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Thiazide diuretics alone or combined with potassium-sparing diuretics to treat hypertension: a systematic review and network meta-analysis of randomized controlled trials

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Background: The magnitude of blood pressure (BP)-lowering effects and decrease of the adverse effects of thiazide diuretics provided by potassium-sparing diuretics remain uncertain. The aim of this study was to compare the BP-lowering efficacy and the incidence of adverse effects of high (T+) and low-dose (T-) thiazide diuretics, alone or combined with high (PS+) or low-dose (PS-) potassium-sparing diuretics in patients with primary hypertension.

Methods: A systematic literature search was performed in PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials, Embase, Web of Science, Scopus and LILACS. Randomized double-blind placebo or active-controlled trials (RCT) with 3 weeks to 1 year of follow-up were included. Sample size, mean and standard deviation from baseline, follow-up and change from baseline values were extracted by two independent reviewers. Pairwise random effect models and Bayesian network meta-analysis models were used to compare the effects of treatments. The risk of bias in individual studies was assessed using the Rob 1.0 tool. The primary outcome was the mean difference in office SBP. Secondary outcomes were the mean difference in biochemical parameters and the incidence of nonmelanoma skin cancer.

Results: Two hundred and seventy-six double-blind RCTs involving 58 807 participants (mean age: 55 years; 45% women) were included. All treatment groups were more effective than placebo in lowering BP, with mean differences (MDs) of change from baseline ranging from −7.66 mmHg [95% credible interval (95% CrI), −8.53 to −6.79] for T- to −12.77 mmHg (95% CrI, −15.22 to −10.31) for T+PS-. T+ alone or combined with potassium-sparing was more effective in reducing BP than T-. The surface under the cumulative ranking curve (SUCRA) estimated ranking showed that the best effectiveness in lowering SBP was found for T+PS- (0.69), T+PS+ (0.65) and T+ (0.54). Compared with placebo, all treatments (except T-PS-) were associated with more potassium reduction and T+ compared with all other treatments and T- when compared with T-PS-. Compared with placebo, all active treatments (except T+PS+) showed higher elevations of uric acid. The increase of plasma glucose promoted by thiazides alone was reduced by potassium-sparing agents.

Conclusion: Thiazides with potassium-sparing diuretics are associated with increased BP-lowering efficacy compared with thiazides alone while minimizing hypokalaemia and hyperglycaemia. These findings demonstrate that thiazide and potassium-sparing diuretic combination is preferable to thiazide alone in treating hypertension.

Keywords: blood pressure, diuretics, hypertension, potassium-sparing, thiazides, treatment

Abbreviations: BP, blood pressure; CrI, credible interval; PRISMA-NMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses for Network Meta-analysis; PROSPERO, International Prospective Register of Systematic Reviews; PS-, low-dose potassium-sparing diuretics; PS+, high-dose potassium-sparing diuretics; RCTs, randomized controlled trials; RoB, Risk of Bias; SUCRA, The surface under the cumulative ranking curve; T-, low-dose thiazide diuretics; T+, high-dose thiazide diuretics

INTRODUCTION

Thiazide diuretics and thiazide-like diuretics (e.g. chlorthalidone and indapamide) were the primary drugs tested in landmark randomized controlled

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trials (RCTs) that demonstrated the high degree of efficacy of blood pressure (BP)-lowering in preventing major cardiovascular events in patients with hypertension [1–5]. However, there are no RCTs comparing the efficacy of different thiazides, alone or combined with potassium-sparing diuretics, to prevent cardiovascular outcomes in patients with hypertension. Indirect comparisons by meta-analyses and evidence from observational studies returned conflicting results [6–8].

Comparisons of the BP-lowering effect of the several thiazides, alone and associated with potassium-sparing agents, have been rarely investigated in head-to-head clinical trials. The effect of amiloride and triamterene on BP remained uncertain and was not identified in a systematic review of six double-blind RCTs with a total of 496 participants [9]. In two isolated trials, however, amiloride increased the BP-lowering effect of hydrochlorothiazide [10,11]. Amiloride may be effective in resistant hypertension [12], particularly at higher doses [13]. Potassium supplementation has a BP-lowering effect [14], and the replacement of a proportion of sodium chloride with potassium chloride in meals reduced BP [15,16]. A pioneering nutritional RCT showed that replacing 25% of the sodium chloride content with potassium chloride was associated with reducing the incidence of major cardiovascular events and death [17]. The antihypertensive efficacy of spironolactone and eplerenone have been well documented [18–20]; however, these drugs are not commonly used with thiazides in fixed combinations.

Thiazides have been associated with adverse metabolic effects, including hypokalaemia, hyperglycaemia, hyponatremia, hyperuricemia, hyperlipidaemia and hypomagnesemia in a dose-dependent fashion [21–23]. The risk of hypokalaemia, impaired glucose tolerance or sudden death may be minimized by combining thiazides with potassium-sparing diuretics (e.g. spironolactone, eplerenone, amiloride or triamterene) [10,24].

The critical role of potassium in BP control and the adverse effects of thiazide diuretics suggest that potassium-sparing diuretics can be effective adjuncts in treating hypertension. The scarcity of direct comparisons between thiazides alone with thiazides associated with potassium-sparing diuretics concerning their BP-lowering and adverse effects motivated this systematic review with a Bayesian network meta-analysis.

MATERIALS AND METHODS

Protocol and registration

A full description of the methodology and protocol of this investigation has been published [25]. The present report was generated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-analysis (PRISMA-NMA) guidelines [26]. The protocol of this network meta-analysis was prospectively registered at the PROSPERO database (CRD42018118492), published [25] and deposited in a public repository (the Open Science Framework) (https://osf.io/tezf8).

Eligibility criteria

Adults with primary hypertension.

Interventions and comparators

Interventions of interest were thiazide diuretics alone (hydrochlorothiazide, chlorothiazide, butizide, bendroflumethiazide, hydroflumethiazide, trichlormethiazide, methyclothiazide, polythiazide, cyclothiazide, cyclopenthiazide, chlorthalidone, metolazone, quinethazone, fenquizone, clorexolone, clopamide, indapamide, diapamide, isodapamide, mefruside, xipamide, bemetizide, benzthiazide or chlorazanil) or combined with a potassium-sparing diuretic (spironolactone, eplerenone, amiloride and triamterene).

Outcomes

The primary outcome was the mean difference in office SBP. Safety outcomes were the mean difference in biochemical abnormalities (potassium, uric acid, fasting plasma glucose, HbA1c, total cholesterol, LDL-C, HDL-C and triglycerides) and the incidence of nonmelanoma skin cancer.

Study design

Double-blind placebo or active-controlled RCTs (parallel, crossover or factorial) with a follow-up period between 3 and 52 weeks were included. Crossover studies were included if there were at least 2 weeks of washout between study phases.

Search strategy and information sources

Searches were performed in the Cochrane Central Register of Controlled Trials, PubMed/MEDLINE, Embase, Web of Science, Scopus and LILACS. ClinicalTrials.gov was searched for possible results in unpublished studies, and the Educational Resources Information Center (ERIC [ProQuest]) was searched for results in nonindexed journals or other reporting forms, all from inception to 15 September 2021, with no language restrictions. To improve search strategy sensitivity, the strategies were developed using Medline subject heading (MeSH) terms, synonyms and Boolean operators (where possible). Keywords and MeSH terms were as follows: 'hydrochlorothiazide', 'chlorothiazide', 'bendroflumethiazide', 'hydroflumethiazide', 'cyclopenthiazide', 'chlorthalidone', 'metolazone', 'indapamide', 'mefruside', 'xipamide', 'bemetizide', 'spironolactone', 'eplerenone,' 'amiloride', 'triamterene', 'thiazide diuretics', 'inhibitor of the epithelial sodium channel', 'potassium sparing diuretic' and 'hypertension'. Comprehensive search strategies are provided in the Supplement, http://links.lww.com/HJH/C179 (Search Strategy).

Study selection

An electronic database was exported to reference manager software (EndNote X9), and duplicates were removed. Titles and abstracts were independently selected by pairs of independent reviewers using the liberal accelerated approach [27]. Disagreements were resolved by consensus or by a third reviewer. Authors were contacted to seek any potential unpublished outcomes.

Data extraction and items

The following data were extracted: study characteristics, baseline characteristics of participants, interventions and comparators, and outcomes.

The interventions of interest were classified as thiazide diuretic alone or thiazide diuretic combined with a potassium-sparing diuretic and further stratified according to the mean daily dose. The doses of the interventions were categorized as proportions of the manufacturer's recommended starting dose: low-dose ($< 2 \times$ start dose) and high-dose ($\geq 2 \times$ start dose). The starting dose of hydrochlorothiazide was 25 mg because chlorthalidone is 1.5–2 times as effective as hydrochlorothiazide for lowering BP [28].

Data on drugs and doses are presented in Table S1, http://links.lww.com/HJH/C179 in the Supplement. The full glossary of extracted variables with their definitions is available at https://osf.io/tezf8.

Risk of bias within individual studies

The risk of bias was assessed using the Risk of Bias for Interventions tool v. 1.0 from the Cochrane Collaboration [29] (i.e. low, unclear or high risk of bias). Two reviewers independently evaluated the following items for each study: selection bias due to random sequence generation, selection bias due to allocation concealment, performance bias, detection bias, attrition bias, reporting bias and other bias (e.g. industry sponsorship). Raw data with commentary from the reviewers can be found at https://osf.io/tezf8.

Summary measures and statistical analysis

Results were pooled using mean change from baseline differences. First, direct pairwise evidence was summarized using frequentist random-effects meta-analysis models for all pairs of treatments. Pooled results were calculated using the inverse of variance method and the DerSimonian & Laird estimator for the variability among studies. Heterogeneity was estimated using I^2 statistics. Asymmetry was evaluated using funnel plots. A Bayesian multiple treatment comparison models with noninformative priors combining all available direct and indirect evidence was used to compare all treatments. For each network, studies with anchor arms that did not contribute to the evidence among interest treatments were excluded from the analysis. Posteriors were estimated using Markov Chain Monte Carlo simulations. Burn-in simulation periods and thin values were chosen by inspecting autocorrelation plots. The number of simulations was determined to guarantee sufficiently small standard time series errors. Fixed and random effect models with homogeneity of variance were adjusted, and the deviance information criterion value was used to decide between them. The validity of the models was assessed using the split-node method with Bonferroni correction for the inconsistency assumption and characteristics of the individual studies for the transitivity assumption. Treatments were ranked using the surface under the cumulative curve (SUCRA) method. Results were presented as mean change from baseline differences with 95% credible intervals using forest plots. Statistical analyses were performed using the *meta* and *gemtc* packages in R software (v. 3.5.2; R Foundation for Statistical Computing, Vienna, Austria). All analyses regarding thiazide diuretics refer to thiazide-type and thiazide-like combined.

Data sharing

The data sharing policy followed The International Committee of Medical Journal Editors Data Sharing Statement. All data and materials related to this study are available at https://osf.io/tezf8 (Creative Commons CC-By Attribution 4.0), without restrictions on timing and purpose of use.

RESULTS

Study selection

The initial search identified 21 161 titles and abstracts, of which 4655 were excluded as duplicates. Another 209 registers and 14 potentially eligible studies were identified in the reference lists of other studies. The remaining 16 729 titles, abstracts and registers were screened for eligibility; 15 819 were excluded. Thus, 910 potentially eligible studies were read in full, of which 634 were excluded (reasons presented in Table S2, http://links.lww.com/HJH/C179 in the Supplement). Finally, 276 studies (References in the Supplement, http://links.lww.com/HJH/C179) were included in the review. The flow diagram of study search and selection is shown in Fig. 1.

Presentation and summary of network structures

Interest and anchor treatment groups were simultaneously compared for each outcome of interest. Figure 2 shows the network of eligible comparisons for SBP (a), potassium (b), uric acid (c) and fasting plasma glucose (d). Figures S1–S5, http://links.lww.com/HJH/C179 in the Supplement show the network for other biochemical parameters. The Supplement (Figures S6–S14, http://links.lww.com/HJH/C179) provides detailed results of the pairwise meta-analyses.

Intervention characteristics

The evidence network comprised 18 eligible interventions, which were further classified into five groups according to the pharmacological class and mean daily dose (T+PS-, T+PS+, T-PS-, T-, T+). Comparisons between all groups of interest and placebo were possible for office SBP, serum potassium, uric acid and fasting plasma glucose. For the other outcomes, the number of pairs obtained for comparison were 10 for total cholesterol, LDL-C and triglycerides, six for HDL-C and one for HbA1c. The most common active treatment arm with a single drug was hydrochlorothiazide (180 studies), followed by chlorthalidone (27 studies) and indapamide (23 studies); the associations of diuretics used most often were hydrochlorothiazide + amiloride (22 studies) and hydrochlorothiazide + triamterene (nine studies). Only three studies included mineralocorticoid receptor antagonists (spironolactone) combined with a thiazide, and none assessed eplerenone.

Study and patient's characteristics

Two hundred and seventy-six double-blind RCTs (comprising 58 807 patients) published between 1964 and 2016 were included. The mean study sample size was 213 participants (range, 9–2776). The mean age was 55 years in 244 studies (32 did not report the age of the participants); 45% of the sample population were women. The mean duration of follow-up was 10 weeks (range, 3–52 weeks). The mean number of arms in the studies was three (range, 2–20), with most studies having two to four arms (243 studies; 88%). Of

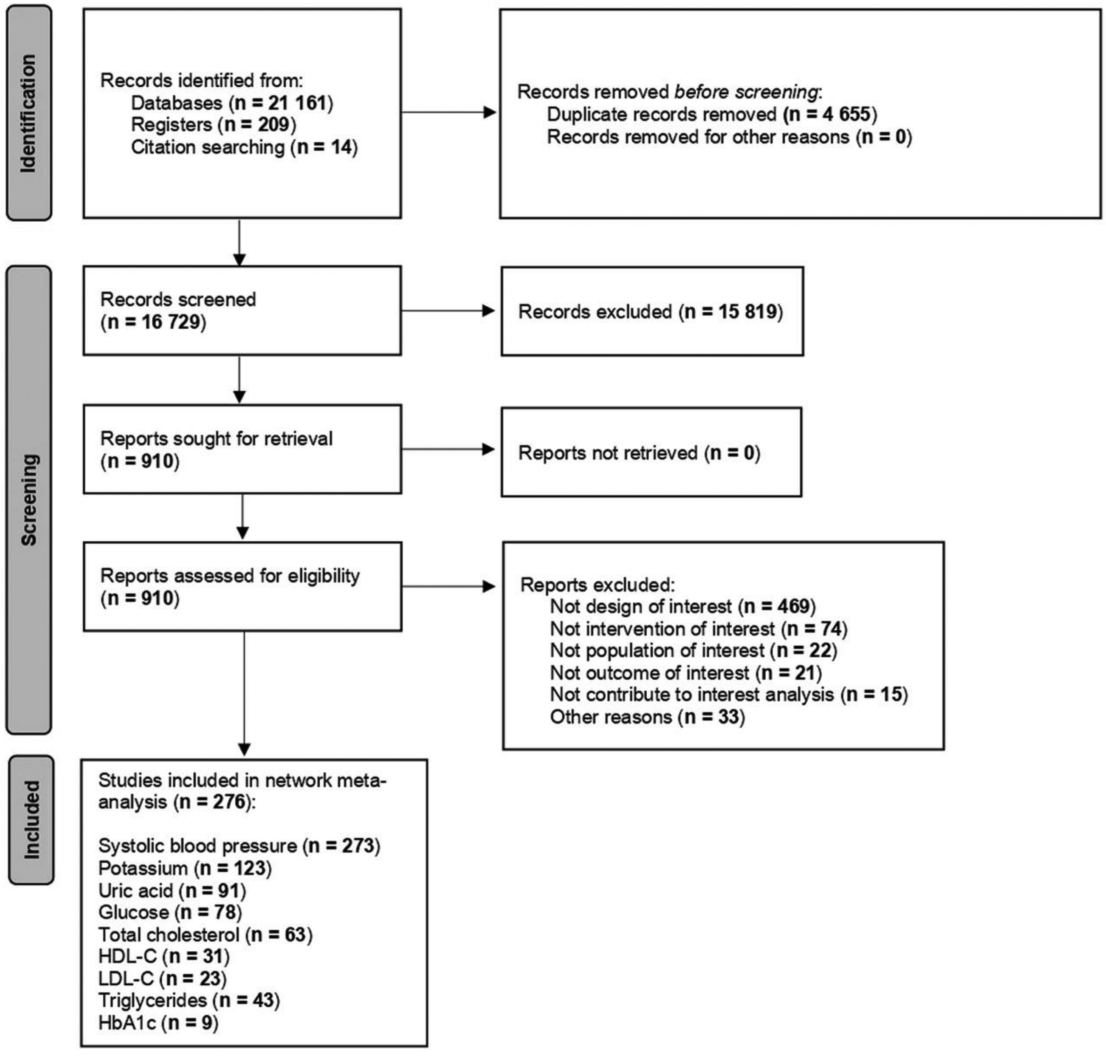

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study.

the 276 studies, 265 (96%) articles were published in English, three (1%) in Italian, four (1%) in German, two (0.7%) in French, one (0.4%) in Spanish and one (0.4%) in Chinese. Regarding the study design, 224 (81%) studies were parallel, 37 (13%) were crossover and 15 (5%) were factorial. Additional characteristics of included studies are summarized in Table S3, http://links.lww.com/HJH/C179 in the Supplement.

Risk of bias within studies

The risk of bias in the studies included in the meta-analysis is presented in Fig. 3; unclear risk of bias was frequent. The summary with individual assessments of each study is available in the Supplement (Figure S15, http://links.lww.com/HJH/C179).

Validity of the models

Inconsistency was not found for all the networks showed ($P > 0.05/c$, where c is the number of pairs with direct and indirect evidence in each network). Transitivity holds, as patients from all studies had hypertension and the treatment arms were classified into groups (high/low dose) according to the original mean daily dose.

Office SBP

When compared with placebo, all active treatments were more effective in lowering BP, with mean difference (MD) ranging between −7.66 mmHg [95% credible interval (95% CrI), −8.53 to −6.79] for T- and −12.77 mmHg (95% CrI, −15.22 to −10.31) for T+PS-. Regarding active treatment comparisons, T+ alone or combined with potassium-sparing was more effective in reducing BP than T- (MD = −2.71 mmHg; 95% CrI, −3.89 to −1.53 for T+; MD = −4.72 mmHg; 95% CrI, −9.23 to −0.21 for T+PS+; and MD = −5.11 mmHg; 95% CrI, −7.47 to −2.75 for T+PS-). The other comparisons were not statically significant (Fig. 4a). According to SUCRA, T+PS- (0.69), T+PS+ (0.65) and T+ (0.54) demonstrated the best effectiveness in lowering SBP (Fig. 5).

Metabolic effects

T+ was associated with greater potassium reduction than the other interventions, ranging from −0.49 mEq/l (95% CrI,

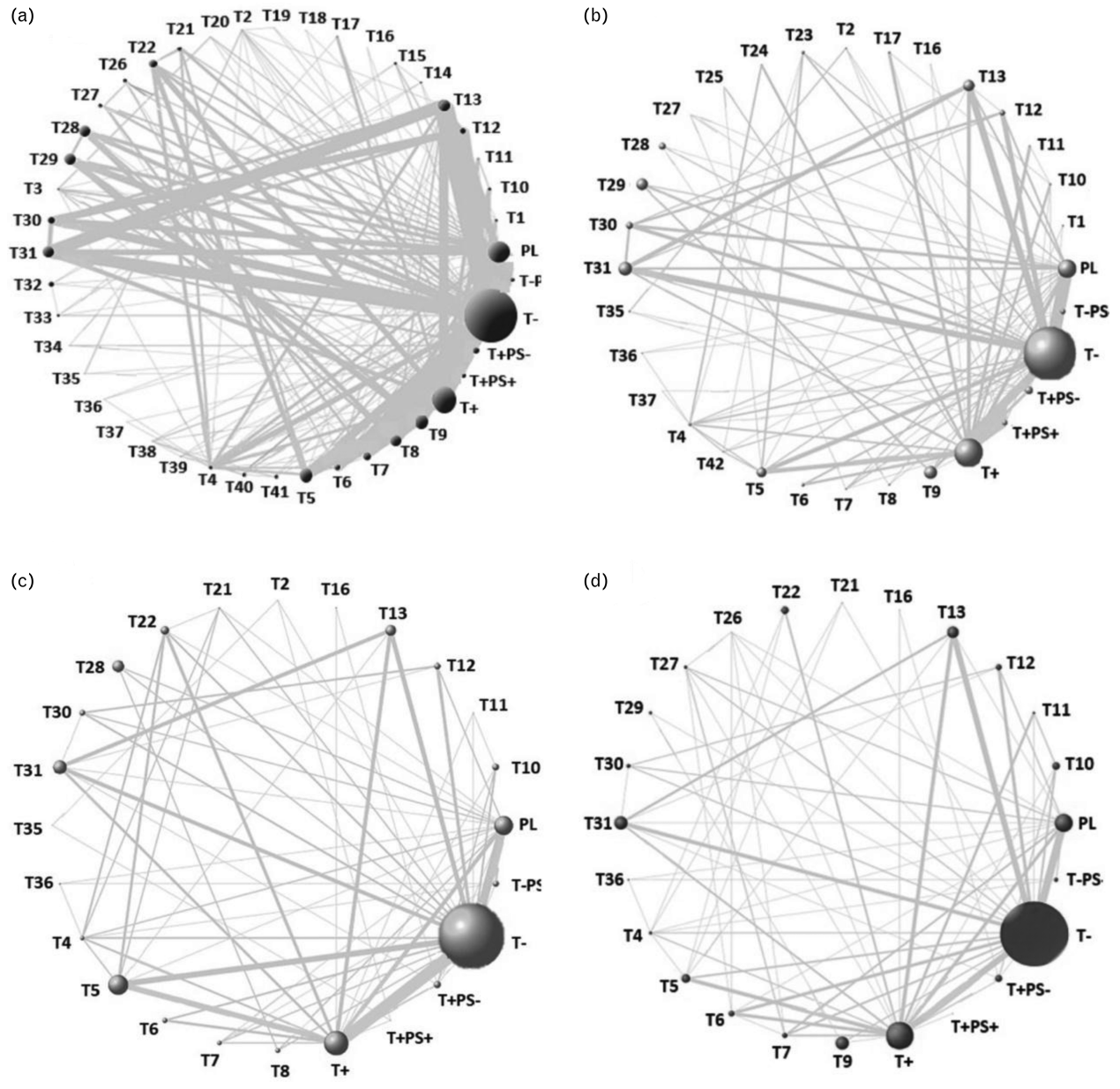

FIGURE 2 Network meta-analysis of eligible comparisons for SBP (a), potassium (b), uric acid (c) and fasting plasma glucose (d). Width of the lines is proportional to the number of trials comparing every pair of treatments, and circle size is proportional to the trials sample size. T1: AB+; T2: AARA-; T4: AARA+; T5: BB-; T6: BB+; T7: CCB-; T8: CCB+; T9: ARB-; T10: ARB+; T11: LD-; T12: LD+; T13: ACEi-; T14: ACEi+; T15: RI-; T16: RI+; T17: PS-; T18: PS+; T19: TAB+; T20: TARAA-; T21: TARAA+; T22: TBB-; T23: TBB+; T24: T-BB+; T25: T+BB-; T26: T+BB+; T27: TCCB-; T28: TCCB+; T29: TARB-; T30: TARB+; T31: TACEi-; T32: TACEi+; T33: TRI-; T34: TRI+; T35: TKCL; T36: TPSAARA+; T37: TPSBB-; T38: TPSBB+; T39: TV-; T40: TV+; T41: V; T42: V+; T43: T-BB-.

−0.56 to −0.42) vs. placebo, to −0.23 mEq/l (95% CrI, −0.29 to −0.17) vs. T-. The magnitude of potassium reduction with T- was greater than in association with a potassium-sparing agent and was greater than placebo (MD = −0.26 mEq/l; 95% CrI, −0.32 to −0.20) and T-PS- (MD = −0.23 mEq/l; 95% CrI, −0.34 to −0.11). When compared with placebo, potassium reduction was not statistically significant only for T-PS- (MD = −0.04 mEq/l; 95% CrI, −0.15 to 0.07) (Fig. 4b). The higher depletion of potassium in the SUCRA analysis was found with thiazides alone at a higher dose, followed by low-dose thiazides alone, and was somewhat lessened by the association with potassium-sparing agents (Fig. 5).

Compared with placebo, all active treatments but T+PS+ showed higher elevation in uric acid, ranging from 0.64 mg/dl (95% CrI, 0.47–0.81) for T- to 1.16 mg/dl (95% CrI, 0.78–1.53) for T+PS-. Among the comparison between active treatments, T+ compared with T- (MD = 0.31 mg/dl; 95% CrI, 0.14–0.48) and T+PS- compared with T- (MD = 0.53 mg/dl; 95% CrI, 0.18–0.88) were associated with greater uric acid elevation (Fig. 4-C).

T+PS- and high and low thiazide doses raised plasma glucose more than placebo: MD = 6.28 mg/dl (95% CrI, 2.29–10.28) for T+PS-, 7.01 mg/dl (95% CrI, 4.21–9.8) for T+ and 4.11 mg/dl (95% CrI, 2.01–6.21) for T- (Fig. 4d). T+

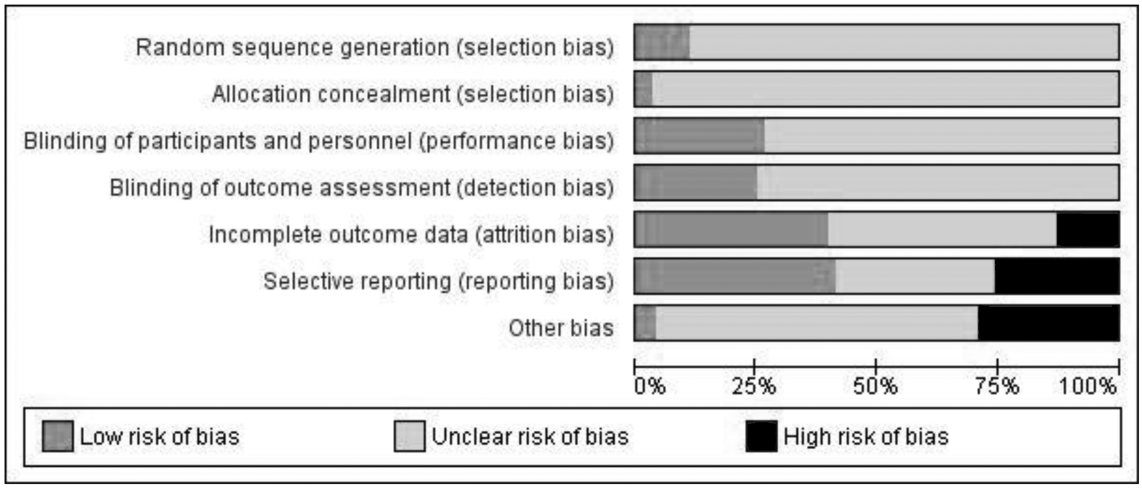

FIGURE 3 Risk of bias of the studies included in the meta-analysis.

was associated with greater glucose elevation than T- (MD = 2.9 mg/dl; 95% CrI, 0.72–5.08).

The average increase in total cholesterol was higher in T+ and T- than in placebo (MD = 7.08 mg/dl; 95% CrI, 0.9–13.27; and MD = 5.05 mg/dl; 95% CrI, 0.73–9.37, respectively). T+PS- showed higher elevation in total cholesterol than placebo (MD = 16.21 mg/dl; 95% CrI, 5.21–27.21) and T- (MD = 11.17 mg/dl; 95% CrI, 0.92–21.42) (Figure S16, http://links.lww.com/HJH/C179 in the Supplement).

No comparison showed a difference concerning HDL-C or LDL-C (Figures S17, http://links.lww.com/HJH/C179 and S18, http://links.lww.com/HJH/C179 in the Supplement).

T+PS- showed higher elevation in triglycerides than placebo (MD = 33.68 mg/dl; 95% CrI, 16.6–50.76), T+

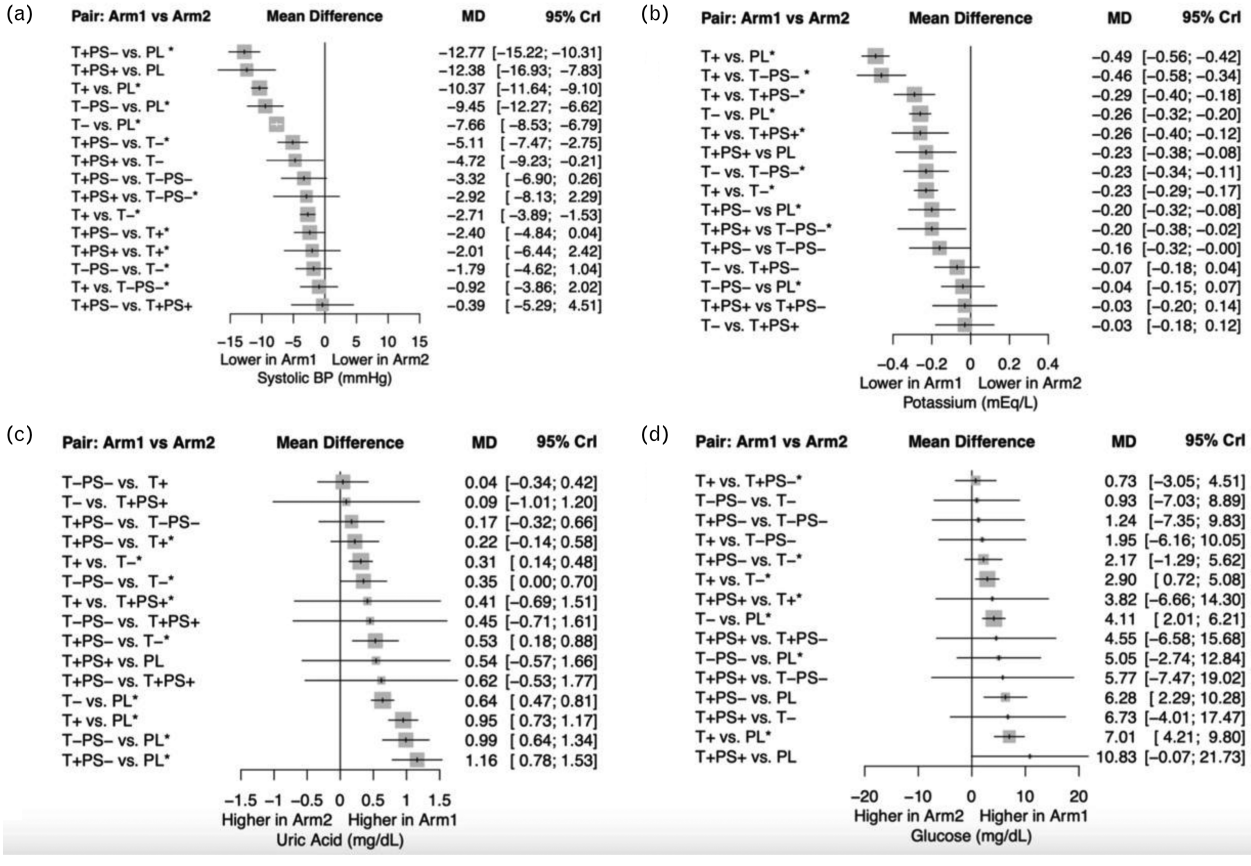

FIGURE 4 Results of the network meta-analysis by classes of drugs for office SBP (a), potassium (b), uric acid (c) and fasting plasma glucose (d), where * indicates that the pair has direct evidence. The figure shows the average difference of reductions after treatment (and its 95% credibility interval) for each outcome. Differences are considered as statistically significant when the 0 is not included in the 95% credibility interval.

Outcomes	T+PS-	T+PS+	T+	T-PS-	T-	PL
Systolic BP	0.69	0.65	0.54	0.46	0.30	0.01
Potassium	0.69	0.73	0.95	0.40	0.81	0.32
Uric Acid	0.93	0.58	0.84	0.86	0.65	0.22
Glucose	0.67	0.83	0.74	0.53	0.46	0.13
Total Cholesterol	0.91		0.66	0.53	0.56	0.26
HDL-C	0.62		0.20		0.50	0.22
LDL-C	0.77		0.48	0.59	0.57	0.27
Triglycerides	0.82		0.45	0.76	0.55	0.19
HbA1c			0.13		0.70	

FIGURE 5 Surface under the cumulative ranking curve (SUCRA). SUCRA values range from 0 to 1. The higher the SUCRA value, the higher the likelihood that an intervention is in the top rank. Table cells are shaded according to SUCRA values, as light gray (high), dark gray (intermediate), or dotted pattern (low).

(MD = 20.59 mg/dl; 95% CrI, 3.86–37.32) and T- (MD = 16.26 mg/dl; 95% CrI, 3.46–29.07). T- showed higher elevation in triglycerides than placebo (MD = 17.46 mg/dl; 95% CrI, 6.11–28.82) (Figure S19, http://links.lww.com/HJH/C179 in the Supplement).

Only one comparison was available for HbA1c: T- vs. T+, showing no difference between treatments (MD = −0.42%; 95% CrI, −1.05 to 0.22) (Figure S20, http://links.lww.com/HJH/C179 in the Supplement).

There were no reports of nonmelanoma skin cancer in the included studies.

Risk of bias across studies

No evidence of asymmetry was found by visual inspection of funnel plots, suggesting no evidence of publication bias (Figures S21–S24, http://links.lww.com/HJH/C179 in the Supplement).

DISCUSSION

This network meta-analysis, with many RCTs and participants, showed that the BP-lowering effect of thiazides increased with higher doses and was enhanced by the association with potassium-sparing diuretics. The potassium-sparing diuretics further mitigated the potassium depletion induced by thiazide diuretics. Potassium-sparing diuretics did not affect uric acid increases. The estimates of the effects on glucose were based on few studies; however, the values tended to be lower in the associations with potassium-sparing diuretics. The association of potassium-sparing agents did not influence the effects of thiazide diuretics on blood lipids.

The importance of high BP in the causation of cardiovascular disease [30] demands effective strategies to mitigate the incidence of noncommunicable diseases. The ideal treatment of patients with hypertension should include drugs with known effectiveness to prevent cardiovascular events, convenient administration and low incidence of adverse effects. Diuretics have the best record in terms of the prevention of cardiovascular events [2–5]. In the SPRINT trial [31], the significant difference in the proportion of BP-lowering classes of drugs in the intensive treatment arm (SBP target below 120 mmHg) and the control group (SBP target below 140 mmHg) was the use of diuretics (approximately 60 vs. 40%, respectively). The BP-lowering effect of diuretics is at least similar to other agents, and their long duration of action is instrumental in circumventing lower adherence to treatment [32–34].

Metabolic adverse events (particularly lowering of serum potassium and increasing uric acid and glucose) are reasons of concern regarding the use of thiazide diuretics. In a case–control study, low blood potassium was associated with lower effectiveness in preventing major cardiovascular events in the SHEP trial [4] and was a risk factor for sudden cardiac death in a case–control study [24]. Moreover, the reduction of potassium was associated with increased blood glucose levels [35]. These findings suggest that treatments that increase potassium (e.g. supplementation of potassium chloride [14] and replacement of sodium chloride by potassium chloride) [36] lower BP. Replacing 25% of the dietary sodium salt with potassium chloride reduced the incidence of stroke and cardiovascular events [17].

The findings of this network meta-analysis suggest that the association of potassium-sparing diuretics increases the BP-lowering effect of thiazides and mitigates some of their adverse effects. The effects of the association of thiazides with potassium-sparing diuretics on potassium and a trend for effects over glucose in this meta-analysis agree with those observed in the PATHWAY-3 trial [10].

Hydrochlorothiazide combined with amiloride had better performance than controls in two RCTs with cardiovascular outcomes [37,38]. In the Medical Research Council

trial of treatment of hypertension in older adults, participants treated with the combination had a lower incidence of stroke and coronary events than participants in the placebo and atenolol arms [37]. In the INSIGHT trial, participants treated with hydrochlorothiazide with amiloride had a lower incidence of fatal myocardial infarction and nonfatal heart failure than patients treated with long-acting nifedipine [38].

The evidence from these RCTs with cardiovascular events, and the effects of the association of thiazide diuretics with potassium-sparing diuretics on BP and metabolic parameters suggest that these combinations should be used more frequently in managing high BP.

Our study has some limitations, such as the use of the Rob 1 version instead of the Rob 2, which provides an assessment of overall bias, but we believe that this limitation is unlikely to compromise the internal validity of our meta-analysis. Second, potassium-sparing diuretics were administered mostly in low dosage; the BP-lowering efficacy of higher doses requires further investigations. The strengths of this meta-analysis are a large number of RCTs and patients evaluated. With the thorough use of network meta-analyses, we believe that this study is the most extensive evidence on this topic.

In conclusion, the combination of thiazides (particularly at higher doses) with potassium-sparing diuretics increases their BP-lowering effectiveness with less potassium depletion. These combinations should be considered when initiating treatment of hypertension.

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Conflicts of interest

None.

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