Effect of sodium-glucose cotransporter-2 inhibitors on patients with essential hypertension and pre-hypertension: a meta-analysis

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Abstract
Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors are novel, hypoglycemic drugs exhibiting cardiovascular protective activities. If SGLT2 inhibitors can be successfully used as antihypertensive drugs, they can be administered to patients with both hypertension and type 2 diabetes, thus diminishing the risk of polypharmacy-related complications. Aim: The aim of this review was to evaluate the hypotensive efficacy of SGLT2 inhibitors in patients with hypertension and pre-hypertension. Data Sources and Methods: We systematically searched PubMed, Embase, and Cochrane for randomized controlled trials comparing SGLT2 inhibitors and a placebo in patients with essential hypertension and pre-hypertension. Our main outcome was the mean change in office blood pressure (BP) and body weight. We assessed the pooled data using a fixed-effects model. Results: After screening 968 articles, nine trials were eligible (n = 2450 participants). Compared to the mean changes in systolic and diastolic BP in patients who were given a placebo, those in patients who used SGLT2 inhibitors were −5.04 mmHg and −1.67 mmHg, respectively. An intensive dose of SGLT2 inhibitors resulted in a stronger BP-lowering effect than the regular dose. Compared to that in the placebo group, the mean change in mean body weight was −1.74 kg in the SGLT2 inhibitor group. There was no significant difference between the two groups regarding the risk of overall adverse events. The pooled effect estimates remained similar across all residual studies and their subgroups in the leave-one-out sensitivity analysis. Conclusion: SGLT2 inhibitors had a statistically significant BP-lowering effect on hypertension and pre-hypertension, which was further enhanced with increased drug dosage. SGLT2 inhibitors have the potential to be used as antihypertensive agents in patients with hypertension complicated by type 2 diabetes.

Keywords: hypertension, meta-analysis, pharmacotherapy, sodium-glucose cotransporter-2 inhibitors

Introduction
Essential hypertension is a prevalent chronic disease that has several risk factors, including obesity and age. Pre-hypertension is a crucial stage in the prevention and treatment of hypertension and is defined as a systolic blood pressure (BP) of 120–139 mmHg and/or a diastolic BP of 80–89 mmHg. Both essential hypertension and pre-hypertension have been proven to increase the risk of cardiovascular disease. Furthermore,
hypertension is often associated with type 2 diabetes mellitus (T2DM), and thus synergistic therapies which reduce polypharmacy are preferred. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are novel antidiabetic drugs. These glucose-lowering agents target the kidney, simultaneously reducing glucose reabsorption and promoting glucose excretion in urine, and thereby decreasing hyperglycemia in patients with T2DM. In addition to their salutary effect on diabetes, SGLT2 inhibitors have demonstrated cardiovascular protective effects in a number of trials. Currently, these drugs are widely used by patients with T2DM to improve glycemic control and reduce the incidence of cardiovascular disease.

SGLT2 inhibitors inhibit the reabsorption of sodium by proximal convolution tubules, which cause natriuresis and osmotic diuresis. This, in turn, results in the reduction of plasma volume and BP. Therefore, SGLT2 inhibitors exhibit both hypotensive and hypoglycemic effects. However, the antihypertensive amplitude of SGLT2 inhibitors for essential hypertension and pre-hypertension has not been fully investigated nor has its potential as an antihypertensive drug. Using SGLT2 inhibitors for hypertension may only not provide cardiovascular protection but also slow down the rise of polypharmacy. The aim of this meta-analysis of randomized controlled trials (RCTs) is to evaluate the hypotensive efficacy of SGLT2 inhibitors on patients with hypertension and pre-hypertension. Furthermore, since obesity is a risk factor for hypertension and SGLT2 inhibitors are associated with weight loss, we also evaluated weight change in our meta-analysis.

Methods
This meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was registered at International Platform of Registered Systematic Review and Meta-analysis Protocols (Number: INPLASY2021 20004).

Literature search
We searched the following databases for relevant English language literature: MEDLINE-PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), and Embase. We included all published RCTs up to June 18, 2021. The medical subject headings (MeSH) and/or keywords used were: ‘Sodium glucose cotransporter 2 inhibitor’, ‘sodium glucose transporter 2 inhibitor’, ‘SGLT2 inhibitor’, ‘gliflozin’, ‘PF-04971729’, ‘TA-7284’, ‘BMS-512148’, ‘Invokana’, ‘Farxiga’, ‘Jardiance’, ‘hypertension’, ‘high blood pressure’, ‘hypertensive’, ‘HTN’, ‘HBP’, ‘blood pressure’, ‘systolic pressure’, ‘diastolic pressure’, ‘pulse pressure’, and ‘arterial pressure’. Reference lists of literature 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.

Study selection and data extraction
Two investigators (RB and CM) independently searched for articles, screened the titles and abstracts of the retrieved articles, reviewed the full texts, and selected articles for inclusion. Disagreements between investigators were resolved by consensus. The inclusion criteria for this meta-analysis were as follows: (1) the participants were adults with resting systolic BP \( \geq 120 \text{ mmHg} \) and/or diastolic BP \( \geq 80 \text{ mmHg} \) or were administered a stable regimen of anti-hypertension for \( \geq 4 \text{ weeks} \) before screening; (2) the intervention group was treated with SGLT2 inhibitors; (3) a control group was included and were administered placebos; (4) change in office BP was assessed; and (5) the study type was an RCT. The exclusion criteria were as follows: (1) the enrolled patients had secondary hypertension; (2) the enrolled patients suffered from chronic kidney disease (CKD) and/or heart failure; (3) with follow-up period \(<4 \text{ weeks}\); and (4) the study was based on animal experiments.

One investigator (RB) extracted the required data from each RCT independently. The data included (1) general information on the study, including name of the first author, year of publication, study type, duration of follow-up, interventions, comparators, number of participants, randomized, mean age of the participants, sex, baseline mean systolic and diastolic BP, baseline mean 24-h ambulatory blood pressure monitoring (ABPM) systolic and diastolic BP, baseline mean body weight, baseline fasting plasma glucose, and baseline hemoglobin A1c (HbA1c); and (2) clinical endpoints, including mean office BP, daytime
systolic BP, nighttime systolic BP, body weight from baseline, number of adverse, hypoglycemic and volume depletion relevant events (e.g. hypotension and dehydration).

Study quality assessment
Two independent investigators (RB and CM) assessed the risk of bias with The Cochrane Collaboration’s Tool. The risks were assessed as ‘Low’, ‘Unclear’, or ‘High’ based on the following aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selected reporting, and other bias. Disagreements between investigators were resolved by consensus. The results of these questions were graphed and assessed using Review Manager 5.4. The quality of the pooled results was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Statistical analysis
Meta-analyses were performed on the mean changes from baseline for office systolic and diastolic BP, body weight, and the number of hypoglycemic and volume depletion events. Results were assessed using forest plots and presented as mean difference (MD) for all continuous data and as odds ratio (OR) for dichotomous data. Between-study heterogeneity was assessed using the Cochran Q statistics. In addition, F testing was performed to determine the magnitude of heterogeneity between studies, with values >50% considered indicative of moderate to high heterogeneity. We calculated the pooled estimates with a fixed-effects model if the heterogeneity of the studies was acceptable. If heterogeneity was found to be unacceptable, we used the random-effects model. Subgroup analyses were performed by pooling data for regular doses (dapagliflozin 10 mg/day, empagliflozin 10 mg/day, and canagliflozin 100 mg/day) and intensive doses (empagliflozin 25 mg/day and canagliflozin 300 mg/day) of SGLT2 inhibitors separately and assessing the pooled between-group variance. The percentage weight contributed by a trial was determined by the precision of its sample estimate for the population parameter. Trials with more precise estimates, as indicated by those with narrower confidence intervals, had a greater weight. The amount that each study contributed was indicated via forest plots. The presence of publication bias and related biases was evaluated via funnel plots.

A sensitivity analysis was performed to ascertain the results of the meta-analysis by excluding each of the individual studies. Then, new meta-analyses were performed to compare the effect statistics and heterogeneity. The study was considered heterogeneous if the heterogeneity changed and the effect statistics were still statistically significant. If heterogeneous, further comparative analysis of the source of heterogeneity was performed. If the effect value and heterogeneity changes were negligible after each study was removed, we interpreted the study results as stable and reliable. Statistical analyses were conducted using Review Manager 5.4.

Results
Search results and study characteristics
The results of our citation search are shown in Figure 1. A total of 968 papers were found: 203 from PubMed, 329 from CENTRAL, and 436 from Embase. After the removal of 238 duplicate reports, 730 articles were analyzed for the title and abstract, from which 648 records were excluded. The remaining 82 articles were retrieved in full-text, with 9 independent RCTs10–18 chosen for this meta-analysis after meeting our inclusion criteria. After screening the references of these studies, no additional articles were added for analysis.

Study duration ranged from 6 to 24 weeks. Three types of SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin) were included in these trials. Among these articles, Lambers Heerspink et al.13 used both hydrochlorothiazide and dapagliflozin for intervention. We only chose dapagliflozin as the intervention group. Tikkanen et al.15 and Townsend et al.16 used two doses of SGLT2 inhibitors, and we analyzed the results with both doses. A total of 2450 patients were enrolled, including 1395 for the SGLT2 inhibitors group and 1055 for the placebo group. Table 1 summarizes the characteristics of the nine included RCTs.
Quality assessment and risk of bias

The risk of bias was evaluated using The Cochrane Collaboration’s Tool (Figure 2). Overall, the risk of bias was low. Ferdinand et al., Sha et al., and Townsend et al. did not give information on random sequence generation and allocation concealment. Lambers Heerspink et al. did not report the change in office diastolic BP. The blinding of participants and personnel and the incomplete outcome data showed no bias. Missing data were imputed using a last-observation-carried-forward approach. The outcome assessment was not influenced by blinding. Upon visual inspection of the funnel plots, we noted minute asymmetry for all outcomes, suggesting a low risk of publication bias (Figure 3).

Office BP

Figure 4 shows the change in office systolic BP in hypertension and pre-hypertension. Statistically significant heterogeneity was not observed among the studies (Cochrane $p=0.04$, $I^2 = 48\%$). Compared to the placebo, SGLT2 inhibitors use was associated with a statistically significant reduction (5.04 mmHg) in systolic BP [95% confidence interval (CI), 3.79–6.30, $p<0.01$]. The subgroup analysis, separated by dose, showed that intensive doses of SGLT2 inhibitors resulted in a stronger effect of lowering systolic BP than the regular dose (MD = −6.12 mmHg; 95% CI, −8.68 to −3.57 vs MD = −4.70 mmHg; 95% CI, −6.14 to −3.26). The quality of the evidence was high according to the GRADE approach.
| Study                  | Year  | Study design | Follow-up (w) | Drug and dose       | n   | Mean Age (y) | Male | Baseline SBP<sup>a</sup> (mmHg) | Baseline DBP<sup>b</sup> (mmHg) | Mean 24-h ABPM SBP<sup>c</sup> (mmHg) | Mean 24-h ABPM DBP (mmHg) | Baseline BW<sup>d</sup> (kg) | Baseline FPG<sup>e</sup> (mmol/L) | Baseline HbA1c<sup>f</sup> (%) |
|-----------------------|-------|--------------|---------------|---------------------|-----|--------------|------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|--------------------------------|-------------------------------|-----------------------------|
| Heerspink et al.      | 2013  | R, DB<sup>g</sup>, PC<sup>i</sup> | 12            | Placebo             | 25  | 58.0 (9.5)   | 18   | 132 (12)                      | 82 (8)                        | 127 (12)                      | 74 (7)                        | 96.2 (19.5)                    | 8.1 (2.4)                      | 7.5 (1.0)                    |
|                       |       |              |               | Dapagliflozin (10 mg/day) | 24  | 53.7 (9.4)   | 16   | 141 (16)                      | 82 (9)                        | 131 (12)                      | 77 (7)                        | 93.2 (18.0)                    | 8.8 (2.0)                      | 7.7 (0.6)                    |
| Sha et al.            | 2014  | R, DB, PC    | 12            | Placebo             | 18  | 62.3 (6.8)   | 15   | 133.8 (10.8)                  | 85.7 (8.4)                     | NR                           | NR                           | 94.7 (12.4)                    | NR                            | 7.7 (0.6)                    |
|                       |       |              |               | Canagliflozin (300 mg/day) | 18  | 63.3 (4.0)   | 16   | 137.1 (12.9)                  | 88.5 (10.4)                    | NR                           | NR                           | 92.3 (16.5)                    | NR                            | 7.6 (0.5)                    |
| Tikkanen et al.       | 2015  | R, DB, PC    | 12            | Placebo             | 271 | 60.3 (8.8)   | 168  | 142.0 (12.4)                  | 83.7 (7.1)                     | 131.7 (11.8)                  | 75.2 (7.5)                    | NR                           | 8.9 (2.0)                      | 7.90 (0.72)                   |
|                       |       |              |               | Empagliflozin (100 mg/day) | 276 | 60.6 (8.5)   | 171  | 142.3 (12.0)                  | 84.1 (7.3)                     | 131.3 (13.0)                  | 75.1 (8.3)                    | NR                           | 8.7 (2.1)                      | 7.87 (0.77)                   |
|                       |       |              |               | Empagliflozin (25 mg/day) | 276 | 59.9 (9.7)   | 156  | 141.9 (12.5)                  | 83.8 (6.8)                     | 131.2 (12.1)                  | 74.6 (7.5)                    | NR                           | 9.0 (2.1)                      | 7.92 (0.72)                   |
| Townsend et al.       | 2016  | R, DB, PC    | 6             | Placebo             | 56  | 59.6 (9.5)   | 33   | 137.7 (8.6)                   | 82.7 (8.6)                     | 136.7 (10.3)                  | 78.4 (7.3)                    | 91.7 (17.5)                   | 9.8 (2.4)                      | 8.2 (0.9)                    |
|                       |       |              |               | Canagliflozin (100 mg/day) | 57  | 57.8 (8.7)   | 34   | 138.5 (11.1)                  | 82.4 (7.7)                     | 136.5 (11.5)                  | 78.0 (8.1)                    | 95.3 (22.2)                   | 9.7 (2.1)                      | 8.1 (0.9)                    |
|                       |       |              |               | Canagliflozin (300 mg/day) | 56  | 58.3 (6.9)   | 31   | 139.2 (8.8)                   | 83.0 (8.2)                     | 139.6 (10.9)                  | 79.3 (7.9)                    | 96.1 (20.2)                   | 9.4 (2.0)                      | 8.0 (0.8)                    |
| Weber et al.          | 2016  | R, DB, PC    | 12            | Placebo             | 311 | 56.2 (8.9)   | 171  | 145.9 (8.0)                   | 90.8 (4.9)                     | NR                           | NR                           | 84.1 (17.5)                   | 8.9 (2.4)                      | 8.0 (0.9)                    |
|                       |       |              |               | Dapagliflozin (10 mg/day) | 302 | 55.6 (8.4)   | 179  | 149.8 (7.5)                   | 91.1 (4.8)                     | NR                           | NR                           | 86.0 (18.4)                   | 8.8 (2.4)                      | 8.1 (1.0)                    |
| Weber et al.          | 2016  | R, DB, PC    | 12            | Placebo             | 224 | 57.0 (5.5)   | 129  | 151.3 (6.7)                   | 91.4 (4.8)                     | NR                           | NR                           | 89.9 (18.4)                   | 8.9 (2.4)                      | 8.0 (1.0)                    |
|                       |       |              |               | Dapagliflozin (10 mg/day) | 225 | 56.0 (6.0)   | 118  | 151.0 (7.9)                   | 91.2 (4.8)                     | NR                           | NR                           | 88.0 (20.3)                   | 9.0 (2.5)                      | 8.1 (0.9)                    |
| Ferdinand et al.      | 2019  | R, DB, PC    | 24            | Placebo             | 72  | 57.2 (9.3)   | 36   | 148.31 (11.12)                | 88.76 (7.72)                   | 145.78 (10.61)                | NR                           | 101.35 (20.96)                | 9.7 (2.6)                      | 8.51 (1.10)                   |
|                       |       |              |               | Empagliflozin (10–25 mg/day) | 78  | 56.5 (9.3)   | 43   | 148.93 (12.89)                | 87.97 (8.57)                   | 146.81 (11.48)                | NR                           | 105.05 (24.29)                | 9.9 (3.1)                      | 8.66 (0.97)                   |
| Kario et al.          | 2019  | R, DB, PC    | 12            | Placebo             | 63  | 69.3 (7.8)   | 33   | 143                           | 77.1                           | 134.2                        | 74.9                         | 64.6 (14.3)                   | NR                            | 6.6 (0.8)                    |
|                       |       |              |               | Empagliflozin (10 mg/day) | 68  | 70.9 (8.7)   | 36   | 141.2                         | 76.7                           | 138.8                        | 75.9                         | 65.4 (11.4)                   | NR                            | 6.6 (0.8)                    |
| Díaz-Cruz et al.      | 2020  | R, DB, PC    | 13            | Placebo             | 15  | 50 (5)       | 7    | 127 (9)                       | 81 (7)                         | 119 (9)                      | 74 (7)                        | 80 (12)                       | 6.0 (0.4)                      | 5.8 (0.3)                    |
|                       |       |              |               | Dapagliflozin (10 mg/day) | 15  | 47 (7)       | 4    | 127 (7)                       | 80 (6)                         | 121 (8)                      | 73 (7)                        | 74 (10)                       | 6.3 (0.3)                      | 5.9 (0.5)                    |

ABPM, ambulatory blood pressure monitoring.
<sup>a</sup>Systolic blood pressure.
<sup>b</sup>Diastolic blood pressure.
<sup>c</sup>Ambulatory blood pressure monitoring.
<sup>d</sup>Body weight.
<sup>e</sup>Fasting plasma glucose.
<sup>f</sup>Haemoglobin A1c.
<sup>g</sup>Randomized.
<sup>h</sup>Double blind.
<sup>i</sup>Placebo controlled.
<sup>j</sup>Not reported.
Figure 5 shows the change in office diastolic BP. Statistically significant heterogeneity was not observed among the studies (Cochrane $p = 0.14$, $I^2 = 34\%$, $p < 0.01$). A statistically significant reduction in office diastolic BP was found in SGLT2 inhibitors use compared to that in the placebo (MD $= -1.67$ mmHg; 95% CI, $-2.45$ to $-0.89$). Subgroup analysis also showed that this efficacy varies with the dose of SGLT2 inhibitors (intensive dose MD $= -2.55$ mmHg; 95% CI, $-4.01$ to $-1.08$ vs regular dose MD $= -1.32$ mmHg; 95% CI, $-2.24$ to $-0.40$). The quality of evidence was high according to the GRADE approach.

Besides, we performed a subgroup analysis to determine whether there were differences among different drugs (dapagliflozin, empagliflozin, and canagliflozin). The results are shown in Figure 6. Notably, the antihypertensive efficacy varies with the type of drug. Dapagliflozin reduced the participants’ systolic BP by $4.71$ mmHg (95% CI, $6.41$–$3.00$, $p < 0.01$). Empagliflozin reduced the participants’ systolic BP by $6.18$ mmHg (95% CI, $8.77$–$3.58$, $p < 0.01$). At the same time, canagliflozin reduced the participants’ systolic BP by $5.27$ mmHg (95% CI, $10.04$–$0.50$, $p = 0.03$).

### Daytime and nighttime BP

After pooling the results of the trials, we found that SGLT2 inhibitors reduced the participants’ daytime systolic BP by $4.57$ mmHg (95% CI, $3.71$–$5.43$, $p < 0.01$; Cochrane $p = 0.53$, $I^2 = 0\%$) compared to that in the placebo. Meanwhile, a decrease in nighttime systolic BP of $2.80$ mmHg (95% CI, $1.84$–$3.76$, $p < 0.01$; Cochrane $p = 0.90$, $I^2 = 0\%$) was also observed (Figure 7). These results confirmed that SGLT2 inhibitors reduced daytime systolic BP more than nighttime BP. The quality of evidence was high according to the GRADE system.

### Body weight

We discovered a statistically significant reduction in body weight for patients who underwent SGLT2-based therapy. The mean body weight change of the SGLT2 inhibitors group compared to that in the placebo group was $-1.74$ kg (95% CI, $-3.05$–$0.05$, $p = 0.005$).
CI, −2.09 to −1.38, \( p < 0.01 \); Cochrane \( p = 0.39, I^2 = 5\% \) as shown in Figure 8. Similarly, weight reduction in the intensive dose group was greater than that in the regular dose group (MD = −2.01 kg; 95% CI, −2.54 to −1.48 vs MD = −1.53 kg; 95% CI, −2.00 to −1.05). The quality of the evidence was moderate according to the GRADE system.

**Adverse events**

A total of 590 and 412 adverse events occurred in the SGLT2 inhibitor and placebo groups, respectively. The OR was 1.08 (95% CI, 0.91–1.28; Cochrane \( p = 0.26, I^2 = 20\% \)). None of the included trials reported the occurrence of euglycemic diabetic ketoacidosis (eDKA). Hypoglycemia occurred in 64 and 36 participants in the SGLT2 inhibitor and the placebo groups, respectively. The OR was 1.19 (95% CI, 0.78–1.82; Cochrane \( p = 0.18, I^2 = 34\% \)). There was no significant difference between the two groups for hypoglycemia risk. However, we found that the significant difference in adverse events was consistent with volume depletion. A total of 59 participants reported volume depletion by SGLT2 inhibitors, and the OR was 4.83 (95% CI, 2.22–10.50, \( p < 0.01 \); Cochrane \( p = 0.27, I^2 = 22\% \)). Besides, a total of 94 and 31 urinary tract or genital infection occurred in the SGLT2 inhibitor and placebo groups, respectively. The OR was 2.26 (95% CI, 1.49–3.42, \( p < 0.01 \); Cochrane \( p = 0.61, I^2 = 0\% \)). The results are shown in Figure 9. The quality of both results was high in the GRADE system.

**Sensitivity analysis**

Even though the heterogeneity of some of the included trials was not statistically significant, we performed sensitivity analysis by independently excluding each trial to test the stability of the results. In the leave-one-out sensitivity analyses of systolic BP, removing the trial of Sha *et al.* \(^{14}\) and pooling residual trials led to a mean change in systolic BP from −3.85 mmHg (95% CI, −4.92 to −2.78, \( p < 0.01 \)) to −3.68 mmHg (95% CI, −4.76 to −2.60, \( p < 0.01 \)) and \( I^2 \) changing from 49% to 29%. We considered that the source of heterogeneity is the small sample size (\( n = 35 \)) and missing data (one participant was lost to follow-up). Moreover, we could not obtain sufficient information about the selection bias of this trial, which might be the source of heterogeneity. The trial of Díaz-Cruz *et al.* \(^{10}\) also affected heterogeneity, which increased \( I^2 \) from 36% to 48%. We considered the small sample size (\( n = 30 \)) and missing data (four participants were lost to follow-up) as the source of heterogeneity. Despite the results of the sensitivity analyses, we still included these two trials as the source of heterogeneity was unclear, and the influence on the pooled effect estimates was small. Particularly, the trial of Díaz-Cruz *et al.* \(^{10}\) included participants who suffered from pre-hypertension, which provided valuable

![Figure 3. Funnel plot of analysis.](image-url)
insights for this meta-analysis. The pooled effect estimates remained similar across all residual studies and their subgroups, which confirmed that the significant difference between the studied groups is the overall effect of all included studies.

Discussion
In our review, SGLT2 inhibitors reduced the participants’ systolic and diastolic BP by 5.04 mmHg and 1.67 mmHg, respectively, compared to that in the placebo group. Despite the included studies having a relatively short follow-up period, the reduction in both systolic and diastolic BP was statistically significant. We also performed a subgroup analysis between different types of SGLT2 inhibitors. The result showed that empagliflozin has the strongest effect. However, due to the small sample size, the results were highly heterogeneous.

SGLT2 inhibitors had a greater effect on daytime BP than nighttime BP. Furthermore, participants in the SGLT2 inhibitors group lost 10 kg of body weight compared to those in the placebo group. Considering the relatively short follow-up period, SGLT2 inhibitors may be more effective for losing weight than the result of our review. Regarding overall adverse events and the risk of hypoglycemic events, SGLT2 inhibitors showed no significant difference from the placebo.

According to our review, SGLT2 inhibitors had a statistically significant BP-lowering effect, whether systolic BP or diastolic BP, on hypertension and pre-hypertension, and the effect was further enhanced with the increase in drug dose. The hypotension events in the experimental group were more than those in the control group, which confirmed the significant antihypertensive effect of SGLT2 inhibitors. Although it was relatively
weak, the effect could not be ignored, especially in cases of pre-hypertension. Although we found that empagliflozin was more effective in lowering BP, the results were highly heterogeneous due to the small sample size. Future studies comparing different drugs with larger sample sizes are needed to show which kind of SGLT2 inhibitors are more effective.

The management of pre-hypertension is vital for the prevention and treatment of hypertension. Its treatment is also associated with cardiovascular diseases, as it is an independent risk factor for the latter. Whelton et al.'s study showed that there was an increase in traditional risk factors for atherosclerotic cardiovascular disease (ASCVD) and incident ASCVD events with increasing systolic BP levels. The adjusted hazard ratio for ASCVD was 1.53 (95% CI, 1.17–1.99) for every 10 mmHg increase in systolic BP levels. Compared to that in the participants with systolic BP levels of 90–99 mmHg, the adjusted hazard ratio for ASCVD risk was 4.58 (95% CI, 1.47–14.27) for systolic BP levels of 120–129 mmHg. Therefore, aggressive antihypertensive therapy in pre-hypertension can significantly reduce the risk of ASCVD. Antihypertensive medications for pre-hypertension are necessary, especially for patients with T2DM. Compared to traditional antihypertensive drugs, such as renin–angiotensin–aldosterone system inhibitors, calcium channel blockers, and diuretics, SGLT2 inhibitors can be milder hypotensive and better tolerated. We found only one trial that was aimed at patients with pre-hypertension. This trial concluded that dapagliflozin significantly decreased office systolic BP by 11 mmHg and office diastolic BP by 6 mmHg. When treated with dapagliflozin at a dose of 5 mg for 14 days, the circadian BP pattern of patients changed from non-dipper to dipper. However, due to the small sample size and the missing data, we considered that the results were not

Figure 5. Forest plots of meta-analysis and subgroup analysis for change in DBP.
Figure 6. Forest plots of subgroup analysis of different drugs.

Figure 7. Forest plots of meta-analysis for change in daytime and nighttime SBP.
representative. Meanwhile, we did not perform subgroup analysis at different stages of hypertension and pre-hypertension due to the lack of information from the included literature. Long-term studies with a larger sample size and broader inclusion criteria are needed to determine whether SGLT2 inhibitors are more suitable as an antihypertensive agent for pre-hypertension.

In addition, we hoped to demonstrate that SGLT2 inhibitors are better at lowering nighttime BP. Nighttime hypertension was found to be a significant factor in worsening end-organ damage as assessed by arterial stiffness and central BP values.20 Nighttime BP management is particularly vital for the prevention of cardiovascular events, especially heart failure, as well as age-related organ damage, such as CKD and cognitive dysfunction.21 Unfortunately, we found that nighttime BP levels were not strongly influenced by SGLT2 inhibitors. Although routine ingestion of SGLT2 inhibitors by hypertensive patients at bedtime may result in improved BP control and diminished occurrence of major CVD events, SGLT2 inhibitors have no known effects in significantly reducing nighttime BP.

In addition, a current study on the effect of SGLT2 inhibitors on BP by Benham et al.23 Revealed that there is insufficient evidence to suggest that BP reduction is a significant contributor to the cardiovascular benefits observed. They examined the association of lower BP with cardiovascular benefits but did not examine whether SGLT2 inhibitors could be used as a BP-lowering drug. Conversely, meta-analyses conducted by Tsapas et al.24 and Mohsen et al.25 analyzed the antihypertensive effect of SGLT2 inhibitors. However, both analyses only looked at clinical BP. The analysis of clinical BP may be influenced by a variety of factors, such as the measurement environment and patients’ emotions, which affects the final results. The present study analyzed the results of ABPM, including daytime BP and nighttime BP, and more

**Figure 8.** Forest plots of meta-analysis and subgroup analysis for change in body weight.
comprehensively analyzed the changes in BP of subjects. Furthermore, while the above studies did not account for the adverse events of the drugs and did not evaluate the safety of SGLT2 inhibitors, the present study complements some of these deficiencies.

Studies have proven that overweight or obesity is an important risk factor for hypertension and prehypertension. Losing weight for individuals with obesity can reduce the risk of hypertension. In the results of our review, SGLT2 inhibitors significantly reduced body weight in

**Figure 9.** Forest plots of meta-analysis for adverse events.
participants. Although there was no statistically significant difference in the MD of body weight after increasing the dose of SGLT2 inhibitors, the weight loss effect of SGLT2 inhibitors is clear. Currently, the types of body composition affected by SGLT2 inhibitors are unclear. Kato et al.'s study depicted that after 12 weeks of using ipragliflozin, body fat mass decreased by $1.31 \pm 1.69$ kg, muscle mass decreased by $0.92 \pm 1.02$ kg, and body water decreased by $0.70 \pm 0.80$ kg. This study showed ipragliflozin mainly decreases body fat mass. However, the evidence is not adequate, and further studies should perform body composition analysis in patients taking different types of SGLT2 inhibitors.

The exact mechanisms responsible for the BP-lowering action of SGLT2 inhibitors remain elusive. The prevailing view is that SGLT2 inhibitors lower BP by natriuresis and osmotic diuresis. Since approximately 85% of glucose renal reabsorption is mediated by the SGLT2 receptors, their inhibition leads to glucose release within the tubular lumen, which is hypothesized to have an osmotic effect, promoting the excretion of sodium and water throughout the length of the tubule. Alongside glucose excretion, SGLT inhibitors also inhibit sodium reabsorption. These two diuretic effects together lead to a decrease in BP. Therefore, we believe that SGLT2 inhibitors have the potential to be used as antihypertensive agents in patients with hypertension complicated by diabetes.

Although SGLT2 inhibitors were tolerated during clinical trials, severe adverse reactions occurred during clinical application, including eDKA. In our analysis, none of the included trials reported the occurrence of eDKA. Dehydration events occurred more in the SGLT2 inhibitors group than in the placebo group, and some of the participants showed symptoms such as thirst, polyuria, fatigue, and nausea. These symptoms may be related to eDKA. More data are needed from targeted clinical trials.

**Limitations**

There are several limitations in our review. First, only three databases were used in our review, resulting in a small number of articles that were included, which may reduce the accuracy of the study. Second, the included studies did not provide relevant information on patients with different BP levels. Hence, it was not possible to perform a subgroup analysis based on the patients’ BP levels and clarify whether the antihypertensive effect of SGLT2 inhibitors was affected by the range of BP levels. Third, our analysis did not include control studies between SGLT2 inhibitors and other antihypertensive drugs, as there were fewer related studies, and the drugs used for comparison varied greatly. Finally, the follow-up period of the included articles was relatively short; hence, there was a lack of evaluation of the long-term antihypertensive effects and safety of SGLT2 inhibitors.

**Conclusion**

Despite the limitations, our review provided evidence that SGLT2 inhibitors had a statistically significant BP-lowering effect in both hypertension and pre-hypertension. This effect was found to be enhanced with increased drug dosage. Thus, SGLT2 inhibitors have the potential to be used as antihypertensive agents in patients with hypertension complicated with diabetes. Further studies are required to compare the hypotensive effect of SGLT2 inhibitors with traditional antihypertensive agents, as well as studies on their effect on patients with different BP levels.

**Declarations**

*Ethics approval and consent to participate*

Not applicable.

*Consent for publication*

Not applicable.

*Author contributions*

**Bangjiaxin Ren**: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft.

**Ming Chen**: Conceptualization; Supervision; Writing – review & editing.

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