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REVIEW ARTICLE

Sodium Glucose Co-Transporter 2 Inhibitors in the Treatment of Type 2 Diabetes Mellitus

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KEYWORDS:

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Renal Glucose Reabsorption

SGLT2 Inhibitors

Efficacy

Safety

Type 2 diabetes mellitus (T2DM) is a chronic, progressive disease, control of which typically requires multiple therapies. Current guidelines suggest that, in addition to improving glycemic control, antihyperglycemic therapy should be chosen on the basis of its effects on body weight and the risk of hypoglycemia. The newest class of oral antihyperglycemic agents, the sodium glucose co-transporter 2 (SGLT2) inhibitors, reduces renal glucose reabsorption and increases urinary glucose excretion via an insulin-independent mechanism of action. SGLT2 inhibitors have been shown to improve glycemic control and to reduce body weight and systolic blood pressure, and their use is associated with a low risk of hypoglycemia. This paper explains the mechanism of action of SGLT2 inhibitors and reviews published efficacy and safety data from phase 3 clinical trials and pooled analyses for the three SGLT2 inhibitors currently approved by the U.S. Food and Drug Administration for use in patients with T2DM: canagliflozin (Invokana[®]), dapagliflozin (Farxiga[™]), and empagliflozin (Jardiance[®]). Implications for clinical osteopathic practice are discussed.

INTRODUCTION

The sodium glucose co-transporter 2 (SGLT2) inhibitors are the first agents to address hyperglycemia by targeting the kidneys in patients with type 2 diabetes mellitus (T2DM). Three medications in this therapeutic class entered the U.S. market within 17 months — canagliflozin in March 2013, followed by dapagliflozin in January 2014, and empagliflozin in August 2014.¹⁻³ SGLT2 inhibitors are included in the 2013 treatment algorithm of the American Association of Clinical Endocrinologists (AACE),⁴ and in the 2015 American Diabetes Association (ADA) Standards of Medical Care.⁵

To offer guidance on the place of SGLT2 inhibitors in osteopathic clinical practice, this review describes the mechanism of action of these agents and summarizes efficacy and safety data from phase 3 clinical trials with the three SGLT2 inhibitors available in the United States.

ROLE OF THE KIDNEYS IN HYPERGLYCEMIA & DIABETES

The kidneys influence glucose homeostasis primarily by reabsorbing glucose from the glomerular filtrate. In healthy individuals, virtually all of the filtered glucose is reabsorbed into the circulation.⁶ The majority of glucose reabsorption (about 90%) occurs through SGLT2, which is located almost exclusively in the proximal tubule.⁶

When the plasma glucose concentration exceeds 180 - 200 mg/dL in healthy adults (the renal threshold),^{7, 8} the reabsorptive capacity of the kidneys is exceeded and glucose is excreted in the urine.⁶ In patients with diabetes, the renal threshold for glucose is increased by as much as 20%, to up to 240 mg/dL.⁸⁻¹⁰ This change is counterproductive because the hyper-reabsorption of glucose leads to maintenance or exacerbation of the hyperglycemic state, rather than spilling excess glucose into the urine.^{6,11}

SGLT2 INHIBITORS

MECHANISM OF ACTION

Canagliflozin, dapagliflozin, and empagliflozin are all highly selective inhibitors of SGLT2.¹²⁻¹⁵ Inhibition of SGLT2 reduces renal glucose reabsorption and lowers the renal threshold for glucose reabsorption, leading to increased urinary glucose excretion (UGE) and reduction of hyperglycemia in patients with T2DM.^{12,16} UGE attributable to SGLT2 inhibition is approximately 80-120 g/day with canagliflozin 100 mg and 300 mg,¹⁷⁻²⁰ approximately 70 g/day with dapagliflozin 10 mg,²¹ and approximately 78 g/day with empagliflozin 25 mg.²² In addition, canagliflozin 300mg has been shown to lower postprandial glucose excursion, likely because local concentrations of canagliflozin in the gut lumen may be sufficient to transiently inhibit intestinal SGLT1.²³⁻²⁵ As SGLT2 inhibitors act independently of beta-cell function or insulin sensitivity,²⁶ this class of medication can be used in all stages of diabetes.^{27, 28}

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Small studies have reported an increase in endogenous glucose production (EGP) with SGLT2 inhibitors,^{23, 29, 30} plasma glucose showed a net decrease despite elevated EGP. The mechanism of this phenomenon is currently unexplained, but elevated EGP may be a compensatory response to support normal plasma glucose levels in the presence of sustained UGE.²³

CLINICAL BENEFITS

A systematic review and meta-analysis of clinical trials comparing SGLT2 inhibitors with placebo (45 studies, n=11,232) or active comparator (13 studies, n=5,175) reported improved glycemic control, reduced body mass, and reduced blood pressure with SGLT2 inhibitor therapy.³¹ These effects have been confirmed by other published reviews.³²⁻³⁴ Although glycated hemoglobin A (A1C) improved in all groups of patients, those with higher baseline A1C values generally experienced greater A1C reductions.^{30, 35-37}

SAFETY

Side effects associated with the SGLT2 inhibitor class and its mechanism of action of increasing UGE include genital mycotic infections (GMIs), urinary tract infections (UTIs), osmotic diuresis-related events, and volume depletion.³² When SGLT2 inhibitors are used as monotherapy, the risk of hypoglycemia is comparable to that of other classes of antihyperglycemic agents (AHA) that are not associated with hypoglycemia.^{31, 36} Rates of serious adverse events (AEs) range between 1.0% and 12.6%, and AEs resulting in discontinuation of therapy range between 0.9% and 9.9%.³²

Glycemic lowering by SGLT2 inhibitors depends on glomerular filtration; therefore, efficacy may be reduced in patients with renal impairment. The prescribing information for each SGLT2 inhibitor includes recommendations specific to patients with reduced renal function. Patients with estimated glomerular filtration rate (eGFR) ≥ 45 to < 60 mL/min/1.73 m² should receive only lower-dose canagliflozin (100 mg), whereas empagliflozin 10 mg and 25 mg can be used in patients with eGFR ≥ 45 mL/min/1.73 m².^{17, 22} Dapagliflozin is not indicated in this patient population.²¹ Canagliflozin and empagliflozin should not be initiated in individuals with an eGFR < 45 mL/min/1.73 m².^{17, 22} Dapagliflozin should not be started in patients with eGFR < 60 mL/min/1.73 m².²¹ Renal function should be monitored and SGLT2 therapy discontinued if eGFR remains persistently below these levels (eGFR: < 45 mL/min/1.73 m² for canagliflozin and empagliflozin, and < 60 mL/min/1.73 m² for dapagliflozin).^{17, 21, 22}

EFFICACY AND SAFETY OF INDIVIDUAL U.S. FOOD AND DRUG ADMINISTRATION-APPROVED AGENTS

CANAGLIFLOZIN:

EFFICACY AND CLINICAL BENEFITS

Table 1 (pages 12-17) summarizes the results of phase 3 trials of canagliflozin.^{35, 36, 38-44} Compared with placebo, canagliflozin 100 mg and 300 mg significantly reduced A1C from baseline to 26 weeks when given as monotherapy, dual therapy (added to metformin), or triple therapy (added to metformin plus a sulfonylurea or metformin plus pioglitazone).^{35, 36, 40, 42}

When compared with glimepiride³⁸ or sitagliptin⁴⁰ as add-on therapy to metformin for 52 weeks, A1C reduction with canagliflozin 300 mg was superior to that of comparators, whereas A1C reduction with canagliflozin 100 mg was non-inferior to comparators. In a study comparing canagliflozin 300 mg with sitagliptin as add-on therapy to metformin plus a sulfonylurea, canagliflozin 300 mg produced A1C reduction superior to that of sitagliptin.⁴¹

As monotherapy, dual therapy (added to metformin), and triple therapy (added to metformin plus a sulfonylurea), canagliflozin 100 mg and 300 mg were associated with significantly greater reductions in body weight at 26 weeks compared with placebo.^{35, 36, 40} As dual therapy (added to metformin), canagliflozin at both doses was associated with significantly greater body weight reduction versus sitagliptin⁴⁰ or glimepiride at 52 weeks.³⁸ As triple therapy (added to metformin plus a sulfonylurea), canagliflozin 300 mg was associated with significantly greater body weight reduction than sitagliptin at 52 weeks.⁴¹ Weight reduction early in canagliflozin treatment is likely, in part, attributable to fluid loss;⁴⁵ however, over time, the reduction in body weight is mainly attributable to reduction in fat mass.³⁸

Compared with placebo, canagliflozin 100 mg and 300 mg significantly reduced systolic blood pressure (SBP) as monotherapy and as dual therapy (added to metformin) at 26 weeks,^{35, 40} and as dual therapy (added to metformin)⁴⁰ and triple therapy (added to metformin plus a sulfonylurea)⁴¹ compared with sitagliptin at 52 weeks. As dual therapy (added to metformin), canagliflozin modestly reduced SBP at 52 weeks compared with glimepiride, which was associated with a small increase.³⁸ As triple therapy (added to metformin plus a sulfonylurea), canagliflozin was associated with numerical SBP reductions at 26 weeks.³⁶

High-density lipoprotein cholesterol (HDL-C) significantly increased with canagliflozin 100 mg and 300 mg at 26 weeks as monotherapy³⁵ and triple therapy,⁴² compared with placebo. In other studies, changes in HDL-C with canagliflozin were either

TABLE 1:

Efficacy and Safety of CANA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy ^a			
		A1C (%)	Body Weight (kg)	SBP (mmHg)	HDL-C (%)
Monotherapy					
Stenlöf et al. 2013 ³⁵	CANA 100mg (n=195)	-0.77 ^b	-2.5 ^b	-3.3 (0.8) ^b	11.2 (1.4) ^b
	CANA 300mg (n=197)	-1.03 ^b	-3.4 ^b	-5.0 (0.8) ^b	10.6 (1.4) ^c
	PBO (n=192) 26 weeks	0.14	-0.5	0.4 (0.8)	4.5 (1.4)
Combination Therapy					
Cefalu et al. 2013 ³⁸	MET + one of: CANA 100mg (n=483)	-0.82 (0.04) ^d	-3.7 (0.2) ^f	-3.3 (0.6)	7.9 (0.8)
	CANA 300mg (n=485)	-0.93 (0.04) ^e	-4.0 (0.2) ^f	-4.6 (0.6)	9.0 (0.8)
	GLIM (n=482) 52 weeks	-0.81 (0.04)	0.7 (0.2)	0.2 (0.6)	0.3 (0.8)
Leiter et al. 2014 ³⁹	MET + one of: CANA 100mg (n=483)	-0.65	-3.6	-2.0	9.4
	CANA 300mg (n=485)	-0.74	-3.6	-3.1	10.0
	GLIM (n=482) 104 weeks	-0.55	0.8	1.7	0.7
Lavalle-González et al. 2013 ⁴⁰	MET + one of: CANA 100mg (n=368)	-0.73 (0.05) ^d	-3.3 (0.2) ^g	-3.5 (0.6) ^g	11.2 (1.0)
	CANA 300mg (n=367)	-0.88 (0.05) ^e	-3.7 (0.2) ^g	-4.7 (0.6) ^g	13.2 (1.1)
	SITA (n=366) 52 weeks	-0.73 (0.05)	-1.2 (0.2)	-0.7 (0.6)	6.0 (1.1)
Scherthner et al. 2013 ⁴¹	MET + SU + one of: CANA 300mg (n=377)	-1.03 ^e	-2.3 ^g	-5.1 ^g	7.6
	SITA (n=378) 52 weeks	-0.66	0.1	-0.9	0.6

Safety					
GMI (%)	UTIs (%)	↑ Urinary Frequency (%)	↑ Urinary Volume (%)	Postural Dizziness (%)	Orthostatic Hypotension (%)
Monotherapy					
2.5 M, 8.8 F	7.2	2.6	0	0.5	0
5.6 M, 7.4 F	5.1	3.0	3.0	1.0	1.0
0 M, 3.8 F	4.2	0.5	0	0	0
Combination Therapy					
7 M, 11 F	6	3	<1	<1	<1
8 M, 14 F	6	3	<1	<1	<1
1 M, 2 F	5	<1	<1	<1	0
9.5 M, 13.9 F	10.6	Not separately assessed	Not separately assessed	Not separately assessed	Not separately assessed
9.1 M, 15.6 F	8.7				
1.9 M, 2.7 F	6.8				
5.2 M, 11.3 F	7.90	5.7	0.5	0.5	0
2.4 M, 9.9 F	4.90	3.0	0.5	0.5	0.3
1.2 M, 2.6 F	6.30	0.5	0	0.3	0
9.2 M, 15.3 F	4.00	1.6	0.8	0	0
0.5 M, 4.3 F	5.60	1.3	0	0.5	0.3

TABLE 1 (CON'T):

Efficacy and Safety of CANA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy ^a			
		A1C (%)	Body Weight (kg)	SBP (mmHg)	HDL-C (%)
Combination Therapy (Continued)					
Wilding et al. 2013 ^{36,h}	MET + SU + one of: CANA 100mg (n=157)	-0.74	-2.0	-3.7 (1.0)	6.6 (1.3)
	CANA 300mg (n=156)	-0.96	-3.1	-2.9 (1.0)	8.2 (1.3)
	PBO (n=156) 52 weeks	0.01	-1.0	0.1 (1.0)	3.3 (1.3)
Forst et al. 2014 ⁴² (26-week core period)	MET + PIO + one of: CANA 100mg (n=113)	-0.89 ^b	-2.6 ^b	-5.3 (1.0) ^c	7.2 (1.4) ⁱ
	CANA 300mg (n=114)	-1.03 ^b	-3.7 ^b	-4.7 (1.0) ⁱ	8.9 (1.3) ^b
	PBO (n=115) 26 weeks	-0.26	-0.2	-1.2 (1.0)	2.4 (1.4)
Forst et al. 2014 ⁴² (full trial period) ^h	CANA 100mg (n=113)	-0.92	-2.5	-3.4 (1.1)	7.0 (1.6)
	CANA 300mg (n=114)	-1.03	-3.6	-3.7 (1.1)	11.4 (1.6)
	PBO/SITA (n=115) 52 weeks	NR	NR	NR	NR
Special Populations					
Bode et al. 2013 ⁴³ (patients aged 55-80 years)	Current treatment + one of: CANA 100mg (n=241)	-0.60 ^b	-2.2 ^b	-3.5 (1.0) ^b	6.8 (1.2) ^b
	CANA 300mg (n=236)	-0.73 ^b	-2.8 ^b	-6.8 (1.1) ^b	6.2 (1.2) ^b
	PBO (n=237) 26 weeks	-0.03	-0.1	1.1 (1.0)	1.5 (1.2)

Safety					
GMI (%)	UTIs (%)	↑ Urinary Frequency (%)	↑ Urinary Volume (%)	Postural Dizziness (%)	Orthostatic Hypotension (%)
Combination Therapy (Continued)					
7.9 M, 18.5 F	8.3				
5.7 M, 18.8 F	8.3	Not separately assessed	Not separately assessed	Not separately assessed	Not separately assessed
1.3 M, 5.0 F	7.7				
Safety data reported only at 52 weeks					
3.9 M, 16.7 F	5.3				
4.8 M, 21.6 F	7.9	Not separately assessed	Not separately assessed	Not separately assessed	Not separately assessed
0 M, 7.7 F	7.8				
Special Populations					
3.2 M, 15.4 F	5.8	2.5	1.7	0.8	0.8
6.2 M, 11.2 F	8.1	5.1	1.7	1.3	0.4
0 M, 2.1 F	5.1	2.1	0	0.4	0

TABLE 1 (CON'T):

Efficacy and Safety of CANA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy ^a			
		A1C (%)	Body Weight (kg)	SBP (mmHg)	HDL-C (%)
Special Populations (Continued)					
Yale et al. 2013 ⁴⁴ (patients with CKD)	CANA 100mg (n=90)	-0.33 ^j	-1.2	-6.1 (1.5)	4.0 (1.7)
	CANA 300mg (n=89)	-0.44 ^b	-1.4	-6.4 (1.5)	3.0 (1.8)
	PBO (n=90) 26 weeks	-0.03	0.2	-0.3 (1.5)	1.5 (1.8)

^a Least-squares mean change from baseline value (with standard error in parentheses where provided).^b $p < 0.001$ vs. PBO, difference vs. baseline.^c $p < 0.01$ vs. comparator or PBO, difference vs. baseline.^d Non-inferior to comparator.^e Superior to comparator.^f $p < 0.0001$ vs. comparator, difference vs. baseline.^g $p < 0.001$ vs. comparator, difference vs. baseline.

(CONTINUED)

EFFICACY AND CLINICAL BENEFITS - CANAGLIFLOZIN

In older adults (aged 55-80 years), canagliflozin 100mg and 300mg as add-on therapy to study participants' current treatment regimens was associated with significant reductions from baseline in A1C, body weight, and SBP, and an increase in HDL-C relative to placebo.⁴³ The A1C reduction in older adults (aged ≥ 65 years) was numerically smaller than in younger patients (aged < 65 years).⁴⁷ It is suggested that reduced renal function in patients aged ≥ 65 years may explain this finding because A1C reductions were comparable between older and younger patients when controlling for eGFR.⁴⁷

Canagliflozin (100mg and 300mg) significantly reduced A1C compared with placebo in adults with T2DM and Stage 3 chronic kidney disease (CKD; eGFR ≥ 30 to < 50 mL/min/173 m²) (Table 1).⁴⁴ Numerical changes in body weight, SBP, and HDL-C favored canagliflozin, but statistical comparisons were not performed. Analysis of pooled data from four randomized, placebo-controlled phase 3 studies showed statistically significant reductions in A1C with canagliflozin 100mg and 300mg in patients with Stage 3a (eGFR ≥ 45 to < 60 mL/min/173 m²) and 3b (eGFR ≥ 30 to < 45 mL/min/173 m²) CKD.⁴⁸

CANAGLIFLOZIN: SAFETY

Safety results of phase 3 trials of canagliflozin are summarized in Table 1 (pages 12-17). In a pooled analysis of four phase 3 trials, the most commonly reported AEs deemed related to canagliflozin are GMIs and UTIs.⁴⁶

GMIs were reported in 3.2% of women with placebo and in 10.4% and 11.4% with canagliflozin 100mg and 300mg, respectively.⁴⁶ GMIs also occurred in men receiving canagliflozin, although less often than in women (0.6% with placebo vs. 4.2% and 3.7% with canagliflozin 100mg and 300mg, respectively).⁴⁶ In both men and women, GMIs were mild or moderate in intensity and resolved with standard antifungal therapy.⁴⁶

Canagliflozin therapy resulted in a slight increase in UTIs relative to placebo (4.0% with placebo vs. 5.9% and 4.3% with canagliflozin 100mg and 300mg, respectively), with low rates of serious UTIs and no increased incidence in upper UTIs.⁴⁶ AEs associated with osmotic diuresis (0.8% with placebo vs. 6.7% and 5.6% with canagliflozin 100mg and 300mg, respectively) and volume depletion (1.1% with placebo vs. 1.2% and 1.3% with canagliflozin 100mg and 300mg, respectively) were also reported.⁴⁶

Safety					
GMI (%)	UTIs (%)	↑ Urinary Frequency (%)	↑ Urinary Volume (%)	Postural Dizziness (%)	Orthostatic Hypotension (%)
Special Populations (Continued)					
1.7 M, 3.1 F	5.6	2.2	0	1.10	0
2.1 M, 2.4 F	7.9	4.5	0	2.20	1.1
0 M, 0 F	5.6	1.1	0	0	0

^h Statistical analysis not performed.

ⁱ $p < 0.025$ vs. PBO.

^j $p < 0.05$ vs. PBO, difference vs. baseline.

A1C, glycated hemoglobin A_{1c}; CANA, canagliflozin; CKD, chronic kidney disease; F, females; GLIM, glimepiride; GMI, genital mycotic infections; HDL-C, high-density lipoprotein cholesterol; M, males; MET, metformin; NR, not recorded; PBO, placebo; PIO, pioglitazone; SBP, systolic blood pressure; SITA, sitagliptin; SU, sulfonylurea; UTIs, urinary tract infections.

The occurrence of serious AEs was similar across treatment groups (< 4%), and treatment discontinuation was low overall with no discernible relation to dose (3.1% in the placebo group vs. 4.3% and 3.6% with canagliflozin 100mg and 300mg, respectively).⁴⁶

The incidence of hypoglycemia was similar between canagliflozin monotherapy and placebo when patients were not on background therapy, including a sulfonylurea (2.2% with placebo vs. 3.8% and 4.3% with canagliflozin 100mg and 300mg, respectively). However, it occurs more frequently, as expected, with canagliflozin dual therapy (with a sulfonylurea) relative to placebo (15.4% with placebo vs. 27.4% and 30.1% with canagliflozin 100mg and 300mg, respectively). This is consistent with the pattern seen when an AHA with a low risk of hypoglycemia is given to patients on an AHA with a high risk of hypoglycemia (e.g. sulfonylurea, insulin).⁴⁶

DAPAGLIFLOZIN: EFFICACY AND CLINICAL BENEFITS

Table 2 (pages 18-21) summarizes results of phase 3 trials of dapagliflozin.^{30, 49-56} Compared with placebo, dapagliflozin 5mg and 10mg significantly reduced A1C as monotherapy,³⁰

and as dual therapy (added to metformin, glimepiride, pioglitazone, or insulin therapy).^{50, 52-54} As triple therapy (added to metformin plus a sulfonylurea), dapagliflozin 10mg resulted in significantly greater A1C reduction relative to placebo; dapagliflozin 5mg was not evaluated.⁵⁵ As dual therapy (added to metformin), dapagliflozin (mean dose 9.2mg) compared with glipizide (mean dose 16.4mg) was statistically non-inferior in A1C reduction.⁵¹

Body weight changes with dapagliflozin monotherapy (5mg or 10mg) did not differ significantly from those observed with placebo after 24 weeks.³⁰ An extension of this study, comparing dapagliflozin 10mg monotherapy with placebo plus low-dose metformin therapy (with metformin added to placebo after 24 weeks) did show a significant difference in body weight change at 102 weeks.⁴⁹ Adding dapagliflozin 5mg or 10mg to metformin, glimepiride, pioglitazone, or insulin therapy resulted in significantly greater body weight reduction from baseline compared with placebo.^{50, 52-54} A 24-week study of dapagliflozin concluded that the weight loss observed (difference from placebo in change from baseline: 2.1kg) was due to decreases in fat mass, visceral adipose tissue, and subcutaneous adipose tissue. Reduction in fat mass (rather than lean body mass) accounted for two-thirds of the weight loss.⁵⁷

TABLE 2:

Efficacy and Safety of DAPA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy ^a			
		A1C (%)	Body Weight (kg)	SBP ^b (mmHg)	HDL-C (%)
Monotherapy					
Ferrannini et al. 2010 ³⁰ (main cohort only)	DAPA 5mg (n=64)	-0.77 (0.11) ^c	-2.8 (0.5)	-2.3 (1.9)	NR by treatment arm
	DAPA 10mg (n=70)	-0.89 (0.11) ^d	-3.2 (0.5)	-3.6 (1.9)	
	PBO (n=75) 24 weeks	-0.23 (0.10)	-2.2 (0.4)	-0.9 (1.8)	
Combination Therapy					
Bailey et al. 2014 ⁴⁹	DAPA 5mg (n=64)	-0.70	-1.59	1.9	NR
	DAPA 10mg (n=70)	-0.61	-3.94	3.9	NR
	PBO + low-dose MET (n=75) 102 weeks	-0.17	-1.34	2.1	NR
Bailey et al. 2013 ⁵⁰	MET + one of: DAPA 5mg (n=137)	-0.58 ^d	-1.70 ^d	-1.1 (13.2) ^e	NR
	DAPA 10mg (n=135)	-0.78 ^d	-1.74 ^d	-0.3 (15.0) ^f	NR
	PBO (n=137) 102 weeks	0.02	1.36	1.5 (13.7)	NR
Nauck et al. 2011 ⁵¹ (dose titration)	MET + one of: DAPA (n=406)	-0.52 ^g	-3.22 ^d	-4.3	5.88
	Glipizide (n=408) 52 weeks	-0.52	1.44	0.8	-0.16
Strojek et al. 2011 ⁵²	GLIM + one of: DAPA 5mg (n=142)	-0.63 ^d	-1.56 ^h	-4.0	4.49
	DAPA 10mg (n=151)	-0.82 ^d	-2.26 ^d	-5.0	5.21
	PBO (n=145) 24 weeks	-0.13	-0.72	-1.2	2.37

Safety			
Events Suggestive of GMI (%)	Events Suggestive of UTIs (%)	Renal Impairment or Failure (%)	Hypotension, Dehydration, or Hypovolemia (%)
Monotherapy			
7.8	12.5	NR	NR
12.9	5.7	NR	NR
1.3	4.0	NR	NR
Combination Therapy			
9.4	12.5	0	0
15.7	8.6	4.3	1.4
1.3	4.0	0	1.3
5.8 M, 23.5 F	8.8	2.9	2.2
6.5 M, 20.7 F	13.3	1.5	1.5
0 M, 11.5 F	8.0	1.5	1.5
5.3 M, 21.1 F	10.8	5.9	1.5
0.4 M, 5.4 F	6.4	3.4	0.7
2.8 M, 9.6 F	6.9	0.7	0
6.1 M, 7.1 F	5.3	0	0.7
0 M, 1.3 F	6.2	1.4	0

TABLE 2 (CON'T.):

Efficacy and Safety of DAPA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy ^a			
		A1C (%)	Body Weight (kg)	SBP ^b (mmHg)	HDL-C (%)
Combination Therapy (Continued)					
Rosenstock et al. 2012 ⁵³	PIO + one of: DAPA 5mg (n=141)	-0.82 (0.08) ⁱ	0.09 (0.28) ^d	-0.8 (1.2)	NR by treatment arm
	DAPA 10mg (n=140)	-0.97 (0.08) ^d	-0.14 (0.28) ^d	-3.4 (1.2)	
	PBO (n=139) 24 weeks	-0.42 (0.08)	1.64 (0.28)	1.3 (1.2)	
Wilding et al. 2012 ⁵⁴	INS + one of: DAPA 5mg (n=211)	-0.96 ^c	-1.00 ^c	-4.33	NR
	DAPA 10mg (n=194)	-1.01 ^c	-1.61 ^c	-4.09	NR
	PBO (n=193) 48 weeks	-0.47	0.82	-1.49	NR
Matthaei et al. 2013 ⁵⁵	MET + SU + one of: DAPA 10mg (n=108)	-0.86 ^d	-2.65 ^d	-4.04 ^j	NR
	PBO (n=108) 24 weeks	-0.17	-0.58	-0.27	NR
Special Populations					
Kohan et al. 2013 ⁵⁶ (patients with moderate renal impairment)	DAPA 5mg (n=83)	-1.21	-0.24	-0.25 (9.5)	NR
	DAPA 10mg (n=85)	-0.75	-1.10	-2.51 (16.3)	NR
	PBO (n=84) 104 weeks	-0.67	2.63	4.14 (14.1)	NR

^aAdjusted mean change from baseline value (with standard error in parentheses where provided).

^bSeated SBP.

^c $p < 0.001$ vs. comparator, difference vs. baseline.

^d $p < 0.0001$ vs. PBO or comparator, difference vs. baseline.

^e $p = 0.0136$ vs. PBO, difference vs. baseline.

^f $p = 0.0067$ vs. PBO, difference vs. baseline.

^gNon-inferiority established.

^h $p = 0.0091$ vs. PBO.

ⁱ $p = 0.0007$ vs. PBO.

^j $p = 0.025$ vs. PBO.

Safety			
Events Suggestive of GMI (%)	Events Suggestive of UTIs (%)	Renal Impairment or Failure (%)	Hypotension, Dehydration, or Hypovolemia (%)
Combination Therapy (Continued)			
9.2	8.5	NR	NR
8.6	5.0	NR	NR
2.9	7.9	NR	NR
2.0 M, 17.0 F	10.8	2.8	2.4
9.1 M, 12.0 F	10.2	2.0	1.5
0 M, 5.1 F	5.1	1.5	1.0
5.5	6.4	NR	NR
0	6.4	NR	NR
Special Populations			
9.6	13.3	2.4	9.6
8.2	14.1	9.4	12.9
3.6	14.3	7.1	6.0

A1C, glycated hemoglobin A_{1c}; DAPA, dapagliflozin; F, females; GLIM, glimepiride; GMIs, genital mycotic infections; HDL-C, high-density lipoprotein cholesterol; INS, insulin; M, males; MET, metformin; NR, not reported; PBO, placebo; PIO, pioglitazone; SBP, systolic blood pressure; SU, sulfonylurea; UTIs, urinary tract infections.

(Continued from page 11)

EFFICACY AND CLINICAL BENEFITS - DAPAGLIFLOZIN

Significantly greater SBP reductions from baseline have been reported with dapagliflozin than with metformin alone⁵⁰ or metformin plus a sulfonylurea.⁵⁵ A separate study reported a non-significant increase in SBP with dapagliflozin 10mg compared with placebo plus low-dose metformin, which may have been due to the fact that this study population had a relatively normal SBP at baseline.⁴⁹ Although changes in HDL-C have not been reported by treatment arm in most of the dapagliflozin phase 3 trials, an analysis of pooled data from four phase 3 studies reported consistent increases in HDL-C with dapagliflozin.⁵⁸ Dapagliflozin has been associated with small increases in LDL-C (mean percentage change from baseline at week 24 ranged from 0.6% to 2.7% with dapagliflozin 2.5 mg, 5 mg, and 10 mg vs. -1.9% with placebo).⁵⁹

Lowering of A1C with dapagliflozin 5 mg and 10 mg in T2DM patients with moderate renal impairment did not differ significantly from placebo at 24 weeks.⁵⁶

DAPAGLIFLOZIN:

SAFETY

Safety results of phase 3 trials of dapagliflozin are summarized in Table 2 (pages 18-21). Separate analyses of pooled data have evaluated the incidence of GMIs and UTIs in 12 randomized, placebo-controlled, phase 2b/3 trials of dapagliflozin (n=4,545).^{60, 61} These analyses included patients who had received placebo or dapagliflozin as monotherapy or as add-on therapy to metformin, insulin, a sulfonylurea, or a thiazolidinedione for 12-24 weeks. The incidence of diagnosed GMIs in women was 1.5% with placebo, and 8.4% and 6.9% with dapagliflozin 5mg and 10mg, respectively. In men, the incidence of GMIs was 0.1% with placebo, and 1.2% and 1.2% with dapagliflozin 5 mg and 10 mg, respectively. The incidence of diagnosed UTIs was 3.7% with placebo, and 5.7% and 4.3% with dapagliflozin 5 mg and 10 mg, respectively.⁶¹ GMIs and UTIs were generally mild to moderate in severity and responded to conventional therapy.⁵⁹

Various terms have been used to report hypotension in dapagliflozin trials; in some, hypotension is combined with hypovolemia and dehydration. In at least one trial, no incidents of orthostatic hypotension were reported.⁵³ Other studies have reported either no change from baseline in the proportion of patients experiencing orthostatic hypotension⁵¹ or few hypotensive events across treatment groups.³⁰ A safety summary of dapagliflozin reported incidences of 0.6% and 0.8% for dapagliflozin 5 mg and 10mg, respectively, vs. 0.4% in the placebo group for events

defined as volume depletion (hypotension, dehydration, and hypovolemia).⁵⁹ Of note, there is currently no data available on volume depletion-related AEs with dapagliflozin in patients with high cardiovascular risk. Patients using loop diuretics, those with eGFR < 60 mL/min/1.73 m², or those aged ≥ 65 years are at increased risk of these AEs.⁶² Dapagliflozin trials did not address urinary frequency or urinary volume as AEs.

Use of dapagliflozin infrequently resulted in hypoglycemia; however, when used in combination with glimepiride⁵² or insulin,⁶³ hypoglycemia incidence was increased compared with placebo.⁶⁴

EMPAGLIFLOZIN:

EFFICACY AND CLINICAL BENEFITS

Table 3 (pages 24-27) summarizes results of phase 3 trials of empagliflozin.^{37, 65-70} A1C reduction with empagliflozin 10 mg or 25 mg was statistically superior to that observed with placebo when given as monotherapy³⁷ and in combination with metformin,⁶⁶ metformin plus a sulfonylurea,⁶⁵ pioglitazone, or pioglitazone plus metformin,⁶⁸ or multi-dose insulin with or without metformin.⁶⁹ As add-on therapy to metformin, empagliflozin 25 mg has been shown to be statistically superior to glimepiride (mean maximum titrated dose 2.71 mg/day) in a 104-week study.⁶⁷ A1C reduction with empagliflozin 10 mg and 25 mg was similar to A1C reduction with sitagliptin 100 mg.³⁷

Statistically significant reductions in body weight and SBP (relative to placebo) have been observed with empagliflozin 10 mg and 25 mg as monotherapy,³⁷ in combination with metformin,⁶⁶ with metformin plus a sulfonylurea,⁶⁵ and with pioglitazone or pioglitazone plus metformin.⁶⁸ Empagliflozin 10 mg and 25 mg added to multi-dose insulin with or without metformin resulted in a statistically significant reduction in body weight and a non-significant reduction in SBP.⁶⁹ In combination with metformin, empagliflozin 25 mg resulted in statistically significant reductions in body weight and SBP compared with glimepiride.⁶⁷

Empagliflozin added to metformin plus pioglitazone has been associated with small increases in HDL-C in placebo-controlled studies: 0.06 mmol/L (2.32 mg/dL) with empagliflozin 10 mg and 0.03 mmol/L (1.16 mg/dL) with empagliflozin 25 mg.⁶⁸ With metformin only, increases in HDL-C of 0.08 mmol/L (3.09 mg/dL) and 0.06 mmol/L (2.32 mg/dL) with empagliflozin 10 mg and 25 mg, respectively, relative to placebo were observed.⁶⁶ Empagliflozin as add-on to metformin has been reported to result in small increases in LDL-C (adjusted mean increase 0.15 mmol/L [5.80 mg/dL] with each dose) relative to placebo (0.03 mmol/L [1.16 mg/dL]).⁶⁶

Empagliflozin 25 mg resulted in an adjusted mean change in A1C from baseline of -0.42% relative to placebo at week 24 in patients with $eGFR \geq 30$ to < 60 mL/min/ 1.73 m².⁷⁰ In patients with Stage 2 and Stage 3 CKD, empagliflozin resulted in significant reductions in A1C, body weight, and SBP compared with placebo after 52 weeks, while in patients with Stage 4 CKD, numerical reductions in body weight and SBP were noted.⁷⁰

EMPAGLIFLOZIN:

SAFETY

Safety results of phase 3 trials of empagliflozin are summarized in Table 3 (pages 24-27). Based on pooled analyses, the most frequently occurring AEs with empagliflozin are UTIs (7.6% with placebo vs. 9.3% and 7.6% with empagliflozin 10 mg and 25 mg, respectively) and GMIs (in female patients: 1.5% with placebo vs. 5.4% and 6.4% with empagliflozin 10 mg and 25 mg, respectively).²² AEs related to osmotic diuresis and volume depletion have been evaluated from pooled data from phase 1, 2, and 3 studies in $> 11,000$ patients.⁷¹ In that analysis, the overall incidence of volume depletion events was 1.4% with empagliflozin 10mg and 1.5% with empagliflozin 25 mg vs. 1.4% with placebo. The incidence of these events was higher in patients aged ≥ 75 years, those with $eGFR < 30$ mL/min/ 1.73 m², and those also receiving diuretic therapy.⁷¹ Empagliflozin therapy is associated with hypoglycemia when used with another AHA that has a high risk of hypoglycemia.^{65,68,69}

IMPLICATIONS FOR PRACTICE

The successful management of patients with T2DM requires holistic care, addressing measures beyond A1C reduction. The ADA/European Association for the Study of Diabetes and the AACE recommend considering the impact on body weight and risk of hypoglycemia, as well as tolerability and cost, when selecting second- and third-line treatment regimens.^{4, 5, 72}

Patient types that might be considered particularly good candidates for SGLT2 inhibitor therapy include overweight or obese individuals and those with high levels of insulin resistance or low levels of pancreatic beta-cell function. Clinicians may wish to exercise caution before prescribing SGLT2 inhibitor therapy for those with risk factors for volume depletion-related AEs and who also face elevated risk for falling or injury due to falls (e.g. osteoporosis, Parkinson disease, dementia).

SGLT2 inhibitors offer a novel mechanism of glycemic control by reducing renal glucose reabsorption and increasing UGE. Use of SGLT2 inhibitors offers the additional benefits of reducing blood pressure and body weight, with a low risk of

hypoglycemia. The three SGLT2 inhibitors available in the United States, canagliflozin, dapagliflozin, and empagliflozin, are oral once-daily medications that improve glycemic control with a convenient dosing schedule. The most common side-effects are GMIs, UTIs, and increased urination. GMIs and UTIs are generally mild to moderate in severity, respond well to conventional treatment, and rarely result in treatment discontinuation. Studies are ongoing to provide further information on the long-term efficacy and safety of SGLT2 inhibitors and data will become available in the coming years. As SGLT2 inhibitors offer an insulin-independent mode of action, they can be used in patients at all stages of type 2 diabetes.²⁶⁻²⁸

TABLE 3:

Efficacy and Safety of EMPA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy ^a		
		A1C (%)	Body Weight (kg)	SBP (mmHg)
Monotherapy				
Rodén et al. 2013 ³⁷	EMPA 10mg (n=224)	-0.66 ^b	-2.26 ^b	-2.9 ^c
	EMPA 25mg (n=87)	-0.78 ^b	-2.48 ^b	-3.7 ^d
	PBO (n=228) 24 weeks	0.08	-0.33	-0.3
Combination Therapy				
Häring et al. 2013 ⁶⁵	MET + SU + one of: EMPA 10mg (n=225)	-0.82 (0.05) ^e	-2.16 ^e	-4.1 ^f
	EMPA 25mg (n=216)	-0.77 (0.05) ^e	-2.39 ^e	-3.5 ^g
	PBO (n=225) 24 weeks	-0.17 (0.05)	-0.39	-1.4
Häring et al. 2014 ⁶⁶	MET + one of: EMPA 10mg (n=217)	-0.70 ^e	-2.08 ^e	-4.5 ^e
	EMPA 25mg (n=213)	-0.77 ^e	-2.46 ^e	-5.2 ^e
	PBO (n=207) 24 weeks	-0.13	-0.45	-0.4
Ridderstråle et al. 2014 ⁶⁷	MET + one of: EMPA 25mg (n=765)	-0.66 ^h	-3.1 ^b	-3.1 ^b
	GLIM 1-4mg (n=780) 104 weeks	-0.55	1.3	2.5
Kovacs et al. 2013 ⁶⁸	PIO ± MET + one of: EMPA 10mg (n=165)	-0.59 (0.07) ^e	-1.62 (0.21) ^e	-3.14 (0.9) ^e
	EMPA 25mg (n=168)	-0.72 (0.07) ^e	-1.47 (0.21) ^e	-4.00 (0.8) ^e
	PBO (n=165) 24 weeks	-0.11 (0.07)	0.34 (0.21)	0.72 (0.9)

Safety		
UTIs (%)	Events Consistent with GMI (%)	Events Consistent with UTIs (%)
Monotherapy		
6	3 M, 4 F	2 M, 15 F
4	1 M, 9 F	1 M, 13 F
4	0 M, 0 F	2 M, 9 F
Combination Therapy		
9.4	0.9 M, 4.5 F	2.7 M, 18.0 F
6.9	0.9 M, 3.9 F	0 M, 17.5 F
6.7	0.9 M, 0.9 F	2.7 M, 13.3 F
5.1	0.8 M, 7.6 F	0 M, 12.0 F
5.6	0.8 M, 9.7 F	0.8 M, 11.8 F
4.9	0 M, 0 F	2.6 M, 7.7 F
14	9 M, 15 F	7 M, 22 F
13	1 M, 3 F	5 M, 23 F
14.5	7.2 M, 9.8 F	3.6 M, 30.5 F
10.7	1.2 M, 6.0 F	2.4 M, 21.7 F
10.9	1.4 M, 3.3 F	8.2 M, 22.8 F

TABLE 3 (CON'T.):

Efficacy and Safety of EMPA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy ^a		
		A1C (%)	Body Weight (kg)	SBP (mmHg)
Combination Therapy (Continued)				
Rosenstock et al. 2014 ⁶⁹	MDI INS ± MET + one of: EMPA 10mg (n=186)	-1.18 (0.08) ^e	-1.95 (0.36) ^e	-3.4 (0.8)
	EMPA 25mg (n=189)	-1.27 (0.08) ^e	-2.04 (0.36) ^e	-3.8 (1.0)
	PBO (n=188) 52 weeks	-0.81 (0.08)	0.44 (0.36)	-2.9 (1.0)
Special Populations				
Barnett et al. 2014 ⁷⁰ (patients with Stage 2 CKD)	Existing treatment + one of: EMPA 10mg (n=98)	-0.57 ^b	-2.00 ⁱ	-1.7
	EMPA 25mg (n=97)	-0.60 ^b	-2.60 ^b	-6.2 ^b
	PBO (n=95) 52 weeks	0.06	-0.44	1.6
Barnett et al. 2014 ⁷⁰ (patients with Stage 3 CKD)	Existing treatment + one of: EMPA 25mg (n=187)	-0.32 ^b	-1.17 ^b	-5.1 ^j
	PBO (n=187) 52 weeks	0.12	0.00	-0.8
Barnett et al. 2014 ⁷⁰ (patients with Stage 4 CKD)	Existing treatment + one of: EMPA 25mg (n=37)	0.11 (1.48)	-1.0 (3.3)	-11.2 (15.7)
	PBO (n=37) 52 weeks	-0.37 (0.79)	0 (3.6)	1.0 (17.4)

^a Adjusted mean change from baseline value (with standard error in parentheses where provided).

^b $p < 0.0001$ for difference vs. PBO or comparator.

^c $p = 0.0231$ for difference vs. PBO.

^d $p = 0.0028$ for difference vs. PBO.

^e $p \leq 0.001$ for difference vs. PBO.

^f $p = 0.005$ for difference vs. PBO.

^g $p = 0.032$ for difference vs. PBO.

^h $p = 0.0153$ (superiority) vs. GLIM.

ⁱ $p = 0.0006$ for difference vs. PBO.

^j $p = 0.0023$ for difference vs. PBO.

Safety		
UTIs (%)	Events Consistent with GMIs (%)	Events Consistent with UTIs (%)
Combination Therapy (Continued)		
12.9	1.0 M, 7.9 F	5.2 M, 27.0 F
12.7	8.3 M, 10.5 F	3.6 M, 24.8 F
12.2	1.3 M, 1.8 F	0 M, 25.7 F
Special Populations		
14.3	10.0 M, 2.6 F	8.3 M, 23.7 F
9.3	0 M, 13.9 F	3.3 M, 19.4 F
15.8	3.6 M, 10.3 F	8.9 M, 25.6 F
16.6	1.9 M, 3.8 F	5.6 M, 31.3 F
15.5	0.9 M, 1.2 F	3.8 M, 30.9 F
18.9	0 M, 6.3 F	9.5 M, 31.3 F
8.1	0 M, 0 F	0 M, 16.7 F

A1C, glycated hemoglobin A_{1c}; CKD, chronic kidney disease; EMPA, empagliflozin; F, females; GLIM, glimepiride; GMIs, genital mycotic infections; INS, insulin; M, males; MDI, multiple daily injections; MET, metformin; open-label; PBO, placebo; PIO, pioglitazone; SBP, systolic blood pressure; SU, sulfonyleurea; UTIs, urinary tract infections.

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