

Impact of sodium–glucose cotransporter 2 inhibitors on blood pressure

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Abstract: SGLT2 inhibitors are glucose-lowering agents used to treat type 2 diabetes mellitus (T2DM). These agents target the kidney to promote urinary glucose excretion, resulting in improved blood glucose control. SGLT2-inhibitor therapy is also associated with weight loss and blood pressure (BP) lowering. Hypertension is a common comorbidity in patients with T2DM, and is associated with excess morbidity and mortality. This review summarizes data on the effect of SGLT2 inhibitors marketed in the US (namely canagliflozin, dapagliflozin, or empagliflozin) on BP in patients with T2DM. Boolean searches were conducted that included terms related to BP or hypertension with terms for SGLT2 inhibitors, canagliflozin, dapagliflozin, or empagliflozin using PubMed, Google, and Google Scholar. Data from numerous randomized controlled trials of SGLT2 inhibitors in patients with T2DM demonstrated clinically relevant reductions in both systolic and diastolic BP, assessed via seated office measurements and 24-hour ambulatory BP monitoring. Observed BP lowering was not associated with compensatory increases in heart rate. Circadian BP rhythm was also maintained. The mechanism of SGLT2 inhibitor-associated BP reduction is not fully understood, but is assumed to be related to osmotic diuresis and natriuresis. Other factors that may also contribute to BP reduction include SGLT2 inhibitor-associated decreases in body weight and reduced arterial stiffness. Local inhibition of the renin–angiotensin–aldosterone system secondary to increased delivery of sodium to the juxtaglomerular apparatus during SGLT2 inhibition has also been postulated. Although SGLT2 inhibitors are not indicated as BP-lowering agents, the modest decreases in systolic and diastolic BP observed with SGLT2 inhibitors may provide an extra clinical advantage for the majority of patients with T2DM, in addition to improving blood glucose control.

Keywords: blood pressure, canagliflozin, dapagliflozin, empagliflozin, sodium–glucose cotransporter 2 inhibitors, type 2 diabetes

Type 2 diabetes mellitus and hypertension

Hypertension is a common comorbidity in patients with type 2 diabetes mellitus (T2DM), with the prevalence of T2DM in US patients ranging from 67% to 87% (where hypertension was defined as blood pressure [BP] $\geq 140/90$, $\geq 130/85$, or $\geq 130/80$ mmHg, and/or the use of antihypertensive medication).^{1–3} Hypertension is a major risk factor for cardiovascular (CV) disease⁴ (such as angina, myocardial infarction, and heart failure) and diabetes microvascular complications.⁵ The pathophysiology of hypertension in patients with diabetes is complex and not currently well understood.⁶ A variety of mechanisms are believed to contribute:⁷ principally, sympathetic nervous system overactivity, renin–angiotensin–aldosterone system (RAAS) activation, and abnormal renal sodium handling, as well as endothelial dysfunction, damage to small and large

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arteries, impaired insulin-mediated vasodilatation, dysfunctional immune responses, and inflammation.

BP reduction is associated with decreased risk of T2DM-related micro- and macrovascular complications.^{8,9} Although exact targets for reduction have not been definitively shown, data from UK Prospective Diabetes Study (UKPDS) 36 (observational analysis cohort, N=3,642, mean systolic BP [after 3-month dietary run-in] 135 mmHg; results compared to those from UKPDS 38 study cohort, N=1,148, baseline mean systolic BP 159 mmHg) suggested that each 10 mmHg reduction in systolic BP was associated with a 12% decrease in the risk of any end point related to diabetes (95% confidence interval [CI] 10%–14%, $P<0.0001$) and a 15% reduction in the risk of diabetes-related death (95% CI 12%–18%, $P<0.0001$).⁹ The benefit of BP reduction was confirmed by a recent meta-analysis involving more than 100,000 participants with T2DM who showed a significantly lower risk of mortality, CV events, coronary heart disease, stroke, albuminuria, and retinopathy for each 10 mmHg systolic BP reduction.¹⁰ When the trials were stratified by mean baseline systolic BP (≥ 140 or <140 mmHg), studies with baseline systolic BP ≥ 140 mmHg had lower risks of outcomes other than stroke, retinopathy, and renal failure.¹⁰

Recommendations for target BP in patients with diabetes have been debated;¹¹ however, recent guidelines from various clinical societies have largely recommended a systolic BP target of <140 mmHg for people with diabetes, with the option to individualize treatment to lower systolic targets (ie, <130 mmHg) if this can be achieved without undue treatment burden.^{5,11–14} Although the lack of evidence from randomized clinical trials to support lower BP targets in diabetes has been recorded,¹⁵ some societies advocate more aggressive BP lowering (ie, $<130/80$ mmHg),^{16–18} as supported by several recent publications.^{10,19,20} Regardless of which goal is used, however, a significant proportion of patients with diabetes fail to achieve their target BP.²¹

The aim of this review is to summarize data on the effect of sodium-glucose cotransporter 2 (SGLT2) inhibitors marketed in the US (namely canagliflozin, dapagliflozin, or empagliflozin) on BP in patients with T2DM. SGLT2 inhibitors that are not marketed in the US and/or those currently in clinical development are not discussed herein.

Methods of evidence acquisition

Boolean searches were conducted that included terms related to BP or hypertension with terms for SGLT2 inhibitors, canagliflozin, dapagliflozin, or empagliflozin using PubMed, Google, and Google Scholar.

SGLT2 inhibitors in the treatment of patients with T2DM

Mechanism of action and rationale

The mechanism of action of SGLT2 inhibitors has been described in detail previously.^{22–24} Briefly, fluid and solutes (eg, glucose) from the plasma are filtered via the kidney glomerulus. The glomerular filtrate then enters the kidney tubule, where much of it is reabsorbed and returned to the blood circulation, while the remainder undergoes urinary excretion. In otherwise-healthy individuals, essentially all of the glucose in the filtrate is reabsorbed, and virtually none is lost in the urine.²² SGLT2, a sodium–glucose cotransporter protein located in the early proximal kidney tubule, is the major pathway for renal glucose reabsorption.^{25,26} An additional sodium–glucose cotransporter protein, SGLT1, has a lesser role in glucose reabsorption in the kidney.^{22,25} The expression and activity of SGLT2 is enhanced in individuals with T2DM, resulting in increased glucose reabsorption and maintenance of hyperglycemia.^{23,27} Pharmacologic inhibition of SGLT2 in the kidney reduces glucose reabsorption and promotes urinary glucose excretion, thereby leading to the correction of hyperglycemia.²³ Inhibition of SGLT2 reduces the capacity for renal glucose reabsorption by 30%–50%.²⁸ Currently, three SGLT2 inhibitors are approved in the US for clinical use in the treatment of T2DM: canagliflozin, dapagliflozin, and empagliflozin.^{29–31} These agents also have marketing approval in the EU, and in other parts of the world.

Summary of efficacy and safety

Data from numerous clinical trials in patients with T2DM have demonstrated that SGLT2 inhibitors reduce the concentration of both glycated hemoglobin (HbA_{1c}) and fasting plasma glucose (FPG),^{32–34} thereby improving glucose control.³⁵ This leads to improved pancreatic β -cell function and decreased insulin resistance.^{36–38} SGLT2-inhibitor therapy is also associated with reductions in body weight of 1.6–2.8 kg versus placebo, per data from meta-analyses of SGLT2-inhibitor clinical trials (duration 12–78 weeks).^{32–34} Reductions in body-fat mass accounted for 68%–90% of the weight loss associated with SGLT2-inhibitor therapy, as reported in further clinical trials (duration 52–104 weeks).^{39–41} A further study observed that SGLT2 inhibitor-induced urinary glucose excretion resulted in the loss of approximately 200 kcal/day (empagliflozin 25 mg once daily for 90 weeks; N=86).⁴² During this study, patients achieved only around 30% of the weight loss predicted by their urinary glucose excretion (ie, -3.2 ± 4.2 kg actual vs -11.3 ± 3.1 kg predicted), which was

attributed to dietary compensation of urinary calorie loss.⁴² Modest reductions in systolic BP (3–6 mmHg) were reported during SGLT2-inhibitor clinical trials.⁴³

SGLT2 inhibitors are generally well tolerated, albeit with some commonly associated adverse events (AEs), such as an increased risk of genital mycotic infections in some patients.^{29–31} Clinical trial data show that SGLT2 inhibitors are associated with a low risk of hypoglycemia, unless coadministered with insulin or an insulin secretagogue.^{32–34} Osmotic diuresis with subsequent intravascular volume contraction induced by SGLT2 inhibitors could potentially pose a risk of volume-depletion AEs (eg, hypotension) in patients prone to these conditions (eg, those with renal impairment, low systolic BP, coadministration of diuretic therapy, and elderly patients).^{29–31} There have also been postmarketing reports of diabetic ketoacidosis (DKA),^{44,45} and product labels were revised to include this safety issue.^{29–31} Blood glucose levels were only slightly or moderately increased (ie, euglycemic ketoacidosis) in a number of occurrences of DKA.^{44,46–48} Potential contributory factors for DKA were identified in many cases (eg, major illness or surgery, reduced intake of food and fluid, reduced insulin dose, alcohol intake, and recent exercise).^{44,46,49} The frequency of reported DKA events in populations from randomized controlled trials (RCTs) of US-marketed SGLT2 inhibitors was <0.1%.^{49,50} There have also been postmarketing reports of urosepsis and pyelonephritis,⁴⁵ a warning on which was added to the respective product labels.^{29–31}

SGLT2 inhibitors and BP control

Potential mechanisms of action of SGLT2 inhibitors relating to BP control

BP reduction by SGLT2 inhibitors is thought possibly to be related to their effects on osmotic diuresis and mild natriuresis.^{51,52} Osmotic diuresis leads to the excretion of glucose and water caused by the presence of unreabsorbed glucose in the kidney-tubule fluid, due to SGLT2 inhibition. Increased urinary output ranging from approximately 110 mL/day to 470 mL/day has been documented in patients treated with SGLT2 inhibitors.⁵³ Enhanced sodium excretion may contribute to reduced plasma volume and lower BP, but data on urinary sodium excretion from clinical trials are limited.⁵¹ In addition, ongoing urinary sodium loss has not been reported with SGLT2 inhibitors, and there is quick compensation for the mild natriuresis that may occur.⁵⁴ A reduction in plasma volume is also consistent with the significant increase in hematocrit observed with SGLT2 inhibitors versus placebo or active comparators in a meta-analysis of 14 RCTs.⁵¹ In a 12-week study of T2DM patients (N=75) receiving

dapagliflozin (10 mg/day) versus placebo or hydrochlorothiazide (HTZ; 25 mg/day), hematocrit increased by 2.2 (95% CI 1.3–3) in the dapagliflozin group versus changes of –0.2 (95% CI –1 to 0.6) and –0.9 (95% CI –2.3 to 0.6) for the placebo and HTZ groups, respectively.⁵⁵ A substudy (N=30) observed loss of plasma volume (median –7.3%; interquartile range [IQR] –12.4 to –4.8) in the dapagliflozin group versus placebo and HTZ groups (median 5.2%, IQR –2.5 to 8.7, and median 2.8%, IQR –10.6 to 25.7, respectively).⁵⁵

SGLT2 inhibitor-associated decreases in body weight may also contribute to BP reduction. This is considered unlikely by some researchers, however, as the BP-lowering effect occurs earlier than any significant weight loss.⁵² BP reductions are associated with weight loss, as evidenced in clinical trials and epidemiologic studies^{56–58} in which reductions in systolic BP associated with weight loss in patients with T2DM have been reported.⁵⁹ The weight loss observed during the first weeks after treatment initiation with an SGLT2 inhibitor is presumed to be mainly due to volume contraction, rather than to the loss of fat and/or lean tissue.⁵⁴ As discussed earlier, a reduction in fat-tissue mass has been observed in long-term studies with SGLT2 inhibitors,^{39–41} but its impact on BP lowering has not been evaluated.⁵⁴ Furthermore, an analysis of data pooled from four placebo-controlled Phase III studies using canagliflozin in patients with T2DM (N=2,250; primary assessment at 26 weeks) estimated that weight loss-associated mechanisms contributed approximately 40% to the overall reduction in systolic BP.⁶⁰ Cefalu et al stated that the exact mechanism of weight loss-independent BP reduction with SGLT2 inhibitors was not fully understood,⁶⁰ and speculated that if osmotic diuresis were the major mechanism, then smaller BP-lowering effects in patients with renal impairment might be anticipated.⁶⁰

An additional explanation for BP reduction by SGLT2 inhibitors is the local inhibition of the RAAS secondary to increased delivery of sodium to the juxtaglomerular apparatus.^{61–63} Data from animal models of diabetes supporting the tubular hypothesis for diabetic nephropathy demonstrated that the SGLT2 inhibitor-associated reduction in proximal tubular reabsorption of sodium caused tubuloglomerular feedback, via increased sodium delivery to the macula densa, and resulted in production of the potent vasoconstrictor adenosine, afferent arteriolar vasoconstriction, and decreased renal blood flow.⁶⁴ This may be related to a postulated renoprotective role for SGLT2 inhibitors,⁶⁴ and dedicated renal outcome trials are ongoing (NCT01989754 and NCT02065791).

Further proposed mechanisms for BP control include possible indirect effects on nitric oxide release secondary to reduced oxidant stress caused by improved glycemic control (observations from preliminary studies only).⁵² The effect of SGLT2

inhibitors on reduction of arterial stiffness and its relationship to BP lowering has been investigated for empagliflozin. In an analysis of patients with T2DM (cohort 1, hypertensive population from one 12-week Phase III study, N=823; cohort 2, pooled population from four 24-week Phase III studies, N=2,477), empagliflozin significantly reduced markers of arterial stiffness in both cohorts.⁶⁵ A study of normotensive patients with T1DM who received empagliflozin (25 mg/day for 8 weeks; N=40) reported that empagliflozin was associated with a reduction in arterial stiffness.⁶⁶ These changes were not explained by activity in the RAAS, endothelial nitrous oxide, or the sympathetic nervous system, and the authors postulated that other factors may be involved.⁶⁶ These may include weight loss, decreased insulin dose, direct effects on vascular smooth muscle, and anti-inflammatory effects associated with SGLT2-inhibitor treatment.⁶⁶

Clinical studies and BP data

A summary of the mean changes in systolic and diastolic BP reported during key Phase III RCTs investigating the efficacy and safety of canagliflozin, dapagliflozin, and empagliflozin in patients with T2DM is presented in Table 1,^{67–81} and includes analyses of pooled data.^{65,82,83} During these studies, seated systolic and diastolic BP (ie, office BP) were commonly measured. The placebo-subtracted mean difference from baseline to the end of treatment (24–26 weeks) ranged from –1.4 to –6.6 mmHg for systolic BP and –0.4 to –2.5 mmHg for diastolic BP. It should be noted that these relatively modest changes in BP reflect the fact that these studies were performed in patients with well-controlled BP at baseline.

Analysis of pooled data from canagliflozin RCTs in patients with T2DM (four Phase III studies; N=2,313) reported the following placebo-subtracted mean differences from baseline to the end of treatment in BP for canagliflozin 100 mg/day and 300 mg/day groups, respectively: systolic BP, –4 mmHg (95% CI –5.1 to –2.8) and –4.7 mmHg (95% CI –5.8 to –3.5); diastolic BP, –1.9 mmHg (95% CI –2.6 to –1.2) and –1.9 mmHg (95% CI –2.6 to –1.1).⁸² Canagliflozin 100 mg and 300 mg were associated with an increased frequency of osmotic diuresis-related AEs (eg, increased urine volume, increased urine frequency) versus placebo (6.7% and 5.6% vs 0.8%, respectively), but the frequency of intravascular volume reduction-related AEs (eg, orthostatic hypotension and postural dizziness) was similar for all groups (1.2% and 1.3% vs 1.1%, respectively).⁸² Minimal mean changes in heart rate were observed (–0.6 bpm, –0.4 bpm, and 0 bpm for canagliflozin 100 mg, 300 mg, and placebo, respectively).⁸² Small increases in hematocrit were observed with canagliflozin 100 mg and 300 mg versus placebo (5.8% and

6.35% vs 0.2%, respectively).⁸² A larger analysis of data pooled from dapagliflozin RCTs (13 Phase IIB/III studies; N=4,655) stratified the patient population into those with and without hypertension at baseline (nonhypertensive was defined as systolic BP ≤140 mmHg and hypertensive as systolic BP >140 mmHg).⁸³ Placebo-subtracted mean differences from baseline to the end of treatment in BP for the dapagliflozin group (10 mg/day) were as follows: systolic BP in hypertensive patients, –3.6 mmHg (95% CI –4.9 to –2.4); systolic BP in nonhypertensive patients, –2.6 mmHg (95% CI –3.4 to –1.8); diastolic BP in hypertensive patients, –1.2 mmHg (95% CI –2 to –0.4); diastolic BP in nonhypertensive patients, –1.2 mmHg (95% CI –1.8 to –0.7).⁸³ No clinically relevant mean change in heart rate was observed for either treatment group.⁸³ A similar proportion of hypertensive patients in both treatment groups had an episode of measured orthostatic hypotension (defined as a decrease of >20 mmHg in systolic BP or >10 mmHg in diastolic BP from a supine to a standing position): 17.4% and 15.5% for dapagliflozin and placebo, respectively.⁸³ Orthostatic hypotension reported as AEs were uncommon (data not stated), and none were classified as serious.⁸³ For empagliflozin, a pooled analysis of four Phase III studies (N=2,477, 10 mg/day and 25 mg/day groups were pooled, seated office BP measured) reported placebo-subtracted mean differences from baseline to the end of treatment in BP of –3.6 mmHg (95% CI –4.5 to –2.7, $P<0.001$) for systolic BP and –1.3 mmHg (95% CI –1.9 to –0.8, $P<0.001$) for diastolic BP.⁶⁵ Minimal mean change in 24-hour heart rate was observed for empagliflozin (–0.9 bpm vs –0.1 bpm for placebo).⁶⁵ Events consistent with volume depletion were reported in 0.2% (two patients) receiving placebo versus 0.3% (five patients) receiving empagliflozin.⁶⁵

To date, three dedicated Phase III RCTs to investigate the efficacy and safety of SGLT2 inhibitors in patients with T2DM and hypertension have been published: the dapagliflozin BP study,⁸⁴ the EMPA-REG BP study,⁸⁵ and the canagliflozin BP study.⁸⁶ The main results from these trials are summarized in Table 2.^{84–86} Unlike the other SGLT2-inhibitor Phase III RCTs, these dedicated BP studies required the dose and regimen of background BP-lowering agents to be stable during the study treatment period, and reported the change from baseline in BP as a coprimary end point. BP investigations for these studies included seated measurements and ambulatory BP monitoring (ABPM). EMPA-REG BP and canagliflozin BP studies used ABPM in the primary BP efficacy outcome,^{85,86} whereas it was used as a secondary BP end point in the dapagliflozin BP trial.⁸⁴ ABPM is becoming increasingly recommended for use in the diagnosis and assessment of hypertension.⁸⁷ ABPM has been shown to be a more sensitive predictor of clinical CV

Table I Summary of efficacy of canagliflozin, dapagliflozin, and empagliflozin in reducing systolic and diastolic BP in patients with T2DM

Clinical trial categories	Placebo-subtracted mean BP change from baseline, mmHg ^a												References
	Canagliflozin				Dapagliflozin				Empagliflozin				
	Systolic BP		Diastolic BP		Systolic BP		Diastolic BP		Systolic BP		Diastolic BP		
	100 mg	300 mg	100 mg	300 mg	5 mg	10 mg	5 mg	10 mg	10 mg	25 mg	10 mg	25 mg	
Phase III trials ^b													
Monotherapy	−3.7	−5.4	−1.6	−2.0	−1.4	−2.7	−1.0	−1.3	−2.6	−3.4	−0.6	−1.5	67–69
Add-on to MET	−5.4	−6.6	−2.5	−2.4	−4.1	−4.9	−2.4	−1.7	−4.1	−4.8	−1.9	−1.6	70–72
Add-on to MET + SU	−2.2	−1.6	−1.1	−0.5	Not used	−3.8 ^c	Not used	Not stated	−2.7	−2.1	−0.4	−0.4	73–75
Add-on to PIO ± MET	−4.1	−3.5	−2.4	−2.6	−2.1	−4.7	−1.7	−3.8	−3.9	−4.7	−1.8	−2.5	76–78
Add-on to INS	−2.3 ^d	−4.1 ^d	−1.0 ^d	−1.7 ^d	−2.4 ^e	−3.1 ^e	−1.2 ^e	−0.8 ^e	−3.4 ^f	−3.0 ^f	−3.3 ^f	−1.7 ^f	79–81
Pooled data from RCTs													65,82,83
Overall population	−4.0	−4.7	−1.9	−1.9	Not stated	Not stated	Not stated	Not stated	−3.6 (pooled for both doses)		−1.3 (pooled for both doses)		
Not hypertensive at baseline	Not reported	Not reported	Not reported	Not reported	Not used	−2.6 ^g	Not used	−1.2 ^g	Not reported		Not reported		
Hypertensive at baseline	−6.0 ^h	−7.4 ^h	+1.5 ^h	−1.6 ^h	Not used	−3.6 ^g	Not used	−1.2 ^g	Not reported		Not reported		

Notes: ^aData presented for patients in the main/primary randomized controlled cohort from each trial listed (ie, not for high glycemic or exploratory cohorts). ^bTime to BP end point 24 or 26 weeks, unless otherwise stated. ^cTime to systolic BP end point 8 weeks. ^dTime to BP end point 18 weeks; INS regimens used: basal only (~10% patients), sliding scale/bolus only (~26% patients), basal + bolus (~62% patients). ^eTime to BP end point 24 weeks; INS regimens used: basal (17% patients), sliding scale/bolus (83% patients). ^fTime to BP end point 18 weeks; all patients used basal INS regimen. ^gStudy defined nonhypertensive as baseline systolic BP ≤140 mmHg and hypertensive as baseline systolic BP >140 mmHg; diastolic BP was also measured in each group.⁸³ ^hPatients with elevated BP at baseline: systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg.⁸²

Abbreviations: BP, blood pressure; INS, insulin; MET, metformin; PIO, pioglitazone; RCT, randomized controlled trial; SU, sulfonylurea; T2DM, type 2 diabetes mellitus.

outcomes than conventional office BP measurement, and also avoids the so-called white-coat effect that may be associated with office BP measurement.⁸⁸

The dapagliflozin BP study (N=449) reported a significant reduction in mean seated systolic BP from baseline to week 12 in the dapagliflozin 10 mg group compared with the placebo group (placebo-subtracted mean difference for dapagliflozin -4.28 mmHg, 95% CI -6.54 to -2.02; $P=0.0002$).⁸⁴ A similar trend was observed for mean seated diastolic BP, but was not statistically significant.⁸⁴ Mean reductions from baseline values were more pronounced in the dapagliflozin 10 mg group than in the placebo group (placebo-subtracted mean difference for dapagliflozin -4.45 mmHg, 95% CI -7.14 to -1.76; $P=0.0012$), as revealed by 24-hour ABPM at week 12.⁸⁴ With regard to safety assessments, AEs were similar between both treatment groups, and AEs related to renal function or volume depletion occurred in ≤1% of patients.⁸⁴ Hyponatremia did not occur in either treatment group, and mean change in hematocrit at week 12 was 1.7% (95% CI 1.3%–2%) for dapagliflozin 10 mg and 0.3% (95% CI 0%–0.7%) for placebo (assessed as a safety end point, thus P -value not reported).⁸⁴ Seated heart rate at week 12 did not differ meaningfully from baseline values in either treatment group (-1.4 bpm for dapagliflozin 10 mg [baseline 77.1 bpm] vs -0.5 bpm for placebo [baseline 77 bpm]).⁸⁴ Orthostatic hypotension (defined as a decrease >20 mmHg

in systolic BP or >10 mmHg in diastolic BP from a supine to a standing position) was not reported by any patients as an AE at week 12, but was measured in seven (3%) patients in the dapagliflozin 10 mg group and four (2%) patients in the placebo group.⁸⁴

EMPA-REG BP (N=825) reported that mean 24-hour systolic BP via ABPM was significantly reduced from baseline to week 12 in both the empagliflozin 10 mg and 25 mg groups compared with the placebo group (placebo-subtracted mean difference -3.44 mmHg [95% CI -4.78 to -2.09] for empagliflozin 10 mg and -4.16 mmHg [95% CI -5.5 to -2.83] for empagliflozin 25 mg, $P<0.001$ for each).⁸⁵ A similar trend was observed for mean 24-hour diastolic BP via ABPM, and the difference for each empagliflozin dose versus placebo was statistically significant ($P<0.001$ for each).⁸⁵ Changes in office systolic and diastolic BP were consistent with ABPM, and were also statistically significant.⁸⁵ In a post hoc subgroup analysis of patients with uncontrolled versus controlled BP at baseline (defined as mean 24-hour systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg vs <130/80 mmHg, respectively), the uncontrolled BP subgroup had greater decreases in both mean 24-hour systolic and diastolic BP compared with placebo at week 12 than the controlled BP subgroup.⁸⁵ In terms of safety, AEs consistent with volume depletion were reported by two patients (placebo, one patient; empagliflozin 10 mg, one patient).⁸⁵ Sodium concentrations showed no meaningful change from

Table 2 Summary of main results from dedicated Phase III trials of SGLT2 inhibitors in patients with T2DM and hypertension

Trial	Study and participant details	Regimen ^a	BP data, mmHg		Safety data			
			Baseline (SD)	PBO-subtracted change to end of DB treatment period (95% CI)	Mean heart rate (bpm), n (SD)	Orthostatic hypotension, n (%)	Renal function-related AEs, n (%)	Volume depletion-related AEs, n (%)
Dapagliflozin MB102077 (NCT01195662) ^{8a}	Design: multicenter, randomized, DB, PBO-controlled Duration: 4-week lead-in, 12-week DB treatment period, 1-week follow-up Participants: T2DM (HbA _{1c} 7%–10.5%) and inadequately controlled HTN (systolic BP 140–165 mmHg and diastolic BP 85–105 mmHg at enrollment and randomization; mean 24-hour BP via ABPM \geq 130/80 mmHg within 1 week of randomization) BP measurements: seated systolic BP, ABPM, seated diastolic BP Coprimary efficacy end point: change from baseline to week 12 in mean seated systolic BP Secondary efficacy end points: change from baseline to week 12 in 24-hour ambulatory systolic BP, seated diastolic BP, and serum uric acid	DAPA 10 mg vs PBO (oral, once daily)						
Full-analysis population								
n=224		PBO	Mean seated systolic BP, mmHg 151.3 (6.7)	–4.28 (–6.54 to –2.02)	–0.5	4 (2%)	1 (<1%)	0
n=225		DAPA	151.0 (7.9)		–1.4	7 (3%)	3 (1%)	1 (<1%)
			Mean 24-hour systolic BP (ABPM), mmHg		As above	As above	As above	As above
n=224		PBO	149.2 (12.7)	–4.45 (–7.14 to –1.76)				
n=225		DAPA	146.5 (10.4)					
			Mean seated diastolic BP, mmHg		As above	As above	As above	As above
n=224		PBO	91.4 (4.8)	–0.97 (–2.32 to 0.39)				
n=225		DAPA	91.2 (4.8)					
Subgroup analysis^f								
Thiazide diuretic (n=77)		PBO	Mean seated systolic BP, mmHg 151.8 (6.9)	–2.38 (–6.16 to –1.4)	NR	NR	0	0
Thiazide diuretic (n=92)		DAPA	151.1 (8.6)		NR	NR	2 (2%)	1 (1%)
Calcium-channel blocker (n=61)		PBO	150.0 (6.4)	–5.13 (–9.47 to –0.79)	NR	NR	0	0
Calcium-channel blocker (n=60)		DAPA	150.1 (7.4)		NR	NR	0	0
β -Blocker (n=59)		PBO	151.4 (6.9)	–5.76 (–10.28 to –1.23)	NR	NR	0	0
β -Blocker (n=57)		DAPA	152.6 (7.3)		NR	NR	1 (2%)	0

Empagliflozin EMPA-REG BP (NCT01370005) ⁶⁵	Design: multicenter, randomized, DB, PBO- controlled Duration: 2-week OL PBO run-in, 12-week DB treatment period, 2-week follow-up Participants: T2DM (HbA _{1c} ≥7%–≤10%) and HTN: mean seated office systolic BP 130–159 mmHg and diastolic BP 80–99 mmHg at screening and successful ABPM ≤1 week prior to randomization BP measurements: 24-hour systolic BP and 24- hour diastolic BP, both via ABPM Coprimary efficacy end point: change from baseline in mean 24-hour systolic BP (via ABPM) at week 12 Key secondary efficacy end point: change from baseline in mean 24-hour diastolic BP (via ABPM) at week 12	EMPA 10 mg vs EMPA 25 mg vs PBO (oral, once daily)	g	h	i	Full-analysis population							
						24-hour mean systolic BP (ABPM), mmHg							
						n=271	PBO	131.7 (11.8)	NA	–0.27 (6.1)	51/254 (20.1%)	NR	I (0.4%)
						n=276	EMPA 10 mg	131.3 (13)	–3.44 (–4.78 to –2.09)	–0.17 (7.7)	67/259 (25.9%)	NR	I (0.4%)
						n=276	EMPA 25 mg	131.2 (12.1)	–4.16 (–5.50 to –2.83)	–0.74 (6.16)	76/259 (29.3%)	NR	0
						24-hour mean diastolic BP (ABPM), mmHg							
						n=271	PBO	75.2 (7.5)	NA	As above	As above	As above	As above
						n=276	EMPA 10 mg	75.1 (8.3)	–1.36 (–2.15 to –0.56)	NR for subgroups	NR for subgroups	NR for subgroups	NR for subgroups
						n=276	EMPA 25 mg	74.6 (7.5)	–1.72 (–2.51 to –0.93)	NR for subgroups	NR for subgroups	NR for subgroups	NR for subgroups
						Subgroup: patients with BP (ABPM) ≥ 130/80 mmHg at baseline						Subgroup: patients with BP (ABPM) ≥ 130/80 mmHg at baseline	
n=150	PBO	NR	NA	NR for subgroups	NR for subgroups	NR for subgroups	NR for subgroups						
n=141	EMPA 10 mg	NR	–4.18 (–6.13 to –2.22)	NR for subgroups	NR for subgroups	NR for subgroups	NR for subgroups						
n=153	EMPA 25 mg	NR	–5.04 (–6.96 to –3.12)	NR for subgroups	NR for subgroups	NR for subgroups	NR for subgroups						
Subgroup: patients with BP (ABPM) < 130/80 mmHg at baseline						Subgroup: patients with BP (ABPM) < 130/80 mmHg at baseline							
n=121	PBO	NR	NA	NR for subgroups	NR for subgroups	NR for subgroups	NR for subgroups						
n=135	EMPA 10 mg	NR	–2.69 (–4.78 to –0.6)	NR for subgroups	NR for subgroups	NR for subgroups	NR for subgroups						
n=123	EMPA 25 mg	NR	–2.66 (–4.8 to –0.53)	NR for subgroups	NR for subgroups	NR for subgroups	NR for subgroups						
Subgroup: patients with BP (ABPM) ≥ 130/80 mmHg at baseline						Subgroup: patients with BP (ABPM) ≥ 130/80 mmHg at baseline							
n=150	PBO	NR	NA	NR for subgroups	NR for subgroups	NR for subgroups	NR for subgroups						
n=141	EMPA 10 mg	NR	–1.85 (–2.96 to –0.74)	NR for subgroups	NR for subgroups	NR for subgroups	NR for subgroups						
n=153	EMPA 25 mg	NR	–1.84 (–2.93 to –0.75)	NR for subgroups	NR for subgroups	NR for subgroups	NR for subgroups						
								(Continued)					

(Continued)

Table 2 (continued)

Trial	Study and participant details	Regimen ^a	BP data, mmHg		Safety data			
			Baseline (SD)	PBO-subtracted change to end of DB treatment period (95% CI)	Mean heart rate (bpm), n (SD)	Orthostatic hypotension, n (%)	Renal function-related AEs, n (%)	Volume depletion-related AEs, n (%)
Canagliflozin (NCT01939496) ⁶⁶	Subgroup: patients with BP (ABPM) <130/80 mmHg at baseline							
	n=121	PBO	24-h mean diastolic BP (ABPM), mmHg	NA	NR for subgroups	NR for subgroups	NR for subgroups	NR for subgroups
	n=135	EMPA 10 mg	NR	NA				
	n=123	EMPA 25 mg	NR	-1.02 (-2.22 to 0.17)				
		CANA 100 mg vs CANA 300 mg vs PBO (oral, once daily)	NR	-1.30 (-2.51 to -0.08)				
	Design: multicenter, randomized, DB, PBO-controlled							
	Duration: 2-week single-blind PBO run-in, 6-week DB treatment period, 30-day follow-up							
	Participants: T2DM (HbA1c $\geq 7\%$ – $<10\%$) and HTN (seated systolic BP ≥ 130 – <160 mmHg and diastolic BP ≥ 70 mmHg at baseline)							
	BP measurements: ABPM, seated and standing BP (systolic and diastolic)							
	Primary efficacy end point: change from baseline to week 6 in mean 24-hour systolic BP (via ABPM)							
	Full-analysis population							
	n=56	PBO	24-hour mean systolic BP (ABPM), mmHg	NA	NR	2 (3.9)	0	0
	n=57	CANA 100 mg	136.5 (11.5)	-3.3 (-6.7 to 0.2)	NR	2 (3.8)	1 (1.8)	0
	n=56	CANA 300 mg	139.6 (10.9)	-4.9 (-8.4 to -1.5)	NR	4 (7.1)	0	2 (3.6)
			24-hour mean diastolic BP (ABPM), mmHg			As above	As above	As above
	n=56	PBO	78.4 (7.3)	NA	NR			
	n=57	CANA 100 mg	78 (8.1)	-1.9 (-4 to 0.1)	NR			
	n=56	CANA 300 mg	79.3 (7.9)	-2.9 (-5 to -0.9)	NR			

Notes: ^aDose and regimen of glucose-lowering agents and BP-lowering agents were stable throughout the study period. ^bChange in seated heart rate from baseline to week 12. ^cMeasured orthostatic BP change (ie, not reported as AEs). ^dBased on list of preferred terms from Medical Dictionary for Regulatory Activities (MedDRA) version 15.1. ^eDefined as hypotension, dehydration, or hypovolemia. ^fPatients who did not take an additional BP-lowering agent from these three subgroups or who received agents from more than one subgroup were excluded from subgroup analysis. ^gChange from baseline to week 12. ^hNumber of patients with a positive orthostatic BP test/number of patients who had an orthostatic BP measurement at baseline and week 12. ⁱBased on eight preferred terms from MedDRA. Includes increased serum creatinine. ^jDefined as postural dizziness, dehydration, and/or orthostatic hypotension.

Abbreviations: ABPM, ambulatory blood pressure monitoring; AE, adverse event; BP, blood pressure; CANA, canagliflozin; CI, confidence interval; DB, double-blind; EMPA, empagliflozin; HbA1c, glycated hemoglobin; HTN, hypertension; NA, not applicable; NR, not reported; OL, open-label; PBO, placebo; SD, standard deviation; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

baseline in the placebo or empagliflozin-treatment groups (mean [SD, standard deviation] mmol/L: 0 [2] for placebo vs 0 [2] and 1 [2] for empagliflozin 10 mg and 25 mg, respectively; *P*-values were not reported, as this was a safety end point).⁸⁵ Mean change from baseline to end of treatment in hematocrit (SI unit expressed as a proportion of 1 [SD]) was 0 [0.02] for placebo versus 0.03 [0.02] and 0.02 [0.02] for empagliflozin 10 mg and 25 mg, respectively.⁸⁵ The proportion of patients with measured orthostatic hypotension (defined as positive if there was a decrease ≥ 20 mmHg in systolic BP or ≥ 10 mmHg in diastolic BP or an increase in pulse rate ≥ 20 bpm between supine and standing readings) was greater in the empagliflozin groups than for placebo. Tikkanen et al reported that no patients in the empagliflozin groups with a positive orthostatic BP test had an AE that was potentially related to hypotension on the same day as the test.⁸⁵ BP reductions were not associated with increased pulse rate from baseline to week 12 (mean changes in 24-hour heart rate via ABPM were -0.27 bpm, -0.17 bpm, and -0.74 bpm for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively).⁸⁵ In addition, a post hoc analysis suggested that empagliflozin may have beneficial effects on arterial stiffness and vascular resistance.⁶⁵

The canagliflozin BP study (N=169) reported that canagliflozin 300 mg and 100 mg provided greater reductions in mean 24-hour systolic BP (via ABPM) than placebo at week 6 (placebo-subtracted least squares [LS] mean changes: -4.9 mmHg [95% CI -8.4 to -1.5], *P*=0.006, and -3.3 mmHg [95% CI -6.7 to 0.2], *P*=0.062, respectively).⁸⁶ Mean 24-hour systolic BP showed numerical reductions for both canagliflozin dose groups compared with placebo at day 2 (placebo-subtracted LS mean changes: -1.7 mmHg [95% CI -4.7 to 1.2] and -2 mmHg [95% CI -5 to 0.9] for canagliflozin 300 mg and 100 mg, respectively).⁸⁶ For diastolic BP, placebo-subtracted LS mean changes in 24-hour ABPM from baseline to week 6 were -2.9 mmHg (95% CI -5 to -0.9 , *P*=0.005) for canagliflozin 300 mg and -1.9 mmHg (95% CI -4 to 0.1 , *P*=0.062) for canagliflozin 100 mg.⁸⁶ The incidence of AEs was higher in the canagliflozin 300 mg and 100 mg dose groups versus the placebo group (26.8% and 26.3% vs 19.6%, respectively).⁸⁶ AEs related to volume depletion occurred in two patients (3.6%); both were from the canagliflozin 300 mg group.⁸⁶ AEs related to osmotic diuresis occurred in five patients (8.9%) from the canagliflozin 300 mg group, two (3.5%) from the canagliflozin 100 mg group, and three (5.4%) from the placebo group.⁸⁶ Significant orthostatic hypotension (defined as symptoms on standing [eg, dizziness, lightheadedness] or reduction in office BP [systolic BP ≥ 20 mmHg or diastolic BP ≥ 15 mmHg] after

2 minutes of standing) at week 6 occurred in 7.1% (n=4), 3.8% (n=2), and 3.9% (n=2) for the canagliflozin 300 mg, 100 mg, and placebo groups, respectively.⁸⁶

It should be noted that circadian BP rhythm was maintained in these dedicated hypertension studies of SGLT2 inhibitors, with greater reductions in daytime versus nighttime measurements observed for systolic BP⁸⁴⁻⁸⁶ and diastolic BP.^{85,86} Blunted nocturnal BP dipping, which is relatively common among patients with T2DM and hypertension, is associated with increased CV risk.⁸⁹

A meta-analysis of 27 RCTs of SGLT2 inhibitors (N=12,960) assessed their BP-lowering ability, and included evaluations of canagliflozin (nine studies, N=5,607), dapagliflozin (12 studies, N=5,280), and empagliflozin (three studies, N=1,359).⁵¹ Compared with the control, SGLT2 inhibitors significantly reduced both systolic BP (weighted mean difference -4 mmHg, 95% CI -4.4 to -3.5) and diastolic BP (weighted mean difference -1.6 mmHg, 95% CI -2.2 to -1) from baseline.⁵¹ A meta-analysis of 19 RCTs evaluating canagliflozin (nine studies, N=5,285) and dapagliflozin (eleven studies, N=4,788) reported that these SGLT2 inhibitors had no significant effect on the incidence of orthostatic hypotension (relative risk 0.72, 95% CI 0.47–1.09).⁵¹

The trials discussed included predominantly white/Caucasian participants, but a pooled analysis has allowed the study of black/African American individuals, a group disproportionately affected by T2DM, as well as diabetes-related complications and hypertension.⁹⁰ In a recent pooled analysis of data from four Phase III RCTs for canagliflozin in patients with poorly controlled T2DM (N=4,158), black/African Americans comprised 4% (N=165) of the study population, and experienced significant reductions in systolic BP with canagliflozin (placebo-subtracted mean difference -2.8 mmHg [95% CI -7.9 to -2.3] for canagliflozin 100 mg and -5.1 mmHg [95% CI -9.8 to -0.4] for canagliflozin 300 mg).⁹¹ The first trial of an SGLT2 inhibitor conducted specifically in black/African American patients is underway, and is recruiting patients with hypertension plus uncontrolled T2DM; as such, it should provide particular insight into effects on BP as well as glucose control.⁹² This trial (NCT02182830) will investigate empagliflozin (10 mg or 25 mg, once daily) versus placebo, and is expected to complete in 2017.⁹²

BP-lowering effects of SGLT2 inhibitors on CV outcomes in T2DM

The ability of SGLT2 inhibitors to reduce BP and lower body weight, in addition to decreasing hyperglycemia, is indicative of their potential to reduce CV risk in patients

with T2DM; however, the impact of their BP-lowering effect on CV outcomes is unknown.⁵¹ Nevertheless, several large RCTs to evaluate the CV safety of SGLT2 inhibitors are underway,^{93–97} and the empagliflozin CV outcomes trial (EMPA-REG OUTCOME) recently reported its results.⁹⁸ CV outcomes trials for canagliflozin and dapagliflozin are estimated to complete in June 2017 and April 2019, respectively.^{93,95} During EMPA-REG OUTCOME, patients with T2DM and at high risk of CV events were randomized and treated with empagliflozin (10 mg or 25 mg once daily) or placebo, in addition to the standard of care.⁹⁸ The primary outcome was a composite of CV death, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke.⁹⁸ EMPA-REG OUTCOME was the first dedicated CV outcomes study to demonstrate that a glucose-lowering agent (ie, of any drug class) lowered CV mortality and all-cause mortality, and reduced hospitalization for heart failure in patients with T2DM at high risk of CV events.⁹⁸ From the study design, it is not possible to determine whether BP changes had any contribution to the CV outcomes, but despite the placebo group being more likely to receive additional BP-lowering drugs than empagliflozin-treated patients, the empagliflozin arms had small reductions in both systolic and diastolic BP for the duration of the trial.⁹⁸ In a post hoc analysis of subgroups, there appeared to be a consistent benefit of empagliflozin treatment in patients with controlled and uncontrolled BP (defined as <140/<90 mmHg and ≥140/≥90 mmHg, respectively) for the primary outcome and for CV death, suggesting empagliflozin might benefit patients with and without hypertension.⁹⁸ It has been suggested that the observed impact on CV events and heart failure could be explained if empagliflozin caused a greater decrease in central aortic pressure than that evident from brachial artery BP measurement, and also reduced aortic stiffness.^{66,99} The reduction in hospitalization for heart failure reported during EMPA-REG OUTCOME is important for hypertensive patients with T2DM, given the association between elevated BP and heart failure.¹⁰⁰ The results of the canagliflozin and dapagliflozin CV outcomes trials will determine if there is a class effect for SGLT2 inhibitors regarding CV outcomes, and may facilitate further analyses of any related BP effects.

Conclusion

Although SGLT2 inhibitors are not indicated as antihypertensive agents, the modest decreases in systolic and diastolic BP observed during SGLT2-inhibitor therapy

may provide an extra clinical advantage for the majority of patients with T2DM, in addition to improving glucose control (via reductions in HbA_{1c} and FPG). Further studies are required to investigate the possible effects of SGLT2 inhibitors on vascular structure and function. Data from the remaining CV outcomes trials with SGLT2 inhibitors, in addition to those obtained from EMPA-REG OUTCOME, will provide clinicians with a clearer picture of the CV benefits of these agents in patients with T2DM, including those with hypertension.

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Disclosure

The author reports no conflicts of interest in this work.

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