Ambulatory Blood Pressure Reduction With SGLT-2 Inhibitors: Dose-Response Meta-analysis and Comparative Evaluation With Low-Dose Hydrochlorothiazide

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OBJECTIVE

Sodium–glucose cotransporter (SGLT)-2 inhibitors lower clinic and ambulatory blood pressure (BP), possibly through their natriuretic action. However, it remains unclear whether this BP-lowering effect is dose dependent and different from that of low-dose hydrochlorothiazide. The purpose of this meta-analysis was to quantify the association of the dose with response of ambulatory BP to SGLT-2 inhibition and to provide comparative evaluation with low-dose hydrochlorothiazide.

RESEARCH DESIGN AND METHODS

PubMed/MEDLINE, Embase, and Cochrane database of clinical trials from inception of each database through 22 August 2018. Randomized controlled trials (RCTs) reporting treatment effects of SGLT-2 inhibitors on ambulatory BP. We extracted data on the mean difference between the active treatment and placebo groups in change from baseline (CFB) of ambulatory systolic and diastolic BP.

RESULTS

We identified seven RCTs (involving 2,381 participants) comparing SGLT-2 inhibitors with placebo. Of these, two RCTs included low-dose hydrochlorothiazide as active comparator. CFB in 24-h systolic BP between SGLT-2 inhibitor and placebo groups was −3.62 mmHg (95% CI −4.29, −2.94) and in diastolic BP was −1.70 mmHg (95% CI −2.13, −1.26). BP lowering with SGLT-2 inhibition was more potent during daytime than during nighttime. The CFB in ambulatory BP was comparable between low-dose and high-dose subgroups and was similar to that for low-dose hydrochlorothiazide. Eligible RCTs did not evaluate cardiovascular outcomes/mortality.

CONCLUSIONS

This meta-analysis shows that SGLT-2 inhibitors provoke an average reduction of systolic/diastolic BP 3.62/1.70 mmHg in 24-h ambulatory BP. This BP-lowering effect remains unmodified regardless of the dose of SGLT-2 inhibitor and is comparable with BP-lowering efficacy of low-dose hydrochlorothiazide.

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META-ANALYSIS

Worldwide, diabetes is a major cause of increased burden of cardiovascular morbidity and mortality. Recently, a new class of drugs, the sodium–glucose cotransporter (SGLT)-2 inhibitors, have been used to treat patients with type 2 diabetes (1). These trials show that SGLT-2 inhibitors may confer cardiovascular protection, including a reduction in cardiovascular death (2,3). Furthermore, these trials also demonstrate a reduced risk of hospitalization due to heart failure (2,3). One mechanism that may account for cardiovascular benefit of this class of drugs appears to be through blood pressure (BP) reduction (1). Prior studies have shown that reducing BP can reduce cardiovascular morbidity and mortality (4). Furthermore, BP reduction has a profound effect on reduction in heart failure hospitalization (4,5). In clinical trials, BP reduction is often measured in the clinic. However, ambulatory BP monitoring (ABPM) has emerged as a more reliable measure to predict adverse cardiovascular events (6).

In this meta-analysis, we ask the following questions: *1*) whether approved SGLT-2 inhibitors in the U.S. can improve ambulatory BP over 24 h, during daytime, and during night; *2*) whether the dose of the SGLT-2 inhibitor is related to an improvement in BP; and *3*) whether the BP-lowering effects of SGLT-2 inhibitors are similar to that seen with hydrochlorothiazide. We reasoned that if these drugs simply improved BP similar to improvement seen with hydrochlorothiazide, then the cardiovascular benefits of SGLT-2 inhibitors may extend beyond BP lowering.

A prior meta-analysis has already examined the mean reduction in 24-h ambulatory BP and reported it as 3.76 mmHg systolic reduction and 1.83 mmHg diastolic reduction compared with placebo (7). However, the two questions that we pose—the dose-response relationship and the comparison of the results with hydrochlorothiazide—were not examined in the prior meta-analysis. Therefore, besides updating the prior meta-analysis, our study provides answers to questions that are relevant and timely.

RESEARCH DESIGN AND METHODS

Literature Search and Selection of Trials

To identify randomized controlled trials (RCTs) evaluating the effect of SGLT-2 inhibitors on ambulatory BP, we performed a systematic literature search of PubMed/MEDLINE, Embase, and Cochrane database of clinical trials using a structured search strategy reported in Supplementary Table 1. Literature search had no language restrictions and was carried out from inception of each database through 22 August 2018. Reference lists of articles retrieved for detailed evaluation, relevant review articles, and earlier meta-analyses were also examined to identify additional studies for potential inclusion in this quantitative review.

Suitability of each identified article for inclusion was independently adjudicated by two authors using prespecified selection criteria. Disagreements between authors were resolved by consensus. We included RCTs with a follow-up of at least 4 weeks enrolling adult patients with diabetes, in which the BP-lowering effect of SGLT-2 inhibitors was compared with placebo or active therapy with other antidiabetes medications and/or hydrochlorothiazide. To be eligible, the study had to report treatment effects on 24-h ambulatory BP in a manner suitable for quantitative data synthesis.

Data Extraction and Study Quality Assessment

A purpose-built data collection form was used to extract the following characteristics of each eligible study: study design, participant characteristics (age, sex, baseline levels of clinic and 24-h ambulatory BP, hypertension status, and background therapy with antihypertensive medications), therapeutic interventions (type of SGLT-2 inhibitor, dose, and background therapy with antidiabetes medications or insulin), duration of follow-up, comparison groups, and outcomes of interest. All data were extracted independently by two investigators and were confirmed for accuracy by the primary investigator (R.A.).

The method quality of each eligible study was assessed by two authors independently using the Risk of Bias (RoB) 2.0 tool (8). This tool includes a description and a judgment in a table that addresses specific sources of bias for every study, including the following: bias arising from the randomization process, bias due to deviations from intended intervention, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result (8).

Statistical Analysis

We used a fixed-effects model to estimate the weighted mean difference between the active treatment and placebo groups in change from baseline (CFB) of ambulatory systolic and diastolic BP. We provide effect estimates separately for 24-h, daytime, and nighttime periods. We used the I^2 statistic in order to quantify statistical heterogeneity among individual studies. For exploration of potential interactions between the dose and response of ambulatory BP to therapy, eligible RCTs were stratified according to the dose of SGLT-2 inhibitor (low versus high dose). Specifically, treatment arms of individual RCTs with the highest recommended daily dose for each SGLT-2 inhibitor (i.e., canagliflozin 300 mg/day, dapagliflozin 10 mg/day, empagliflozin 25 mg/day, and ertugliflozin 25 mg/day) were stratified in the high-dose subgroup. All other treatment arms using a dose lower than the highest recommended dose were combined in the low-dose subgroup. For comparison of the BP-lowering effect of SGLT-2 inhibitors with that of low-dose hydrochlorothiazide, eligible RCTs were stratified according to active treatment (SGLT-2 inhibitor versus low-dose hydrochlorothiazide). To explore the association of baseline ambulatory BP with the reduction in ambulatory BP provoked by SGLT-2 inhibitors, we performed random-effects meta-regression analysis. All analyses were performed using the metan and metareg commands in Stata 14.2 (StataCorp LLC, College Station, TX).

RESULTS

Trial Flow and Study Characteristics

The literature search and flow diagram of study selection are depicted in Fig. 1. Of the 289 studies initially identified and screened, 64 studies were considered potentially relevant and were retrieved for detailed evaluation. Of these, 57 studies were excluded for the following reasons: no use of ABPM in assessment of the BP-lowering effect of SGLT-2 inhibitors (n = 46), absence of randomization (n = 8), protocol of an ongoing trial (n = 1), and duplicate publication (n = 2). A total of seven RCTs, enrolling 2,381

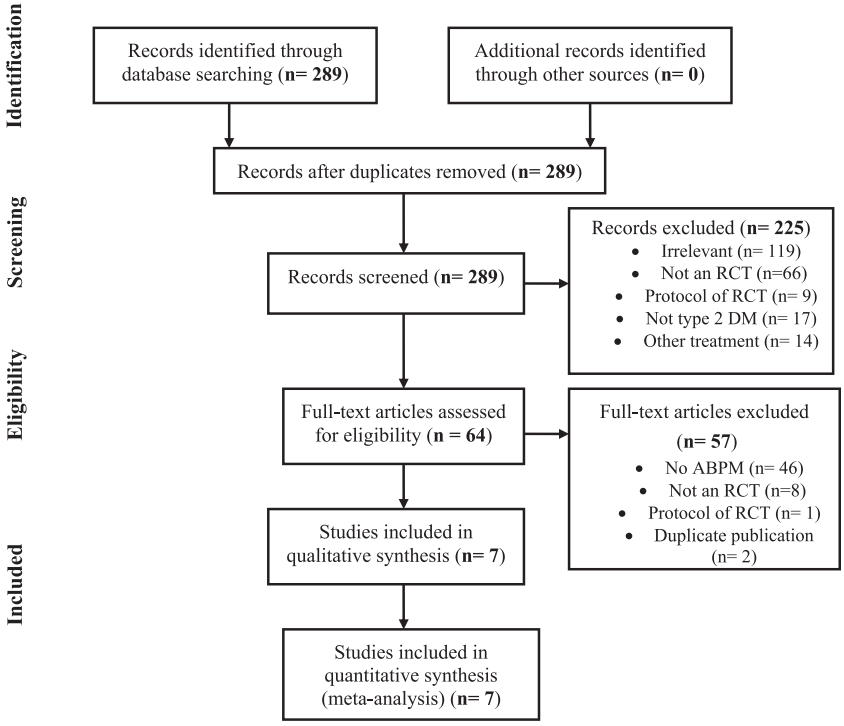

Figure 1—Flow diagram of studies considered for inclusion. DM, diabetes.

adult participants with type 2 diabetes, were finally included in quantitative data synthesis (9–15).

As shown in Table 1, of the seven double-blind, placebo-controlled RCTs included, six followed a parallel-group assignment (9,11–15) and one followed a crossover design (10). Of these, four studies used dapagliflozin administered at a single dose of 10 mg/day (10,11,14,15), one study used empagliflozin administered at doses of 10 and 25 mg/day (12), one study used canagliflozin at doses of 100 and 300 mg/day (13), and one study used ertugliflozin at doses ranging from 1 to 25 mg/day (9). In two of seven studies, low-dose hydrochlorothiazide (12.5–25 mg/day) was used as active comparator (9,11). The number of participants randomly assigned to SGLT-2 inhibitor therapy ranged from 24 to 302, the number of placebo-treated participants ranged from 25 to 311, and the number of participants randomized to low-dose hydrochlorothiazide ranged from 26 to 39. Duration of follow-up ranged from 4 to 12 weeks. Additional data on background antihypertensive therapy are depicted in Supplementary Table 3. Background antihypertensive therapy was continued during follow-up in six out of seven eligible RCTs (9,11–15), but modifications in the intensity of therapy were prohibited by protocol on all occasions.

Method quality was assessed for all studies using the RoB 2.0 tool (Supplementary Table 2); no studies were excluded as a result of suboptimal method quality.

Effect on 24-h Ambulatory Systolic and Diastolic BP

We identified seven RCTs (9–15) that compared SGLT-2 inhibitors with placebo and reported data on 24-h systolic BP. CFB in 24-h systolic BP between the SGLT-2 inhibitors and placebo was −3.62 mmHg (95% CI −4.23, −2.94) (Fig. 2) and for 24-h diastolic BP, reported in five RCTs (9,10,12–14), was −1.70 mmHg (95% CI −2.13, −1.26) (Fig. 3). There was no evidence of heterogeneity across studies with respect to both 24-h systolic BP (I^2 = 0, P = 0.936) and diastolic BP (I^2 = 0, P = 0.435).

As shown in Fig. 4, for exploration of potential dose-response associations, RCTs were stratified by dose of SGLT-2 inhibitor. In the low-dose subgroup, CFB in 24-h systolic BP between SGLT-2 inhibitors and placebo differed by −3.50-mmHg (95% CI −4.67, −2.32); in the high-dose subgroup, the difference was −3.73 mmHg (95% CI −4.57, −2.88). There was no evidence of heterogeneity between subgroups (P = 0.756). In the low-dose subgroup, CFB in 24-h diastolic BP between SGLT-2 inhibitors and placebo was −1.62 mmHg (95% CI −2.32, −0.91); in the high-dose subgroup, it was −1.67 mmHg (95% CI −2.25, −1.10). Once again, no heterogeneity between subgroups was evident (P = 0.903) (Supplementary Figs. 1 and 2 for forest plots).

For comparison of the BP-lowering effect of SGLT-2 inhibitors with that of low-dose hydrochlorothiazide, RCTs were stratified by active treatment. CFB in 24-h systolic BP between the SGLT-2 inhibitors and placebo was −3.62 mmHg (95% CI −4.29, −2.94) and for low-dose hydrochlorothiazide was −3.46 mmHg (95% CI −6.15, −0.77). CFB in 24-h diastolic BP averaged −1.70 mmHg (95% CI −2.13, −1.26) for SGLT-2 inhibitor and −2.23 mmHg (95% CI −4.34, −0.12) for low-dose hydrochlorothiazide (Fig. 4). Thus, the BP-lowering effect of SGLT-2 inhibitors was comparable with that of low-dose hydrochlorothiazide (see Supplementary Figs. 3 and 4 for forest plots).

In meta-regression analysis, 24-h systolic and diastolic BP at baseline had no association with the reduction in 24-h BP provoked by SGLT-2 inhibitors (see Supplementary Figs. 17 and 18).

Effect on Daytime Systolic and Diastolic BP

CFB in daytime systolic BP between the SGLT-2 inhibitors and placebo was reported in six RCTs (9,11–15) and averaged −4.32 mmHg (95% CI −5.06, −3.57). CFB in daytime diastolic BP between the SGLT-2 inhibitors and placebo was reported in four RCTs (9,12,13,15) and averaged −2.03 mmHg (95% CI −2.53, −1.53). When the analysis was stratified by low versus high SGLT-2 inhibitor dose, no significant interaction between the dose and response of daytime systolic and diastolic BP to SGLT inhibitor therapy was evident. When the analysis was stratified according to the type of active comparator, the magnitude of decrease in daytime systolic and diastolic BP relative to placebo was similar in the SGLT-2 and low-dose hydrochlorothiazide subgroups (Fig. 4) (see Supplementary Figs. 5–10 for forest plots).

Random-effects meta-regression showed no association of daytime systolic and diastolic BP at baseline with the reduction

Table 1—Characteristics of studies included in systematic review and quantitative data synthesis

Trial	Year	Study design	Follow-up (weeks)	Groups	*N*	Age (yrs)	Sex (M/F)	Duration of diabetes (yrs)	HbA_{1c} at baseline (%)	24-h BP at baseline (mmHg)	CFB in 24-h BP (mmHg)
Lambers Heerspink et al. (11)	2013	Double-blind, parallel	12	Placebo	25	58.0	18/7	6.5	7.5	131.0/74.0	−0.7*
				Dapa (10 mg/day)	24	53.7	16/8	6.5	7.7	133.0/76.0	−5.6*
				HCTZ (25 mg/day)	26	54.8	15/11	6.0	7.4	122.0/69.0	−4.9*
Tikkanen et al. (12)	2015	Double-blind, parallel	12	Placebo	271	60.3	168/103	NA	7.9	131.7/75.2	0.48/0.32
				Empa (10 mg/day)	276	60.6	171/105	NA	7.9	131.3/75.1	−3.44/−1.04
				Empa (25 mg/day)	276	59.9	156/120	NA	7.9	131.2/74.6	−4.16/−1.72
Weber et al. (14)	2015	Double-blind, parallel	12	Placebo	311	56.2	171/140	7.6	8.0	146.6/87.2	−6.7/−5.5
				Dapa (10 mg/day)	302	55.6	179/123	8.2	8.1	145.9/87.0	−9.6/−6.2
Amin et al. (9)	2015	Double-blind, parallel	4	Placebo	38	55.1	24/14	6.4	8.2	136.1/81.9	—
				Ertu (1 mg/day)	39	54.4	27/12	7.5	8.4	133.1/78.7	−2.97/−2.7**
				Ertu (5 mg/day)	38	53.8	25/13	5.5	8.1	135.1/80.2	−4.0/−3.18**
				Ertu (25 mg/day)	39	52.5	27/12	5.8	8.3	135.6/80.4	−3.69/−2.3**
				HCTZ (12.5 mg/day)	39	56.5	28/11	8.2	8.2	139.5/82.7	−3.2/−2.23**
Townsend et al. (13)	2016	Double-blind, parallel	6	Placebo	56	59.6	33/23	NA	8.2	136.7/78.4	−1.2/−0.3
				Cana (100 mg/day)	57	57.8	34/23	NA	8.1	136.5/78	−4.5/−2.2
				Cana (300 mg/day)	56	58.3	31/25	NA	8.0	139.6/79.3	−6.2/−3.2
Weber et al. (15)	2016	Double-blind, parallel	12	Placebo	224	57.0	129/95	7.3	8.0	149.2*	—
				Dapa (10 mg/day)	225	56.0	118/107	7.7	8.1	146.5*	−4.45**
Karg et al. (10)	2018	Double-blind, crossover	6	Placebo							−0.5/0
				Dapa (10 mg/day)	59	60.3	36/29	5.5	6.7	129.0/77.0	−3.0/−2.0

Cana, canagliflozin; Dapa, dapagliflozin; Empa, empagliflozin; Ertu, ertugliflozin; HCTZ, hydrochlorothiazide; F, female; M, male; NA, not available; yrs, years. *Data on diastolic BP were not reported. **Placebo-adjusted CFB is reported.

in daytime BP provoked by SGLT-2 inhibitors (see Supplementary Figs. 19 and 20).

Effect on Nighttime Systolic and Diastolic BP

CFB in nighttime systolic BP between the SGLT-2 inhibitors and placebo was reported in six RCTs (9,11–15) and averaged −2.62 mmHg (95% CI −3.46, −1.78). CFB in nighttime diastolic BP between the SGLT-2 inhibitors and placebo was reported in four RCTs (9,12,13,15) and averaged −1.39 mmHg (95% CI −1.96, −0.81). Analyses stratified by dose of SGLT-2 inhibitors revealed similar CFB in nighttime systolic and diastolic BP between low-dose and high-dose SGLT-2 inhibitors, indicating absence of dose-response relationship (Fig. 4). The magnitude of decrease in nighttime systolic and diastolic BP relative to placebo did not differ between the SGLT-2 and low-dose hydrochlorothiazide subgroups (see Supplementary Figs. 11–16 for forest plots).

Random-effects meta-regression showed no association of nighttime systolic and diastolic BP at baseline with the reduction in nighttime BP provoked by SGLT-2 inhibitors (see Supplementary Figs. 21 and 22).

CONCLUSIONS

This systematic review and meta-analysis aimed to explore the BP-lowering action of SGLT-2 inhibitors by combining RCTs reporting treatment-induced changes in ambulatory BP. The effect of these agents on clinic BP was quantified in a 2017 meta-analysis of 43 RCTs (16) in which SGLT-2 inhibitors provoked an average systolic/diastolic BP reduction of 2.4/1.46 mmHg relative to placebo. A subsequent meta-analysis of six RCTs (involving 2,098 participants) showed that compared with placebo, SGLT-2 inhibitors lowered 24-h BP by 3.76/1.83 mmHg (7). Despite the fact that our updated literature search led to the identification of only one additional ABPM trial, this study expands the results of prior meta-analyses providing the following findings: *1*) compared with placebo, SGLT-2 inhibitors lowered 24-h BP by 3.62/1.70 mmHg, a BP-lowering action that was more potent during daytime than during nighttime; *2*) the magnitude of ambulatory BP reduction was similar regardless of the dose of

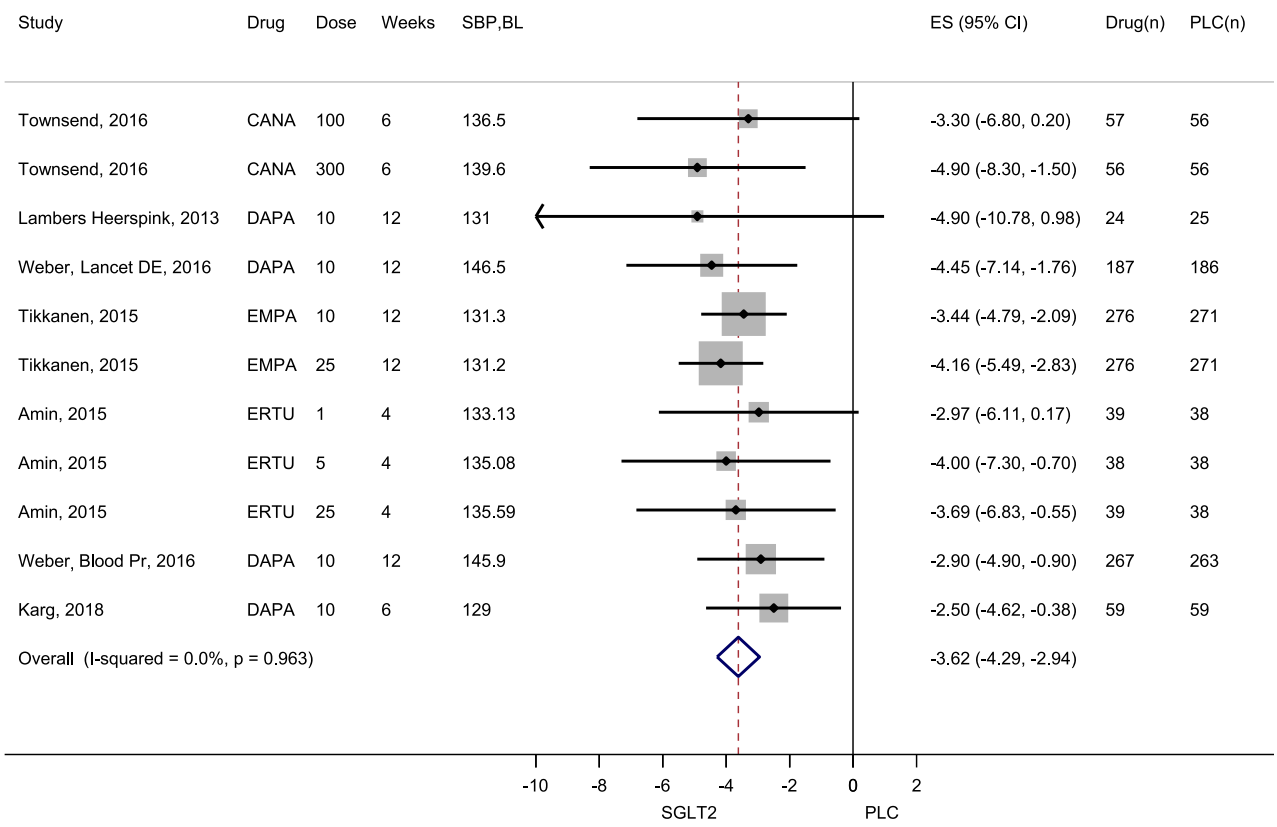

Figure 2—Forest plot depicting the CFB in 24-h ambulatory systolic BP (SBP) in the SGLT-2 group minus CFB in the placebo group. Blood Pr: Weber et al. (14); Lancet DE: Weber et al. (15). BL, baseline; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; ERTU, ertugliflozin; ES, effect size; PLC, placebo.

SGLT-2 inhibitor, suggesting a rather flat dose-response relationship; *3*) the magnitude of ambulatory BP reduction with SGLT-2 inhibition was comparable with the BP-lowering effect of low-dose hydrochlorothiazide; and *4*) ambulatory BP at baseline had no association with the treatment-induced reduction in ambulatory BP.

Two large randomized trials designed to test the cardiovascular safety of SGLT-2 inhibitors provided evidence in favor of a cardioprotective action of this drug class. In the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial (3), compared with placebo, empagliflozin lowered by 32%, 38%, and 35% the risk of all-cause mortality, cardiovascular mortality, and hospitalization due to worsening heart failure, respectively (3). Similarly, in the CANagliflozin cardioVascular Assessment Study (CANVAS) Program (2), canagliflozin lowered by 14% the risk of cardiovascular death and by 33% the risk of heart failure hospitalization relative to placebo (2). The extent to which this cardiovascular risk reduction is mediated through the BP-lowering action of SGLT-2 inhibitors is an issue of substantial controversy. If this BP-lowering effect is similar to that of low-dose hydrochlorothiazide, as is evident in the present meta-analysis, then the hypothesis of a BP-mediated cardiovascular benefit of these agents appears to be a less likely explanation. Meta-analyses of RCTs showed that monotherapy with low-dose hydrochlorothiazide is inferior to monotherapy with all other antihypertensive drug categories in reducing ambulatory BP (17). Notably, a benefit of monotherapy with low-dose hydrochlorothiazide on cardiovascular outcomes is not supported by "hard" clinical trial evidence. In addition, the overall cardiovascular risk reduction offered by diuretics—as class effect—may be not applicable to low-dose hydrochlorothiazide owing to its less potent natriuretic and BP-lowering action (18,19). Meta-regression analysis of 123 studies (incorporating data from 613,815 participants) showed that the relative risk reduction in major cardiovascular outcomes is proportional to the treatment-induced reduction in BP levels (20). Accordingly, an average reduction of 3.62/1.70 mmHg in 24-h BP with SGLT-2 inhibitors, seen in the present meta-analysis, can only partially explain the results of the EMPA-REG OUTCOME trial and CANVAS. If BP lowering was the prominent mediator of cardiovascular risk reduction, then an improvement in atherosclerotic cardiovascular events also should have occurred. In contrast, no such benefit on the risk of nonfatal myocardial infarction or stroke was evident in these trials (2,3).

The exact mechanisms responsible for the BP-lowering action of SGLT-2 inhibitors still remain elusive. Contraction in plasma volume mediated through natriuresis suggests a diuretic-like BP-lowering effect of SGLT-2 inhibitors (1,21). However, SGLT-2 inhibitors differ from thiazides in that they have a relatively flat dose-response relationship. In a 2011 dose-response meta-analysis including 11 RCTs using low-dose (12.5–25 mg/day) and 5 RCTs using high-dose (50 mg/day) hydrochlorothiazide, the CFB in 24-h BP averaged −6.5/−4.5 mmHg

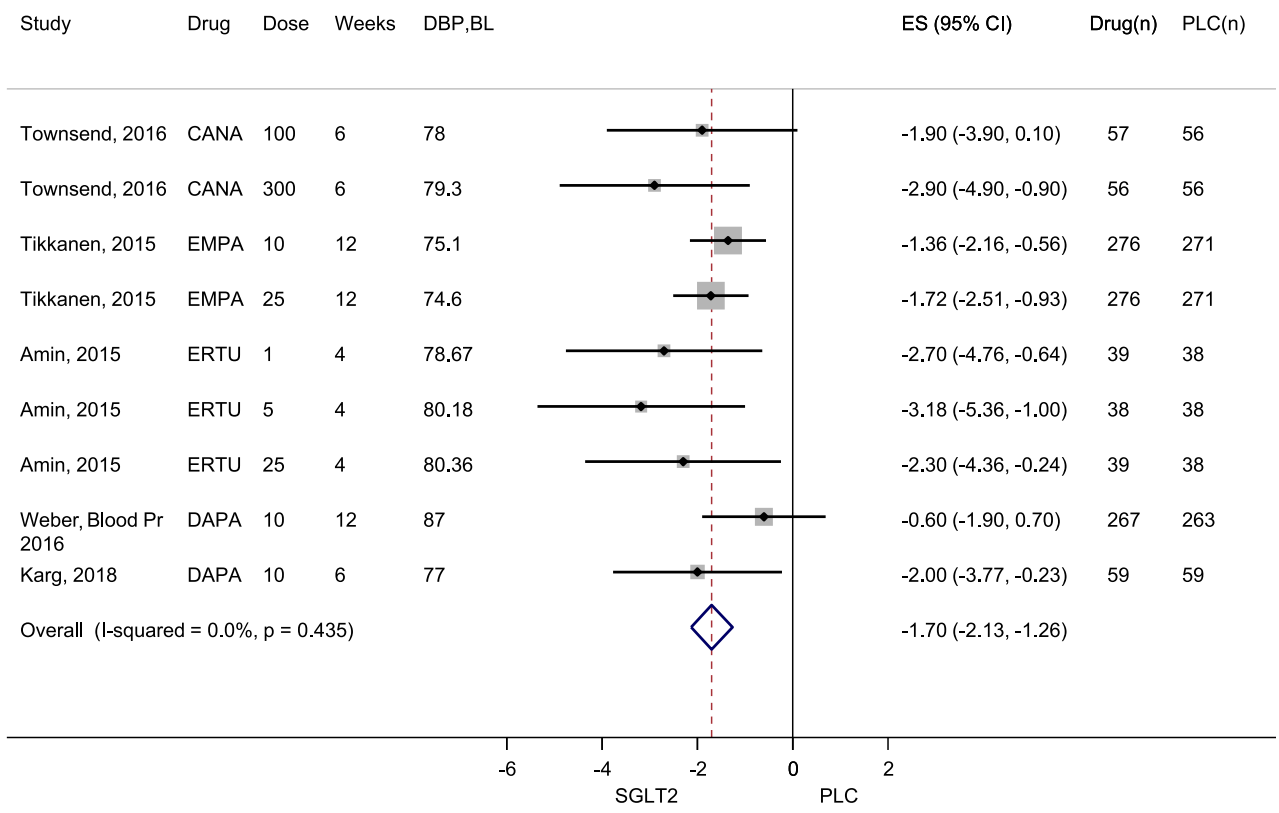

Figure 3—Forest plot depicting the CFB in 24-h ambulatory diastolic BP (DBP) in the SGLT-2 group minus CFB in the placebo group. Blood Pr: Weber et al. (14). BL, baseline; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; ERTU, ertugliflozin; ES, effect size; PLC, placebo.

with low-dose hydrochlorothiazide (17); however, the CFB in 24-h BP was −12.0/−5.4 mmHg with high-dose hydrochlorothiazide (17). A dose-dependent BP-lowering action of hydrochlorothiazide is also supported by a 2014 Cochrane meta-analysis of 33 RCTs (22), in which the placebo-subtracted CFB in clinic BP with hydrochlorothiazide doses of 6.25, 12.5, 25, and 50 mg/day was −4/−2 mmHg, −6/−3 mmHg, −8/−3 mmHg, and −11/−5 mmHg, respectively (22).

Both SGLT-2 inhibitors and hydrochlorothiazide have a greater effect on daytime rather than nighttime BP. It is thought that SGLT-2 inhibitors have an attenuated glycosuric/natriuretic effect at night (1). Among patients with stage I hypertension, low-dose hydrochlorothiazide (12.5 mg/day) was inferior to chlorothalidone (6.25 mg/day) in lowering nighttime BP (23). By contrast, extended-release formulation hydrochlorothiazide was equally effective with chlorothalidone in improving nocturnal hypertension (23). Given that the cardiovascular protective effects of SGLT-2 inhibitors surpassed even chlorothalidone, the salutary effects cannot be attributed to BP reduction or the patterns of BP reduction per se.

Several non–BP-lowering benefits of SLGT-2 inhibitors have been proposed. Randomized trials have shown that SGLT-2 inhibitors reduce aortic pulse wave velocity and other measures of arterial stiffness (24,25), generating the hypothesis that improvement in arterial stiffness may be another plausible mechanistic explanation for cardiovascular benefit. Long-term weight loss and improvement in body fat distribution are proposed as additional pathways (26). Notably, clinical data dissociate long-term weight reduction with BP lowering, suggesting that only the initial weight loss—that is mediated through plasma volume contraction—may partially explain the BP-lowering effect of SGLT-2 inhibitors (1,21,27). Suppression of the renin-angiotensin-aldosterone and sympathetic nervous systems and improvement in nitric oxide bioactivity are less likely mechanistic explanations for cardiovascular protection in light of studies showing that these neuro-hormonal pathways remain unchanged in response to SGLT-2 inhibition (1,24,27).

This study has strengths and limitations. A strength of this study is that its design prespecified comparative analysis of included RCTs stratified by the dose of SGLT-2 inhibitor and type of active treatment. Accordingly, this meta-analysis not only updates but also expands the results of prior meta-analyses, providing novel data on the dose-response relationship of SGLT-2 inhibitors with ambulatory BP reduction as well as comparison of the BP-lowering effect of SGLT-2 inhibitors with low-dose hydrochlorothiazide. However, this study also has some limitations that need to be acknowledged. As commonly occurring in any quantitative review, RCTs combined in this meta-analysis differed in terms of design, participant characteristics, duration of follow-up, type of active treatment, and intensity of background antidiabetes and antihypertensive therapy. We have reasons to believe that these unavoidable differences across individual RCTs have not influenced the strength of our findings in the absence of statistically significant

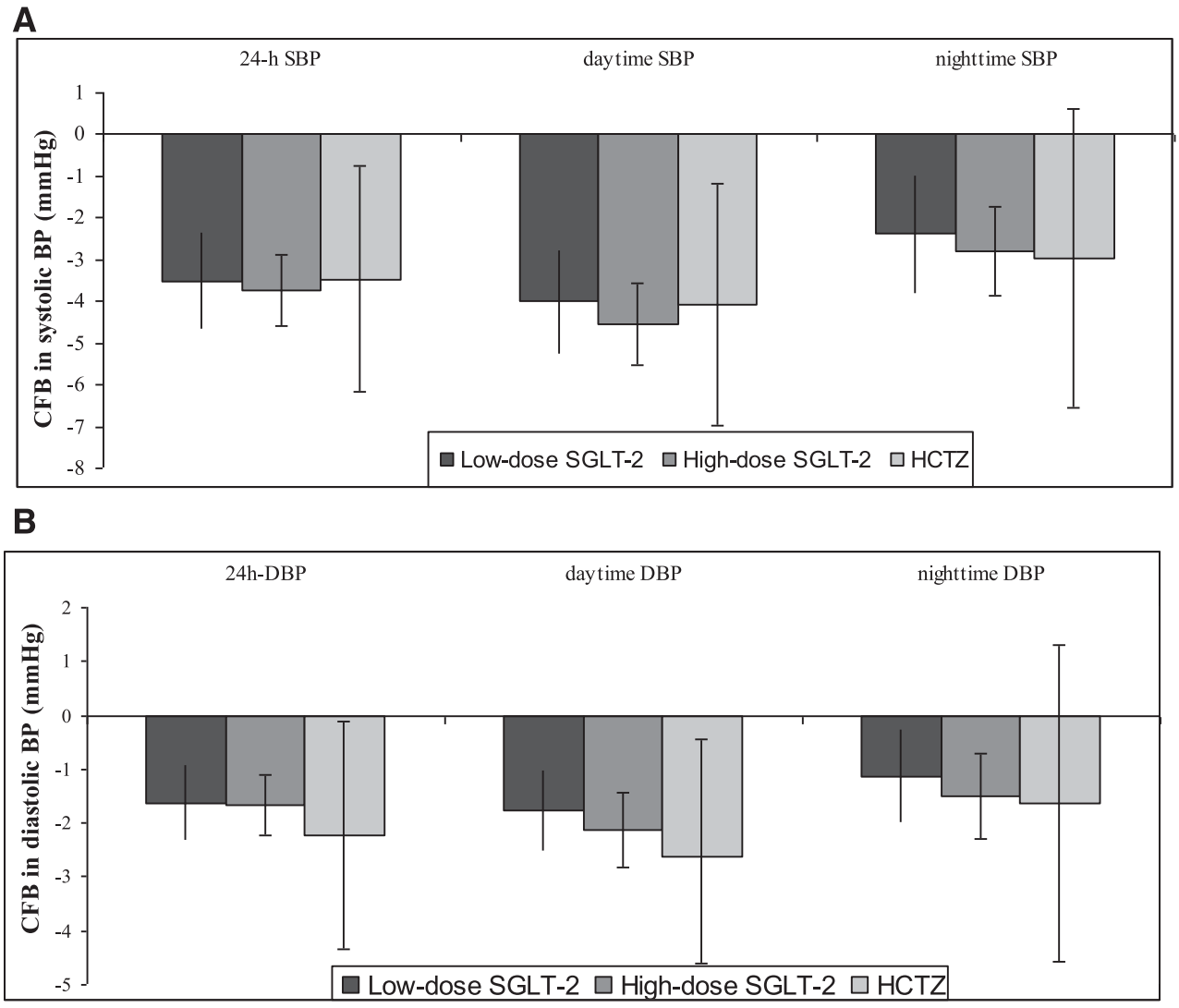

Figure 4—Placebo-subtracted CFB in 24-h, daytime, and nighttime systolic (*A*) (SBP) and diastolic (*B*) BP (DBP) with low-dose SGLT-2 inhibitors, high-dose SGLT-2 inhibitors, and low-dose hydrochlorothiazide (HCTZ). The *y*-axis shows the CFB in ambulatory BP. The *x*-axis shows the period of BP monitoring (24-h, daytime, and nighttime). The error bars represent the 95% CI of the placebo-subtracted CFB in ambulatory BP.

heterogeneity in quantitative data synthesis. Another possible limitation is that eligible RCTs did not examine the effect of SGLT-2 inhibitors on cardiovascular outcomes and mortality. Accordingly, the association of BP lowering with the cardiovascular risk reduction offered by SGLT-2 inhibitors cannot be quantified in this meta-analysis.

In conclusion, this meta-analysis shows that among patients with type 2 diabetes, SGLT-2 inhibitors provoke an average reduction of 3.62/1.70 mmHg in 24-h ambulatory BP. This BP-lowering effect is more potent during daytime than during nighttime and is not modified by the dose of SGLT-2 inhibitor. Importantly, the effect of SGLT-2 inhibitors on ambulatory BP is comparable with that of low-dose hydrochlorothiazide. If BP-lowering efficacy of these two drug categories is truly equal, BP lowering per se only partially explains the impressive cardioprotective action demonstrated in large-scale outcome trials testing the cardiovascular safety of SGLT-2 inhibitors.

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Duality of Interest. R.A. is a member of data safety monitoring committees for AstraZeneca and Ironwood Pharmaceuticals; a member of steering committees of randomized trials for Akebia Therapeutics, Bayer, Janssen, GlaxoSmithKline, Relypsa, and Sanofi Genzyme; a member of adjudication committees for Bayer, Boehringer Ingelheim, and Janssen; and a member of scientific advisory boards or a consultant for Celgene, Daiichi Sankyo, Inc., Eli Lilly, Relypsa, Reata Pharmaceuticals, Takeda Pharmaceuticals U.S.A., and ZS Pharma. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. P.I.G. contributed to literature search, data extraction, and study quality assessment and wrote the first draft of the manuscript. R.A. contributed to concept and design, literature search, data extraction, study quality assessment, statistical analysis, and manuscript revision.

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