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness) and seek medical attention immediately if they experience symptoms. Clinicians should evaluate for the presence of acidosis, including ketoacidosis, in patients experiencing these signs or symptoms and discontinue SGLT2 inhibitors if acidosis is confirmed.

Table 2. FDA-Approved SGLT2 Inhibitors

Agent	Recommended Starting Dose	Maximum Daily Dose	Contraindications	Common Adverse Events
Canagliflozin[50+]	100 mg once daily, before the day's first meal	300 mg*	eGFR < 30 mL/min/1.73 m^2**	• Female genital mycotic infections • Urinary tract infection (UTI) • Increased urination
Canagliflozin/ metformin hydrochloride[52‡]	Individualized to patient; twice daily with meals	300 mg canagliflozin/ 2,000 mg metformin[†]	• eGFR < 45 mL/min/1.73 m^2 • Creatinine levels ≥ 1.5 mg/dL (males) or 1.4 mg/dL (females)	• Canagliflozin: as above • Metformin: ∼ Diarrhea ∼ Nausea/indigestion ∼ Vomiting ∼ Flatulence ∼ Asthenia ∼ Abdominal discomfort ∼ Headache
Dapagliflozin[51]	5 mg; once daily; in the morning w/ or w/o food	10 mg	eGFR < 60 mL/min/1.73 m^2[§]	• Female genital mycotic infections • UTI • Nasopharyngitis
Dapagliflozin/ metformin hydrochloride[53‡]	Individualized to patient; once daily in the morning w/food	10 mg dapagliflozin/ 2,000 mg metformin	• eGFR < 60 mL/min/1.73 m^2 • Creatinine levels ≥ 1.5 mg/dL (males) or 1.4 mg/dL (females)	• Dapagliflozin: as above • Metformin: as above
Empagliflozin[49]	10 mg; once daily; in the morning w/ or w/o food	25 mg	eGFR < 45 mL/min/1.73 m^2[§]	• Female genital mycotic infections • UTI

Legend: eGFR = estimated glomerular filtration rate.

[+]Canagliflozin exposure is reduced in individuals who take UDP-glucuronosyltransferase inducers (e.g., rifampin), and digoxin levels should be monitored in individuals who take both canagliflozin and digoxin.

*In individuals with an eGFR > 60 mL/min/1.73 m^2. Individuals with an eGFR of 45 to less than 60 mL/min/1.73 m^2 should not take more than 100 mg of canagliflozin once daily.

**Canagliflozin should be discontinued if the eGFR level falls persistently below 45 mL/min/1.73 m^2.

[‡]The package inserts for the canagliflozin/metformin hydrochloride and the dapagliflozin/metformin hydrochloride tablets contain a "black box" warning that states that lactic acidosis can occur due to metformin accumulation. The statement notes that the risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure. Symptoms may be non-specific and can include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. Clinicians who suspect acidosis are advised to discontinue the canagliflozin and metformin hydrochloride tablets and to hospitalize the patient immediately.

[†]Individuals with an eGFR of 45 to less than 60 mL/min/1.73 m^2 should not take more than 50 mg of canagliflozin twice daily. Assess renal function before initiating canagliflozin and metformin hydrochloride tablets.

[§]Discontinue use if eGFR falls persistently below this level.

INTEGRATING SGLT2 INHIBITORS INTO A PATIENT-CENTERED TYPE 2 DIABETES MANAGEMENT PLAN

As clinical experience with SGLT2 inhibitors grows, this new class of agents is becoming incorporated into clinical guidelines and evidence-based treatment algorithms. For example, in 2013, the American Association of Clinical Endocrinologists (AACE) included SGLT2 inhibitors as an option for treating type 2 diabetes, either as monotherapy for patients with A_{1c} < 7.5% or in combination regimens for patients with A_{1c} ≥ 7.5.[23] In 2015, the ADA and the European Association for the Study of Diabetes (EASD) released a joint position statement on type 2 diabetes management that recommends SGLT2 inhibitors as an option in combination with metformin when dual therapy is necessary

and with metformin plus a sulfonylurea, thiazolidinedione, DPP-4 inhibitor, or insulin when triple therapy is warranted to achieve glycemic goals **(Figure 2)**.[38] This recommendation is included in the ADA's 2015 *Standards of Medical Care in Diabetes*.[54]

DIABETES SELF-MANAGEMENT: A PARTNERSHIP BETWEEN THE PATIENT AND PROVIDER. In 2012, the ADA and the EASD released a joint position statement advocating for patient involvement in decision making with regard to type 2 diabetes management,[55] which was updated in 2015 to reflect current therapeutic options.[38] The ADA/EASD recommendations support a shared decision-making approach that applies to primary care practices and those that incorporate the patient-centered medical home (PCMH). The PCMH is based on a "partnership" between the patient and healthcare providers that incorporates skills such as problem solving, decision making, resource utilization, action planning, and self-tailoring of inter-

Figure 2. ADA/EASD General Recommendations for Antihyperglycemic Therapy for Type 2 Diabetes.[38]

The ADA suggests that providers select agents based on patient preferences and various patient-, disease-, and drug-based characteristics, with an aim to reduce glucose concentrations while minimizing hypoglycemia and other side effects.

Healthy eating, weight control, increased physical activity & diabetes education

MONOTHERAPY

METFORMIN

Efficacy*	high
Hypo risk	low risk
Weight	neutral/loss
Side effects	GI/lactic acidosis
Costs	low

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

DUAL THERAPY†

	Metformin + Sulfonylurea	Metformin + Thiazolidinedione	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + Insulin (basal)
Efficacy*	high	high	intermediate	intermediate	high	highest
Hypo risk	moderate risk	low risk	low risk	low risk	low risk	high risk
Weight	gain	gain	neutral	loss	loss	gain
Side effects	hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
Costs	low	low	high	high	high	variable

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

TRIPLE THERAPY

Metformin +	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
	TZD	SU	SU	SU	SU	TZD
or	DPP-4-i	DPP-4-i	TZD	TZD	TZD	DPP-4-i
or	SGLT2-i	SGLT2-i	SGLT2-i	DPP-4-i	Insulin§	SGLT2-i
or	GLP-1-RA	GLP-1-RA	Insulin§	Insulin§		GLP-1-RA
or	Insulin§	Insulin§				

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

COMBINATION INJECTABLE THERAPY‡

Metformin +

Basal Insulin + Mealtime Insulin **or** GLP-1-RA

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

ventions. For the patient, effectively managing type 2 diabetes requires collaboration, a personalized management plan, self-management education, adherence to treatment, and appropriate follow-up and monitoring. Successful approaches aimed at improving self-management are planned and feature defined targets and established goal-setting. Several approaches, including diabetes "mini-clinics," structured behavioral interventions, multidisciplinary disease programs, and methods to improve organization and delivery of patient education, have been explored in primary care settings to improve care for patients with diabetes.[56, 57] Patients with diabetes who have been managed through various PCMH programs have demonstrated improvements in disease-related factors such as A_{1c}, blood pressure, and low-density lipoprotein (LDL) cholesterol, with concomitant reductions in medical costs and inpatient admissions.[57]

BEHAVIORAL MODIFICATIONS REQUIRE ACTIVE PATIENT PARTICIPATION. Successful behavioral modification requires that the patient take responsibility for his/her actions by setting specific health/lifestyle goals and achieving them in large part through self-management. Numerous patient-based factors, including motivation level, support systems, time, stress level, and attitude toward physical activity can influence adherence to a given regimen. As such, the provider must assess the patient's readiness to undertake a lifestyle regimen.

Adherence relies on accountability; therefore, patients must be encouraged to use all possible tools to maintain momentum. When encouraging patients, the clinician should recognize the emotional effect of living with diabetes—stress can affect insulin and blood glucose levels and undermine healthy eating, activity and self-monitoring schedules, and adherence to medications. Suggested strategies to facilitate adherence to a regimen include:

- *Maintain a daily diet/exercise diary*
- *Identify (and, where possible, avoid) high-risk situations (e.g., situations that will promote unhealthy diet, a lack of activity, or less rigorous self-monitoring)*
- *Reward success*
- *Identify a social network and support system (e.g., family and friends, group-visit intervention sessions, established organizations such as Weight Watchers™)*
- *Set realistic goals and a specific, patient-generated plan*
- *Establish a self-management action plan based on what the patient feels that he/she can achieve with high confidence.*

Numerous self-management goal-setting forms and tools for patients and clinicians (in English and Spanish) are available from the Robert Wood Johnson Foundation's Diabetes Initiative at: *http://diabetesnpo.im.wustl.edu/resources/topics/GoalSetting.html*

For those patients who are undertaking lifestyle transitions but do not wish to join established social support groups, the provider should schedule frequent follow-up visits to assess progress.

COMMUNICATION AND TEAM EFFORTS ENHANCE SUCCESS. Managing long-term complications of type 2 diabetes requires continuing care and education; the patient and provider must communicate in an interactive, collaborative and ongoing process. When possible, care should be administered by a multi-disciplinary, provider-facilitated team that may include a registered dietitian, a behaviorist, an exercise physiologist, an ophthalmologist, a pharmacist, a physician, a podiatrist, a diabetes educator and other healthcare professionals. It is imperative that the patient interact frequently and regularly with team members. Certain healthcare professionals have special expertise in diabetes education; assistance in locating certified diabetes educators (CDEs) and creating a team is available from the American Association of Diabetes Educators (AADE) at 1-800-TEAMUP4.

REIMBURSING DIABETES SELF-MANAGEMENT TRAINING

Reimbursing diabetes self-management education or training depends on the policies of the payor as well as the location in which the services are provided (e.g., each state has its own requirement). Specificity and accuracy are the keys to successful billing. Visits can be billed using Evaluation and Management (E&M) methods employed in standard one-on-one office visits.[58] Thorough documentation is essential and should correspond to the level of service provided, and the various components of the visit (e.g., history, vital signs, general assessment, educational discussion, assessment and plan, and time spent) should be distinctly documented. In most cases, either a Level 3 or Level 4 E&M billing code (e.g., 99213 or 99214) with ICD-10 diabetes diagnosis code (e.g., E11) will be appropriate.

Medicare will reimburse diabetes self-management training (DSMT) for up to 10 hours during the first year and 2 hours/year each year thereafter.[59] DSMT services are covered if the treating physician or qualified non-physician practitioner who is managing the Medicare beneficiary with diabetes certifies that such services are needed. Medicare has assigned specific codes (G0108 and G0109) for DSMT services that can be used to bill most government and commercial payors. The Centers for Medicare & Medicaid Services (CMS) will reimburse for DSMT programs that are accredited by the ADA or the AADE. The AADE provides a detailed summary of reimbursement for diabetes education in primary care practice,[60] and the National Council on Aging has also developed a DSMT resource to help practices operate cost-effective, accredited DSMT programs that can meet CMS requirements for Medicare reimbursement.[59]

ADDITIONAL RESOURCES FOR PATIENTS AND PROVIDERS

Numerous resources for patients and healthcare providers are available online for the management of type 2 diabetes and the maintenance of cardiovascular and metabolic health **(Table 3)**.

Table 3. Online Resources for Patients and Providers

ORGANIZATION	URL	RESOURCES
American Diabetes Association	***www.diabetes.org***	• General information about diabetes • Nutrition and recipes • Weight loss/ exercise strategies • Preventive tools (risk calculators) • Current statistics and research findings
American Academy of Family Physicians	***www.aafp.org***	• CME materials • Clinical practice guidelines
American Association of Diabetes Educators	***www.diabeteseducator.org***	• Information on diabetes education accreditation • Location of diabetes educators • CME/online courses
American Association of Clinical Endocrinologists/ American College of Endocrinology	***www.aace.com***	• Treatment guidelines and algorithms • CME materials

CONCLUSION

Type 2 diabetes is a progressive disorder that affects numerous organs and tissues. Achieving glycemic control is essential to managing diabetes and its complications; many patients can reach and maintain glycemic goals by implementing lifestyle changes (e.g., diet, physical activity) and using oral antihyperglycemic agents. However, the progressive nature of the disease often necessitates multiple agents with complementary mechanisms of action. The SGLT2 inhibitors, a new class of oral agents that reduce renal glucose reabsorption independently of insulin, can be used as a component of diabetes management in the primary care setting. Since 2013, three oral SGLT2 inhibitors—canagliflozin, dapagliflozin, and empagliflozin–have been approved by the US FDA, with several other agents currently in Phase II and III clinical trials. These agents are indicated as adjuncts to diet and exercise to improve glycemic control in adults who have type 2 diabetes. SGLT2 inhibitors do not intrinsically promote hypoglycemia, and this class of agents is associated with weight loss and reduction in blood pressure. Because diabetes is a chronic condition, management strategies should treat-to-target and involve the patient in the process of his/her disease management as early as possible. By identifying those patients who will benefit from SGLT2 inhibitors, the primary care clinician can help patients manage their type 2 diabetes, thereby reducing complications and enhancing quality of life.

Case Study #1: Gloria

Gloria is a 58-year-old African-American woman who was diagnosed with type 2 diabetes two years ago and is at the office for a routine follow-up visit. Since her diagnosis, she has taken metformin, although she now has difficulty controlling her hyperglycemia despite taking the maximum dose. She also takes an angiotensin-converting enzyme (ACE) inhibitor (administered at night), a statin, and daily low-dose (81 mg) aspirin. She reports that she received diabetes education at the time of her initial diagnosis. She states that she wishes to lose weight, but despite walking 30 minutes each day and trying to monitor her diet, she gains approximately three pounds each year. Gloria currently has a BMI of 31 kg/m^2, and her A_{1c} is 8.0%. Her blood pressure is 142/90 mm Hg. Her laboratory workup and physical examination reveal no signs of volume depletion. Her eGFR is 85 mL/min/1.73 m^2. She reports that she is not sexually active.

You ask Gloria about reaching her goals, and she states that she is committed to monitoring her diet and activity level. However, it is clear that she will require more than metformin alone to control her blood sugar.

According to ADA guidelines, which of the following is a reasonable A_{1c} goal for Gloria?

a) 5.8%
b) 6.0%
c) 6.5%
d) 7.0%
e) 8.0%

[Answer: d. The ADA recommends a goal of 7.0% for most adults with diagnosed diabetes].

You discuss blood sugar with Gloria and agree with her about her A_{1c} target. According to the ADA, which of the following classes of agents could be added to metformin to help control Gloria's hyperglycemia?

a) DPP-4 inhibitor
b) Sulfonylurea
c) Thiazolidinedione
d) Insulin
e) SGLT2 inhibitor
f) GLP-1 receptor agonist
g) All of the above

[Answer: g. According to ADA, any of these agent classes is acceptable to consider as second-line therapy.]

Gloria expresses concerns about initiating insulin at this point, given that she is trying to lose weight and that she views insulin therapy as a last-line effort that indicates that she is succumbing to her disease. While you agree that insulin is not strictly necessary at this point in her management, you should use this opportunity to:

a) Tell Gloria that she will never have to take insulin if she meets her A_{1c} goal with oral medications.
b) Tell her that she will likely eventually require insulin as part of her management; it can be considered as an option at any point going forward.
c) State that insulin is a highly effective treatment; its use will enable her to control her diabetes.
d) Agree with her that insulin should be postponed as long as possible, given the emotional toll associated with it use.
e) a and d only
f) b and c only

[Answer: f. Considering the progressive nature of pancreatic β-cell decline associated with type 2 diabetes, it is likely that Gloria will require insulin at some point in her long-term disease management. It is a highly effective treatment that will enable her to control her blood sugar and reduce the risk of complications.]

Gloria has expressed her desire to lose weight. Which of the following agents are associated with weight loss?

a) DPP-4 inhibitor
b) Sulfonylurea
c) Thiazolidinedione
d) SGLT2 inhibitor
e) GLP-1 receptor agonist
f) a, b, and c
g) a, b, and d
h) d and e

[Answer: h]

Gloria prefers to use an oral agent rather than an injectable at this point, so you recommend adding SGLT2 to her regimen of metformin. What SGLT2-specific potential side effects or issues should you discuss with Gloria before initiating treatment?

a) Kidney stones
b) Diarrhea
c) Mycotic or urinary tract infection
d) Vomiting
e) Increased urination
f) a, c, and e
g) c and e
h) b and d

[Answer: g. SGLT2 inhibitors are associated with increased urination and mycotic/urinary tract infections. They are not associated with kidney stones, diarrhea, or vomiting].

Based on the mechanism of action of SGLT2 inhibitors, would you expect Gloria to experience significant hypoglycemia with the new regimen?

a) Yes. Because SGLT2 inhibitors promote urinary excretion of glucose, they are associated with increased risk of hypoglycemia, especially in combination with other antihyperglycemic agents.
b) No. The insulin-independent mechanism of action of SGLT2 inhibitors suggests that the agents have a low intrinsic capacity to promote hypoglycemia.

[Answer: b.]

While you do not expect to see significant hypoglycemia when Gloria initiates SGLT2 therapy, you nonetheless advise her to be aware of symptoms (e.g., dizziness, confusion, blurred vision). You also suggest that she may experience an increase in urinary volume and recommend that she stay hydrated. Finally, you arrange for her to receive counseling from a Certified Diabetes Educator (CDE) on principles of self-managing her condition and with a dietitian to help her achieve weight loss. Given her relatively low risk of complications, you schedule a follow-up visit in three months.

Gloria calls the office two weeks after initiating SGLT2 treatment, complaining of vaginal itching and discharge. What should you recommend?

a) Discontinue the SGLT2 immediately.
b) Continue SGLT2 treatment, treat the infection topically for a week with an over-the-counter medication, and follow-up.
c) Recommend that she come to the office immediately for glucose monitoring.

[Answer: b. SGLT2 inhibitors are associated with an increased incidence of urinary and genital tract infections, mostly likely caused by glycosuria. These infections are generally mild to moderate and respond to standard treatment.]

When you call Gloria a week later, she reports that the infection has cleared. At her 3 –month follow-up visit, Gloria's A_{1c} is 7.2%, and she has lost three pounds. Her blood pressure is 138/88 mm Hg, and her eGFR is 83 mL/min/1.73 m^2. You recommend that she continue the current regimen and follow-up every three months. You could also consider maximizing the dose of the SGLT2 inhibitor to help Gloria attain her glycemic goal, given that she is unlikely to experience side effects that would warrant lower doses.

Case Study #2: Shirley

Shirley, who is 55 years old, was diagnosed with type 2 diabetes ten years ago. She has tried various approaches to control her glycemia over the years, including oral medications and lifestyle interventions. She reports that her efforts have been met with varying success. Although she has attended diabetes education classes, she admits difficulty maintaining her resolve with

regard to diet and exercise (although she takes her medications regularly). She arrives at the office asking about losing weight, noting that she has seen several television commercials touting various new medications for diabetes and/or weight control.

Shirley currently takes pioglitazone and a sulfonylurea, although her A_{1c} has reached 8.1% on these two medications. Her BMI is 32 kg/m^2, and her eGFR is 61 mL/min/1.73 m^2. She has also taken an ACE inhibitor for approximately five years.

According to ADA guidelines, which of the following is a reasonable A_{1c} goal for Shirley?

a) 5.2%
b) 6.2%
c) 6.5%
d) 7.0%
e) 8.0%
f) 9.0%

[Answer: d. The ADA recommends a goal of 7.0% for most adults with diabetes. Given that Shirley's eGFR suggests chronic kidney disease, it will be imperative to control her blood sugar more tightly than is currently achieved.]

Shirley requests a third oral medication rather than initiation of insulin (she reports a phobia of needles). Based on her glycemic goals, her preferences, and these data, which is the best option at this point?

a) Metformin
b) SGLT2 inhibitor
c) DPP-4 inhibitor
d) GLP-1 receptor agonist
e) Any of the above

[Answer: b. Although metformin, SGLT2 inhibitors, and DPP-4 inhibitors are all to be used cautiously in renally-impaired individuals, SGLT2 inhibitors are associated with weight loss, whereas DPP-4 inhibitors and metformin are weight-neutral. GLP-1 receptor agonists are injectable.]

Adding an SGLT2 inhibitor lowers Shirley's A_{1c} to 6.5% within three months, but she experiences multiple hypoglycemic episodes. How should you proceed?

a) Discontinue sulfonylurea
b) Discontinue SGLT2 inhibitor
c) Discontinue pioglitazone
d) Add insulin
e) Add metformin

[Answer: a. Adding another agent (especially insulin) to this regimen will increase the likelihood of hypoglycemia, which is the factor that drives this management decision. Since Shirley is well below her A_{1c} target, it is reasonable to consider discontinuing an agent. Of the three agents, the sulfonylurea is the class most associated with hypoglycemia.]

Once the sulfonylurea is discontinued, Shirley's A_{1c} stabilizes at 7.0% for two years (with routine checkups every three months) using the combination of pioglitazone and an SGLT2 inhibitor, and she loses ten pounds during that period. She reports no hypoglycemia during this time. However, a routine checkup reveals that her eGFR has dropped to 29 mL/min/1.73 m^2.

Given Shirley's concern about using needles, which of the following options represents a viable immediate step?

a) Discontinue pioglitazone
b) Add metformin
c) Discontinue SGLT2 inhibitor and add metformin
d) Discontinue SGLT2 inhibitor and add GLP-1 receptor agonist
e) Discontinue SGLT2 inhibitor and monitor blood sugar on Shirley's follow-up visit.

[Answer: e. All SGLT2 inhibitors and metformin are contraindicated at eGFR values below 30 mL/min/1.73 m^2. GLP-1 receptor agonists are injectable agents. While it is likely that Shirley may need to become comfortable with injectable agents in the near future, choice e is viable for this juncture.]

Over the next three months, the pioglitazone monotherapy proves unsustainable for Shirley, as her A_{1c} rises to 8.0%. She gains four pounds, and her blood pressure shows an incremental rise. How should you counsel Shirley at this point?

a) Help her locate a Certified Diabetes Educator (CDE) who can teach her about diabetes self-management and a dietitian who can help her promote healthy eating habits
b) Reiterate the importance of maintaining a healthy lifestyle
c) Emphasize that insulin will likely be necessary to manage her disease
d) Discuss the importance of monitoring her blood glucose to avoid hypoglycemia
e) All of the above

[Answer: e. At this point, Shirley will require more than oral agents to manage her diabetes. She should be made aware of realistic expectations and receive instruction in principles of disease management.]

While insulin remains a likely future treatment, it is associated with weight gain and hypoglycemia, two issues of concern to Shirley. Prior to initiating insulin, which category of agent could be considered for Shirley at this point?

a) DPP-4 inhibitor
b) GLP-1 receptor agonist
c) Sulfonylurea
d) Metformin
e) SGLT2 inhibitor
f) a or b.

[Answer: f. GLP-1 receptor agonists are associated with weight loss and a low risk of hypoglycemia. DPP-4 inhibitors are weight-neutral and could also potentially be considered.

Metformin and SGLT2 inhibitors are contraindicated due to Shirley's renal function, and sulfonylureas are associated with hypoglycemia. However, it should be noted that Shirley's degree of renal insufficiency will require caution if proceeding with GLP-1 receptor agonists or DPP-4 inhibitors. Also, some GLP-1 agents are contraindicated at Shirley's eGFR level.]

At this point, Shirley's non-insulin-based options are becoming limited, and it is likely that she will require insulin at some point in the near future. To this end, which of the following options is inappropriate to discuss with her?

a) Explain that she will likely eventually require insulin as part of her management; it should be considered as an option sooner rather than later

b) State that insulin is a highly effective treatment; its use will enable her to control her diabetes

c) Agree with her that insulin should be postponed as long as possible, given the emotional toll associated with it use

d) Help her locate a CDE to instruct her on self-management and possibly a support group to help her manage the psychological adjustment to initiating insulin

[Answer: c. It will be imperative to help Shirley make the adjustment to insulin, which will ultimately be necessary to control her diabetes. Postponing insulin will serve no viable purpose at this point.]

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CME Accreditation Procedures

This Enduring Material activity, *CME Report: Sodium-Glucose Cotransporter 2 (SGLT2) Inhibition in Type 2 Diabetes Management: A New Therapeutic Option in Primary Care*, has been reviewed and is acceptable for up to 2.00 Prescribed credit(s) by the American Academy of Family Physicians. Term of approval begins 05/15/2015. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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If you do not wish to take the post test online, complete the test and evaluation and mail to:

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224 West State Street, Trenton, NJ 08608
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CME Report: Sodium-Glucose Cotransporter 2 (SGLT2) Inhibition in Type 2 Diabetes Management: A New Therapeutic Option in Primary Care

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I claim _____ AAFP Prescribed Credits

1. What is the A_{1c} target recommended by the American Diabetes Association for most adults who have type 2 diabetes (with the understanding that this goal may need to be more or less stringent, as determined by the needs of the individual patient)?

a) 5.0% *c) 6.0%* *e) 7.0%*
b) 5.7% *d) 6.5%* *f) 8.0%*

2. Which of the following organs/tissues is impacted by type 2 diabetes?

a) pancreas *d) liver* *f) all of the above*
b) kidney *e) adipocytes* *g) a and b only*
c) muscle

3. What is the predominant mechanism through which the kidneys affect circulating glucose concentration?

a) generating glucose from various substrates through the gluconeogenesis pathway
b) breaking down glycogen stores
c) reabsorbing glucose that is filtered by the glomeruli

4. Approximately what percentage of glucose that is filtered in the kidney of a healthy adult is excreted in the urine?

a) 1% c) 25% e) 75%
b) 10% d) 50%

5. The SGLT2 inhibitors reduce renal glucose reabsorption independently of insulin.

a) True b) False

6. SGLT2 inhibitors have been associated with weight gain and elevated blood pressure.

a) True b) False

7. Which of the following side-effects are associated with SGLT2 inhibitors?

a) vomiting *e) kidney stones*
b) increased urination *f) b and c only*
c) mycotic/urinary tract infections *g) b, c, and e only*
d) hypoglycemia

8. Factors to consider when tailoring a diabetes management plan to an individual patient include:

a) glycemic control d) cardiovascular considerations
b) weight gain e) patient preferences/concerns
c) risk of hypoglycemia f) all of the above

9. Practitioners should use caution and clinical judgment when prescribing SGLT2 inhibitors to individuals with eGFR values less than 60 mL/min/1.73 m².

a) True b) False

10. True/False: The progressive nature of type 2 diabetes often necessitates the use of multiple antihyperglycemic agents with complementary mechanisms of action.

a) True b) False

Program Evaluation

(Rating Scale: 5 is the highest rating; 1 is the lowest rating.)

	5	4	3	2	1
Relevance of this topic to my practice.....	❑	❑	❑	❑	❑
Clinical material was current and useful....	❑	❑	❑	❑	❑
This activity was free of commercial bias...	❑	❑	❑	❑	❑
Overall rating for this activity.....	❑	❑	❑	❑	❑

Please state two changes to your practice that you are committed to make based on your experience with this CME Activity.

1. _____

2. _____

What barriers could you encounter that could prevent you from implementing these changes?

1. _____

2. _____

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