Use of Canagliflozin in Combination With and Compared to Incretin-Based Therapies in Type 2 Diabetes

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IN BRIEF Sodium–glucose cotransporter 2 (SGLT2) inhibitors and incretin-based therapies (dipeptidyl peptidase-4 [DPP-4] inhibitors and glucagon-like peptide-1 [GLP-1] receptor agonists) are widely used to treat patients with type 2 diabetes. In clinical and real-world studies, canagliflozin, an SGLT2 inhibitor, has demonstrated superior A1C lowering compared to the DPP-4 inhibitor sitagliptin. Canagliflozin can also promote modest weight/fat loss and blood pressure reduction. The addition of canagliflozin to treatment regimens that include a DPP-4 inhibitor or a GLP-1 receptor agonist has been shown to further improve glycemic control, while still maintaining beneficial effects on cardiometabolic parameters such as body weight and blood pressure. Overall, the available clinical and real-world evidence suggests that canagliflozin is a safe and well-tolerated treatment option that can be considered either in addition to or instead of incretin-based therapies for patients with type 2 diabetes.

Chronic elevations in blood glucose levels in patients with type 2 diabetes may lead to long-term organ damage, including microvascular diseases such as retinopathy, neuropathy, and nephropathy, and may accelerate macrovascular disease, affecting the coronary artery and cerebrovascular and peripheral vascular circulation (1). Improvement in glycemic control can significantly reduce the risks of development and progression of microvascular and, to a lesser extent, macrovascular complications (2,3). However, results from the National Health and Nutrition Examination Survey from 1999 to 2010 and from 2007 to 2010 indicated that almost half of all adults with type 2 diabetes were not at the generally recommended A1C goal of <7.0% (4,5).

The difficulty in achieving glycemic goals may be due, in part, to therapeutic approaches that do not target the underlying pathophysiology. In type 2 diabetes, glucose regulation is disrupted through several different mechanisms, including progressive loss of β-cell function, insulin resistance, inappropriate glucagon secretion, accelerated lipolysis, incretin deficiency and/or resistance, and enhanced glucose reabsorption by the kidneys (6–8). As these disturbances accumulate and worsen, a state of chronic hyperglycemia develops. In recent years, insight into the multiple mechanisms contributing to hyperglycemia in type 2 diabetes has led to the development of new medications targeting one or more of the pathways that are disrupted in type 2 diabetes. Incretin-based therapies, including dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists (7,9), and the newest class of antihyperglycemic agents, the sodium–glucose cotransporter 2 (SGLT2) inhibitors, are prime exam-

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https://doi.org/10.2337/cd16-0063

ples of targeted therapies for type 2 diabetes (8).

In clinical studies of patients with type 2 diabetes, treatment with the SGLT2 inhibitor canagliflozin has been shown to provide clinically meaningful reductions in A1C, body weight, and blood pressure. These effects were consistently observed in a broad range of patients on different background antihyperglycemic agents, including DPP-4 inhibitors and GLP-1 receptor agonists (10,11). This article provides an overview of the available clinical and real-world data on canagliflozin treatment in patients with type 2 diabetes, both in combination with and compared to incretin-based therapies.

Mechanism of SGLT2 Inhibition

In healthy individuals, the kidneys filter and subsequently reabsorb ~160–180 g of glucose per day. Most renal glucose reabsorption is mediated by SGLT2, which couples sodium and glucose active transport in the early proximal tubule (Figure 1A) (8,12).

In patients who develop chronic hyperglycemia, the renal threshold for glucose excretion (RTG) increases from the normal threshold of ~10.0–11.1 mmol/L (~180–200 mg/dL) in healthy adults to ~13.3 mmol/L (240 mg/dL) in patients with type 2 diabetes, thereby increasing the rate of tubular glucose reabsorption. As a result of these changes, excess glucose is reabsorbed rather than excreted in urine, perpetuating and exacerbating hyperglycemia (8,12).

SGLT2 inhibitors lower the RTG, decreasing the kidneys' capacity to reabsorb glucose, increasing urinary glucose excretion, and consequently decreasing plasma glucose levels. The ensuing glucosuria also results in a net loss of calories, which can promote weight loss (13). As shown in Figure 1B, in addition to their renal effects, SGLT2 inhibitors have been shown to improve insulin resistance and β-cell function by reducing glucotoxicity (14–16). Canagliflozin also decreases postprandial glucose excursions through a nonrenal mechanism. Immediately after morning dosing, the intestinal concentration of canagliflozin may be high enough to transiently inhibit SGLT1, which may slow glucose absorption from the morning meal and delay the appearance of glucose in plasma (16). Recent studies have also shown that SGLT2 inhibitors increase postprandial plasma glucagon levels, perhaps through inhibition of the SGLT2 transporter on pancreatic α-cells. By decreasing plasma insulin levels and stimulating glucagon secretion, SGLT2 inhibitors may increase endogenous glucose production (14,17). This result suggests that SGLT2 inhibition triggers a physiological response to avoid hypoglycemia, increasing endogenous glucose production such that patients with type 2 diabetes can achieve normal blood glucose levels with minimal risk of hypo-

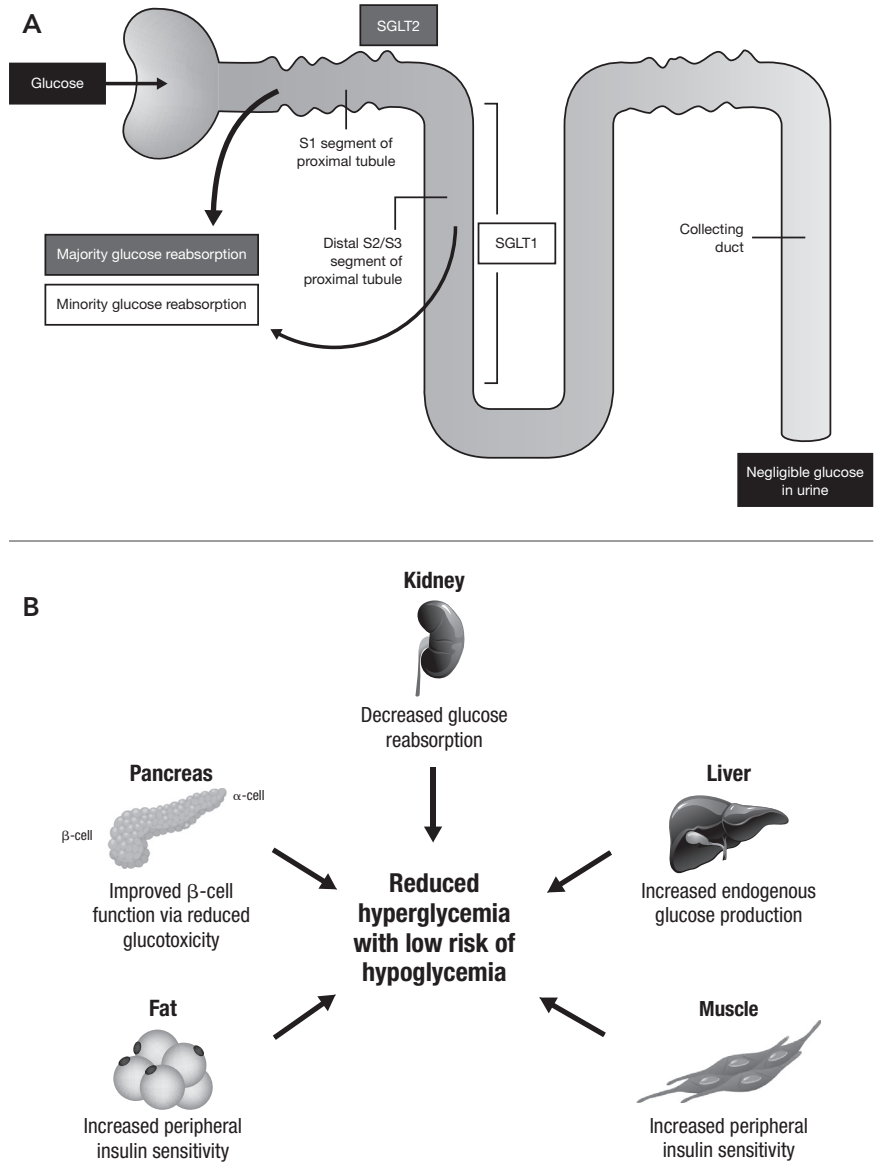

FIGURE 1. Overview of the actions of SGLT2, including the role of SGLT2 in glucose reabsorption in the proximal tubule (A) and sites of action at which SGLT2 inhibitors alter glycemia (B). Figure A is reprinted with permission from Macmillan Publishers Ltd.: Nature Reviews Drug Discovery (ref. 67), copyright 2010. Figure B is adapted from ref. 68.

glycemia (14,17). Because SGLT2 inhibitors act independently from insulin, their mechanism of action is complementary to a range of other antihyperglycemic agents.

Mechanism of Incretin-Based Therapies

Incretins (e.g., GLP-1 and gastric inhibitory polypeptide [GIP]) are gut hormones that are secreted in response to food intake and stimulate pancreatic insulin secretion in a glucose-dependent manner (18,19). In addition, GLP-1 has been associated with glucose-dependent inhibition of glucagon secretion, decreased endogenous glucose production, delayed gastric emptying, and increased satiety (18,19).

In healthy individuals, GLP-1 and GIP account for up to 60% of postprandial insulin secretion; however, this effect is markedly reduced in patients with poorly controlled type 2 diabetes (20). In studies of patients with type 2 diabetes, administration of exogenous GLP-1 improved insulin secretion and decreased glucagon secretion in a glucose-dependent manner (21,22). Exogenous GLP-1 was also shown to decrease both fasting and postprandial glucose levels. However, GLP-1 has a short half-life because it is rapidly degraded by DPP-4, making it unsuitable as a pharmacological therapy (20). This result led to the development of GLP-1 receptor agonists, which are resistant to degradation by DPP-4, for the treatment of type 2 diabetes. In parallel, DPP-4 inhibitors were also developed; these agents increase levels and prolong the half-life of active GLP-1 and GIP in circulation (9,19,23).

Incretin-based therapies, including GLP-1 receptor agonists and DPP-4 inhibitors, are now widely recommended and used to treat patients with type 2 diabetes (18,24,25). In addition to providing strong antihyperglycemic efficacy, GLP-1 receptor agonists are associated with weight loss and reductions in systolic blood pressure (26). In contrast, DPP-4 inhibitors are generally considered to be weight neutral because they do not promote satiety or decrease appetite (9).

Clinical Studies of Canagliflozin Versus Sitagliptin

Two active-controlled, phase 3 studies evaluated canagliflozin compared to the DPP-4 inhibitor sitagliptin in dual therapy with metformin and in triple therapy with metformin plus a sulfonylurea. The study designs and patient populations for these studies, as well as for studies that evaluated clinical outcomes with canagliflozin in combination with incretin-based therapies, are summarized in Table 1. Table 2 provides a summary of the overall safety and adverse events (AEs) reported with canagliflozin in combination with and compared to incretin-based therapies. To date, there have been no head-to-head studies of canagliflozin compared to GLP-1 receptor agonists or to DPP-4 inhibitors other than sitagliptin.

In a randomized, double-blind, four-arm, parallel-group study (ClinicalTrials.gov identifier, NCT01106677), patients with type 2 diabetes inadequately controlled on metformin (n = 1,284) received canagliflozin 100 or 300 mg, sitagliptin 100 mg, or placebo during a 26-week core treatment period; patients in the placebo group were then switched to sitagliptin 100 mg, while those initially on canagliflozin or sitagliptin remained on randomized treatment for an additional 26 weeks (27). At week 52, canagliflozin 100 mg demonstrated noninferiority, and canagliflozin 300 mg demonstrated superiority to sitagliptin 100 mg in A1C lowering (–0.73, –0.88, and –0.73%, respectively). Significant reductions in body weight (–3.3, –3.7, and –1.2 kg, respectively) and systolic blood pressure (–3.5, –4.7, and –0.7 mmHg, respectively) were also seen with canagliflozin 100 and 300 mg versus sitagliptin 100 mg. Consistent with the known safety profile of SGLT2 inhibitors, rates of genital mycotic infections and osmotic diuresis–related AEs were higher with canagliflozin 100 and 300 mg than with sitagliptin 100 mg or placebo/sitagliptin (Table 2).

In a separate randomized, double-blind, active-controlled study (ClinicalTrials.gov identifier, NCT01137812), patients with type 2 diabetes inadequately controlled on metformin plus a sulfonylurea (n = 755) received canagliflozin 300 mg or sitagliptin 100 mg for 52 weeks (28). Canagliflozin 300 mg demonstrated superiority in A1C lowering compared to sitagliptin 100 mg at week 52 (–1.03 vs. –0.66%) and provided significant reductions in body weight (–2.3 vs. 0.1 kg) and systolic blood pressure (–5.1 vs. 0.9 mmHg) (28). Canagliflozin also provided greater reductions in 2-hour postprandial glucose compared to sitagliptin (–3.3 vs. –2.2 mmol/L). Incidences of genital mycotic infections and osmotic diuresis–related AEs were higher with canagliflozin 300 mg than with sitagliptin 100 mg (Table 2). The incidences of documented hypoglycemia were similar with canagliflozin 300 mg and sitagliptin 100 mg, despite an ~0.4% larger reduction in A1C with canagliflozin.

Clinical Studies of Canagliflozin in Combination With Incretin-Based Therapies

Two randomized, double-blind, placebo-controlled studies evaluated canagliflozin used in combination with incretin-based therapies for the treatment of type 2 diabetes. The first was a 26-week study (ClinicalTrials.gov identifier, NCT02025907) to assess the efficacy and safety of canagliflozin administered using a dose-titration algorithm in 218 patients with type 2 diabetes inadequately controlled on metformin and sitagliptin (29). The second was a post hoc analysis of the CANagliflozin cardioVascular Assessment Study (CANVAS; ClinicalTrials.gov identifier, NCT01032629) to evaluate the efficacy and safety of canagliflozin

TABLE 1. Design and Patient Populations of Studies of Canagliflozin Compared to and in Combination With Incretin-Based Therapies

Study	Key Inclusion Criteria	*n*	Design
Add-on to MET versus PBO/SITA (26/52 weeks) (27)	• Age: 18–80 years • A1C ≥7.0 to ≤10.5% • On stable MET ≥2,000 mg/day (or ≥1,500 mg/day if unable to tolerate higher dose)	Total = 1,284 • PBO = 183 • SITA = 366 • CANA 100 mg = 368 • CANA 300 mg = 367	26-week, double-blind, PBO- and active-controlled, core treatment phase and 26-week, double-blind, active-controlled, extension treatment period after a 2-week, single-blind, PBO run-in period
Add-on to MET + SU versus SITA (52 weeks) (28)	• Age: ≥18 years • A1C ≥7.0 to ≤10.5% • On a stable regimen of MET ≥2,000 mg/day (or ≥1,500 mg/day if unable to tolerate higher dose) + SU (at half-maximal labeled dose or greater)	• Total = 756 • SITA 100 mg = 378 • CANA 300 mg = 378	52-week, double-blind, active-controlled treatment period after a 2-week, single-blind, PBO run-in period
Add-on to MET + SITA (26 weeks) (29)	• Age: 18–75 years • A1C ≥7.5 to ≤10.5% • On stable MET ≥1,500 mg/day and SITA 100 mg/day	Total = 213 • PBO = 106 • CANA = 107	26-week, double-blind treatment phase after a 1-week screening period and a 2-week, single-blind, PBO run-in period
CANVAS post hoc analysis of patients on DPP-4i/GLP-1RA (18 weeks) (11)	• A1C ≥7.0 to ≤10.5% (45) • History/high risk of CVD (45) • On stable dose of DPP-4i or GLP-1RA through 18 weeks	Total = 411 • DPP-4i + PBO = 102 • DPP-4i + CANA 100 mg = 103 • DPP-4i + CANA 300 mg = 111 • GLP-1RA + PBO = 30 • GLP-1RA + CANA 100 mg = 35 • GLP-1RA + CANA 300 mg = 30	Post hoc analysis of 18-week data in patients taking CANA versus PBO as add-on to incretin-based therapy enrolled in CANVAS (an ongoing randomized, double-blind, placebo-controlled study of the cardiovascular safety of CANA in 4,330 patients with type 2 diabetes)

CANA, canagliflozin; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; MET, metformin; PBO, placebo; SITA, sitagliptin; SU, sulfonylurea.

over 18 weeks in the subset of patients who were on background therapy that included DPP-4 inhibitors or GLP-1 receptor agonists, with or without other antihyperglycemic agents (11). Key efficacy findings from these 2 studies are presented in Figure 2.

In the 26-week canagliflozin dose-titration study, patients inadequately controlled on metformin and sitagliptin were eligible to increase their dose of canagliflozin from 100 to 300 mg or from placebo to matching placebo starting at week 6 based on prespecified criteria (29). In this study, 90.7% of patients in the canagliflozin group increased their dose from 100 to 300 mg, and 80.2% of patients in the placebo group underwent a mock dose increase. Titrated canagliflozin (pooled 100 and 300 mg) provided superior A1C lowering, weight loss, and systolic blood pressure reduction compared to placebo at 26 weeks as add-on to metformin and sitagliptin (Figure 2). The incidence of female genital mycotic infections and osmotic diuresis–related AEs was numerically higher with canagliflozin than with placebo (Table 2).

In the post hoc analysis of 18-week data from patients enrolled in the CANVAS trial who were on background incretin-based therapy (with or without other antihyperglycemic agents), 316 patients comprised the DPP-4 inhibitor subset and 95 patients comprised the GLP-1 receptor agonist subset (11). In the DPP-4 inhibitor subset, reductions from baseline in A1C, body weight, and systolic blood pressure were seen with canagliflozin 100 and 300 mg compared to placebo. Similar results were observed with canagliflozin 100 and 300 mg compared to placebo in the GLP-1 receptor agonist subset. The incidence of female and male genital mycotic infections and of osmotic diuresis–related AEs was generally higher with canagliflozin compared to placebo in both the DPP-4 inhibitor and GLP-1 receptor agonist subsets (Table 2).

TABLE 2. Summary of Overall Safety and Selected AEs With Canagliflozin Compared to and in Combination With Incretin-Based Therapies

	Add-On to MET Versus PBO/SITA (52 weeks) (27)				Add-On to MET + SU Versus SITA (52 weeks) (28)		Add-On to MET + SITA Versus PBO (26 weeks) (29)		CANVAS Add-On to Incretin-Based Therapies Versus PBO: DPP-4i Subset (18 weeks) (11)			CANVAS Add-On to Incretin-Based Therapies Versus PBO: GLP-1RA Subset (18 weeks) (11)		
	PBO/ SITA, *n* = 183	SITA 100 mg, *n* = 366	CANA 100 mg, *n* = 368	CANA 300 mg, *n* = 367	SITA 100 mg, *n* = 378	CANA 300 mg, *n*= 377	PBO, *n* = 108	CANA, *n* = 108	PBO, *n* = 102	CANA 100 mg, *n* = 103	CANA 300 mg, *n* = 111	PBO, *n* = 30	CANA 100 mg, *n* = 35	CANA 300 mg, *n* = 30
Any AE	122 (66.7)	236 (64.5)	266 (72.3)	230 (62.7)	293 (77.5)	289 (76.7)	48 (44.4)	43 (39.8)	60 (58.8)	66 (64.1)	70 (63.1)	23 (76.7)	22 (62.9)	22 (73.3)
AEs leading to discontinuation	8 (4.4)	16 (4.4)	19 (5.2)	12 (3.3)	11 (2.9)	20 (5.3)	3 (2.8)	1 (0.9)	1 (1.0)	1 (1.0)	6 (5.4)	0 (0)	2 (5.7)	3 (10.0)
AEs related to study drug*	23 (12.6)	72 (19.7)	97 (26.4)	73 (19.9)	105 (27.8)	128 (34.0)	9 (8.3)	12 (11.1)	14 (13.7)	21 (20.4)	29 (26.1)	7 (23.3)	10 (28.6)	11 (36.7)
Serious AEs	7 (3.8)	18 (4.9)	15 (4.1)	12 (3.3)	21 (5.6)	24 (6.4)	2 (1.9)	2 (1.9)	2 (2.0)	3 (2.9)	5 (4.5)	1 (3.3)	2 (5.7)	5 (16.7)
Deaths	1 (0.5)	1 (0.3)	0 (0)	1 (0.3)	0 (0)	2 (0.5)	0 (0)	0 (0)	2 (2.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Selected AEs														
UTIs	12 (6.6)	23 (6.3)	29 (7.9)	18 (4.9)	21 (5.6)	15 (4.0)	2 (1.9)	2 (1.9)	1 (1.0)	7 (6.8)	5 (4.5)	2 (6.7)	2 (5.7)	4 (13.3)
Genital mycotic infections														
Men†	1 (1.1)	2 (1.2)	9 (5.2)	4 (2.4)	1 (0.5)	19 (9.2)	0	1 (1.5)	1 (1.7)	3 (4.5)	5 (6.2)	1 (5.3)	1 (3.6)	2 (10.5)
Women‡	1 (1.1)	5 (2.6)	22 (11.3)	20 (9.9)	7 (4.3)	26 (15.3)	1 (2.0)	5 (12.2)	1 (2.4)	5 (13.5)	5 (16.7)	0	0	5 (45.5)
Osmotic diuresis–related AEs§	1 (0.5)	7 (1.9)	30 (8.2)	16 (4.4)	9 (2.4)	19 (5.0)	4 (3.7)	6 (5.6)	1 (1.0)	6 (5.8)	9 (8.1)	1 (3.3)	5 (14.3)	4 (13.3)
Volume depletion–related AEs‖	1 (0.5)	7 (1.9)	4 (1.1)	3 (0.8)	8 (2.1)	7 (1.9)	2 (1.9)	1 (0.9)	0 (0)	0 (0)	4 (3.6)	1 (3.3)	0 (0)	3 (10.0)
Hypoglycemia episodes														
Documented¶,#	5 (2.7)	15 (4.1)	25 (6.8)	25 (6.8)	154 (40.7)	163 (43.2)	2 (1.9)	4 (3.7)	12 (16.2)	17 (24.3)	29 (33.3)	4 (15.4)	11 (37.9)	11 (50.0)
Severe#	0(0)	1 (0.3)	1 (0.3)	0 (0)	13 (3.4)	15 (4.0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)	0 (0)	1 (4.5)

All data are shown as number of patients (%).
**Possibly, probably, or very likely related to study drug, as assessed by investigators.*
†Includes balanitis, balanitis candida, balanoposthitis, genital candidiasis, genital infection fungal, penile infection, and posthitis.
‡Includes genital infection female, genital candidiasis, genital infection fungal, vaginal infection, vaginal inflammation, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis.
§Includes dry mouth, micturition disorder and urgency, nocturia, pollakiuria, polydipsia, polyuria, thirst, and urine output increased.
‖Includes blood pressure decreased, dehydration, postural dizziness, hypotension, orthostatic hypotension, presyncope, syncope, and urine output decreased.
¶Including biochemically documented episodes (fingerstick or plasma glucose ≤3.9 mmol/L [≤70 mg/dL] with or without symptoms and severe episodes [i.e., those requiring the assistance of another individual or resulting in seizure or loss of consciousness]).
#For the CANVAS study, hypoglycemia episodes are reported for the subset of patients on background insulin or insulin secretagogues; documented hypoglycemia was infrequent in patients who were not on background insulin or insulin secretagogues (≤1 episode in all treatment groups; no episodes were severe).
CANA, canagliflozin; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; MET, metformin; PBO, placebo; SITA, sitagliptin; SU, sulfonylurea; UTI, urinary tract infection.

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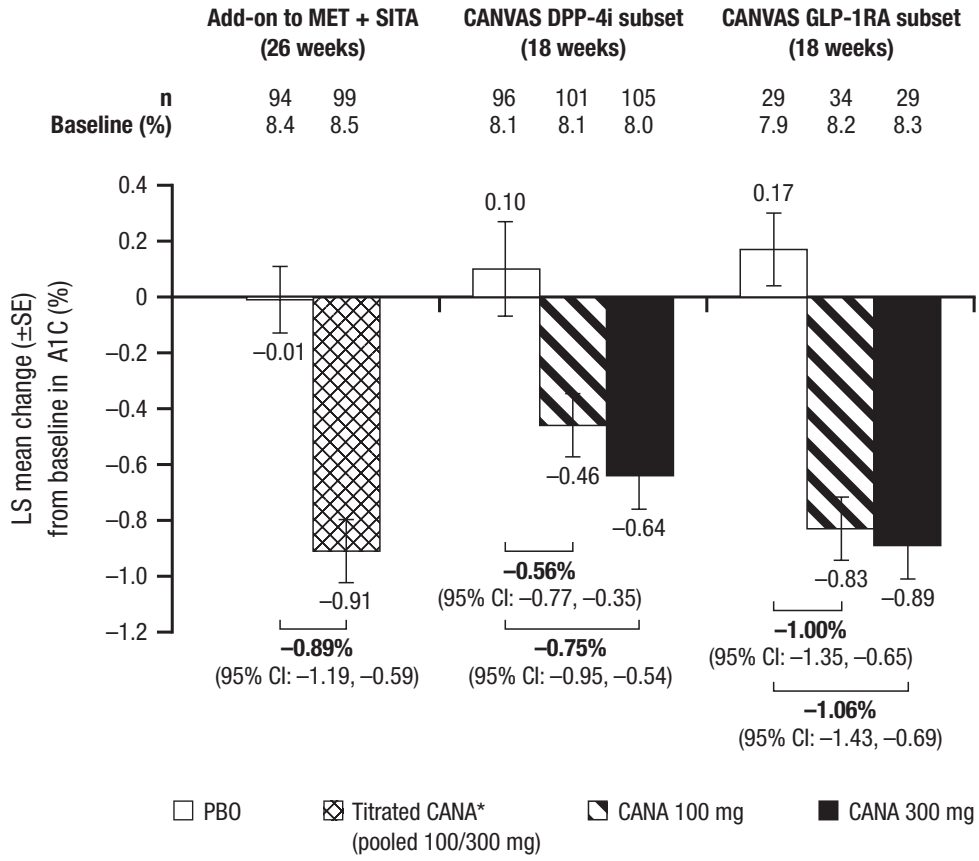
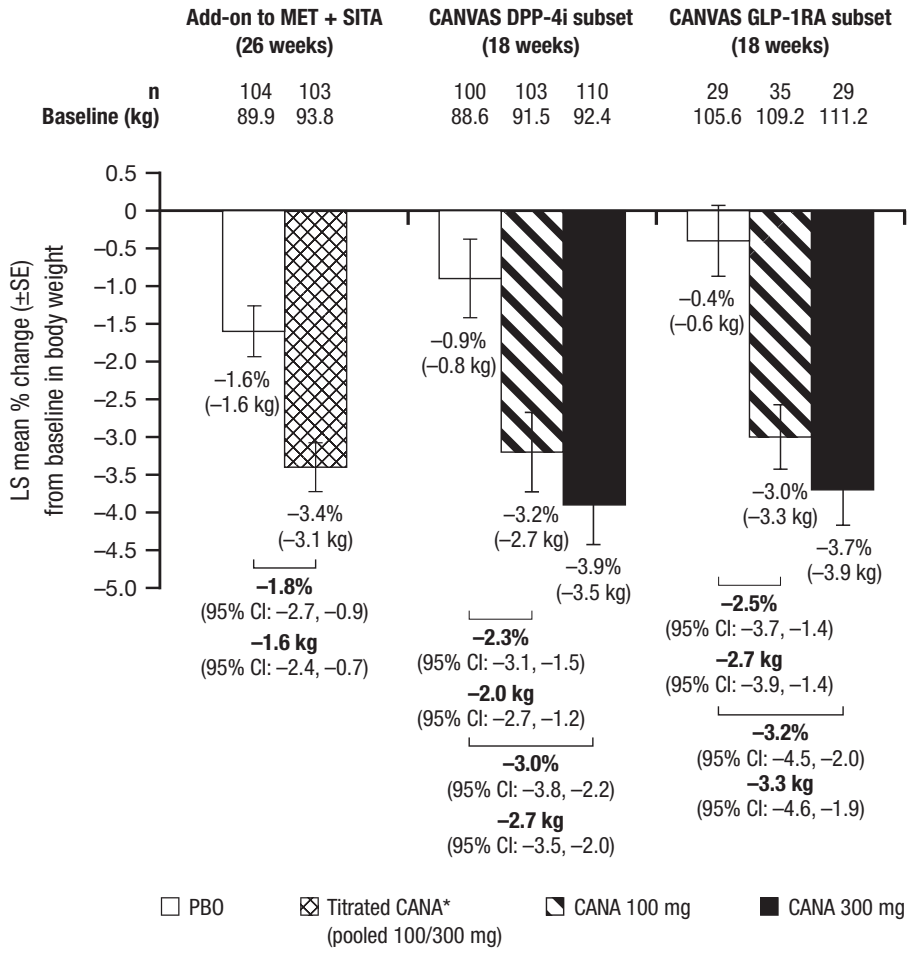

Add-on to MET + SITA (26 weeks)
CANVAS DPP-4i subset (18 weeks)
CANVAS GLP-1RA subset (18 weeks)
n 94 99 96 101 105 29 34 29
Baseline (%) 8.4 8.5 8.1 8.1 8.0 7.9 8.2 8.3
LS mean change (±SE) from baseline in A1C (%)
0.4
0.2
0
–0.2
–0.4
–0.6
–0.8
–1.0
–1.2
–0.01
–0.91
0.10
–0.46
–0.64
0.17
–0.83
–0.89
–0.89%
(95% CI: –1.19, –0.59)
–0.56%
(95% CI: –0.77, –0.35)
–0.75%
(95% CI: –0.95, –0.54)
–1.00%
(95% CI: –1.35, –0.65)
–1.06%
(95% CI: –1.43, –0.69)
PBO
Titrated CANA* (pooled 100/300 mg)
CANA 100 mg
CANA 300 mg

B


Add-on to MET + SITA (26 weeks)
CANVAS DPP-4i subset (18 weeks)
CANVAS GLP-1RA subset (18 weeks)
n 104 103 100 103 110 29 35 29
Baseline (kg) 89.9 93.8 88.6 91.5 92.4 105.6 109.2 111.2
LS mean % change (±SE) from baseline in body weight
0.5
0
–0.5
–1.0
–1.5
–2.0
–2.5
–3.0
–3.5
–4.0
–4.5
–5.0
–1.6% (–1.6 kg)
–3.4% (–3.1 kg)
–0.9% (–0.8 kg)
–3.2% (–2.7 kg)
–3.9% (–3.5 kg)
–0.4% (–0.6 kg)
–3.0% (–3.3 kg)
–3.7% (–3.9 kg)
–1.8%
(95% CI: –2.7, –0.9)
–1.6 kg
(95% CI: –2.4, –0.7)
–2.3%
(95% CI: –3.1, –1.5)
–2.0 kg
(95% CI: –2.7, –1.2)
–3.0%
(95% CI: –3.8, –2.2)
–2.7 kg
(95% CI: –3.5, –2.0)
–2.5%
(95% CI: –3.7, –1.4)
–2.7 kg
(95% CI: –3.9, –1.4)
–3.2%
(95% CI: –4.5, –2.0)
–3.3 kg
(95% CI: –4.6, –1.9)
PBO
Titrated CANA* (pooled 100/300 mg)
CANA 100 mg
CANA 300 mg

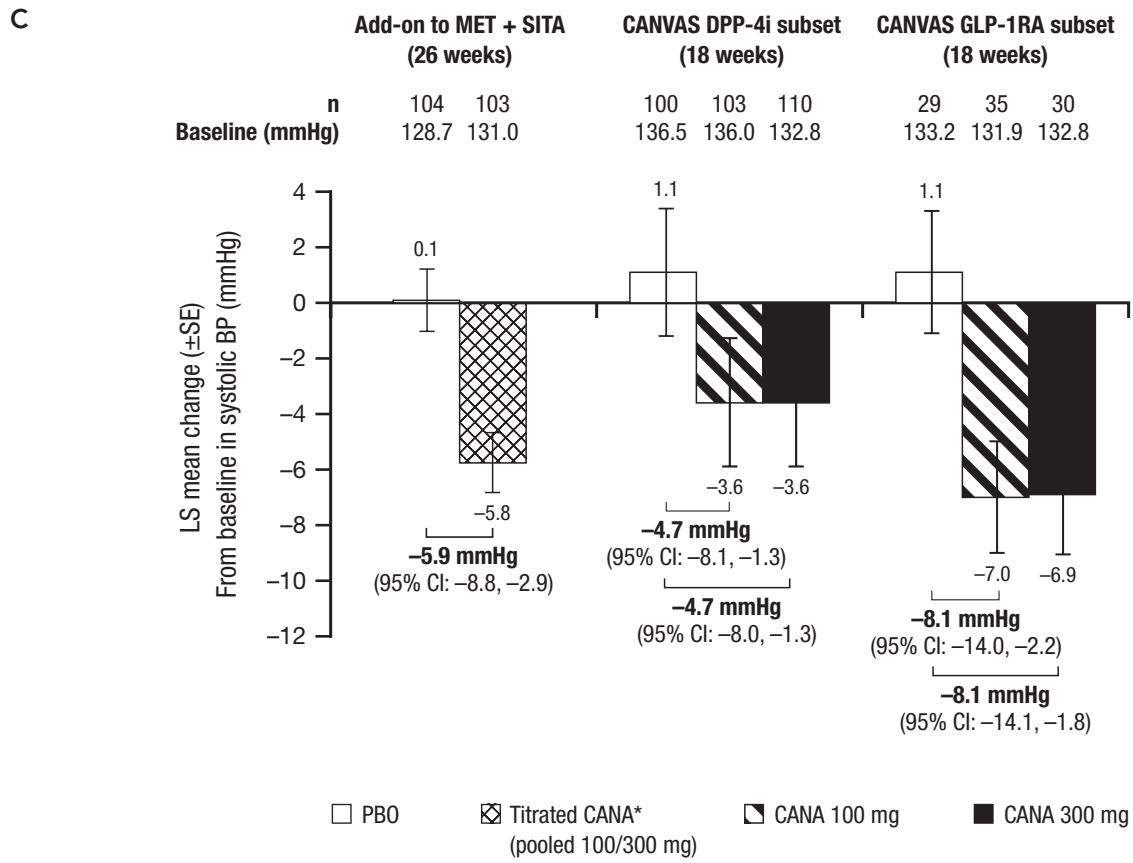


FIGURE 2. Changes in A1C (A), body weight (B), and systolic blood pressure (C) with canagliflozin in combination with incretin-based therapies. *In the dose-advancement study, all patients in the canagliflozin arm started with the 100-mg dose; 85% of patients increased their dose to 300 mg during the study. BP, blood pressure; CANA, canagliflozin; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; LS, least squares; MET, metformin; PBO, placebo; SE, standard error; SITA, sitagliptin.

Interpretation of findings from the CANVAS post hoc analysis was limited by the relatively small numbers of patients on background therapy with DPP-4 inhibitors or GLP-1 receptor agonists and by the relatively short duration of treatment (11). However, findings from this analysis (11) and from the 26-week add-on to metformin/sitagliptin dose-titration study (29) provide evidence of clinically meaningful reductions in A1C, body weight, and systolic blood pressure in patients with type 2 diabetes on regimens that include incretin-based therapies. The benefits of SGLT2 inhibitors in combination with DPP-4 inhibitors are also supported by data from studies of dapagliflozin in combination with metformin and sitagliptin or saxagliptin (30–32) and of a fixed-dose combination of empagliflozin 10 mg with linagliptin 5 mg, which has been shown to be more effective than either agent as monotherapy or as add-on to metformin (33,34).

Real-World Evidence Comparing Canagliflozin and Incretin-Based Therapies

In a retrospective, matched-control cohort study (n = 5,532) that used integrated claims and laboratory data from a large, geographically diverse U.S. population of patients enrolled in commercial and Medicare Advantage health plans, the effectiveness of canagliflozin (pooled 100 and 300 mg) compared to DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin) was evaluated over a 9-month period (35). The analysis included adults with ≥1 pharmacy claim for canagliflozin or a DPP-4 inhibitor as monotherapy or combination therapy and ≥1 medical claim with a diagnosis of type 2 diabetes during the study period; there were no selection criteria related to estimated glomerular filtration rate (eGFR). Patients in each cohort were stratified based on A1C status, and then propensity score matching was used to match patients by incorporating various parameters.

Among matched patients with a baseline A1C ≥7.0% (n = 1,656), mean time to follow-up was 184.2 days and 182.3 days in the canagliflozin and DPP-4 inhibitor cohorts, respectively (35). At follow-up, canagliflozin treatment was associ-

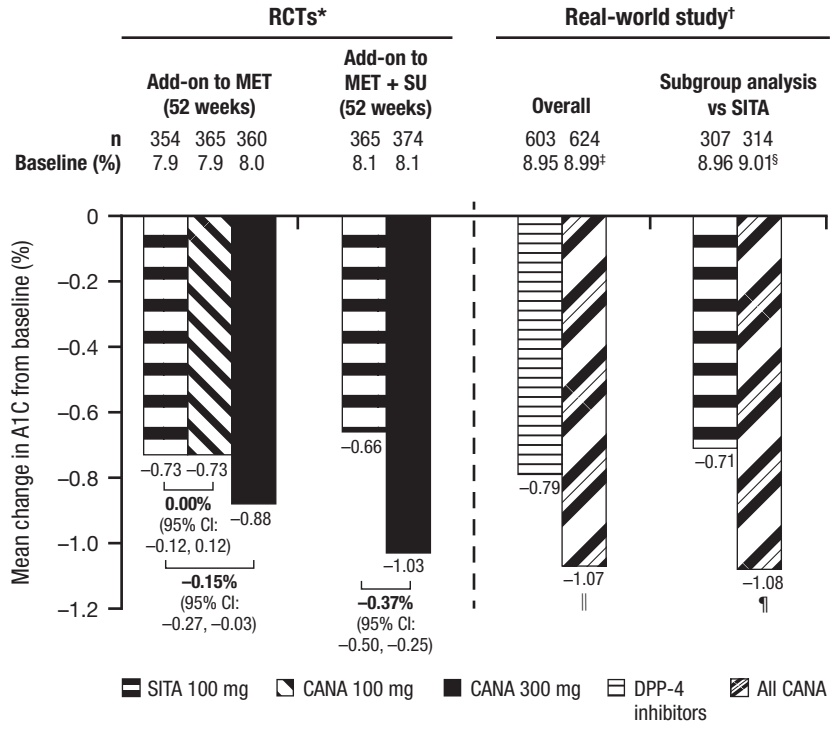


FIGURE 3. Side-by-side comparison of change in A1C with canagliflozin versus DPP-4 inhibitors in randomized clinical trials and the real-world study. *Data are LS mean change from baseline. †Data are mean change from baseline for patients with baseline A1C ≥7.0% who had A1C data at baseline and follow-up. ‡P = 0.686 for CANA versus DPP-4 inhibitor cohort. §P = 0.706 for CANA versus SITA cohort. ||P = 0.004 for CANA versus DPP-4 inhibitor cohort. ¶P = 0.010 for CANA versus SITA cohort. BP, blood pressure; CANA, canagliflozin; LS, least squares; MET, metformin; RCT, randomized controlled trial; SITA, sitagliptin; SU, sulfonylurea.

ated with a greater mean reduction in A1C compared to DPP-4 inhibitors (Figure 3). After adjusting for residual differences in baseline characteristics, mean reductions in A1C remained greater for patients treated with canagliflozin 100 and 300 mg than for those treated with DPP-4 inhibitors. In a subgroup analysis of canagliflozin compared to sitagliptin, A1C reductions in matched patients with a baseline A1C ≥7.0% were consistent with the analysis versus all DPP-4 inhibitors (Figure 3).

No direct head-to-head comparisons are available between canagliflozin and GLP-1 receptor agonists. A recent retrospective U.S. claims database analysis examined treatment persistence with canagliflozin compared to incretin-based therapies in patients who had a first claim in 2013 for canagliflozin, sitagliptin, saxagliptin, linagliptin, liraglutide, exenatide, or long-acting exenatide. Findings from this analysis indicate that patients taking canagliflozin tend to stay on treatment longer than those taking DPP-4 inhibitors or GLP-1 receptor agonists. Data from the Truven database of commercially insured patients (n = 66,206) showed that, after 12 months, 64.0% of patients prescribed canagliflozin 100 mg and 65.0% of patients prescribed canagliflozin 300 mg remained on treatment, compared to 30.2% with linagliptin, 51.1% with sitagliptin, 24.3% with exenatide, and 43.0% with liraglutide (P <0.0001 for all comparisons) (36). The likelihood of treatment discontinuation (based on mean adjusted hazard ratios) was shown to be higher for sitagliptin, saxagliptin, linagliptin, exenatide, long-acting exenatide, and liraglutide than for canagliflozin. A limitation of this analysis is that, for much of the timeframe evaluated, canagliflozin was the only SGLT2 inhibitor approved for use in the United States, so patients had only one treatment option in this drug class but had several choices of DPP-4 inhibitors and GLP-1 receptor agonists.

Considerations for Use of Canagliflozin and Incretin-Based Therapies in Clinical Practice

Consistent with current type 2 diabetes practice guidelines, clinicians should implement a patient-centered approach to disease management. When setting individualized glycemic goals and selecting therapies, treatment strategies should be designed to optimize the patient's overall benefit/risk profile. Key factors to consider when developing individualized treatment plans include age, disease duration, comorbidities, renal function, patient preferences for and attitudes toward treatment, and availability of health care resources and support (18,24,25).

The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) and American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) treatment algorithms recommend SGLT2 inhibitors both as monotherapy, when metformin is contraindicated or not tolerated, and as part of dual and triple combination therapy with metformin (18,24,25). After metformin, AACE/ACE guidelines recommend the following agents as initial monotherapy (in order of preference): GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, thiazolidinediones, α-glucosidase inhibitors, and sulfonylureas (25).

The effects of SGLT2 inhibitors are independent of insulin secretion, thus making them a suitable option for patients with more advanced type

TABLE 3. Patient Populations That May Benefit Most From Treatment With an SGLT2 Inhibitor Instead of or in Addition to Incretin-Based Therapies

Patients likely to benefit from treatment:

- Patients with normal kidney function
- Patients intolerant to metformin
- Patients requiring add-on therapy to metformin because they are not at goal
- Newly diagnosed patients with an A1C >9% requiring initial combination therapy with metformin plus a second antihyperglycemic agent
- Patients requiring a third antihyperglycemic agent because they are not at goal with dual therapy

Patients for whom canagliflozin should be used with caution:

- Patients with moderate renal impairment
- Elderly patients
- Patients prone to genital mycotic infections
- Patients taking loop diuretics or with other risk factors for dehydration

2 diabetes. However, given their renal mechanism of action, patient kidney function should be assessed before and periodically during treatment with these agents. In patients with an eGFR <45 mL/min/1.73 m^2, clinical data indicate that the efficacy of canagliflozin is reduced (25) and the risk of volume-related AEs is increased. Therefore, use of canagliflozin is not recommended in patients with an eGFR <45 mL/min/1.73 m^2. In such cases, treatment with adjusted doses of some DPP-4 inhibitors may be a suitable alternative. GLP-1 receptor agonists should be used with caution in patients with renal impairment because there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, usually in patients who experienced nausea, vomiting, diarrhea, or dehydration.

In addition to improving glycemic control, canagliflozin has demonstrated beneficial effects on multiple risk factors commonly observed in patients with type 2 diabetes, including reducing body weight and visceral adiposity, blood pressure, albuminuria, and uric acid levels. Canagliflozin has shown favorable effects on some lipid parameters, including reducing triglycerides and increasing HDL cholesterol; however, canagliflozin is associated with dose-related increases in LDL cholesterol levels (37–43). The mechanism of increased LDL cholesterol is unknown but may be related to modest hemo-concentration due to osmotic diuresis (44). Additional information on the overall and cardiovascular safety of canagliflozin will be obtained from the CANVAS Program, including CANVAS and CANVAS-R (renal endpoints; ClinicalTrials.gov identifier, NCT01989754), upon completion in 2017 (45–47).

Overall, canagliflozin is generally well tolerated, with favorable real-world persistence rates compared to incretin-based therapies (36). The most common side effects observed in patients treated with canagliflozin are related to the mechanism of SGLT2 inhibition (i.e., genital mycotic infections and volume depletion–related AEs); these AEs are usually mild or moderate in intensity, tend to occur early in the course of treatment and decrease over time, and can be managed using standard treatments (13).

There have been postmarketing reports of urosepsis and pyelonephritis in patients receiving SGLT2 inhibitors (48). Across pooled placebo-controlled studies, the incidence of urinary tract infections was modestly higher with canagliflozin 100 and 300 mg compared to placebo; however, there was no increase in serious urinary tract infections with canagliflozin versus placebo (43,49).

The U.S. Food and Drug Administration has also issued safety warnings for SGLT2 inhibitors based on postmarketing reports of acute kidney injury and diabetic ketoacidosis (DKA) with all marketed SGLT2 inhibitors (50–52), and bone fractures with canagliflozin (53). In addition, interim results from CANVAS showed higher rates of amputations (mostly toes) with canagliflozin than with placebo (54). After the postmarketing reports of DKA and bone fractures, post hoc analyses of pooled clinical trial data were conducted to better understand these risks. In an analysis of data from completed and ongoing randomized controlled trials of canagliflozin (n = 17,596 patients with nearly 24,000 patient-years of exposure), the incidence of DKA was 0.07% with canagliflozin 100 mg, 0.11% with canagliflozin 300 mg, and 0.03% with comparators (55). These rates are consistent with observed rates of DKA in general populations of patients with type 2 diabetes (55).

In a separate analysis of >10,000 patients enrolled in nine phase 3 studies, a non–dose-dependent increase in fractures was seen with canagliflozin versus comparators that was driven by results in the CANVAS trial (56). Fractures generally occurred early after treatment initiation, and most fractures were located in distal parts of the upper

and lower extremities and not in typical osteoporotic regions, such as the hips and spine. Although it is unknown whether the increased fracture risk seen with canagliflozin is an SGLT2 inhibitor class effect, an imbalance in upper limb fractures (i.e., humerus, wrist, upper limb, and forearm) was reported with empagliflozin versus placebo in the EMPA-REG OUTCOME (ClinicalTrials.gov identifier, NCT01131676) trial, although the overall rate of fractures was similar between groups (57,58). An early increased risk of fractures was also seen with dapagliflozin in a 104-week study in 252 patients with type 2 diabetes and moderate renal impairment (51).

Incretin-based therapies are also generally well tolerated. DPP-4 inhibitors have favorable safety profiles, with much lower rates of gastrointestinal side effects compared to GLP-1 receptor agonists and a low propensity to cause hypoglycemia. However, cases of serious hypersensitivity reactions, including Stevens-Johnson syndrome, as well as angioedema, urticaria, bronchial hyperreactivity, and other immune-mediated dermatological effects have been reported rarely with DPP-4 inhibitors (26). Common side effects of GLP-1 receptor agonists are nausea and vomiting, and hypoglycemia has been reported in clinical studies of these agents, especially when used in combination with sulfonylureas or insulin (59). For many patients, the benefits of GLP-1 receptor agonists outweigh the risks, given their favorable effects on body weight, blood pressure, and lipids (59). Pancreatitis may be a concern with incretin-based therapies, although reported events with GLP-1 receptor agonists and DPP-4 inhibitors have been rare. Ongoing studies are being performed to clarify this potential risk (26).

Table 3 provides an overview of the types of patients for whom treatment with an SGLT2 inhibitor in addition to or instead of incretin-based therapies may be most beneficial. Based on the current understanding of the mechanism of action, as well as safety and efficacy data, and considering patient convenience and personal choices, it appears that SGLT2 inhibitors would be a reasonable alternative for any patient with type 2 diabetes who is not at goal (i.e., A1C >7.0%) when treated with ≥1 oral antihyperglycemic agent. Candidates must have adequate renal function (i.e., eGFR >60 mL/min/1.73 m^2) and no known allergies to the drugs. SGLT2 inhibitors may also be appropriate for use earlier in the course of the disease, as long as patients are aware of the risks of genital mycotic infections, transient polyuria with mild dehydration, and infections of the lower urinary tract. In general, the durability of the glucose-lowering effect with the potential for delaying the deterioration of β-cell function, in addition to reductions in body weight and blood pressure, are appealing attributes that support the selection of SGLT2 inhibitors as early therapy in patients with type 2 diabetes.

Potential for Cardiometabolic Benefits With Incretins and SGLT2 Inhibitors

Results from large-scale cardiovascular safety studies of incretin-based therapies and SGLT2 inhibitors in patients at high risk for cardiovascular events are starting to emerge and, coupled with those from several ongoing studies, will provide a more complete picture of the cardiometabolic effects of these classes of antihyperglycemic agents.

Recently published results from the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ClinicalTrials.gov identifier, NCT01179048) study demonstrated that liraglutide significantly reduced the rate of the first occurrence of a composite of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke compared to placebo in patients with type 2 diabetes (60). These data suggest that some GLP-1 receptor agonists may have the potential to improve long-term cardiovascular outcomes in patients with diabetes and high cardiovascular risk. Studies with DPP-4 inhibitors (i.e., SAVOR-TIMI 53 [Saxagliptin Assessment of Vascular Outcomes Recorded on Patients with Diabetes Mellitus; ClinicalTrials.gov identifier, NCT01107886] [61], EXAMINE [EXamination of cArdiovascular outcoMes with alogliptIN versus standard of care; ClinicalTrials.gov identifier, NCT00968708] [62], and the TECOS [Trial Evaluating Cardiovascular Outcomes with Sitagliptin; ClinicalTrials.gov identifier, NCT00790205] [63]) have shown that DPP-4 inhibitors do not appear to increase the risk of overall cardiovascular events compared to placebo in patients with type 2 diabetes and established cardiovascular disease. However, saxagliptin was associated with an increased risk of hospitalization for heart failure compared to placebo (61).

Encouraging results on the cardiometabolic benefits of SGLT2 inhibitors have been reported from the EMPA-REG OUTCOME trial. Results of this study showed that empagliflozin was associated with a 14% reduction in the three-point major adverse cardiovascular event primary outcome, which was primarily driven by a 38% reduction in cardiovascular death (57). Additionally, results from a secondary prespecified analysis of renal outcomes showed that patients treated with empagliflozin for a median duration of 2.6 years experienced slower progression of kidney disease compared to placebo (64). Findings from this analysis are consistent with the hypothesis that SGLT2 inhibitors have the potential to provide renoprotection, perhaps through direct effects on renal hypertension and hyperfiltration and on renal tubular inflammation and hypertrophy, as well as via indirect effects on glycemic control, body weight, and systolic blood pressure reduc-

tions, improved insulin sensitivity, and lowering of serum uric acid levels (65,66). Additional data on possible renoprotective mechanisms of SGLT2 inhibition are expected from the phase 3 CREDENCE study (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; ClinicalTrials.gov identifier, NCT02065791), which is evaluating whether canagliflozin 100 mg can slow the progression of diabetic nephropathy in patients with type 2 diabetes and stage 2 or stage 3 chronic kidney disease and macroalbuminuria who are receiving therap;y aqccording to standards of care.

Conclusion

SGLT2 inhibitors and incretin-based therapies have emerged as excellent choices to control hyperglycemia in a broad range of patients with type 2 diabetes (18,24,25). In clinical and real-world studies, canagliflozin has demonstrated superior A1C lowering compared to sitagliptin. Unlike sitagliptin and other DPP-4 inhibitors, treatment with canagliflozin can promote modest weight loss and blood pressure reduction. Adding canagliflozin to treatment regimens that include a DPP-4 inhibitor or a GLP-1 receptor agonist has been shown to further improve glycemic control and to have additional beneficial effects on cardiometabolic parameters such as body weight and blood pressure. Overall, the available clinical and real-world evidence on the use of canagliflozin compared to or in addition to incretin-based therapies supports canagliflozin as a safe and well-tolerated treatment option to be considered for use with or instead of incretin-based therapies.

Acknowledgments

Medical writing support for this article was provided by Cherie Koch, PhD, of MedErgy and funded by Janssen Scientific Affairs, LLC. The authors retained full editorial control over the contents.

Duality of Interest

E.C. has served on speakers bureaus for the Boehringer Ingelheim/Eli Lilly Alliance, Janssen Pharmaceuticals, AstraZeneca, and Sanofi; has served on advisory boards for the Boehringer Ingelheim/Eli Lilly Alliance and Sanofi; and has received research funding from Janssen Pharmaceuticals and AstraZeneca. No other potential conflicts of interest were reported.

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