

Clinical Implications of Canagliflozin Treatment in Patients With Type 2 Diabetes

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■ **IN BRIEF** Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of antihyperglycemic agents that lower blood glucose levels in patients with type 2 diabetes. SGLT2 inhibitors have an insulin-independent mechanism of action, acting to inhibit the reabsorption of glucose in the kidney, which leads to increases in urinary glucose excretion in individuals with elevated blood glucose levels. This article provides an overview of the role of the kidney in type 2 diabetes, describes the rationale for renal SGLT2 as a new target for glycemic control, and focuses on the clinical implications of incorporating the SGLT2 inhibitor canagliflozin into type 2 diabetes treatment regimens based on data from phase 3 studies.

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of antihyperglycemic agents that lower blood glucose levels in patients with type 2 diabetes. SGLT2 inhibitors have an insulin-independent mechanism of action, acting to inhibit the reabsorption of glucose in the kidney, which leads to increases in urinary glucose excretion (UGE) in individuals with elevated blood glucose levels (1,2).

Canagliflozin (3) was the first SGLT2 inhibitor to be approved in the United States to improve glycemic control in adults with type 2 diabetes; it is also approved for this indication in other countries. Another SGLT2 inhibitor, dapagliflozin (4), is approved in the United States and other countries. Empagliflozin has recently been approved in the European Union, and several other SGLT2 inhibitors are in various stages of clinical development (5–8).

Role of the Kidney in Type 2 Diabetes

A key function of the kidney in healthy individuals is to help ensure

that the body's energy needs are met during fasting periods through reabsorption of filtered glucose and gluconeogenesis (9). In individuals without type 2 diabetes, the kidneys filter ~180 g of glucose per day; nearly all of this is reabsorbed to maintain normal fasting blood glucose levels, with ≤1% excreted in urine (1). The majority of this renal glucose reabsorption is mediated by SGLT2, a glucose transport protein found in the early portion of the proximal renal tubule, whereas a smaller amount of renal glucose reabsorption is mediated by SGLT1, a transporter found in the distal segment of the proximal tubule and in the mucosa of the small intestine, where it plays a primary role in intestinal glucose absorption (Fig. 1) (10,11).

Increased blood glucose levels result in an increased amount of glucose being filtered and reabsorbed by the kidney until the renal capacity to reabsorb glucose is reached, at which point excess glucose is excreted in the urine (9). The blood glucose concentration at which this occurs is referred

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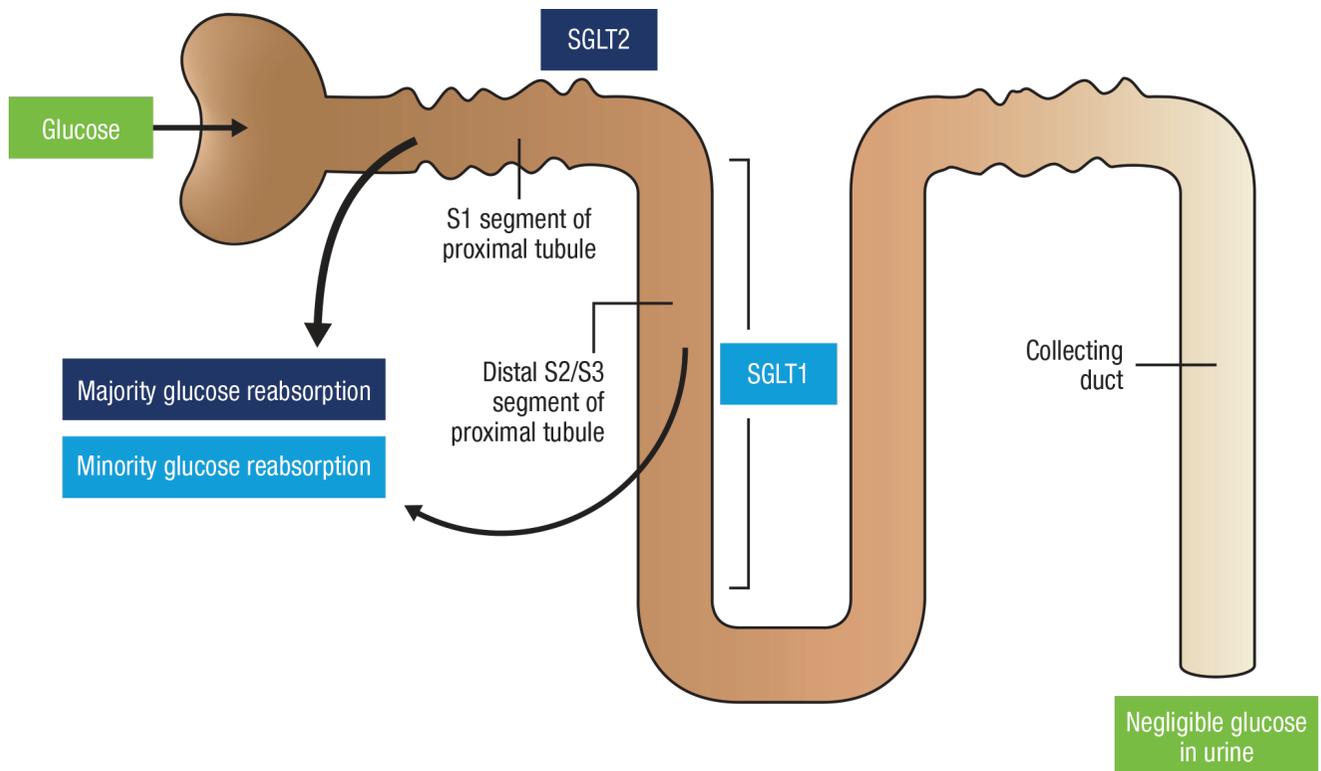


FIGURE 1. Glucose reabsorption in the renal proximal tubule. Reprinted from Ref. 28 with permission from Macmillan Publishers Ltd., copyright 2010.

to as the renal threshold for glucose excretion (RT_G).

Studies have found that renal glucose reabsorptive capacity increases in type 2 diabetes (12,13), and this has begun to be recognized as a mechanism that contributes to hyperglycemia (9,14). In patients with type 2 diabetes, increased mean RT_G values of up to ~240 mg/dL have been reported (15,16), which is ~40–60 mg/dL higher than the commonly reported values of 180–200 mg/dL in healthy subjects (2,9,15,17). This increase is likely related to increased expression of glucose transporters including SGLT2 (18,19). Assuming a typical glomerular filtration rate (GFR) of 90 mL/min and a body weight of 90 kg, it is estimated that the average increase in RT_G in patients with type 2 diabetes can result in an amount of additional glucose reabsorption similar to the increased hepatic glucose output observed when the plasma glucose concentration is elevated (20).

Lowering of Plasma Glucose With SGLT2 Inhibitors

SGLT2 inhibitors lower the RT_G , thereby decreasing the kidney’s capacity to reabsorb glucose, resulting in increased UGE and reduced blood glucose concentrations (measured as A1C and fasting plasma glucose [FPG]) (12,21). Canagliflozin has also been shown to reduce postprandial glucose excursions via two mechanisms: 1) increased UGE due to SGLT2 inhibition and 2) delayed appearance of oral glucose in plasma that is likely due to local (rather than systemic) transient intestinal SGLT1 inhibition, which ultimately provides a small contribution to overall A1C reduction (22). During the once-daily periods of drug absorption, intestinal concentrations of canagliflozin may be high enough to locally and transiently inhibit intestinal SGLT1 and thereby delay intestinal glucose absorption at the morning meal only, which could contribute to glucose lowering by a nonrenal mechanism (22).

Increased UGE with SGLT2 inhibition may provide other benefits in addition to improved glycemia, including body weight reduction due to net calorie loss (~4 kcal/g of glucose excreted) and reduced blood pressure (BP), which may be associated with a mild osmotic diuresis and reduced body weight (23). SGLT2 inhibition is expected to be associated with a low risk for hypoglycemia because the amount of UGE decreases as plasma glucose is reduced (24,25), and studies of canagliflozin have shown that RT_G is reduced to above the level at which hypoglycemia occurs (15,21). Recently, SGLT2 inhibition has been shown to be associated with an increase in endogenous glucose production via increased ratio of circulating glucagon to insulin levels (26,27); in the event of hypoglycemia, this increased endogenous glucose production could provide a source for glycemic “rescue” (9).

Because SGLT2 inhibitors lower blood glucose in an insulin-independent manner, they are

expected to provide glycemic improvements across a wide spectrum of patients, including those with newly diagnosed type 2 diabetes who have mildly impaired β -cell function and those with a longer duration of disease who have severely impaired β -cell function. In addition, the treatment effect of SGLT2 inhibitors is expected to persist as diabetes progresses and β -cell function declines (9). Because of their novel mechanism of action, SGLT2 inhibitors may provide additional glycemic benefit when used with other antihyperglycemic

agents that have different mechanisms of action (9,28).

Implications for the Use of the SGLT2 Inhibitor Canagliflozin in Clinical Practice

In the United States, canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (3). It is administered orally as 100- or 300-mg tablets, with a recommended starting dose of 100 mg once daily taken before the first meal of the day. Dosage can be increased to 300 mg once daily in patients who

have an estimated GFR (eGFR) ≥ 60 mL/min/1.73 m² who require additional glycemic control and are tolerating this therapy well. Canagliflozin is not indicated in patients with an eGFR < 45 mL/min/1.73 m².

The efficacy and safety of canagliflozin 100 and 300 mg have been evaluated in patients with type 2 diabetes in phase 3 studies of various regimens: as monotherapy, as dual therapy added to metformin or sulfonylurea, as triple therapy added to metformin plus sulfonylurea or metformin plus thiazolidinedione (pioglitazone), and in combination

TABLE 1. Summary of the Efficacy and Safety of Canagliflozin as Add-On to Metformin, Metformin Plus Sulfonylurea, and Insulin in Patients With Type 2 Diabetes Over 52 Weeks (3,30–33,50,53)

	Canagliflozin as:		
	Add-on to MET	Add-on to MET + SU	Add-on to insulin
Changes in key efficacy parameters			
A1C (%)	GLIM	PBO	PBO
	Baseline: 7.8	Baseline: 8.1	Baseline: 8.2
	Change: -0.81	Change: +0.01	Change: +0.13
	CANA 100 mg	CANA 100 mg	CANA 100 mg
	Baseline: 7.8	Baseline: 8.1	Baseline: 8.3
	Change: -0.82	Change: -0.74	Change: -0.58
	CANA 300 mg	CANA 300 mg	CANA 300 mg
	Baseline: 7.8	Baseline: 8.1	Baseline: 8.3
	Change: -0.93	Change: -0.96	Change: -0.68
	SITA	SITA	
	Baseline: 7.9	Baseline: 8.1	
	Change: -0.73	Change: -0.66	
CANA 100 mg	CANA 300 mg		
Baseline: 7.9	Baseline: 8.1		
Change: -0.73	Change: -1.03		
CANA 300 mg			
Baseline: 8.0	Patients with baseline A1C $\geq 9.0\%$		
Change: -0.88	SITA		
	Baseline: 9.5		
	Change: -1.44		
	CANA 300 mg		
	Baseline: 9.6		
	Change: -1.99		

TABLE CONTINUED ON P. 8 →

TABLE 1. Summary of the Efficacy and Safety of Canagliflozin as Add-On to Metformin, Metformin Plus Sulfonylurea, and Insulin in Patients With Type 2 Diabetes Over 52 Weeks (3,30–33,50,53), continued from p. 7

	Canagliflozin as:		
	Add-on to MET	Add-on to MET + SU	Add-on to insulin
Body weight (kg)	GLIM	PBO:	PBO
	Baseline: 86.6	Baseline: 90.8	Baseline: 97.7
	Change: +1.0% (+0.7)	Change: –0.9% (–1.0)	Change: +0.1% (+0.1)
	CANA 100 mg	CANA 100 mg	CANA 100 mg
	Baseline: 86.8	Baseline: 93.5	Baseline: 96.9
	Change: –4.2% (–3.7)	Change: –2.2% (–2.0)	Change: –2.4% (–2.3)
	CANA 300 mg	CANA 300 mg	CANA 300 mg
	Baseline: 86.6	Baseline: 93.5	Baseline: 96.7
	Change: –4.7% (–4.0)	Change: –3.2% (–3.1)	Change: –3.1% (–3.0)
	SITA	SITA	
	Baseline: 87.6	Baseline: 89.6	
	Change: –1.3% (–1.2)	Change: +0.3% (+0.1)	
CANA 100 mg	CANA 300 mg		
Baseline: 88.7	Baseline: 87.6		
Change: –3.8% (–3.3)	Change: –2.5% (–2.3)		
CANA 300 mg			
Baseline: 85.4			
Change: –4.2% (–3.7)			
Systolic BP (mmHg)	GLIM	PBO	PBO
	Baseline: 129.5	Baseline: 130.1	Baseline: 138.2
	Change: +0.2	Change: +0.1	Change: –1.4
	CANA 100 mg	CANA 100 mg	CANA 100 mg
	Baseline: 130.0	Baseline: 130.4	Baseline: 137.0
	Change: –3.3	Change: –3.7	Change: –4.7
	CANA 300 mg	CANA 300 mg	CANA 300 mg
	Baseline: 130.0	Baseline: 130.8	Baseline: 138.2
	Change: –4.6	Change: –2.9	Change: –7.6
	SITA	SITA	
	Baseline: 128.0	Baseline: 130.1	
	Change: –0.7	Change: +0.9	
CANA 100 mg	CANA 300 mg		
Baseline: 128.0	Baseline: 131.2		
Change: –3.5	Change: –5.1		
CANA 300 mg			
Baseline: 128.7			
Change: –4.7			

TABLE CONTINUED ON P. 9 →

TABLE 1. Summary of the Efficacy and Safety of Canagliflozin as Add-On to Metformin, Metformin Plus Sulfonylurea, and Insulin in Patients With Type 2 Diabetes Over 52 Weeks (3,30–33,50,53), continued from p. 8

	Canagliflozin as:		
	Add-on to MET	Add-on to MET + SU	Add-on to insulin
Selected safety parameters			
Hypoglycemia	Low incidence, similar to SITA, significantly lower than GLIM	Incidence similar to SITA	Higher incidence compared to PBO
Genital mycotic infections	<ul style="list-style-type: none"> • Higher incidence than PBO, GLIM, and SITA • Mild or moderate, respond to standard treatments 		
Urinary tract infections	<ul style="list-style-type: none"> • Higher incidence than PBO and GLIM • Similar incidence than SITA • Upper urinary tract infections rare 		
Osmotic diuresis-related AEs	<ul style="list-style-type: none"> • Higher incidence than PBO and SITA • Incidence low with few study discontinuations 		
Volume depletion-related AEs	<ul style="list-style-type: none"> • Incidence low with few study discontinuations 		
Lipids	<ul style="list-style-type: none"> • Increases in HDL cholesterol (PBO-subtracted changes of 5.4 and 6.3% with CANA 100 and 300 mg, respectively, in the pooled PBO-controlled studies) • Increases in LDL cholesterol (PBO-subtracted changes of 4.5 and 8.0% with CANA 100 and 300 mg, respectively, in the pooled PBO-controlled studies) • Increases in non-HDL cholesterol smaller than those in LDL cholesterol (PBO-subtracted changes of 1.5 and 3.6% with CANA 100 and 300 mg, respectively, in the pooled PBO-controlled studies) • No notable trends in change from baseline in LDL/HDL cholesterol ratio 		
Laboratory parameters	<ul style="list-style-type: none"> • Modest improvements in liver function parameters • Increases in bilirubin and BUN • Reductions in serum urate • Transient decreases in eGFR with reciprocal increases in serum creatinine • Small increases in hemoglobin 		
<p><i>BUN, blood urea nitrogen; CANA, canagliflozin; GLIM, glimepiride; MET, metformin; PBO, placebo; SITA, sitagliptin; SU, sulfonylurea.</i></p>			

with insulin (alone or with other oral antihyperglycemic agents). Across phase 3 studies, canagliflozin 100 and 300 mg doses have improved glycemic control and reduced body weight and systolic BP (29–35). Canagliflozin has also demonstrated glycemic efficacy in older patients (aged 55–80 years) and in those with moderate renal impairment (eGFR ≥ 30 and < 50 mL/min/1.73 m²) (36,37). In addition, canagliflozin generally provided greater reductions in A1C in patients with elevated baseline A1C levels across clinical trials (29,31,32,37).

Canagliflozin is well tolerated, with a pattern of specific adverse events (AEs) likely associated with its mechanism of action (e.g., genital mycotic infections, urinary tract infections, and osmotic diuresis-related AEs). These AEs were generally mild or moderate in intensity, infrequently resulted in discontinuation of treatment (3,38,39), and have also been reported with other SGLT2 inhibitors (4,8,40–42). In a pooled analysis of placebo-controlled studies, the incidence of urinary tract infections was slightly higher with canagliflozin 100 and 300 mg than with placebo (5.9, 4.3, and 4.0%,

respectively) (3,39). Patients aged ≥ 75 years, those with moderate renal impairment, and those taking loop diuretics may be at an increased risk for volume depletion-related AEs (e.g., postural dizziness and hypotension), although incidence of these AEs was generally low across the canagliflozin research program (3).

The following patient vignettes illustrate how canagliflozin may be used in clinical practice. Results of phase 3 canagliflozin studies are summarized in Table 1 and at the beginning of each vignette to provide context for the outcomes described.

Vignette 1: Patient on Metformin

Supporting Information From Phase 3 Clinical Studies

In a clinical study of canagliflozin compared with placebo at week 26 or sitagliptin at week 52 in patients with type 2 diabetes who were being treated with background metformin, canagliflozin 100 and 300 mg significantly reduced A1C compared with placebo over 26 weeks (33). At week 52, canagliflozin 100 mg demonstrated non-inferiority, and canagliflozin 300 mg demonstrated superiority to sitagliptin in A1C lowering (from baseline A1C of 7.9% in all groups, changes were -0.73 , -0.88 , and -0.73% with canagliflozin 100 and 300 mg and sitagliptin, respectively). Both canagliflozin doses reduced FPG, body weight, and systolic BP compared with placebo at week 26 and sitagliptin at week 52. Canagliflozin was generally well tolerated; the overall incidence of AEs and AEs leading to discontinuation was generally similar across groups but was higher with canagliflozin 100 mg over 52 weeks. The incidence of genital mycotic infections was higher with canagliflozin than with sitagliptin, and urinary tract infection incidences were similar across treatment groups. The incidence of hypoglycemia was low and similar with canagliflozin (6.8% with both canagliflozin doses) and sitagliptin (4.1%).

In a separate phase 3 study, the efficacy and safety of canagliflozin added to metformin were compared with the sulfonylurea glimepiride (30). At week 52, canagliflozin 100 mg demonstrated noninferiority, and canagliflozin 300 mg demonstrated superiority to glimepiride (from baseline A1C of 7.8% in all groups, changes were -0.82 , -0.93 , and -0.81% with canagliflozin 100 and 300 mg and glimepiride, respectively). Patients in the canagliflozin groups experienced significant body weight reduction compared with a slight weight gain with glimepiride. Reductions in systolic BP were also

seen with canagliflozin compared with glimepiride. The incidence of genital mycotic infections was higher with canagliflozin than with glimepiride. The incidence of urinary tract infections was slightly higher with canagliflozin than with glimepiride. The incidence of hypoglycemia was significantly lower with both canagliflozin doses compared with glimepiride.

Clinical Implications

Metformin is the standard first-line treatment option for patients with type 2 diabetes. However, many patients taking metformin alone do not achieve an A1C $<7.0\%$. Typically, health care providers choose to add either a dipeptidyl peptidase-4 (DPP-4) inhibitor or a sulfonylurea to help patients achieve glycemic goals. Additional antihyperglycemic agents that will provide significant A1C reduction without weight gain or risk of hypoglycemia would be desirable for patients requiring add-on therapy to metformin.

These phase 3 trial data show that canagliflozin treatment in tandem with metformin provides robust A1C reductions along with weight loss compared with a DPP-4 inhibitor (sitagliptin) and a sulfonylurea (glimepiride). These results suggest that canagliflozin may provide an attractive option as an add-on to metformin therapy to support patients' glycemic goals, with the added benefit of weight loss and a low risk of hypoglycemia.

Glucagon-like peptide-1 (GLP-1) receptor agonists provide another option for glycemic management that is associated with weight loss. Although canagliflozin has not been directly compared with a GLP-1 receptor agonist, both have provided weight reductions in clinical studies. For example, in a 52-week study evaluating the effects of canagliflozin as add-on to metformin (33), mean body weight reductions of 3.3 and 3.7 kg were observed with the 100- and 300-mg doses, respectively. Average

weight loss over 52 weeks of treatment with the GLP-1 receptor agonist liraglutide 1.8 mg was reported to be 2.5 kg (43). Although both canagliflozin and GLP-1 receptor agonists provide improved glycemic control and weight loss, the oral antihyperglycemic agent canagliflozin may be preferred by patients to an injectable GLP-1 receptor agonist.

Vignette 2: Patient on Metformin Plus Sulfonylurea

Supporting Information From Phase 3 Clinical Studies

In a phase 3 study of patients receiving metformin plus sulfonylurea, canagliflozin was associated with significant A1C reductions compared with placebo at 26 weeks (-0.85 , -1.06 , and -0.13% for canagliflozin 100 and 300 mg and placebo, respectively) (32). Over 52 weeks, A1C reductions with canagliflozin 100 and 300 mg were sustained, whereas a slight increase was seen with placebo (-0.74 , -0.96 , and 0.01% , respectively). Canagliflozin also reduced FPG and body weight over 52 weeks compared with placebo. The overall incidence of AEs across treatment groups was similar over 52 weeks. Both canagliflozin doses were associated with an increased incidence of genital mycotic infections and osmotic diuresis-related AEs, whereas the incidence of urinary tract infections was similar across groups. Canagliflozin 100 and 300 mg were associated with an increased incidence of hypoglycemia compared with placebo (33.8, 36.5, and 17.9%, respectively), and the incidence of severe hypoglycemic episodes was 0.6% across groups (32).

In a head-to-head study of canagliflozin 300 mg compared with sitagliptin in patients receiving metformin plus sulfonylurea, canagliflozin 300 mg demonstrated superiority to sitagliptin in A1C lowering over 52 weeks (mean changes from baseline of -1.03 and -0.66% , respectively) (31). Canagliflozin 300 mg provided greater A1C reductions in patients with higher baseline A1C

(changes in subgroups with baseline A1C <8%: -0.57 and -0.31%; A1C ≥8 to <9%: -1.15 and -0.73%; A1C ≥9%: -1.99 and -1.44% with canagliflozin 300 mg and sitagliptin, respectively). Canagliflozin 300 mg also significantly reduced FPG, body weight, and systolic BP compared with sitagliptin. Canagliflozin 300 mg and sitagliptin were both associated with improvements in indices of β -cell function; in general, these improvements were numerically greater with canagliflozin 300 mg.

Canagliflozin 300 mg was generally well tolerated, with a safety/tolerability profile consistent with that described above. The incidence of hypoglycemia was similar with canagliflozin 300 mg (43.2%) and sitagliptin (40.7%), despite -0.4% greater A1C lowering with canagliflozin 300 mg compared with sitagliptin; the incidence of hypoglycemia with canagliflozin was higher than that seen in studies of canagliflozin in patients not on background therapy with a sulfonyleurea (29,30,33). These findings are consistent with previous reports of increased hypoglycemia incidence with agents not inherently associated with hypoglycemia when they are used in combination with a sulfonyleurea or insulin (44–48).

Clinical Implications

Concomitant use of canagliflozin with metformin plus sulfonyleurea background therapy provides a reduction in A1C, with additional benefits of body weight and BP reduction compared with triple therapy with the DPP-4 inhibitor sitagliptin with metformin plus sulfonyleurea. Of note, despite greater A1C reduction with canagliflozin, a similar incidence of hypoglycemia was seen with canagliflozin and sitagliptin. These data show that canagliflozin may provide efficacy in triple therapy without an added risk of hypoglycemia. Furthermore, canagliflozin may provide glycemic improvements in patients across a range of baseline

A1C values, with potential for greater A1C reductions in patients with an elevated baseline A1C.

Vignette 3: Patient With Advanced Type 2 Diabetes (i.e., Add-On to Insulin)

Supporting Information From Phase 3 Clinical Studies

In patients with type 2 diabetes on insulin alone or in combination with other antihyperglycemic agents (mean insulin dose of 83 IU/day), canagliflozin 100 and 300 mg improved glycemic control and reduced body weight and systolic BP compared with placebo over 18 weeks (3,49). Over 52 weeks, canagliflozin 100 and 300 mg were associated with sustained reductions in A1C compared with an increase with placebo (-0.58, -0.68, and 0.13%, respectively) (50). Both canagliflozin doses also provided reductions in FPG, body weight, and systolic BP compared with placebo over 52 weeks.

Canagliflozin was generally well tolerated, with a safety/tolerability profile consistent with that described above. The incidence of hypoglycemia was higher in the canagliflozin groups than with placebo, as expected given the improved glycemic control and the background insulin therapy.

Clinical Implications

Many patients are on one or more oral antihyperglycemic agents plus insulin, and diabetes management can become increasingly difficult when the disease progresses to this stage, particularly when A1C goals have not been met. Clinicians face the challenge of knowing that increasing the insulin dose can lead to increases in weight that may perpetuate the need for further insulin dose adjustments. Canagliflozin uses a renal mechanism that is independent of insulin to provide reductions in A1C, body weight, and systolic BP; in particular, the outcome of weight loss is attractive because it may lower insulin requirements. In addition, canagliflozin is administered orally, and patients

may prefer this to adding another injectable agent (e.g., a GLP-1 receptor agonist) to insulin therapy.

Conclusion

The 2013 American Association of Clinical Endocrinologists diabetes management algorithm includes SGLT2 inhibitors as a treatment option as monotherapy or as part of dual- and triple-therapy regimens because of their potential to improve glycemic control and promote weight loss and BP reduction with a low risk of hypoglycemia (51). A limitation of canagliflozin is that it does not have a well-established long-term safety profile. However, forthcoming data from longer-term clinical trials and from real-world clinical experience will be helpful in confirming the long-term safety of canagliflozin and other SGLT2 inhibitors and in determining the types of patients who may benefit most from SGLT2 inhibitor therapy.

Canagliflozin should not be used in patients with severe renal impairment (i.e., eGFR <30 mL/min/1.73 m², end-stage renal disease, or dialysis). Patients with moderately impaired renal function (eGFR <60 mL/min/1.73 m²) should be evaluated frequently for signs of worsening kidney function and hyperkalemia (3). However, results from analyses of pooled data from the canagliflozin phase 3 research program in patients across a range of baseline renal function showed that mean increases in serum potassium were small (0.6–2.8%) (52). The frequency of potassium elevations meeting outlier criteria (i.e., greater than the upper limit of normal [5.4 mmol/L] and a >15% increase from baseline) at any time post-baseline was higher with canagliflozin 300 mg compared with canagliflozin 100 mg and placebo (6.8, 4.5, and 4.7%, respectively, in patients with baseline eGFR ≥60 mL/min/1.73 m²; 9.1, 5.2, and 5.5%, respectively, in patients with baseline eGFR ≥45 and <60 mL/min/1.73 m²), but potassium elevations >6.5 mmol/L were rare

(52). Small increases in magnesium and phosphate were observed with canagliflozin compared with placebo; however, the proportion of patients with outlier levels of these electrolytes was not different between groups (52). The incidence of AEs related to changes in electrolytes was low with canagliflozin and placebo (52).

Patients with renal impairment, elderly patients, and patients taking antihypertensive medications (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers) should be monitored for signs of hypotension (3). Patients taking canagliflozin should also be monitored for changes in LDL cholesterol because increases of 4.5 and 8.0% compared with placebo were seen with canagliflozin 100 and 300 mg, respectively, in the pooled placebo-controlled studies. All patients should be informed of the increased risk for genital mycotic infections associated with SGLT2 inhibitors (3).

The vignettes presented here highlight some potential applications for the use of canagliflozin in clinical practice, in a range of varying patient characteristics and circumstances. Canagliflozin provides reductions in A1C, body weight, and systolic BP and is generally well tolerated across a broad range of patients. Because of its unique insulin-independent mechanism of action, canagliflozin is suitable for use in combination with a variety of other antihyperglycemic agents to optimize glycemic control. Thus, canagliflozin may provide an attractive option for patients and clinicians facing the challenge of type 2 diabetes management.

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Duality Of Interest

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References

1. Neumiller JJ, White JR Jr, Campbell RK. Sodium-glucose co-transport inhibitors: progress and therapeutic potential in type 2 diabetes mellitus. *Drugs* 2010;70:377–385
2. Abdul-Ghani MA, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. *Endocr Rev* 2011;32:515–531
3. Invokana [package insert]. Titusville, NJ, Janssen Pharmaceuticals, 2013
4. Farxiga [package insert]. Princeton, NJ, Bristol-Myers Squibb, 2014
5. Jardiance [summary of product characteristics]. Ingelheim, Germany, Boehringer Ingelheim, 2014
6. Kurosaki E, Ogasawara H. Ipragliflozin and other sodium-glucose cotransporter-2 (SGLT2) inhibitors in the treatment of type 2 diabetes: preclinical and clinical data. *Pharmacol Ther* 2013;139:51–59
7. Kapur A, Connor-Semmes O, Hussey EK, et al. First human dose-escalation study with remogliflozin etabonate, a selective inhibitor of the sodium-glucose transporter 2 (SGLT2), in healthy subjects and in subjects with type 2 diabetes mellitus. *BMC Pharmacol Toxicol* 2013;14:26
8. Rosenstock J, Seman LJ, Jelaska A, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. *Diabetes Obes Metab* 2013;15:1154–1160
9. Defronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. *Diabetes Obes Metab* 2012;14:5–14
10. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. *Physiol Rev* 2011;91:733–794
11. Gorboulev V, Schurmann A, Vallon V, et al. Na(+)-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. *Diabetes* 2012;61:187–196
12. Defronzo RA, Hompesch M, Kasichayanula S, et al. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. *Diabetes Care* 2013;36:3169–3176
13. Farber SJ, Berger EY, Earle DP. Effect of diabetes and insulin of the maximum capacity of the renal tubules to reabsorb glucose. *J Clin Invest* 1951;30:125–129
14. Defronzo RA: Banting Lecture 2008: From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009;58:773–795
15. Devineni D, Morrow L, Hompesch M, et al. Canagliflozin improves glycemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. *Diabetes Obes Metab* 2012;14:539–545
16. Devineni D, Curtin CR, Polidori D, et al. Pharmacokinetics and pharmacodynamics of canagliflozin, a sodium glucose co-transporter 2 inhibitor, in subjects with type 2 diabetes mellitus. *J Clin Pharmacol* 2013;53:601–610
17. Nair S, Wilding JP. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. *J Clin Endocrinol Metab* 2010;95:34–42
18. Freitas HS, Anhe GF, Melo KF, et al. Na(+)-glucose transporter-2 messenger ribonucleic acid expression in kidney of diabetic rats correlates with glycemic levels: involvement of hepatocyte nuclear factor-1alpha expression and activity. *Endocrinology* 2008;149:717–724
19. Rahmoune H, Thompson PW, Ward JM, Smith CD, Hong G, Brown J. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. *Diabetes* 2005;54:3427–3434
20. Beck-Nielsen H, Hother-Nielsen O, Staehr P. Is hepatic glucose production increased in type 2 diabetes mellitus? *Curr Diab Rep* 2002;2:231–236
21. Rosenstock J, Aggarwal N, Polidori D, et al.; Canagliflozin DIA 2001 Study Group. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care* 2012;35:1232–1238
22. Polidori D, Sha S, Mudaliar S, et al. Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion: results of a randomized, placebo-controlled study. *Diabetes Care* 2013;36:2154–2161
23. Blonde L, Wilding J, Chiasson J-L, Polidori D, Meininger G, Stein P. Canagliflozin (CANa) lowers A1C and blood pressure (BP) through weight loss-independent (WL-I) and weight loss-associated (WL-A) mechanisms (Abstract). *Diabetes* 2013;62(Suppl. 1):A1110-P
24. Liang Y, Arakawa K, Ueta K, et al. Effect of canagliflozin on renal threshold for glucose, glycemia, and body weight in normal and diabetic animal models. *PLoS One* 2012;7:e30555
25. Sha S, Devineni D, Ghosh A, et al. Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects. *Diabetes Obes Metab* 2011;13:669–672
26. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin

- sensitivity but enhances endogenous glucose production. *J Clin Invest* 2014;124:509–514
27. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest* 2014;124:499–508
28. Chao EC, Henry RR. SGLT2 inhibition: a novel strategy for diabetes treatment. *Nat Rev Drug Discov* 2010;9:551–559
29. Stenlöf K, Cefalu WT, Kim K-A, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab* 2013;15:372–382
30. Cefalu WT, Leiter LA, Yoon K-H, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet* 2013;382:941–950
31. Scherthner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week, randomized trial. *Diabetes Care* 2013;36:2508–2515
32. Wilding JP, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. *Int J Clin Pract* 2013;67:1267–1282
33. Lavalley-Gonzalez F, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia* 2013;56:2582–2592
34. Stenlof K, Cefalu WT, Kim KA, et al. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. *Curr Med Res Opin* 2014;30:163–175
35. Forst T, Guthrie R, Goldenberg R, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. *Diabetes Obes Metab* 2014;16:467–477
36. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab* 2013;15:463–473
37. Bode B, Stenlof K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract* 2013;41:72–84
38. Nyirjesy P, Sobel JD, Fung A, et al. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. *Curr Med Res Opin* 2014;30:1109–1119
39. Nicolle LE, Capuano G, Fung A, Usiskin K. Urinary tract infection in randomized phase III studies of canagliflozin, a sodium glucose co-transporter 2 inhibitor. *Postgrad Med* 2014;126:7–17
40. Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF. Urinary tract infections in patients with diabetes treated with dapagliflozin. *J Diabetes Complications* 2013;27:473–478
41. Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF. Vulvovaginitis and balanitis in patients with diabetes treated with dapagliflozin. *J Diabetes Complications* 2013;27:479–484
42. Haring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care* 2013;36:3396–3404
43. Jendle J, Nauck MA, Matthews DR, et al. Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. *Diabetes Obes Metab* 2009;11:1163–1172
44. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 2004;27:2628–2635
45. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 2005;28:1083–1091
46. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes Obes Metab* 2007;9:733–745
47. Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab* 2011;13:928–938
48. Wilding JP, Woo V, Soler NG, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med* 2012;156:405–415
49. Matthews D, Fulcher G, Perkovic V, et al. Efficacy and safety of canagliflozin (CANa), an inhibitor of sodium glucose co-transporter 2 (SGLT2), added-on to insulin therapy +/- oral agents in type 2 diabetes (T2D) (Abstract). *Diabetologia* 2012;55:A764
50. Neal B, Matthews D, Fulcher G, et al. 52-week effects of canagliflozin, an inhibitor of sodium glucose co-transporter 2 (SGLT2), added to insulin therapy in type 2 diabetes (T2D). Poster presented at the 22nd Biennial World Diabetes Congress of the International Diabetes Federation, 2–6 December 2013, Melbourne, Australia
51. Garber AJ, Abrahamson MJ, Barzilay JI, et al.; American Association of Clinical Endocrinologists. AACE comprehensive diabetes management algorithm 2013. *Endocr Pract* 2013;19:327–336
52. Weir MR, Kline I, Xie J, Edwards R, Usiskin K. Effect of canagliflozin on serum electrolytes in patients with type 2 diabetes in relation to estimated glomerular filtration rate (eGFR). *Curr Med Res Opin* 2014;30:1759–1768
53. Usiskin K, Kline I, Fung A, Mayer C, Meininger G. Safety and tolerability of canagliflozin in patients with type 2 diabetes: pooled analysis of phase 3 study results. *Postgrad Med* 2014;126:16–34