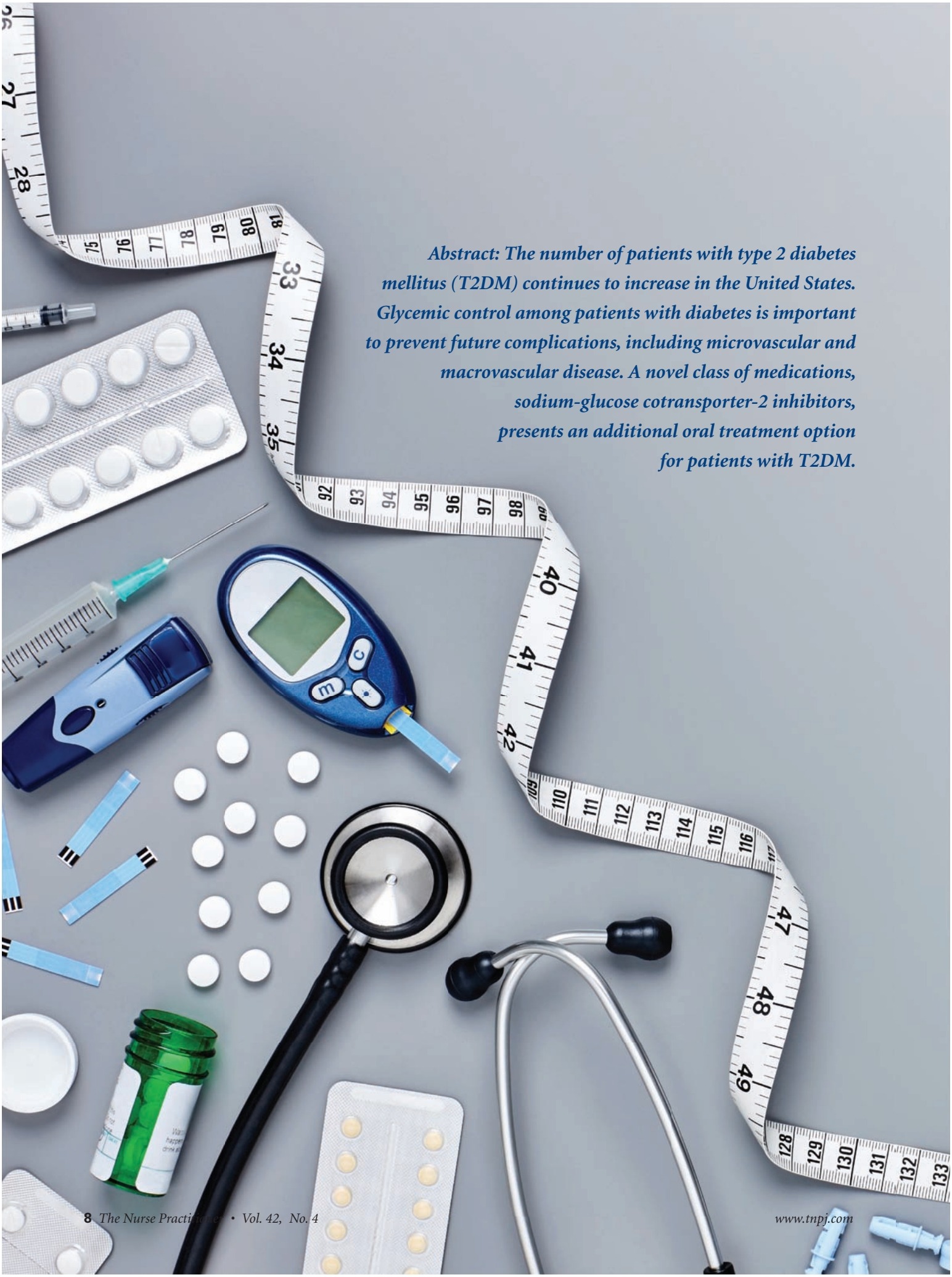

Abstract: *The number of patients with type 2 diabetes mellitus (T2DM) continues to increase in the United States. Glycemic control among patients with diabetes is important to prevent future complications, including microvascular and macrovascular disease. A novel class of medications, sodium-glucose cotransporter-2 inhibitors, presents an additional oral treatment option for patients with T2DM.*

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Sodium-glucose cotransporter-2 inhibitors

Expanding oral treatment options for type 2 diabetes mellitus

By Emily Ashjian, PharmD, BCPS, BCACP and Jeffrey Tingen, PharmD, MBA, BCPS, BCACP, CDE

Type 2 diabetes mellitus (T2DM) affects over 29.1 million individuals in the United States, including an estimated 25.9% of older adults.[1] The prevalence of diabetes is projected to double between the years 2000 and 2030.[2] Complications and comorbidities associated with T2DM, including neuropathy, nephropathy, retinopathy, and cardiovascular disease negatively affect quality of life and significantly increase healthcare costs.[1] It is important to appropriately treat and manage T2DM at diagnosis in order to prevent the development of complications.

Since 2012, several medications for T2DM have been approved by the FDA, expanding both oral and injectable treatment options. These include the glucagon-like peptide-1 agonists albiglutide, dulaglutide, exenatide extended release (ER), and lixisenatide; the dipeptidyl peptidase-4 (DPP-4) inhibitor alogliptin; several new insulin formulations; the combination GLP-1 agonist lixisenatide and insulin glargine; the combination GLP-1 agonist liraglutide and insulin degludec; and the sodium-glucose cotransporter-2 (SGLT2) inhibitors canagliflozin, dapagliflozin, and empagliflozin (see *FDA-approved SGLT2 inhibitors*).[3-17] The SGLT2 inhibitors have been incorporated into the American Diabetes Association (ADA) 2017 Standards of Care as pharmacotherapy options for use after initiation of metformin and implementation of lifestyle changes, including healthy eating, weight control, increased physical activity, and diabetes education.[18]

SGLT2 inhibitors

SGLT2 inhibitors work through an insulin-independent mechanism of action to prevent reabsorption of glucose in the proximal tubule of the kidney, leading to increased urinary excretion of glucose.[19] In addition to improved glycemic control, use of SGLT2 inhibitors may result in weight loss and improvements in BP, with a recent meta-analysis suggesting a mean reduction in systolic BP of 4 mm Hg, mean reduction in diastolic BP of 1.6 mm Hg, and weight loss of 4.2 lb (1.9 kg).[20]

SGLT2 inhibitors provide an additional oral option for glycemic control in patients with T2DM with minimal risk for hypoglycemia when used as monotherapy. Due to volume depletion that may occur with SGLT2 inhibitors, these medications should be used with caution in older adults, those with a history of hypotension, or those who are concurrently taking a diuretic, angiotensin-converting enzyme inhibitor (ACEI), or angiotensin II receptor blocker (ARB). SGLT2 inhibitors may cause hyperkalemia and should be used judiciously in patients taking an ACEI, ARB, or potassium-sparing diuretic such as spironolactone.[15-17] SGLT2

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Keywords: canagliflozin, dapagliflozin, empagliflozin pharmacotherapy, SGLT2 inhibitors, sodium-glucose cotransporter-2 inhibitors, T2DM, type 2 diabetes mellitus

inhibitors are contraindicated in patients with a history of severe hypersensitivity to the drug and those with severe kidney impairment, end-stage kidney disease, and patients on dialysis.[15-17]

FDA-approved SGLT2 inhibitors

Canagliflozin. The first SGLT2 inhibitor to become available with initial FDA approval in April 2013, canagliflozin is approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It is not recommended for patients with type 1 diabetes mellitus (T1DM) or those with ketoacidosis.[7] A once-daily oral medication, the starting dose of canagliflozin is 100 mg taken prior to the first meal of the day. The dose may be increased to 300 mg daily if additional glycemic control is needed.[15] Baseline assessment of kidney function should be completed, as renal dose adjustments are recommended with a maximum dose of 100 mg daily for patients with an estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73 m^2 to 60 mL/min/1.73 m^2.[15] Canagliflozin is also available in a combination tablet with metformin and metformin ER.[21,22]

The most common adverse reactions reported with the use of canagliflozin include urinary tract infections (UTIs; 4.4% to 5.9%), increased urination (4.6% to 5.1%), thirst (2.4% to 2.8%), constipation (1.8% to 2.4%), nausea (2.1% to 2.3%), genital mycotic infections (10.6% to 11.6% in females, 3.8% to 4.2% in males), and vulvovaginal pruritus (1.6% to 3.2%).[13] Canagliflozin was associated with a small increase in low-density lipoprotein cholesterol (LDL-C) in clinical trials. Overall, the LDL-C increase seen in pooled data from four placebo-controlled clinical trials was 4.4 mg/dL and 8.2 mg/dL with canagliflozin 100 mg and 300 mg daily, respectively.[15]

Rosenstock and colleagues investigated the use of canagliflozin in a randomized, double-blind, placebo-controlled, dose-ranging study including 451 participants with T2DM and an A1C of 7.5% to 10.5%.[23] Patients were randomized to canagliflozin 50 mg, 100 mg, 200 mg, or 300 mg once daily, 300 mg twice daily, sitagliptin 100 mg daily, or placebo for 12 weeks.

The primary outcome was the change in A1C at week 12; change in body weight after 12 weeks of therapy was included as a secondary outcome. The mean A1C at baseline ranged from 7.6% to 8%; mean body mass index at baseline was 31.5 kg/m^2. Overall, canagliflozin 100 mg daily and canagliflozin 300 mg daily were shown to reduce A1C by 0.76% and 0.92%, respectively, with a decrease of 0.74% seen in patients taking sitagliptin and 0.22% in patients taking placebo (P <0.001).

Participants taking canagliflozin also had greater decreases in body weight at 12 weeks when compared with those taking placebo (-2.6% and -3.4% versus -1.1%;

FDA-approved SGLT2 inhibitors[15-17,21,22,28,32-34]

	Canagliflozin	Dapagliflozin	Empagliflozin
Oral dosing and renal recommendations	• Starting dose is 100 mg daily, taken before the first meal of the day • Do not use for eGFR <45 mL/min/1.73 m^2 • Increase the dose to 300 mg daily if additional glycemic control is needed and eGFR ≥60 mL/min/1.73 m^2 • Correct volume depletion before starting the drug • Maintain adequate fluid intake	• Starting dose is 5 mg daily, taken in the morning with or without food • Increase the dose to 10 mg daily if additional glycemic control is needed • Do not use for eGFR <60 mL/min/1.73 m^2 • Correct volume depletion before starting the drug • Maintain adequate fluid intake	• Starting dose is 10 mg daily, taken in the morning with or without food • Increase the dose to 25 mg daily if additional glycemic control is needed • Do not use if eGFR <45 mL/min/1.73 m^2 • Correct volume depletion before starting the drug • Maintain adequate fluid intake
Monitoring	• Renal function or acute kidney injury • Potassium • Volume status • Hypotension • Ketoacidosis • Genital mycotic infection • UTI • LDL-C	• Renal function or acute kidney injury • Potassium • Volume status • Hypotension • Ketoacidosis • Genital mycotic infection • UTI • LDL-C	• Renal function or acute kidney injury • Potassium • Volume status • Hypotension • Ketoacidosis • Genital mycotic infection • UTI • LDL-C
Combination therapy	• Canagliflozin-metformin • Canagliflozin-metformin ER	• Dapagliflozin-metformin ER	• Empagliflozin-metformin • Empagliflozin-metformin ER • Empagliflozin-linagliptin

P <0.001 for canagliflozin 100 mg daily and canagliflozin 300 mg daily versus placebo, respectively). Rates of hypoglycemia were minimal, and there was a higher incidence of genital infections reported in females taking canagliflozin. Overall, the authors concluded that canagliflozin assisted with glycemic control and resulted in weight loss while causing minimal hypoglycemia.[23]

A randomized, double-blind, active controlled trial compared canagliflozin 100 mg or 300 mg daily with glimepiride 6 mg to 8 mg daily among 1,452 participants taking at least 2,000 mg of metformin.[24] The average A1C in this group at baseline was 7.8%. After 1 year of therapy, there was no statistically significant difference in A1C reduction between glimepiride and canagliflozin 100 mg daily. Canagliflozin 300 mg daily resulted in an A1C reduction of 0.12% more than glimepiride, which was a statistically significant finding, but may not be clinically significant. Overall, the trial demonstrated canagliflozin 100 mg to be noninferior to glimepiride and canagliflozin 300 mg to be superior to glimepiride as an add-on therapy to metformin in patients with T2DM.[24]

Forst and colleagues compared canagliflozin 100 mg and 300 mg with placebo in a phase 3, double-blind, randomized controlled trial among 342 patients with an A1C of 7% to 10.5%.[25] Patients were required to take at least 1,500 mg of metformin daily and pioglitazone 30 mg to 45 mg daily. Outcomes including change in A1C, weight, and systolic BP after 26 weeks of therapy were assessed. Canagliflozin 100 mg daily and 300 mg daily resulted in A1C reductions of 0.89% and 1.03%, respectively, compared with a reduction of 0.26% with placebo (P <0.001).[25]

In terms of weight loss, canagliflozin 100 mg and 300 mg daily resulted in an average weight loss of 5.7 lb (2.6 kg) and 8.2 lb (3.7 kg), respectively, as compared with weight loss of 0.4 lb (0.2 kg) with placebo (P <0.001). Canagliflozin 100 mg and 300 mg daily also resulted in an overall reduction in systolic BP of 5.3 mm Hg and 4.7 mm Hg, respectively, compared with a 1.2 mm Hg reduction with placebo (P <0.01 for canagliflozin 100 mg, P <0.025 for canagliflozin 300 mg). Overall, the authors concluded that canagliflozin at a dose of 100 mg or 300 mg daily resulted in improved glycemic control, reduced body weight, and decreased systolic BP.[25]

More recently, the efficacy and safety of canagliflozin used in combination with insulin was evaluated as part of a substudy of the CANagliflozin cardioVascular Assessment Study (CANVAS).[26] The larger CANVAS trial is currently ongoing with a scheduled completion date of February 2017.[27] The insulin substudy was a randomized, double-blind, placebo-controlled trial among 2,072 participants with a mean A1C of 8.3% who were receiving at least 20 units of insulin (basal, bolus, or a combination basal-bolus regimen).[26] Inclusion criteria required participants to have established cardiovascular disease or an increased risk of developing cardiovascular disease. Participants were randomized to either canagliflozin 100 mg daily, 300 mg daily, or placebo and allowed to continue other medications for treatment of T2DM.

The primary outcome was the mean change in A1C at 18 weeks. Those receiving canagliflozin 100 mg or 300 mg daily had a greater reduction in A1C after 18 weeks as compared with placebo (-0.62%, -0.73%, respectively, P <0.001), a difference that persisted at 1 year (-0.58%, -0.73%, respectively). Participants receiving canagliflozin experienced decreased weight and BP at 18 weeks, which also persisted at 1 year. Higher rates of hypoglycemia, hypovolemia, and genital mycotic infections were seen in participants taking canagliflozin. Overall, this study demonstrated that canagliflozin may be safely used in combination with insulin.[26]

Dapagliflozin. Approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, dapagliflozin is not recommended for patients with T1DM or those with risk factors for ketoacidosis.[16] The starting dose of dapagliflozin is 5 mg once daily, which may be increased to 10 mg daily if additional glycemic control is needed.[16] Dapagliflozin is not labeled for use in patients with an eGFR less than 60 mL/min/1.73 m^2.[16] Dapagliflozin is not recommended for use in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.[16] The most common adverse reactions seen with dapagliflozin in clinical trials include genital mycotic infections (6.9% to 8.4% in females, 2.7% to 2.8% in males), nasopharyngitis (6.3% to 6.6%), and UTIs (4.3% to 5.7%).[14] Dapagliflozin was associated with a small increase in LDL-C in pooled data from 13 clinical trials (2.9% versus -1.0% for dapagliflozin 10 mg versus placebo, respectively).[16] Dapagliflozin is available in a combination tablet with metformin ER.[28]

Dapagliflozin was studied in a phase 3, double-blind, placebo-controlled, parallel group trial. Treatment-naive participants (n = 485) with T2DM and a mean A1C of 8% were randomized to receive dapagliflozin 2.5 mg, 5 mg, or 10 mg once daily or placebo.[29] Participants were also provided with recommendations on diet and exercise during the course of the study.

After 24 weeks of therapy, the mean reduction in A1C from baseline was 0.23% in the placebo group, 0.58% with dapagliflozin 2.5 mg daily (P = 0.0005 compared with placebo), 0.77% with dapagliflozin 5 mg daily (P = 0.0005 compared with placebo), and 0.89% with dapagliflozin 10 mg daily (P <0.0001 compared with placebo). A greater number of participants reached an A1C less than 7% in the dapagliflozin groups. The authors concluded that dapagliflozin resulted in improvements in A1C with no increased risk of hypoglycemia as compared with placebo.[29]

Subsequently, Bailey and colleagues investigated the use of dapagliflozin 2.5 mg, 5 mg, or 10 mg daily as compared with placebo among 546 participants with a mean A1C of 8% who were already taking at least 1,500 mg of metformin per day.[30] The primary endpoint was a change in A1C at 24 weeks. Compared with a 0.3% reduction in A1C with placebo, dapagliflozin 2.5 mg, 5 mg, and 10 mg daily resulted in A1C reductions of 0.67% ($P = 0.0002$), 0.7% ($P < 0.0001$), and 0.84% ($P < 0.0001$), respectively. No difference in the rate of hypoglycemia was noted between groups. The results of this study demonstrated the additive benefit of dapagliflozin on lowering A1C when used with metformin in patients with uncontrolled T2DM.[30]

Dapagliflozin has also been studied as an add-on therapy to metformin and a sulfonylurea. Matthaei and colleagues evaluated the change in A1C after 24 weeks of dapagliflozin 10 mg daily or placebo in combination with metformin and a sulfonylurea.[31] Patients were eligible to participate in the trial if their A1C was 7% to 10.5% after taking metformin 1,500 mg or greater daily and at least the half maximal dose of a sulfonylurea daily for 8 weeks. At baseline, the mean A1C was 8.1% in the dapagliflozin group and 8.2% in the placebo group.

Overall, those receiving dapagliflozin experienced an average decrease in A1C of 0.69% as compared with placebo ($P < 0.0001$). Participants in the dapagliflozin group also experienced a 4.6 lb (2.1 kg) weight loss over the 24-week study compared with those receiving placebo ($P < 0.0001$). Dapagliflozin resulted in a greater incidence of genital infections (5.5% with dapagliflozin, 0% with placebo, $P = 0.029$) and hypoglycemia (12.8% with dapagliflozin, 3.7% with placebo, $P = 0.024$) and was also associated with increased levels of total, LDL, and high-density lipoprotein cholesterol, but not triglycerides.[31]

Empagliflozin. Approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, empagliflozin is also approved to reduce the risk of cardiovascular death in adult patients with T2DM who have known cardiovascular disease.[17] The drug is not recommended for patients with T1DM or those with risk factors for ketoacidosis.[17] Like canagliflozin and dapagliflozin, empagliflozin is a once-daily oral therapy. Empagliflozin is recommended to be initiated at a dose of 10 mg daily, and may be increased to 25 mg daily if additional glycemic control is needed beyond that achieved with the initial dose.[17]

Empagliflozin should not be used in patients with an eGFR less than 45 mL/min/1.73 m^2. The most common adverse reactions seen with empagliflozin include genital mycotic infections (5.4% to 6.4% in females, 1.6% to 3.1% in males) and UTIs (7.6% to 9.3%; 15.1% to 15.7% in older adults).[17] Similar to canagliflozin and dapagliflozin, empagliflozin resulted in small increases in LDL-C (4.6% and 6.5% with empagliflozin 10 mg and 25 mg, respectively, as compared with 2.3% with placebo).[17] Empagliflozin is available in combination with metformin, metformin ER, and the DPP-4 inhibitor linagliptin.[32-34]

Häring and colleagues demonstrated the benefit of adding empagliflozin to metformin using the primary outcome of change in A1C as well as the secondary outcome of weight and exploratory outcome of systolic BP.[35] In a study of 637 adults with a mean A1C of 7.9% on at least 1,500 mg of metformin per day, the mean A1C reduction at week 24 was 0.13% in the placebo group, 0.7% with empagliflozin 10 mg daily ($P < 0.001$ compared with placebo), and 0.77% with empagliflozin 25 mg daily ($P < 0.001$ compared with placebo).

Empagliflozin 10 mg daily resulted in weight loss of 4.59 lb (2.08 kg), and empagliflozin 25 mg daily resulted in weight loss of 5.42 lb (2.46 kg) as compared with 0.99 lb (0.45 kg) with placebo ($P < 0.001$). Empagliflozin 10 mg daily and 25 mg daily were also associated with a statistically significant reduction in BP as compared with placebo (-4.5 mm Hg and -5.2 mm Hg, respectively, compared with -0.4 mm Hg with placebo, $P < 0.001$).[35]

Similar to studies with canagliflozin and dapagliflozin combined with metformin, empagliflozin added to metformin was demonstrated to improve glycemic control and contributed to reductions in weight and BP.[35] Subsequently, empagliflozin 25 mg daily was directly compared with glimepiride 1 mg to 4 mg daily in a phase 3, randomized, double-blind study. This trial involved 1,549 patients with T2DM and a mean A1C of 7.9% at baseline who were taking at least 1,500 mg of metformin daily. The primary outcome of A1C reduction at 1 year and 2 years after the initiation of therapy was used.[36]

Overall, empagliflozin was found to be noninferior to glimepiride at both time points and superior to glimepiride at 2 years. The change in A1C with empagliflozin as compared with glimepiride at 2 years was -0.11% ($P = 0.0153$). A much higher rate of hypoglycemia was seen in the glimepiride group compared with empagliflozin (24% in the glimepiride group versus 2% with empagliflozin). This trial confirmed the role of empagliflozin as an alternative to sulfonylureas as add-on therapy for patients with uncontrolled T2DM on metformin monotherapy.[36]

Empagliflozin also demonstrated beneficial effects on 24-hour ambulatory BP when used for T2DM. Tikkanen and colleagues randomized 825 patients with an average A1C of 7.9% and hypertension (systolic BP 130 to 159 mm Hg and diastolic BP 80 to 99 mm Hg) to placebo or empagliflozin 10 mg or 25 mg daily.[37] BP was evaluated over a 12-week period.

Empagliflozin was associated with a statistically significant improvement in systolic and diastolic BP at doses of

Discussion points for patient-provider shared decision-making[15-17,21,22,28,32-34,38-40,42,46]

Potential benefits of SGLT2 inhibitors	Potential risks of SGLT2 inhibitors
• Once daily, oral therapy • Potential for reductions in BP • Potential for weight loss • Insulin-independent mechanism of action • Demonstrated reduction in major cardiovascular events, slower progression of kidney disease, and lower rates of clinically relevant renal events in patients at high risk for cardiovascular events (empagliflozin) • Available combination products (canagliflozin-metformin, canagliflozin-metformin ER, dapagliflozin-metformin ER, empagliflozin-metformin, empagliflozin-metformin ER, empagliflozin-linagliptin) • Patient assistance programs available to help reduce the cost of therapy	• Volume depletion: Use with caution in older adults, patients with a history of hypotension, and patients concurrently taking a diuretic • Increased incidence of genital mycotic and UTIs • Risk of hyperkalemia, especially in patients taking other medications that may increase potassium • Dependence on kidney function for efficacy • Lack of long-term safety and efficacy data • Reported cases of diabetic ketoacidosis require further investigation • Effects on bone mineral density and incidence of fractures require further investigation • Increased risk of leg and foot amputations with canagliflozin requires further investigation

10 mg and 25 mg daily (systolic BP: -3.44 mm Hg, -4.16 mm Hg for 10 mg and 25 mg, respectively, P <0.001; diastolic BP: -1.36 mm Hg, -1.72 mm Hg for 10 mg and 25 mg, respectively, P <0.001). Overall reductions in A1C similar to those in previously published studies were also seen (empagliflozin 10 mg daily: -0.62%, P <0.001; empagliflozin 25 mg daily: -0.65%, P <0.001).[37]

Most recently, empagliflozin use resulted in a reduced risk of cardiovascular events as compared with placebo when added to standard care in patients with a high risk of cardiovascular events.[38] The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial randomized 7,020 patients with established cardiovascular disease to either empagliflozin 10 mg or 25 mg daily or placebo with a median follow-up period of 3.1 years.[38]

There was a statistically significant reduction in the primary composite outcome of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction (MI) among patients treated with empagliflozin as compared with placebo (hazard ratio in the empagliflozin group 0.86; 95% confidence interval 0.74 to 0.99; P = 0.04 for superiority), which was driven by significant reductions in death from cardiovascular causes, death from any cause, and hospitalization for heart failure.

There was no significant difference in rates of MI or stroke between the two groups.[38] The results of the EMPA-REG OUTCOME trial led to a recommendation in the 2017 ADA Standards of Care that empagliflozin be considered in patients with established cardiovascular disease who need additional A1C lowering.[18]

In addition, in a prespecified analysis of the long-term renal effects of empagliflozin in the EMPA-REG OUTCOME trial, patients treated with empagliflozin were observed to have slower progression of kidney disease and renal events as compared with those treated with placebo.[39] Specifically, patients treated with empagliflozin were demonstrated to have lower rates of doubling of serum creatinine, incident or worsening nephropathy, and initiation of renal replacement therapy.

There was no significant difference in the rate of incident albuminuria.[39] Approximately 81% of the patients were already treated with an ACEI or ARB, suggesting that empagliflozin may provide additional benefits above those provided by renin-angiotensin-aldosterone blockade.[39]

Place in therapy

SGLT2 inhibitors offer several advantages as a new class of medications for the treatment of T2DM. Their insulin-independent mechanism of action allows them to be used in all stages of disease. SGLT2 inhibitors are associated with minimal risk of hypoglycemia when used as monotherapy but should be used cautiously in patients taking other medications known to cause hypoglycemia, such as sulfonylureas and insulin.

This class of medication provides an additional oral option for the treatment of T2DM, and once-daily dosing is beneficial in promoting patient adherence to therapy. In addition, SGLT2 inhibitors have demonstrated efficacy in reducing BP and body weight, which may be highly beneficial, as hypertension and obesity are common comorbidities in patients with T2DM. Patient assistance programs are available for all three SGLT2 inhibitors as well as combination products.

Despite their potential advantages, the use of SGLT2 inhibitors is not without risks and limitations. A recent FDA drug safety communication reported 20 cases of ketoacidosis among patients treated with SGLT2 inhibitors between March 2013 and June 2014.[40] These cases presented atypically, as

patients with T1DM are more likely to experience diabetic ketoacidosis; blood glucose readings among those taking SGLT2 inhibitors and presenting with ketoacidosis were not significantly elevated.[40]

A recent perspective paper suggested several potential mechanisms by which SGLT2 inhibitors may increase the risk of ketoacidosis.[41] Until additional safety information and guidance from the FDA is available, clinicians should monitor for this potential adverse reaction, and patients should be counseled on the signs and symptoms of ketoacidosis (nausea, vomiting, abdominal pain, confusion, fatigue, dyspnea) at the initiation of therapy.[40]

The mechanism of action of SGLT2 inhibitors may also affect bone metabolism and fracture risk.[42,43] During a 104-week study of dapagliflozin in patients with moderate kidney dysfunction (eGFR 30 to 59 mL/min/1.73 m^2), 13 fractures were seen in the dapagliflozin group, whereas no fractures occurred in the placebo group.[44] A pooled analysis of eight canagliflozin studies also demonstrated an increase in the incidence of fractures.[45] Overall, further investigations into the effect of SGLT2 inhibitors on bone mineral density and fracture risk are necessary to make definite conclusions.

Most recently, the FDA issued an alert based on an interim analysis of the CANVAS trial demonstrating an increased incidence of leg and foot amputations in patients treated with canagliflozin as compared with placebo (7 out of every 1,000 patients treated with canagliflozin 100 mg daily, 5 out of every 1,000 patients treated with canagliflozin 300 mg daily, and 3 out of every 1,000 patients treated with placebo over 1 year).[46]

Additional limitations of SGLT2 inhibitors include dependence on eGFR for efficacy, with renal dosing adjustments recommended among patients with decreased eGFR, and increased risk for genital mycotic and UTIs. Volume depletion and the potential for electrolyte imbalances warrant careful monitoring of these agents when they are initiated in patients prone to hypotension or taking other medications, such as ACEIs, ARBs, or spironolactone for hypertension, heart failure, or renal protective effects.

Until long-term safety and efficacy data are available for SGLT2 inhibitors, it is important for patients and providers to discuss the potential risks and benefits associated with the use of this class of medications when considering treatment options for T2DM (see *Discussion points for patient-provider shared decision-making*).

Future directions

Ongoing studies are currently evaluating the use of SGLT2 inhibitors with other classes of medications for the treatment of T2DM. With an anticipated completion date of 2017, CANVAS will provide important information regarding the safety and efficacy of SGLT2 inhibitors among patients with cardiovascular disease.[27] Additionally, the CANVAS-R (a study of the effects of Canagliflozin on renal endpoints in adult participants with T2DM) and CREDENCE (evaluation of the effects of canagliflozin on renal and cardiovascular outcomes in participants with diabetic nephropathy) will provide additional information on any renal benefits associated with the use of canagliflozin.[47,48] The effect of dapagliflozin on the incidence of cardiovascular events is also being investigated.[49]

Additional information from longer studies evaluating the effects of SGLT2 inhibitors on bone mineral density and fractures as well as the risk of ketoacidosis is necessary to ensure the safety of this class of medications. Finally, several SGLT2 inhibitors are currently in development and may be FDA-approved in the future, expanding the number of potential options available in this new class of medications for use in the growing population of patients affected by T2DM. NP

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