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Effects of Sodium-Glucose Cotransporter 2 Inhibitors on 24-Hour Ambulatory Blood Pressure: A Systematic Review and Meta-Analysis

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***Background*—**Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of antihyperglycemic agents that improve glycemic control by increasing glycosuria. Additional benefits beyond glucose lowering include significant improvements in seated clinic blood pressure (BP), partly attributed to their diuretic-like actions. Less known are the effects of this class on 24-hour ambulatory BP, which is a better predictor of cardiovascular risk than seated clinic BP.

***Methods and Results*—**We performed a meta-analysis of randomized, double-blind, placebo-controlled trials to investigate the effects of SGLT2 inhibitors on 24-hour ambulatory BP. We searched all studies published before August 17, 2016, which reported 24-hour ambulatory BP data. Mean differences in 24-hour BP, daytime BP, and nighttime BP were calculated by a random-effects model. SGLT2 inhibitors significantly reduce 24-hour ambulatory systolic and diastolic BP by −3.76 mm Hg (95% CI, −4.23 to −2.34; I^2=0.99) and −1.83 mm Hg (95% CI, −2.35 to −1.31; I^2=0.76), respectively. Significant reductions in daytime and nighttime systolic and diastolic BP were also found. No association between baseline BP or change in body weight were observed.

***Conclusions*—**This meta-analysis shows that the reduction in 24-hour ambulatory BP observed with SGLT2 inhibitors is a class effect. The diurnal effect of SGLT2 inhibitors on 24-hour ambulatory BP may contribute to their favorable effects on cardiovascular outcomes. **(*J Am Heart Assoc*. 2017;6:e005686. DOI: 10.1161/JAHA.117.005686.)**

Key Words: ambulatory blood pressure monitoring • diabetes mellitus • diabetic therapy/glitazones • high blood pressure • hypertension • metformin • sodium-glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter 2 (SGLT2) mediates glucose uptake in the early proximal tubule of the kidney and is responsible for the majority (80–90%) of glucose reabsorption at the glomerulus level.[1] The remaining 10% to 20% is then reabsorbed by SGLT1. In patients with diabetes mellitus, inhibitors of SGLT2 improve hyperglycemia by increasing glycosuria. Currently, 3 SGLT2 inhibitors have been approved by the US Food and Drug Administration for the treatment of type 2 diabetes mellitus as adjuncts to diet and exercise to improve glycemic control: canagliflozin, dapagliflozin, and empagliflozin. Notably, empagliflozin has the highest selectivity for SGLT2 compared with canagliflozin and dapagliflozin.[2]

In the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial,[3] empagliflozin reduced total and cardiovascular mortality in patients with type 2 diabetes mellitus compared with placebo, an effect that was mainly driven by the beneficial effects on heart failure. These impressive data have recently resulted in a label change for empagliflozin to highlight the reduction in cardiovascular mortality risk.[4] However, the cardiovascular benefits of empagliflozin cannot be justified by the improvement in glycemic control alone, which suggests the presence of non-glucose-lowering effects of empagliflozin.

One of the most consistently reported non-glucose-lowering effects of SGLT2 inhibitors is the reduction of systemic arterial blood pressure (BP). A recent meta-analysis of 27 randomized controlled trials (RCTs) concluded that, in patients with type 2 diabetes mellitus, SGLT2 inhibitors improve systolic BP by −4 mm Hg (95% CI, −4.4 to −3.5) and diastolic BP by −1.6 mm Hg (95% CI, −1.9 to −1.3).[5] The exact BP reduction-related mechanisms of SGLT2 inhibitors have not been fully elucidated. However, it

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Clinical Perspective

What is New?

- This meta-analysis demonstrates that Sodium-glucose cotransporter 2 inhibitors, as a class, significantly reduce 24-hour ambulatory blood pressure, which further supports their favorable cardiovascular profile.

What are the Clinical Implications?

- The decrease in 24-hour ambulatory blood pressure observed with Sodium-glucose cotransporter 2 inhibitors further emphasizes the need for close monitoring of blood pressure and volume status, especially in patients receiving concomitant diuretic therapy.

has been suggested that inhibition of glucose-sodium reabsorption in the proximal tubule results in an osmotic diuresis and decreased BP.[6]

Additional studies have also observed that SGLT2 inhibitors improve 24-hour ambulatory BP. Importantly, 24-hour ambulatory BP is a better predictor of cardiovascular risk and mortality than seated clinic BP and therefore, possibly, a more-appropriate therapeutic target.[7] Moreover, 24-hour ambulatory BP can identify subjects with masked hypertension, which is associated with increased cardiovascular risk and is more prevalent in patients with diabetes mellitus.[8,9] Data on the effects of SGLT2 inhibition on 24-hour ambulatory BP are confined to relatively small studies. The purpose of this meta-analysis was to determine the magnitude of the effect SGLT2 inhibitors exert on 24-hour ambulatory BP.

Methods

This meta-analysis conforms to standard guidelines and was written in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[10]

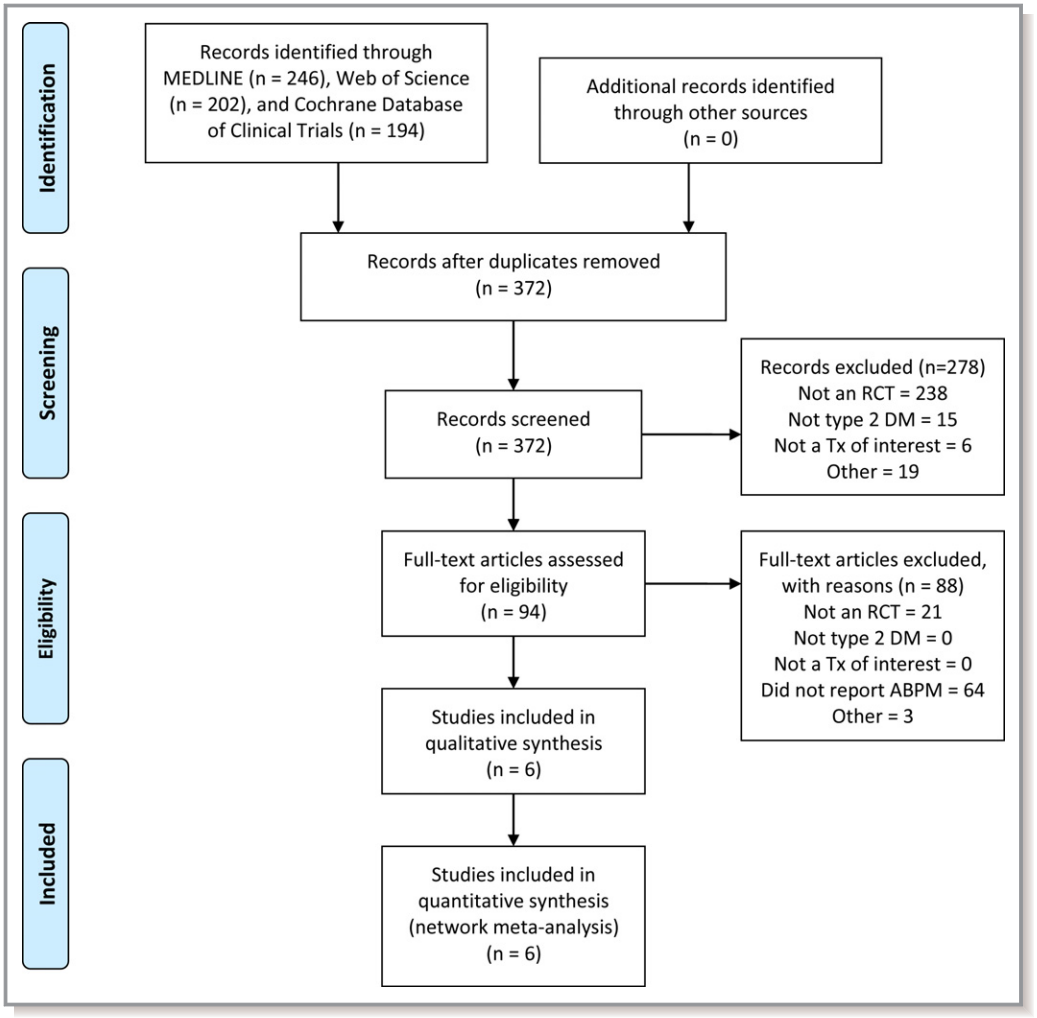

Figure 1. PRISMA diagram of study selection process. ABPM indicates ambulatory blood pressure monitoring; DM, type 2 diabetes mellitus; RCT, randomized, controlled trial; Tx, treatment.

Literature Search

A systematic search of 3 databases was conducted along with a search of the reference lists of the retrieved publications, in order to identify published articles addressing the topic. Databases searched included PubMed/Medline, Web of Science, and The Cochrane Database of Clinical Trials. The articles included were limited to the English language and those published anytime from the inception of each database to present. The search was broken into 3 concept groups. One group encompassed the terminology used to describe "sodium-glucose cotransporter 2 inhibitors," another covered the terms relevant to "blood pressure," and a third addressed "randomized controlled trials." Medical Subject Headings (MeSH) and equivalent controlled vocabulary and keywords were utilized in each database. The last search of the databases was conducted on August 17, 2016.

Study Selection

Three authors (D.L.D., W.L.B., and L.F.B.) reviewed all potentially relevant articles in a parallel manner by using a priori defined criteria. Studies were eligible for inclusion in the meta-analysis if they met the following criteria: (1) RCT in humans; (2) evaluated a SGLT2 inhibitor compared with either placebo or an active control; and (3) reported data on changes in 24-hour ambulatory BP from baseline in a form suitable for pooling. Only data from peer-reviewed publications were considered for inclusion in this analysis.

Data Abstraction and Validity Assessment

For each included study, 2 authors (D.L.D., L.F.B.) used a standardized abstraction tool to extract data for the analysis, with disagreements resolved by a third investigator (M.K.). Information collected from each study included author, year of publication, study design, duration of follow-up, population and setting, sample size, SGLT2 inhibitor evaluated, and concomitant antihyperglycemic therapies. Data on changes in 24-hour BP were obtained. Missing data were collected through a search of the study results reported on clinicaltrials.gov. Two reviewers (D.L.D., L.F.B.) assessed the quality of each study by answering "yes," "no," or "unclear" to 11 questions regarding similarity of baseline populations, randomization, allocation concealment, blinding of study participants and personnel, outcome adjudication, completeness of follow-up, and conflicts of interest using the Methods Guide for Comparative Effectiveness Reviews.[11] Studies were given an overall score of good, fair, or poor with disagreements resolved through discussion.

Table 1. Baseline Characteristics of Trials Evaluating SGLT2 Inhibitors and 24-Hour Ambulatory Blood Pressure

Study Name	Study Design	SGLT2 Group	n	Duration (Weeks)	Average Age (Y)	Baseline 24-Hour SBP	Baseline 24-Hour DBP	Baseline Daytime SBP	Baseline Nighttime SBP
Lambers-Heerspink et al (2013)[16]	R, DB, PC	DAPA 10 mg/d	24	12	52.7±9.4	131±12	77±7	138±12	120±13
		Placebo	25		58.0±9.5	127±12	74±7	131±12	117±15
Amin et al (2015)[20]	R, DB, PC	ERTU 1 mg/d	39	4	54.4±7.0	133.1±1.7	78.6±1.3	NR	NR
		ERTU 5 mg/d	38		53.8±9.9	135.0±1.9	80.1±1.4		
		ERTU 25 mg/d	39		52.5±6.6	135.5±1.9	80.3±1.3		
		Placebo	38		55.1±6.7	136.1±2.5	81.8±1.5		
Tikkanen et al (2015)[19]	R, DB, PC	EMPA 10 mg/d	276	12	60.6±8.5	131.3±13.0	75.1±8.3	NR	NR
		EMPA 25 mg/d	276		59.9±9.7	131.2±12.1	74.6±7.5		
		Placebo	271		60.3±8.8	131.7±11.8	75.2±7.5		
Townsend et al (2016)[15]	R, DB, PC	CANA 100 mg/d	57	6	57.8±8.7	136.5±11.5	78.0±8.1	NR	NR
		CANA 300 mg/d	56		58.3±6.9	139.6±10.6	79.3±7.9		
		Placebo	56		59.6±9.5	136.7±10.3	78.4±7.3		
Weber et al (2016)[18]	R, DB, PC	DAPA 10 mg/d	187	12	56.0 (51–62)	146.5±10.4	NR	NR	NR
		Placebo	186		57.0 (50–62)	149.2±12.7			
Weber et al (2016)[17]	R, DB, PC	DAPA 10 mg/d	267	12	55.6±8.4	145.9±11.7	87.0±6.9	149.1±11.6	139.7±14.7
		Placebo	263		56.2±8.9	146.6±11.7	87.2±6.7	150.4±1.2	139.1±15.1

CANA indicates canagliflozin; DAPA, dapagliflozin; DB, double-blind; DBP, diastolic blood pressure; EMPA, empagliflozin; ERTU, ertugliflozin; NR, not reported; PC, placebo-controlled; R, randomized; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2 inhibitor.

Statistical Analysis

Meta-analyses were performed on the mean changes from baseline in 24-hour systolic and diastolic BP, daytime systolic and diastolic BP, and nighttime systolic and diastolic BP. All continuous data are reported as a mean difference and accompanying 95% CI and was pooled using a Hartung-Knapp method[12] random-effects model using the "meta" package in R (version 3.1.3; The R Project for Statistical Computing). We reported doses for each drug, regardless of its regulatory status. We assessed presence of statistical heterogeneity using the Cochrane *P* value ($P<0.10$ significant) and the degree of heterogeneity using the I^2 statistic with a value >50% considered substantial.[13] Contour plots were constructed as a visual representation of bias in the main results (24-hour systolic and diastolic BP), and we used Egger's test of asymmetry of the plots.[14]

Subgroup analyses were performed by pooling data for each individual SGLT-2 inhibitor separately and assessing the pooled between-group variance. We also conducted random-effects metaregression to evaluate whether the BP effects observed with the SGLT-2 inhibitors were associated with either baseline 24-hour ambulatory BP or changes in body weight during the trial. Additional variables, such as percent patients with hypertension at baseline and urinary sodium excretion, were not sufficiently reported to allow for metaregression to be performed.

Results

Study Selection and Characteristics

The literature search process and results are shown in Figure 1. A total of 6 randomized, double-blind, placebo-controlled studies were included in the analysis (Table 1).[15–20] Of these, 3 RCTs (n=952) evaluated dapagliflozin,[16–18] 1 RCT (n=823) evaluated empagliflozin,[19] 1 RCT (n=169) evaluated canagliflozin,[15] and 1 RCT (n=154) evaluated ertugliflozin.[20] The dose of dapagliflozin used in each study was 10 mg/day, and sample sizes ranged from 49 to 530 participants.[16–18] Doses of empagliflozin, canagliflozin, and ertugliflozin ranged from 10 to 25, 100 to 300, and 1 to 25, respectively.[15,19,20] Key clinical data for each of the included studies are provided in detail in Table 2.[15–20] The quality of each study was determined to be "good" with no disagreements between the reviewers.

Table 2. Reported Clinical End Point Data

Study Name	SGLT2 Group	n	Change in 24-Hour SBP From Baseline	Change in 24-Hour DBP From Baseline	Change in Daytime SBP From Baseline	Change in Daytime DBP From Baseline	Change in Nighttime SBP From Baseline	Change in Nighttime DBP From Baseline
Lambers-Heerspink et al (2013)[16]	DAPA 10 mg/d	24	−5.6±11.62	NR	−8.8±12.25	NR	−1.9±12.5	NR
	Placebo	25	−0.7±9.18		−0.8±9.31		−0.6±11.48	
Amin et al (2015)[20]	ERTU 1 mg/d	39	−2.97±4.62	−1.9±3.03	−2.9±4.78	−2.1±3.19	−2.6±5.89	−1.6±4.3
	ERTU 5 mg/d	38	−4±4.87	−2.3±3.15	−3.6±5.35	−1.9±3.46	−3.6±6.45	−2.6±4.72
	ERTU 25 mg/d	39	−3.69±4.62	−1.5±3.03	−4.2±4.64	−1.7±3.19	−2.4±6.05	−0.9±4.46
	Placebo	38	0.1±4.4	0.8±3.30	0.8±5.19	0.9±3.3	−0.4±6.29	0.9±4.40
Tikkanen et al (2015)[19]	EMPA 10 mg/d	276	−2.99±8.86	−1.1±4.96	−3.4±9.55	−1.28±5.41	−2.22±10.21	−0.8±6.21
	EMPA 25 mg/d	276	−3.59±9.30	−1.32±4.96	−4.12±9.55	−1.58±5.35	−2.47±11.09	−0.75±6.32
	Placebo	271	0.42±8.25	0.3±5.06	0.38±8.74	0.26±5.36	0.51±10.22	0.36±6.8
Townsend et al (2016)[15]	CANA 100 mg/d	57	−4.78±8.33	−2.18±4.87	−5.05±8.66	−2.39±5.41	−4.33±11.51	−1.73±6.48
	CANA 300 mg/d	56	−7.31±11.41	−3.27±6.46	−7.36±11.66	−3.23±6.56	−6.98±12.88	−3.42±8.06
	Placebo	56	−1.26±9.86	−0.26±5.35	−0.65±9.87	−0.2±5.26	−3.49±12.47	−0.98±7.75
Weber et al (2016)[18]	DAPA 10 mg/d	187	−11.33±21.9	−7.56±13.95	NR	NR	NR	NR
	Placebo	186	−6.88±21.5	−5.57±13.64				
Weber et al (2016)[17]	DAPA 10 mg/d	267	−9.62±20.1	−6.15±13.73	−10±20.43	NR	−8.8±22.88	NR
	Placebo	263	−6.73±20.1	−5.53±13.78	−6.9±20.69		−6.5±23.17	

CANA indicates canagliflozin; DAPA, dapagliflozin; DBP, diastolic blood pressure; EMPA, empagliflozin; ERTU, ertugliflozin; NR, not reported; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2 inhibitor.

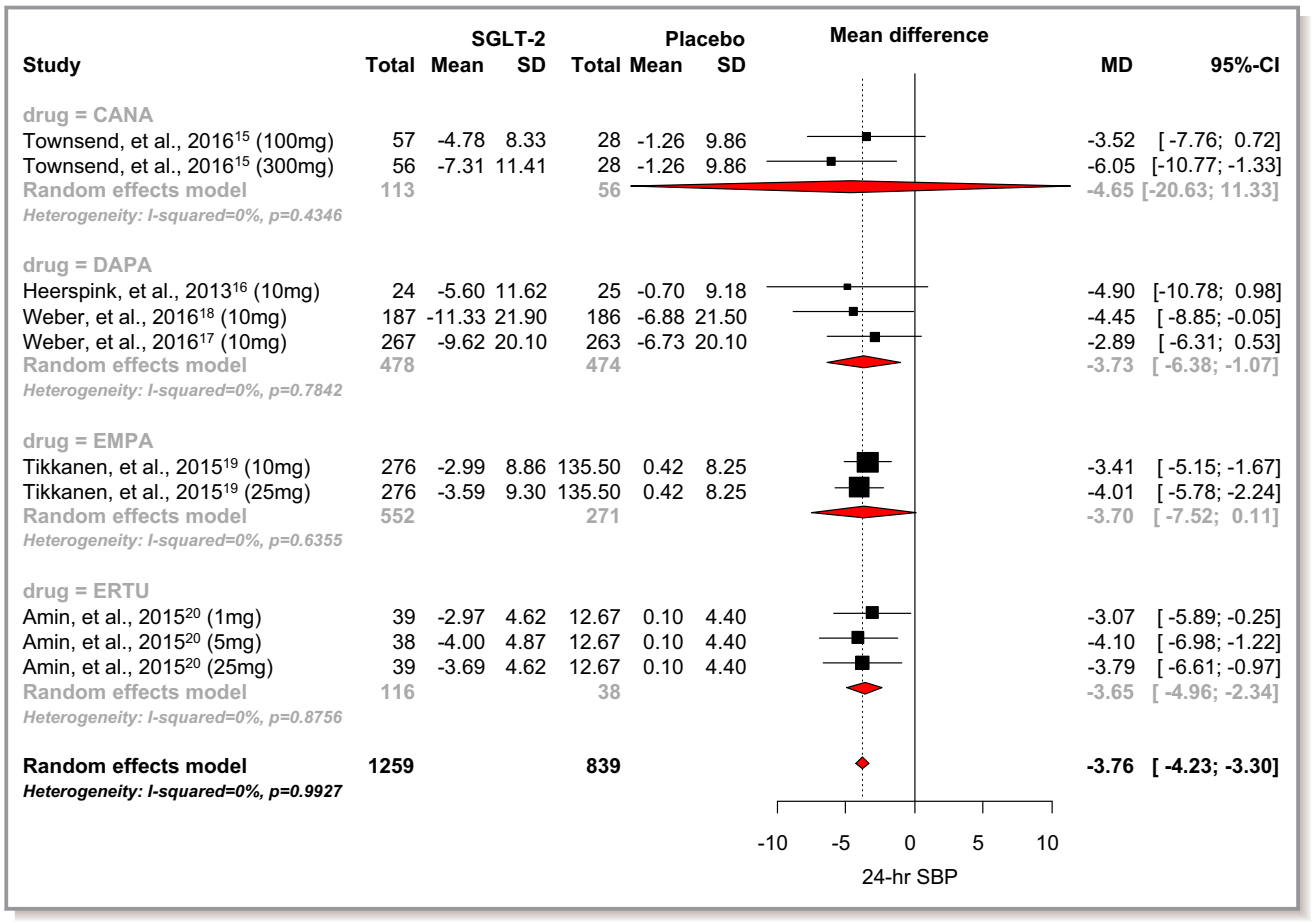

Figure 2. Effect of SGLT2 inhibitors on 24-hour systolic blood pressure. CANA indicates canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; ERTU, ertugliflozin; MD, mean difference; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2 inhibitor.

Quantitative Data Synthesis

24-hour BP

When the 6 RCTs were pooled, SGLT2 inhibitor use was associated with a statistically significant 3.76 mm Hg reduction in 24-hour systolic BP when compared with placebo (95% CI, −4.23 to −2.34; I^2=0.99; Figure 2).[15–20] The mean differences observed with canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin were −4.65 mm Hg (95% CI, −20.63 to 11.33), −3.73 mm Hg (95% CI, −6.38 to

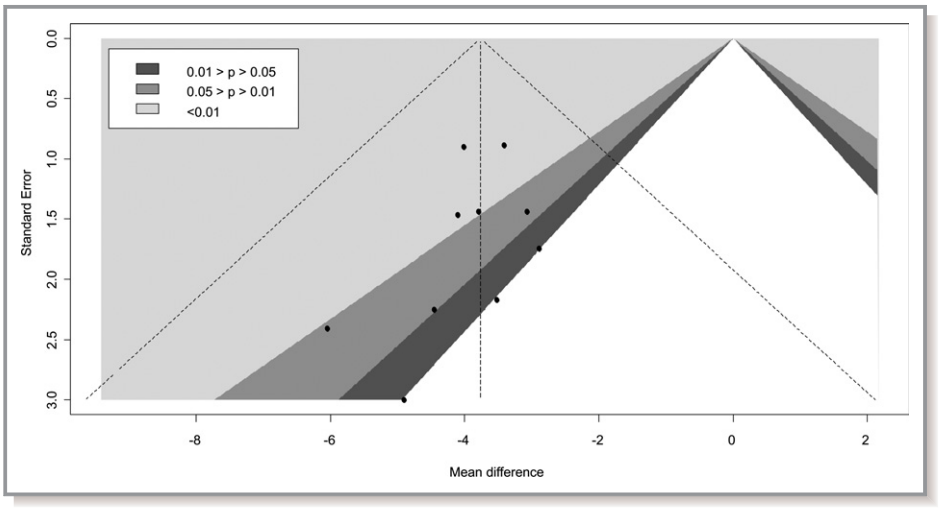

Figure 3. Contour-enhanced funnel plots of 24-hour systolic blood pressure.

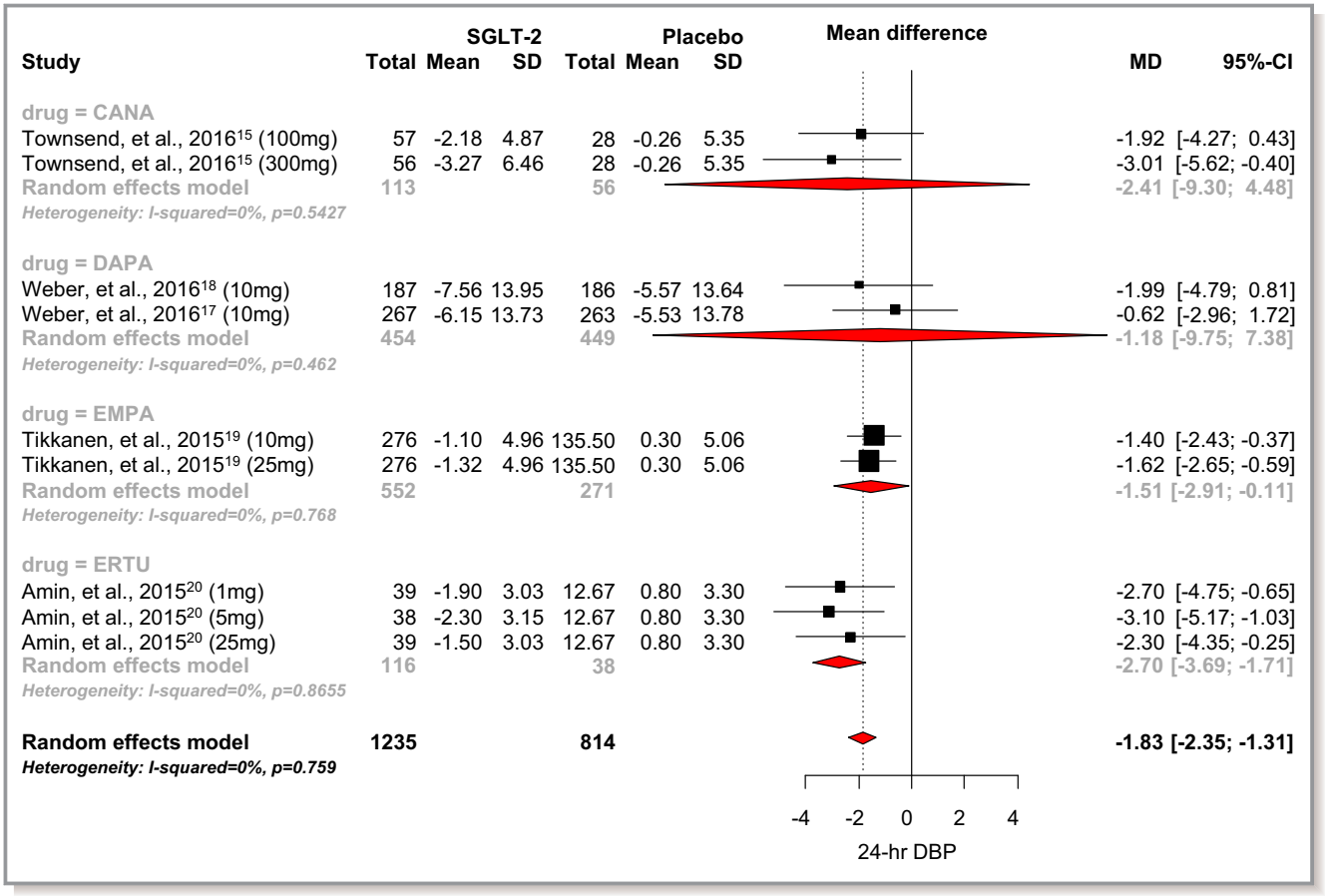

Figure 4. Effect of SGLT2 inhibitors on 24-hour diastolic blood pressure. CANA indicates canagliflozin; DAPA, dapagliflozin; DBP, diastolic blood pressure; EMPA, empagliflozin; ERTU, ertugliflozin; MD, mean difference; SGLT2, sodium-glucose cotransporter 2 inhibitor.

−1.07), −3.70 mm Hg (95% CI, −7.52 to 0.11), and −3.65 mm Hg (95% CI, −4.96 to −2.34), respectively. No significant difference between individual SGLT-2 inhibitors was noted (P=0.90). There was also no strong evidence of small-study effects (Egger's test, P=0.25; Figure 3).

Only 4 of the 6 RCTs reported data for 24-hour diastolic BP. SGLT2 inhibitor use was associated with a statistically significant 1.83 mm Hg reduction in 24-hour diastolic BP when compared with placebo (95% CI, −2.35 to −1.31; I^2=0.76; Figure 4).[15,17–20] The mean differences observed

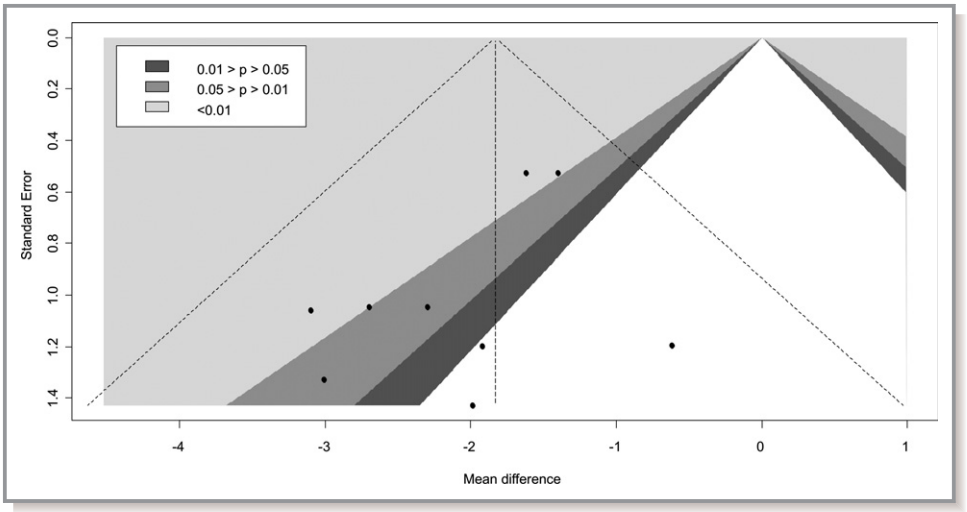

Figure 5. Contour-enhanced funnel plots of 24-hour diastolic blood pressure.

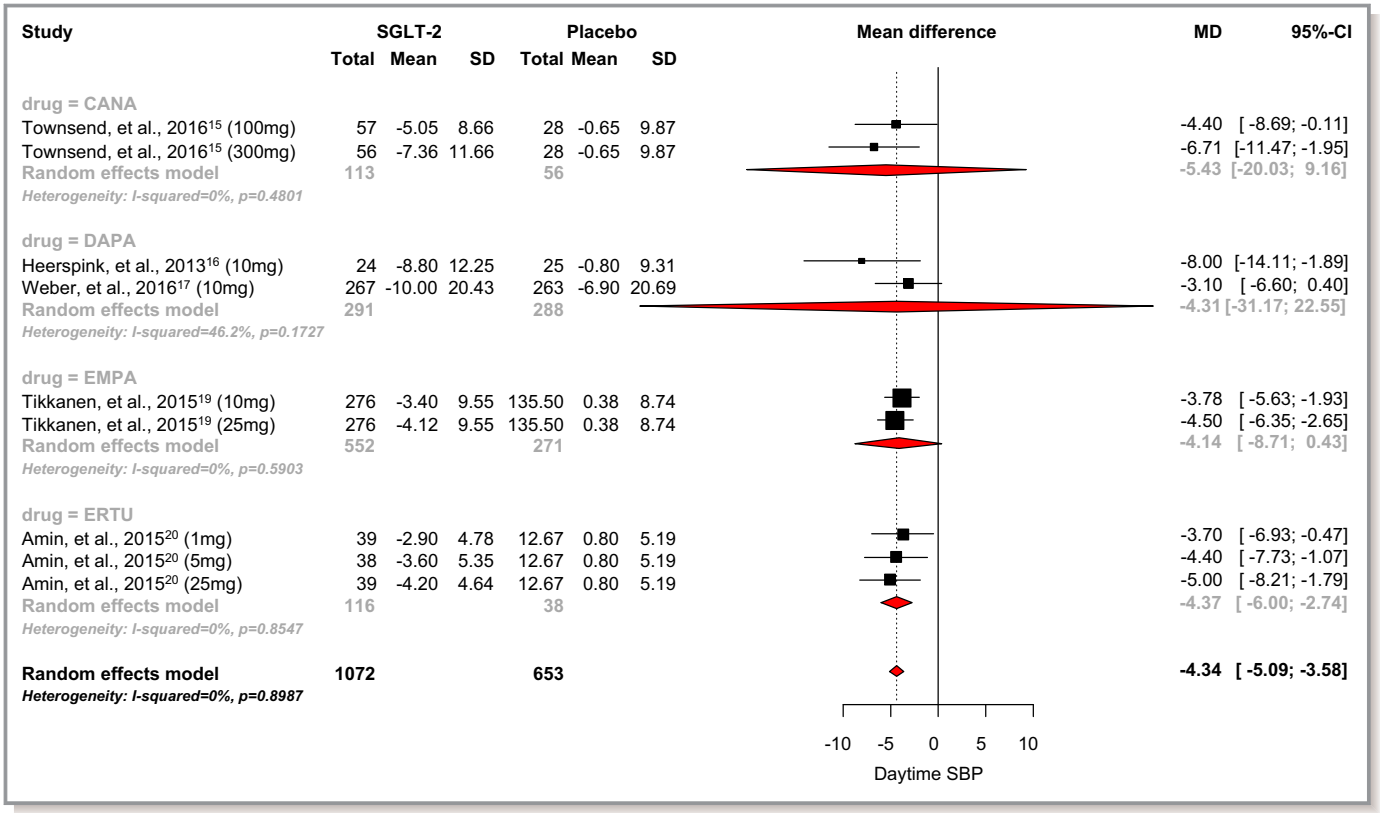

Figure 6. Effect of SGLT2 inhibitors on daytime systolic blood pressure. CANA indicates canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; ERTU, ertugliflozin; MD, mean difference; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2 inhibitor.

with canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin were −2.41 mm Hg (95% CI, −9.30 to 4.48), −1.18 mm Hg (95% CI, −9.75 to 7.38), −1.51 mm Hg (95% CI, −2.91 to −0.11), and −2.70 mm Hg (95% CI, −3.69 to −1.71), respectively. A significant difference between individual SGLT-2 inhibitors was noted (P<0.0001). No strong evidence of small-study effects was observed (Egger's test P=0.15; Figure 5).

Daytime BP

An analysis of the 5 RCTs that reported daytime systolic BP showed that SGLT2 inhibitor use was associated with a statistically significant 4.34 mm Hg reduction when compared with placebo (95% CI, −5.09 to −3.58; I^2=0.90; Figure 6).[15–17,19,20] The mean differences observed with canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin were −5.43 mm Hg (95% CI, −20.03 to 9.16), −4.31 mm Hg (95% CI, −31.17 to 22.55), −4.14 mm Hg (95% CI, −8.71 to 0.43), and −4.37 mm Hg (95% CI, −6.00 to −2.74), respectively. No significant difference between individual SGLT-2 inhibitors was observed (P=0.75).

Only 3 RCTs reported data for daytime diastolic BP. We found no studies that evaluated the effects of dapagliflozin on daytime diastolic BP. SGLT2 inhibitor use was associated with a statistically significant 2.09 mm Hg reduction in daytime diastolic BP when compared with placebo (95% CI, −2.63 to −1.54; I^2=0.80; Figure 7).[15,19,20] The mean differences observed with canagliflozin, empagliflozin, and ertugliflozin were −2.58 mm Hg (95% CI, −7.90 to 2.74), −1.69 mm Hg (95% CI, −3.60 to 0.22), and −2.80 mm Hg (95% CI, −3.30 to −2.30), respectively. A significant difference between individual SGLT-2 inhibitors was noted (P<0.0001).

Nighttime BP

An analysis of the 5 RCTs that reported nighttime systolic BP showed that SGLT2 inhibitor use was associated with a statistically significant 2.61 mm Hg reduction when compared with placebo (95% CI, −3.08 to −2.14; I^2=0.99; Figure 8).[15–17,19,20] The mean differences observed with canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin were −2.11 mm Hg (95% CI, −18.94 to 14.71), −2.05 mm Hg (95% CI, −7.58 to 3.48), −2.85 mm Hg (95% CI, −4.44 to −1.26), and −2.46 mm Hg (95% CI, −4.04 to −0.87), respectively. No significant difference between individual SGLT-2 inhibitors was observed (P=0.25).

Only 3 RCTs reported data for nighttime diastolic BP. We found no studies that evaluated the effects of dapagliflozin on nighttime diastolic BP. SGLT2 inhibitor use was associated

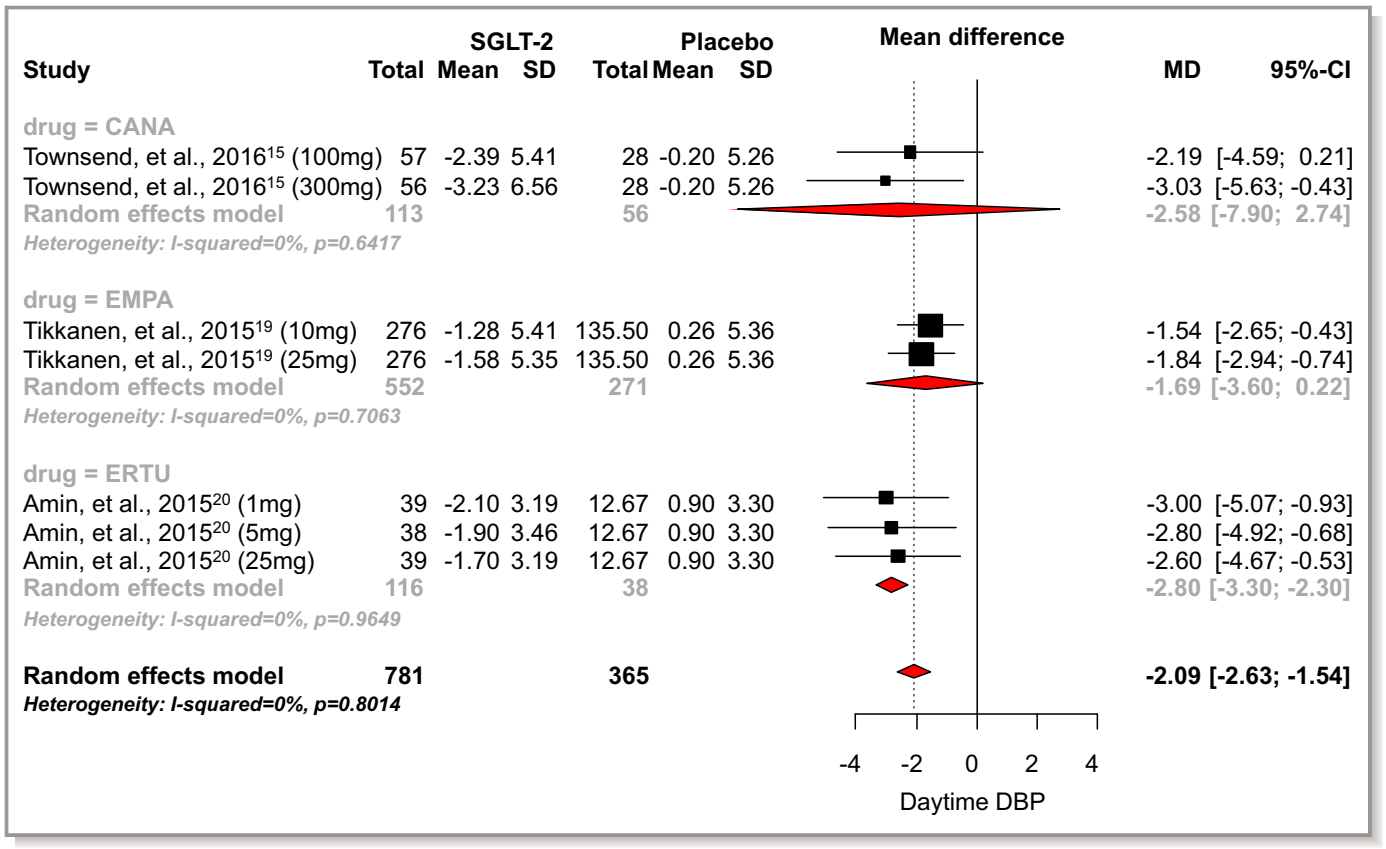

Figure 7. Effect of SGLT2 inhibitors on daytime diastolic blood pressure. CANA indicates canagliflozin; DAPA, dapagliflozin; DBP, diastolic blood pressure; EMPA, empagliflozin; ERTU, ertugliflozin; MD, mean difference; SGLT2, sodium-glucose cotransporter 2 inhibitor.

with a statistically significant 1.49 mm Hg reduction in nighttime diastolic BP when compared with placebo (95% CI, −2.20 to −0.78; I^2=0.79; Figure 9).[15,19,20] The mean differences observed with canagliflozin, empagliflozin, and ertugliflozin were −1.54 mm Hg (95% CI, −12.25 to 9.17), −1.14 mm Hg (95% CI, −1.45 to −0.82), and −2.49 mm Hg (95% CI, −4.60 to −0.38), respectively. A significant difference between individual SGLT-2 inhibitors was observed (*P*=0.02).

Metaregression

Random-effects metaregression analysis showed no significant association between the 24-hour ambulatory systolic or diastolic BP and either baseline BP (*P*=0.96, *P*=0.69, respectively) or changes in body weight (*P*=0.44; *P*=0.88, respectively). Because relatively few studies for each drug reported 24-hour ambulatory BP data, we could not perform metaregression by individual drug dose.

Discussion

This meta-analysis involving 2098 participants showed that SGLT2 inhibitors significantly reduce 24-hour ambulatory systolic BP by −3.76 mm Hg and 24-hour ambulatory diastolic BP by −1.83 mm Hg. These results are similar to a previous meta-analysis of seated clinic BP, which showed a reduction in systolic BP of −3.8 mm Hg and diastolic BP of −1.6 mm Hg.[5] Additionally, our results show that SGLT2 inhibitors significantly reduce daytime systolic and diastolic BP and, to a lesser extent, nighttime systolic and diastolic BP. The effects of SGLT2 inhibitors on 24-hour ambulatory BP were consistent across the doses used in clinical trials. No association was found between baseline BP and change in body weight. Because direct comparisons between individual agents could not be made, the reduction in 24-hour ambulatory BP observed with SGLT2 inhibitors should be considered a class effect.

The exact mechanism(s) through which SGLT2 inhibitors lower BP are not completely understood, but are likely multifactorial. SGLT2 inhibitors induce volume contraction because of natriuretic and osmotic diuretic effects.[1] Because of chronic caloric deficit as a result of glucose excretion in the urine, SGLT2 inhibitors can also induce weight loss and, more important, body composition improvements by reduction of fat mass with minor changes in lean mass.[1,21] Fat mass reduction has been reported to improve BP, proposing this as an additional mechanism of BP reduction with SGLT2

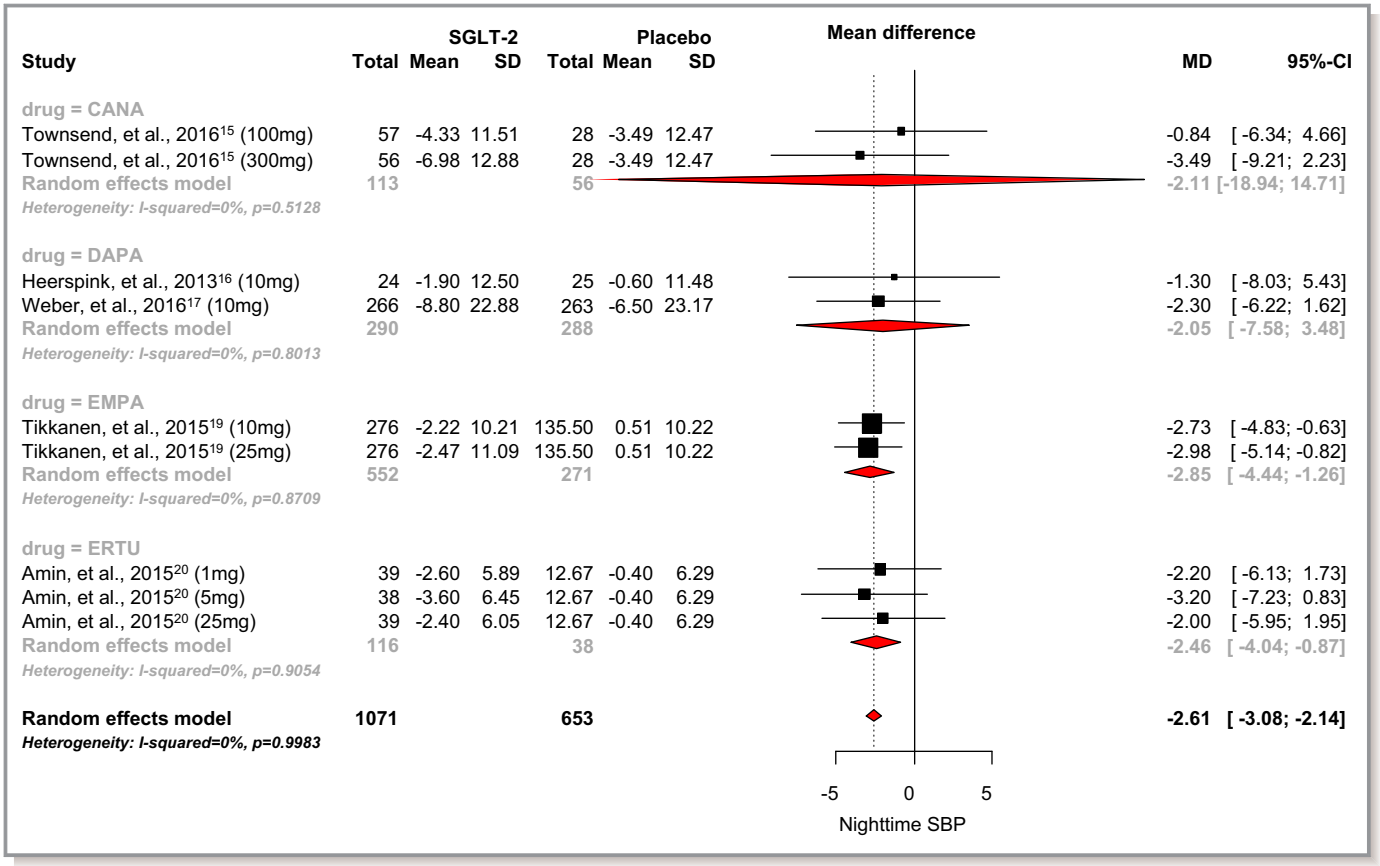

Figure 8. Effect of SGLT2 inhibitors on nighttime systolic blood pressure. CANA indicates canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; ERTU, ertugliflozin; MD, mean difference; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2 inhibitor.

inhibitors.[1] Treatment with SGLT2 inhibitors also improves arterial compliance, which is associated with improved BP.[1] Furthermore, SGLT2 inhibitors reduce sympathetic nervous system activity and, as recently suggested, renin-angiotensin-aldosterone system activity by increasing sodium delivery at the macula densa level in the kidney, both of which are important determinants of BP.[1,22] Further study is warranted to identify the underlying mechanism(s) that contribute to the apparent effects of SGLT2 inhibitors on BP.

In the current meta-analysis, it appears that the observed BP reduction with SGLT2 inhibitors persists throughout a 24-hour day with a greater percent reduction in BP during the daytime compared with nighttime. This may be, in part, attributed to the glucose-dependent nature of how SGLT2 inhibitors improve glycemic control, considering that osmotic diuresis is likely increased during daytime periods of higher caloric and fluid intake. Reduced urine production at night attributed to circadian rhythms in kidney function may also explain the reduced BP-lowering effect at nighttime. Of course, the BP-lowering effect of SGLT2 inhibitors may also be independent of diuresis, and differences in diurnal and nocturnal BP regulation may reflect differences in sympathetic tone.

The effects of other antihyperglycemic therapies on 24-hour ambulatory BP have also been reported. In a study of 220 patients, metformin was shown to have no significant effect on 24-hour ambulatory BP.[23] Sitagliptin, at doses of 50 mg twice-daily and 100 mg twice-daily, produced a small, but significant, reduction in 24-hour ambulatory systolic and diastolic BP of −2.0 to −2.2 mm Hg and −1.6 to −1.8 mm Hg, respectively, when compared with placebo.[24] Twice-daily exenatide[25] and once-daily liraglutide[26] have not been shown to significantly reduce 24-hour ambulatory BP, whereas dulaglutide 1.5 mg once-weekly significantly reduced 24-hour systolic BP by −2.8 mm Hg (95% CI, −4.6 to −1.0, $P \leq 0.001$) compared with placebo.[27] Interestingly, rosiglitazone significantly reduced 24-hour ambulatory systolic BP (−3.8 mm Hg) at both 6 and 12 months, when compared with adding metformin (−1.2 to −1.3 mm Hg; 6 months, $P=0.015$; 12 months, $P=0.031$) to background sulfonylurea therapy.[28] Similar reductions with rosiglitazone were also observed for 24-hour ambulatory diastolic BP. It is well established that hyperinsulinemia resulting from insulin resistance is associated with elevated BP; however, the effects of exogenous insulin on BP are variable.[29,30] Despite the favorable effects of select antihyperglycemic therapies on

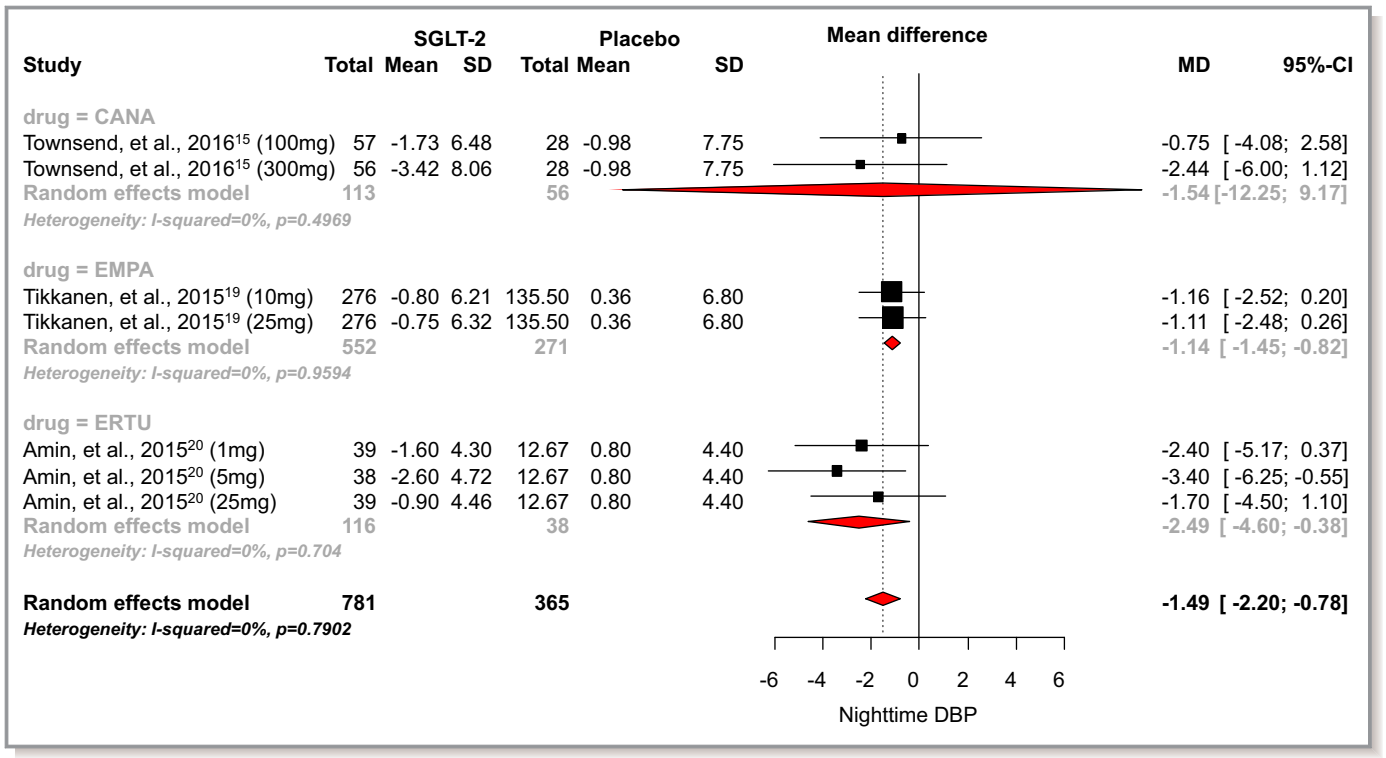

Figure 9. Effect of SGLT2 inhibitors on nighttime diastolic blood pressure. CANA indicates canagliflozin; DAPA, dapagliflozin; DBP, diastolic blood pressure; EMPA, empagliflozin; ERTU, ertugliflozin; MD, mean difference; SGLT2, sodium-glucose cotransporter 2 inhibitor.

24-hour ambulatory BP, none have been shown to improve cardiovascular outcomes. This is possibly attributed to other deleterious effects that may offset any benefit from a reduction in 24-hour ambulatory BP, such as the increase in plasma volume observed with thiazolidinediones.[31] Our analysis demonstrates that the SGLT2 inhibitors are the only known class to have a consistent and significant reduction in 24-hour ambulatory BP regardless of which agent is used.

The EMPA-REG OUTCOME trial[3] was the first study to demonstrate that an antihyperglycemic therapy, empagliflozin, significantly reduces death from cardiovascular causes, death from any cause, and hospitalization for heart failure. Additionally, a prespecified analysis of the EMPA-REG OUTCOME trial showed that empagliflozin also reduces progression of diabetic nephropathy.[32] In the EMPA-REG OUTCOME study, empagliflozin reduced seated clinic systolic BP by −4 to −6 mm Hg at week 16, whereas diastolic BP was similar to placebo.[3,33] Ongoing cardiovascular safety trials with canagliflozin (CANVAS [CANagliflozin cardioVascular Assessment Study], NCT01032629) and dapagliflozin DECLARE-TIMI 58 ([Dapagliflozin Effect on CardiovascuLAR Events-TIMI 58], NCT01730534) will determine whether the cardiovascular benefit of empagliflozin is a class effect. Much remains to be determined regarding the specific mechanism for how empagliflozin improves mortality and decreases heart failure hospitalizations, yet it seems feasible that the reductions in BP would contribute.

It is important to note the limitations of this analysis. Study protocols related to the measurement of 24-hour ambulatory BP varied between studies, as did baseline BP. However, metaregression showed no effects of SGLT2 inhibitors on BP according to baseline BP. Additional heterogeneity in the study populations also exists, such as presence or absence of a hypertension diagnosis and use and duration of background antihyperglycemic and antihypertensive therapies. Moreover, we were unable to test whether the observed reduction in 24-hour ambulatory BP would result in improvement in cardiovascular outcomes. The power of the statistical tests for funnel plot symmetry is likely to be low because of less than 10 trials being included.

Conclusions

This meta-analysis shows that SGLT2 inhibitors significantly improve overall 24-hour ambulatory BP and daytime and nighttime BP in a diurnal fashion. The linear relationship between 24-hour ambulatory BP and risk of cardiovascular events, especially in patients with diabetes mellitus, suggests that the favorable effects of SGLT2 inhibitors on 24-hour ambulatory BP may, at least in part, contribute to a reduction in cardiovascular risk.[7,34,35] While additional study is warranted to investigate mechanisms to describe the BP-lowering effects of SGLT2 inhibitors and the impact of these effects on clinical outcomes, these data highlight a unique characteristic of this

class. It also emphasizes the need for monitoring BP outside of the clinic through the use of home BP monitoring or 24-hour ambulatory BP monitoring, when available, to better monitor for hypotension. Caution is warranted in individuals with lower baseline BP and/or those already receiving diuretic therapies, whereas volume status should also be monitored closely.[36] Together with cardiovascular outcomes data from EMPA-REG and this meta-analysis on 24-hour ambulatory BP, the evidence continues to suggest a favorable effect of SGLT2 inhibitors on cardiovascular outcomes in patients with diabetes mellitus.

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Disclosures

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Effects of Sodium–Glucose Cotransporter 2 Inhibitors on 24–Hour Ambulatory Blood Pressure: A Systematic Review and Meta–Analysis

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