Differentiating Among the SGLT-2 Inhibitors: Considering Cardiovascular and Other Safety Outcomes

Eden M. Miller, DO; Carol H. Wysham, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Provide an overview of the rationale and role of SGLT-2 inhibitor therapy
- Describe the results of cardiovascular outcome trials with canagliflozin and empagliflozin
- Describe the evidence related to the safety of available SGLT-2 inhibitors

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management SGLT-2i and CV outcomes.

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Gregory Scott, PharmD, RPh, editorial support, discloses he has no real or apparent conflicts of interest to report.

Michael Hanak, MD, CME Reviewer, discloses that he has no real or apparent conflicts of interest to report.

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Release Date: 1 August 2018
Expiration Date: 31 July 2019

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

Eden M. Miller, DO, Executive Director and co-founder of Diabetes Nation, High Lakes Health Care, St. Charles Hospital, Bend, Oregon

Carol H. Wysham, MD, Clinical Professor of Medicine, University of Washington School of Medicine, Section Head Multicare/Rockwood Center for Diabetes and Endocrinology, Spokane, Washington

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ACKNOWLEDGEMENT
Editorial support was provided by Gregory Scott, PharmD, RPh. The authors were responsible for all content and editorial decisions.

SUPPORT
This article is sponsored by Primary Care Education Consortium and supported by an educational grant from Janssen Pharmaceuticals, Inc., administered by Janssen Scientific Affairs, LLC.

The availability of several new classes of medications for diabetes over the past decade or so provides greater opportunity to individualize treatment based on a patient's needs and characteristics. Among these new options, the effect of the sodium glucose cotransporter-2 inhibitors (SGLT-2i) on the kidney to lower blood glucose offers a unique, yet complementary mechanism of action to all other classes of medications, including basal insulin. This benefit, coupled with important glycemic and nonglycemic effects that include modest weight loss and an incidence of hypoglycemia similar to metformin, dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and thiazolidinediones (**TABLE 1**),[1-3] makes the SGLT-2i class of medications an important option for type 2 diabetes mellitus (T2DM) as an alternative to metformin[4-7] or as part of dual and triple therapy.[1,2] Four SGLT-2i are currently available in the United States: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin.

CARDIOVASCULAR SAFETY TRIALS

Historical overview

A cardiovascular (CV) event is the leading cause of death among persons with T2DM, serving to underscore the importance of managing other CV risk factors beyond blood glucose, including blood pressure, blood lipids, and body weight. More than a decade ago, evidence emerged indicating an elevated risk of myocardial infarction with rosiglitazone.[8-10] Although further investigation allayed some concerns, the US Food and Drug Administration issued guidance in 2008 requiring industry sponsors of new medications for T2DM to demonstrate in a clinical trial that a new medication is not associated with an unacceptable increase in CV risk relative to a control group at higher risk of a CV event.[11] A finding of noninferiority, ie, similarity, is demonstrated if the upper limit of the two-sided 95% confidence interval (CI) for the estimated risk ratio is less than 1.8, indicating that the new medication poses no increased CV risk versus the control (usually placebo as part of standard care). A risk ratio of less than 1 indicates superiority, demonstrating that the new medication reduces CV risk.

Nine CV safety trials investigating a DPP-4i, GLP-1 RA, or SGLT-2i have been completed. Additional trials are ongoing with other DPP-4i, GLP-1RA, and SGLT-2i, including dapagliflozin and ertugliflozin, with results available over the next 1 to 3 years. All 9 completed trials demonstrated the CV safety of the DPP-4i (alogliptin, saxagliptin, sitagliptin), GLP-1RA (exenatide once-weekly, liraglutide, lixisenatide, semaglutide), or SGLT-2i (canagliflozin, empagliflozin) to be noninferior to placebo as part of standard care.[12-20] In other words, the CV safety of each of these 9 medications is similar to placebo as part of standard care. However, canagliflozin and empagliflozin, as well as the GLP-1RA liraglutide and semaglutide, were shown to reduce CV risk compared to placebo as part of standard care (**TABLE 2**).[16,18-20] The CV safety trials for these 4 medications involved patients with a history or at high risk of CV disease, except empagliflozin, which involved only patients with a history of CV disease (**TABLE 3**).[16,18-20]

Canagliflozin

The CV benefit observed with canagliflozin appears to be a cumulative effect of the 3 components of the primary composite outcome, ie, CV death, nonfatal myocardial infarction, and nonfatal stroke, since changes in these components did not reach statistical significance individually.[19] The CV benefits were generally consistent across a wide range of subgroups at baseline, including age, HbA_{1c}, duration of T2DM, estimated glomerular filtration rate, and history of CV disease, but not beta-blocker or diuretic use. Post hoc analysis suggests that the CV benefits may result from reductions in one or more of the following: systolic blood pressure, diastolic blood pressure, pulse pressure, mean arterial pressure, and double product.[21]

The risk of hospitalization for heart failure alone (hazard ratio [HR], 0.67; 95% CI, 0.52-0.87), as well as combined with CV death (HR, 0.78; 95% CI, 0.67-0.91), was significantly reduced with canagliflozin compared with placebo. Of key importance is that renal outcomes were significantly improved with canagliflozin compared with placebo. These included lower risk of progression of albuminuria (HR 0.73; 95% CI, 0.67-0.79), as well as the composite of a 40% reduction in the estimated glomerular filtration rate, initiation of renal-replacement therapy, or renal death (HR, 0.60; 95% CI, 0.47-0.77).

There was a significantly higher risk of amputation of toes, feet, or legs with canagliflozin than with placebo (6.3 vs 3.4 persons with amputation/1000 patient-years; HR 1.97; 95% CI, 1.41-2.75).[19] Nearly three-quarters (71%) of the amputations were at the level of the toe or metatarsal. The highest absolute risk of amputation occurred among patients who had a history of amputation or peripheral vascular disease. The etiology for amputation is uncertain but may involve poor perfusion due to osmotic diuresis and lower blood pressure in compromised patients.

Empagliflozin

Among patients with T2DM and established CV disease, the CV benefit in the composite endpoint observed with empagliflozin was primarily due to a significant reduction in CV death compared with placebo (HR, 0.62; 95% CI, 0.49-0.77), with no significant between-group differences in the risks of myocardial infarction or stroke.[20] The reductions in the risk

TABLE 1 **Key glycemic and nonglycemic effects of sodium glucose contransporter-2 inhibitors[1-3,26]**

HbA_{1c} lowering*	FPG:PPG lowering	Hypoglycemia	Weight change*	SBP	CV effects		DKD
					ASCVD	HF	
-0.35% to -0.77%	FPG<PPG	No	-1.37 to -2.9 kg	-2.4 to -8.5 mm Hg	Benefit: canagliflozin, empagliflozin		

Abbreviations: HbA_{1c}, glycated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DKD, diabetic kidney disease; FPG, fasting plasma glucose; HF, heart failure; PPG, postprandial glucose; SBP, systolic blood pressure.

*As add-on to metformin vs metformin; data are from trials involving canagliflozin, dapagliflozin, or empagliflozin.

TABLE 2 **Medications for type 2 diabetes mellitus that have been shown to offer a cardiovascular benefit vs placebo as part of standard care[16,18-20]**

Endpoint	Rate/100 patient-years		Hazard ratio (95% CI)
	Medication	Placebo	
Canagliflozin			
CV death, nonfatal MI, nonfatal stroke[a]	2.69	3.15	0.86 (0.75-0.97)
HF hospitalization	0.55	0.87	0.67 (0.52-0.87)
CV death or HF hospitalization	1.63	2.08	0.78 (0.67-0.91)
Progression of albuminuria	8.94	12.87	0.73 (0.67-0.79)
40% reduction of eGFR, renal dialysis or transplantation, renal death	0.55	0.9	0.60 (0.47-0.77)
Empagliflozin			
CV death, nonfatal MI, nonfatal stroke[a]	3.74	4.39	0.86 (0.74-0.99)
All-cause death[b]	1.94	2.86	0.68 (0.57-0.82)
CV death	1.24	2.02	0.62 (0.49-0.77)
HF hospitalization	0.94	1.45	0.65 (0.50-0.85)
HF hospitalization or CV death (excluding fatal stroke)	1.97	3.01	0.66 (0.55-0.79)
Liraglutide			
CV death, nonfatal MI, nonfatal stroke[a,c]	3.4	3.9	0.87 (0.78-0.97)
CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for UA or HF	5.3	6	0.88 (0.81-0.96)
All-cause death[d]	2.1	2.5	0.85 (0.74-0.97)
CV death	1.2	1.6	0.78 (0.66-0.93)
Microvascular event	2	2.3	0.84 (0.73-0.97)
Nephropathy	1.5	1.9	0.78 (0.67-0.92)
Semaglutide			
CV death, nonfatal MI, nonfatal stroke[a,e]	3.24	4.44	0.74 (0.58-0.95)
CV death, nonfatal MI, nonfatal stroke, revascularization, hospitalization for UA or HF	6.17	8.36	0.74 (0.62-0.89)
All-cause death, nonfatal MI, nonfatal stroke	3.66	4.81	0.77 (0.61-0.97)
Nonfatal stroke	0.8	1.31	0.61 (0.38-0.99)
Revascularization	2.5	3.85	0.65 (0.50-0.86)
New or worsening nephropathy	1.86	3.06	0.64 (0.46-0.88)

Abbreviations: CV, cardiovascular, eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; UA, unstable angina.

[a]Primary endpoint.

[b]Number needed to treat = 39 over 3 years.

[c]Number needed to treat = 66 over 3 years.

[d]Number needed to treat = 98 over 3 years.

[e]Number needed to treat = 45 over 2 years.

TABLE 3 Key methodologic features and baseline characteristics of cardiovascular safety trials of sodium glucose cotransporter-2 inhibitors that have been shown to offer a cardiovascular benefit vs placebo as part of standard care[16,18-20]

Medication (Trial)	Participants	Randomization/treatment	Notes
Canagliflozin (CANVAS & CANVAS-R)	Men, women with T2DM; age ≥30 y with symptomatic ASCVD[a] or age ≥50 y with ≥2 CVD risk factors[b] HbA_{1c} ≥7% to ≤10.5%	2-wk single-blind, placebo-run-in Background glucose-lowering treatment allowed CANVAS Cana 300 mg/d or Cana 100 mg/d or Placebo OR CANVAS-R Cana 100 mg/d (optional increase to 300 mg/d at wk 13) or Placebo	N=10,142 (CANVAS 4330; CANVAS-R 5812) Age (mean)[c]: 63.3 y T2DM duration (mean)[c]: 13.5 y CVD history[c]: 65.6% HbA_{1c} (mean)[c]: 8.2% Treatment D/C rate[d]: cana 29.2%, placebo 29.9% Follow-up: 188.2 wks (mean); 126.1 wks (median)
Empagliflozin (EMPA-REG OUTCOME)	Men, women with T2DM and established CVD[e] HbA_{1c} ≥7% to ≤10%	2-wk single-blind, placebo-run-in Background glucose-lowering treatment allowed Empa 10 mg/d or Empa 25 mg/d or Placebo	N=7020 Age (mean)[c]: 63.1 y T2DM duration >10 y[c]: 57% CVD history[c]: 99% HbA_{1c} (mean)[c]: 8.1% Treatment D/C rate: empa 10 mg 23.7%, empa 25 mg 23.1%, placebo 29.3% Follow-up (median): 3.1 y

Abbreviations: HbA_{1c}, glycated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; Cana, canagliflozin; CVD, cardiovascular disease; D/C, discontinuation; Empa, empagliflozin; T2DM, type 2 diabetes mellitus.

[a]Stroke; myocardial infarction; hospitalization for unstable angina; coronary artery bypass graft; percutaneous coronary intervention; peripheral revascularization; symptomatic with hemodynamically-significant carotid or peripheral vascular disease; amputation secondary to vascular disease.

[b]T2DM duration ≥10 y; systolic blood pressure >140 mmHg while receiving ≥1 blood pressure-lowering medication; current smoking; microalbuminuria or macroalbuminuria; high-density lipoprotein cholesterol <38.7 mg/dL.

[c]Baseline.

[d]Canvas: canagliflozin 41.1%, placebo 49%; CANVAS-R: canagliflozin 17.4%, placebo 20.4%.

[e]Coronary artery disease; history of myocardial infarction or stroke; coronary artery bypass graft; peripheral artery disease; cardiac failure.

of CV death in the empagliflozin group were independent of baseline characteristics, including age, body mass index, estimated glomerular filtration rate, and history of CV disease.

The reductions in the risks of CV death and all-cause death occurred early in the trial (within 12 months) and continued thereafter. A dose-response effect, which has been observed for metabolic responses, was not evident with respect to CV outcomes. Of note, the adjusted mean HbA_{1c} at week 206 was 7.81% in the pooled empagliflozin group and 8.16% in the placebo group, suggesting that mechanisms beyond glucose-lowering contributed to the CV benefits observed with empagliflozin.

Additional analysis revealed that patients treated with empagliflozin had a significantly lower risk of a composite microvascular outcome than did those who received placebo (HR, 0.61; 95% CI, 0.55-0.69).[22] Approximately 80% of patients in both groups received concomitant renin-angiotensin-aldosterone system inhibitors at baseline. The between-group difference in the composite microvascular outcome was primarily due to a lower risk of progression of kidney disease with empagliflozin. New or worsening nephropathy occurred in 12.7% of empagliflozin and 18.8% of placebo patients (HR, 0.61; 95% CI, 0.53-0.70). Although empagliflozin did not prevent new albuminuria, patients treated with empagliflozin had a significantly lower risk of progression to macroalbuminuria (11.2% vs 16.2%), doubling of the serum creatinine (1.5% vs 2.6%), or initiation of renal-

TABLE 4 Key safety outcomes with SGLT-2 inhibitors[3,23-26]

Safety outcome	FDA drug safety communication	Included in product labeling			
		Cana	Dapa	Empa	Ertu
Blood pressure reduction		X	X	X	X
Genital mycotic infection		X	X	X	X
Acute kidney injury	Cana, Dapa	X	X	X	X
Urosepsis, pyelonephritis		X	X	X	X
Leg/foot amputation	Cana	X			X
Bone fracture	Cana	X			
Ketoacidosis	Cana, Dapa, Empa	X	X	X	X
Bladder cancer			X		

Abbreviations: Cana, canagliflozin; Dapa, dapagliflozin; Empa, empagliflozin; Ertu, ertugliflozin; FDA, US Food and Drug Administration.

replacement therapy (0.3% vs 0.6%) than patients in the placebo group, respectively.

OTHER SAFETY CONSIDERATIONS

The SGLT-2i are generally well tolerated with small increases in treatment-related adverse events (see below) compared with placebo.[23-25] When compared to metformin, a meta-analysis of 7 short-term trials as add-on therapy to metformin showed a similar risk of total hypoglycemia compared to metformin monotherapy.[3]

Genital mycotic and urinary tract infection

The unique mechanism of action to increase urinary glucose excretion results in a variety of adverse events, including genital mycotic infection (6% to 13%) and urinary tract infection (0% to 2%), particularly in females who have had a previous infection (**TABLE 4**).[3,23-26] Urinary tract infection may progress to urosepsis and pyelonephritis; hydration can aid in preventing progression.[27] To minimize the risk of genital mycotic infection, patients should be advised to keep the genital area clean and dry and, if necessary, apply topical antifungal , A+D ointment, zinc oxide ointment, or similar barrier method.

Blood pressure

The increased urinary glucose excretion caused by SGLT-2i results in an osmotic diuresis and increased urinary frequency. As a consequence, volume depletion may occur in <1% to 4%, lowering systolic blood pressure, which may result in postural hypotension and dizziness. Volume-depletion-related falls have been reported in 1.9%, 3.3%, and 1.5% of patients treated with canagliflozin 100 mg and 300 mg and placebo, respectively.[28] Therefore, it is especially important that patients maintain adequate hydration. In addition, patients should be advised to avoid bending at the waist and to rise slowly from sitting or lying down. Caution is advised with concomitant use with medications that lower blood pressure, especially diuretics; adjustment of antihypertensive therapy may be necessary based on clinical judgment.

Kidney function

Kidney-related adverse events, eg, acute kidney injury and impaired renal function, may occur with SGLT-2i therapy in 1% to 3% of patients with normal renal function and up to 5% to 6% with moderate renal impairment at baseline.[4-7,29] Although renal function generally improves after discontinuation or hydration, hospitalization and dialysis may occur.[29] Caution is advised with concomitant use of a diuretic, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or nonsteroidal anti-inflammatory drug.[29]

Diabetic ketoacidosis

Diabetic ketoacidosis with SGLT-2i therapy also may occur, although rare in patients with T2DM.[4-7,27] Factors predisposing to ketoacidosis include insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency, and alcohol abuse.[4-7] Treatment in an emergency department or hospitalization may be required. In some cases, the diabetic ketoacidosis was present with only modestly elevated blood glucose.

Fractures

The incidence of fractures has been reported to be significantly higher with canagliflozin compared to other medications for T2DM.[30] A pooled analysis showed that the incidence rates were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator (placebo and active comparators), canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively.[28] Fractures were observed as early as 12 weeks after treatment initiation, were more likely to result from minimal trauma, and predominately affected the hands, humerus, ankles, and feet.[28,30] The increased fracture risk was driven primarily by the results of the Canagliflozin Cardiovascular Assessment Study (CANVAS), which involved older patients with a prior history or risk of CV disease and with lower baseline renal function and higher diuretic use. While uncertain, it is possible that the increased risk of fracture in CANVAS may have resulted from volume depletion-related falls, although no adverse events of volume depletion (including syncope and

presyncope) were reported in patients just before or within 30 days of experiencing a fracture.[28] Additional investigation showed that canagliflozin caused significantly greater loss of bone mineral density at the hip (~1%) but not femoral neck, lumbar spine, or distal forearm, compared with placebo over 104 weeks of treatment.[31]

Leg and foot amputation

In the CANVAS program, leg and foot amputations occured about twice as often in patients treated with canagliflozin compared to placebo.[19,32] Over 1 year, the risk of amputation ranged from 5.9 to 7.5 per 1000 patients treated with canagliflozin and 2.8 to 4.2 per 1000 patients treated with placebo. Amputation of the toe and middle of the foot were the most common. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.[5] The etiology for amputation is uncertain, but may involve poor perfusion due to osmotic diuresis and lower blood pressure in compromised patients.

Bladder cancer

Dapagliflozin is associated with an increased incidence of cancer. During the FDA review for the approval of dapagliflozin, the possibility of increased risks of breast and bladder cancers were identified.[33] Further investigation revealed no increased risk for breast cancer, but an imbalance in bladder cancer with dapagliflozin remained. Therefore, dapagliflozin should not be used in patients with active bladder cancer and used with caution in patients with a history of bladder cancer.[4]

IMPLICATIONS FOR PRACTICE

The SGLT-2i class of medications possesses many glycemic and nonglycemic characteristics that make them an important option for individualizing therapy in patients with T2DM. SGLT-2i are generally well-tolerated, with a low incidence of hypoglycemia. Adverse events related to osmotic diuresis and volume depletion are among the most common. A key benefit of canagliflozin and empagliflozin is their ability to reduce CV risk compared to placebo as part of standard care. Whether this is a class effect, eg, that dapagliflozin and ertugliflozin may demonstrate a similar CV risk reduction, is not yet known. Therefore, it remains unclear if patients should be switched from another medication not shown to provide CV risk reduction to a medication with demonstrated CV risk reduction, eg, canagliflozin and empagliflozin. At the very least, the CV benefits observed thus far with canagliflozin and empagliflozin are important to consider when initiating glucose-lowering therapy in patients with T2DM. ●

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