

Systematic Review

Efficacy & safety of chlorthalidone vs. hydrochlorothiazide in hypertension: A systematic review & meta-analysis

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Background & objectives: Diuretics are among the most cost-effective therapies for hypertension, yet uncertainty remains regarding the comparative efficacy and safety of chlorthalidone *versus* hydrochlorothiazide.

Methods: A search was conducted in PubMed, Cochrane, Scopus, and Embase. RCTs involving hypertensive patients were included, with chlorthalidone as the intervention and hydrochlorothiazide as the comparator. Risk of bias was assessed using the ROB 2 tool. The mean difference (MD) and relative risk (RR) were used as summary estimates. Safety outcomes were assessed by pooling the incidence of hypokalaemia, using RR.

Results: Ten RCTs (n = 1,182) were included. Chlorthalidone achieved greater reductions in 24-h ambulatory systolic blood pressure (BP) [MD: -4.21 mmHg, 95% confidence interval (CI): -4.73 to -4.05] and diastolic BP (MD: -2.23 mmHg, 95% CI: -3.13 to -1.32; both $P < 0.01$). Office systolic BP was also lower with chlorthalidone (MD: -4.10 mmHg, 95% CI -6.11 to -2.08; $P < 0.01$), whereas office diastolic BP showed no significant difference (MD: -1.70 mmHg, 95% CI -3.40 to 0; $P = 0.05$). The risk of hypokalaemia did not differ significantly (RR: 1.51, 95% CI 0.83-2.72; $P = 0.17$). Hypokalaemia was numerically more frequent with chlorthalidone.

Interpretation & conclusions: Chlorthalidone lowers systolic and diastolic BP more effectively than hydrochlorothiazide without significantly increasing the risk of hypokalaemia. These findings support chlorthalidone as the more efficacious thiazide option, particularly where cost-effective BP control is critical. Larger, long-term RCTs are needed to determine whether these BP benefits translate into superior cardiovascular outcomes.

Key words Blood pressure - diuretics - chlorthalidone - hydrochlorothiazide - hypertension - meta-analysis

Treatment of hypertension includes non-pharmacological strategies that prioritise reducing salt consumption, increasing potassium intake

through fruits, and limiting alcohol intake with proper weight management¹. Pharmacological treatment generally begins with angiotensin-converting enzyme

inhibitors, angiotensin receptor blockers, calcium channel blockers, or diuretics, as recommended by the International Society of Hypertension. Diuretics effectively control blood pressure (BP), reduce cardiovascular risk, and are the most cost-effective antihypertensive agents, making them particularly valuable in resource-limited settings².

Diuretics are classified as thiazide-type (e.g., hydrochlorothiazide) or thiazide-like (e.g., chlorthalidone). Although both lower BP, they differ pharmacologically as chlorthalidone is taken up by red blood cells, where it binds to carbonic anhydrase, increasing its volume of distribution and prolonging its duration of action^{3,4}. Evidence comparing their efficacy and safety remains conflicting. A 2012 network meta-analysis reported superior cardiovascular protection with chlorthalidone, whereas a 2020 cohort study reported no significant difference^{5,6}. Other studies also present conflicting results; a network meta-analysis found chlorthalidone to be superior in BP control, while a cohort study suggested both drugs have comparable effectiveness^{7,8}. Safety data are also inconsistent; some studies have linked chlorthalidone to more electrolyte disturbances, although recent meta-analyses have found no significant safety differences between the two^{6,7}.

Given these discrepancies, an updated review focusing exclusively on randomized controlled trials (RCTs) directly comparing chlorthalidone and hydrochlorothiazide is warranted. Prior reviews have emphasized surrogate outcomes such as BP reduction, but large-scale RCTs adequately powered to assess cardiovascular endpoints such as myocardial infarction, stroke, and mortality are lacking. This gap leaves uncertainty about whether the modest differences in BP translate into meaningful improvements in the long term. Considering their global use and importance in low-resource settings, this systematic review and meta-analysis aim to provide robust evidence on the comparative efficacy and safety of chlorthalidone and hydrochlorothiazide in the management of hypertension.

Materials & Methods

Protocol and registration: This review followed PRISMA ("Preferred Reporting Items for Systematic Reviews and Meta-Analyses") guideline (Supplementary Table I) and was registered in PROSPERO ("International Prospective Register of Systematic Reviews") database with CRD42024503838.

Search strategy and selection criteria: Guidelines from the Cochrane Handbook for Systematic Reviews of Interventions were followed⁹. The included RCTs met all the following criteria: (i) Population: patients with hypertension. (ii) Intervention: Chlorthalidone alone or in combination. (iii) Comparison: hydrochlorothiazide alone or in combination with the same drug as the intervention group. All the reviews, observational studies, and non-randomized interventional studies were excluded (Supplementary Table II).

A search strategy using keywords for the population (hypertension), intervention (chlorthalidone), and comparison (hydrochlorothiazide) was developed by two authors. Two investigators (PA, RO) independently searched Medline (via PubMed), Cochrane, Scopus, and Embase from inception to December 22, 2024, without year restrictions (Supplementary Table III); only English-language studies were eligible. Clinical trial registries, including ClinicalTrials.gov, WHO ICTRP, and the Clinical Trials Registry – India, were screened for unpublished or ongoing trials. References of eligible articles were also checked. Titles and abstracts were independently screened to identify potentially eligible studies, followed by full-text review. Discrepancies were resolved by consensus with a third investigator.

Data extraction: The data from the selected trials, including the first author's name, year of publication, study design, participant characteristics, intervention and control group details, and follow up schedule, were extracted and entered into a pre-determined proforma.

Study objectives and parameters: The primary objective focused on 24-h ambulatory (systolic and diastolic) BP changes. Secondary objectives concentrate on changes in office (systolic and diastolic) BP and safety endpoints, including the incidence of hypokalaemia.

Data analysis: Two researchers independently extracted data from eligible studies, with disagreements resolved by consultation with an expert. Dichotomous outcomes were pooled as relative risks (RR) and continuous outcomes as mean differences (MD) using Review Manager (RevMan) 5.4 (RRID: SCR_003581; Copenhagen: The Nordic Cochrane Centre, 2020). Statistical significance was set at $P < 0.05$, with 95 per cent confidence intervals (CIs). Heterogeneity was assessed using I^2 ; values > 50 per cent indicated substantial heterogeneity¹⁰. Fixed-effects models were used for $I^2 \leq 50$ per cent, and random-effects models for $I^2 > 50$ per cent.

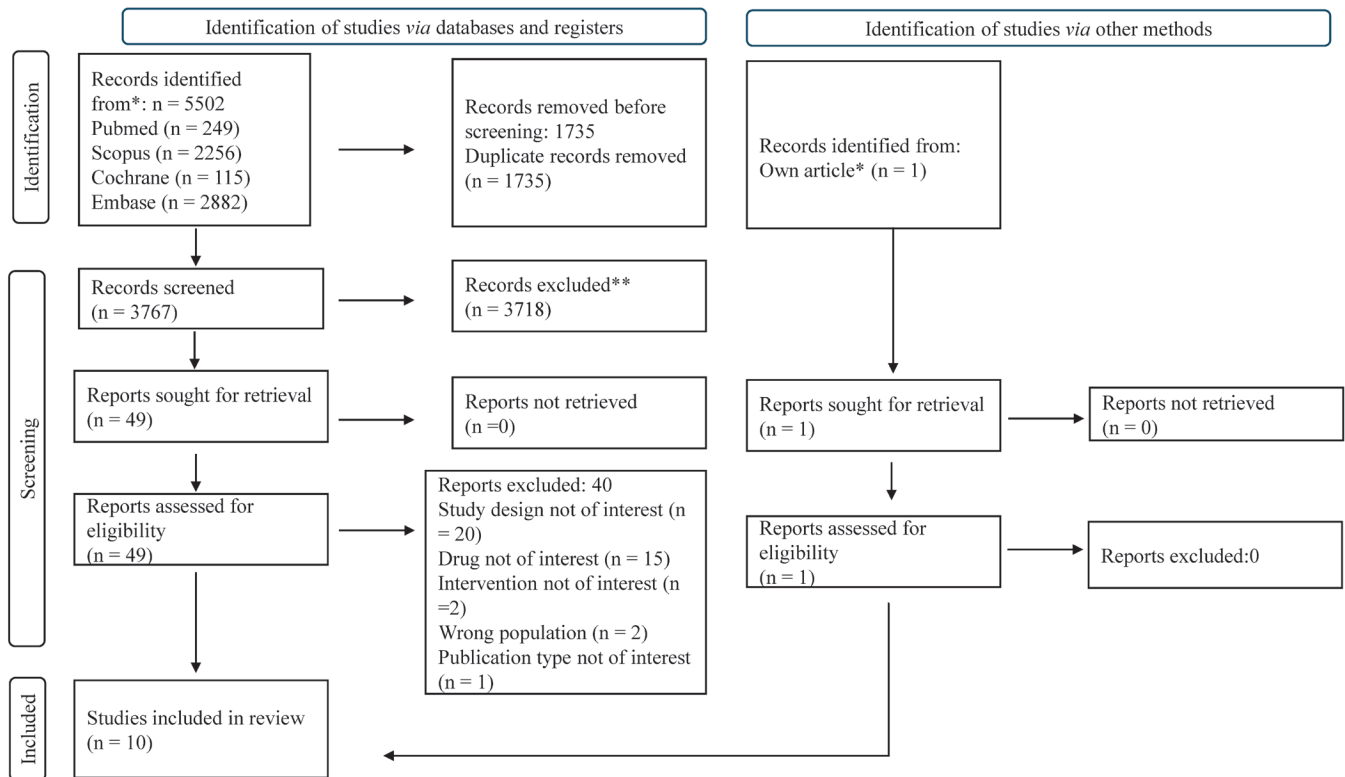


Fig. 1. PRISMA flowchart of study selection. Flow diagram illustrating the systematic identification, screening, eligibility assessment, and inclusion of studies in the review. Numbers of records removed, screened, excluded (with reasons), and included in the final review are indicated at each stage. Here *One article is from the study (unpublished) conducted by first author (PA). PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; n, number of studies.

Quality assessment of studies: Two authors (PA, RO) independently assessed the quality of RCTs using the Cochrane risk of bias 2 (ROB-2) tool, categorizing studies as low risk, high risk, or with some concerns^{11,12}. Risk-of-bias plots were generated with Robvis, and discrepancies resolved by consensus with a third investigator. The overall evidence quality was evaluated using GRADEpro GDT, classifying outcomes as high, moderate, or low quality¹³. The GRADEpro-GDT software was accessed online from <https://grade.pro.org/>.

Results

A total of 5,502 articles were identified from Medline (*via* PubMed), Cochrane, Scopus, and Embase. After removing 1,735 duplicates and 3,718 records that differed from our research question or had inappropriate study designs, 49 articles were screened by title and/or abstract. Of these 10 studies¹⁴⁻²² were included in the analysis, including one (unpublished) conducted by PA (first author of this review) (Fig. 1).

Studies with the same drug combination (*e.g.*, azilsartan + chlorthalidone *vs.* azilsartan +

hydrochlorothiazide) are included, while studies with different drug combinations (*e.g.*, azilsartan + chlorthalidone *vs.* olmesartan + hydrochlorothiazide) were excluded from the meta-analysis²³⁻²⁶.

Study characteristics: The extracted data, covering the year of publication, population age, sample size, intervention and comparator arms, and follow up duration, are summarised in table I.

Efficacy outcomes:

Primary efficacy outcome: 24-h ambulatory BP: Four trials (chlorthalidone: 290; hydrochlorothiazide: 299) assessed changes in 24-hour ambulatory BP. chlorthalidone showed a greater reduction in systolic BP (MD = -4.21; 95% CI -4.73 to -4.05; $P < 0.001$; $I^2 = 9\%$) and diastolic BP (MD = -2.23; 95% CI -3.13 to -1.32; $P < 0.001$; $I^2 = 51\%$), favouring chlorthalidone over hydrochlorothiazide (Supplementary Fig. 1).

Secondary efficacy outcome: Office BP: The pooled analysis of nine trials (chlorthalidone: 517; hydrochlorothiazide: 530) showed a greater reduction

Table I. Characteristics of included studies. Summarizes key features of included studies: author, year, design, population, sample size, age, baseline blood pressure, interventions, comparators, and follow up duration. Reports end-of-study systolic and diastolic BP for each group

First author, yr	Population		Baseline blood pressure		Intervention	Comparison	Follow up (wk)	
	Design	Age (yr)	Sample size	Intervention SBP/ Comparison SBP				Intervention DBP/ Comparison DBP
Bowlus <i>et al</i> ¹⁴ , 1964	RCT	33-72	38	181/178	110/110	Chlorthalidone 50 mg	Hydrochlorothiazide 100 mg	6
Ernst <i>et al</i> ¹⁵ , 2006	RCT	18-79	30	145±9.8/140±12.7	96±7.2/91±11.5	Chlorthalidone 12.5 mg	Hydrochlorothiazide 25 mg	8
Pareek <i>et al</i> ¹⁶ , 2009	RCT	≥18	130	155±9.9/159±15.9	96±5.1/98±6.5	Metoprolol XL 25mg/ Chlorthalidone 6.25 mg	Metoprolol XL 25 mg/ Hydrochlorothiazide 12.5 mg	12
Pareek, Basavanagowdappa <i>et al</i> ¹⁷ , 2009	RCT	18-75	131	154 ± 8/153 ± 8	95 ± 3.7/95± 4.5	Losartan 25 mg + Chlorthalidone 6.25 mg	Losartan 25 mg + Hydrochlorothiazide 12.5 mg	12
Bakris <i>et al</i> ¹⁸ , 2012	RCT	≥18	609	165±0.6/164±0.6	96±0.5/96±0.6	Azilsartanmedoxomil 40 mg/Chlorthalidone 12.5 mg	Azilsartanmedoxomil 40 mg/Hydrochlorothiazide 12.5 mg	10
Kwon <i>et al</i> ¹⁹ , 2013	RCT	30 -69	32	131±12/128±14	84±9/81±11	Candesartan 8 mg + Chlorthalidone 12.5 mg	Candesartan 8 mg + Hydrochlorothiazide 25 mg	8
Pareek <i>et al</i> ²⁰ , 2016	RCT	18-65	54	147±4.5/150±4.5	94±2.8/93±2.4	Chlorthalidone 6.25 mg	Hydrochlorothiazide 12.5 mg	12
Bashir <i>et al</i> ²¹ , 2022	Cross over trial	≥19	34	Not reported	Not reported	Chlorthalidone	Hydrochlorothiazide	6
Krittayaphong <i>et al</i> ²² , 2023	RCT	≥18	56	152/154	90/93	Chlorthalidone 25 mg	Hydrochlorothiazide 50 mg	12
Aggarwal <i>et al</i> , 2024 (unpublished)	RCT	18-60	68	154 ± 5.3/153 ± 4.9	88 ± 8.1/89 ± 6.5	Telmisartan 40 mg + Chlorthalidone 12.5 mg	Telmisartan 40 mg + hydrochlorothiazide 12.5 mg	12

RCT, randomized controlled trial

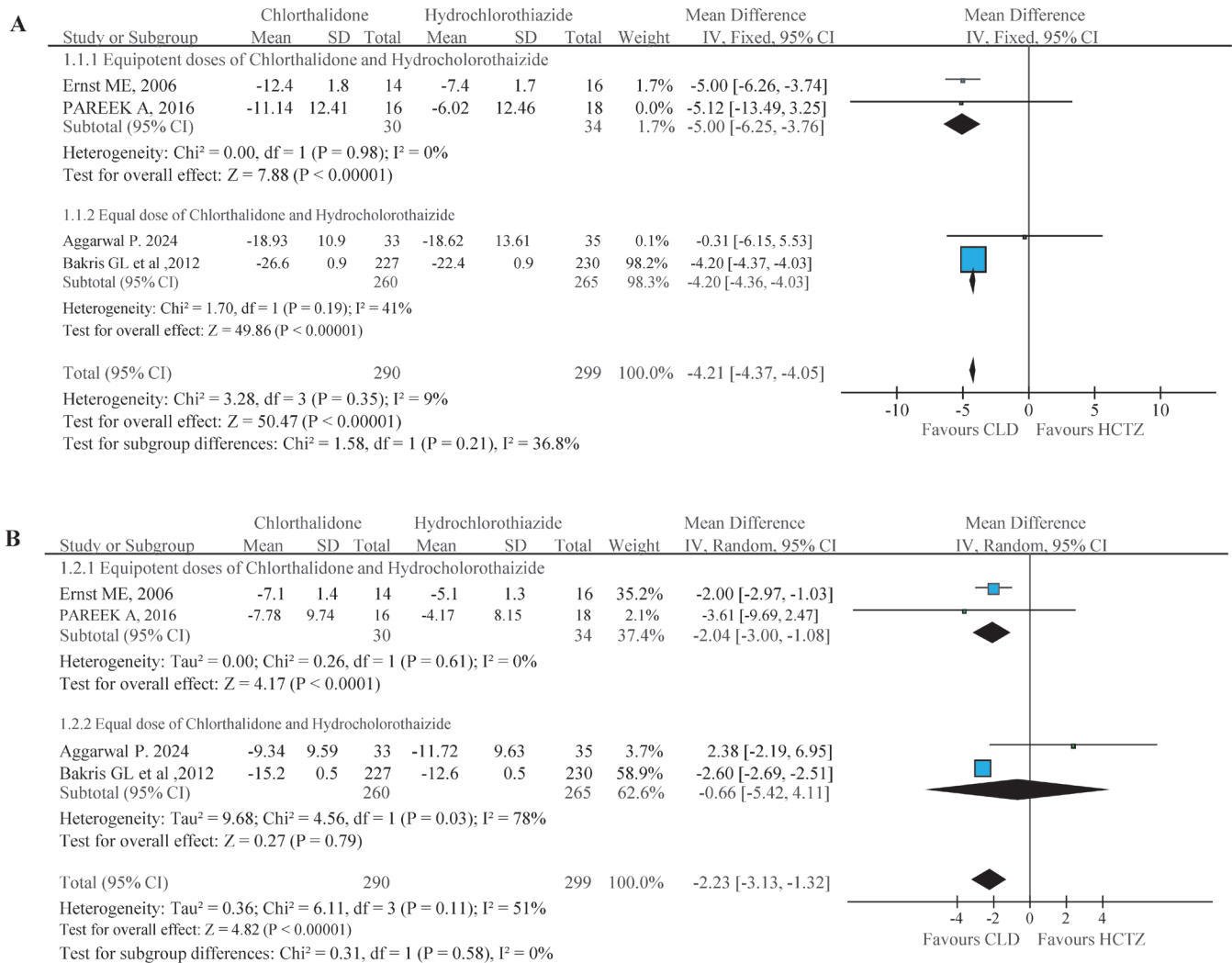


Fig. 2. (A) 24-hour ambulatory systolic BP: chlorthalidone vs. hydrochlorothiazide. Forest plot showing mean differences (95% CI) by dosage and overall effect. **(B)** 24-h ambulatory diastolic BP: chlorthalidone vs. hydrochlorothiazide. Forest plot showing mean differences (95% CI) by dosage and overall effect. CI, confidence interval; SD, standard deviation.

in office systolic BP with chlorthalidone (MD = -4.64; 95% CI -5.98 to -3.29; *P* < 0.01; *I*² = 44%). No significant difference was observed in diastolic BP (MD = -1.7; 95% CI -3.40 to 0; *P* = 0.05; *I*² = 77%) (Supplementary Fig. 2).

Safety outcomes: Incidence of hypokalaemia: The incidence of hypokalaemia was reported in four trials (chlorthalidone: 358; hydrochlorothiazide: 357), with 21 and 14 events, respectively. No significant difference was observed between treatments (RR = 1.51; 95% CI 0.83–2.72; *I*² = 0%; *P* = 0.17), favouring neither chlorthalidone nor hydrochlorothiazide (Supplementary Fig. 2).

Subgroup analysis: A subgroup analysis was done based on whether the doses used were equipotent or equal.

For 24-h ambulatory SBP, equipotent-dose studies showed a reduction of -5.00 mmHg (95% CI: -6.25 to -3.76) and equal-dose studies -4.20 mmHg (95% CI: -4.37 to -4.06), both favouring chlorthalidone (Fig. 2A).

For 24-h ambulatory DBP, equipotent-dose studies showed a pooled MD of -2.04 mmHg (95% CI: -3.00 to -1.08) favouring chlorthalidone, while equal-dose studies showed a non-significant difference of -0.66 mmHg (95% CI: -5.42 to 4.11) (Fig. 2B).

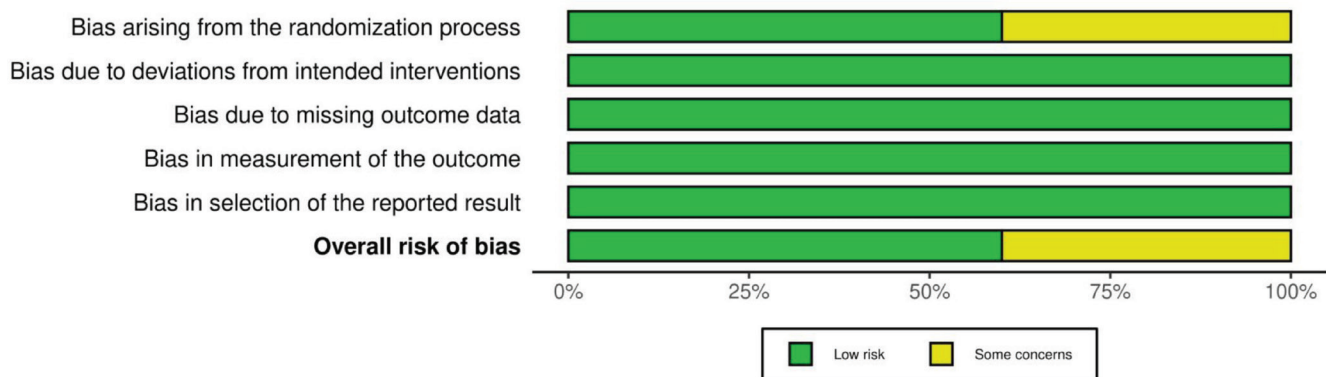


Fig. 3. Risk of Bias: Summary plot. Summary plot showing the proportion of studies with low, unclear, and high risk across each bias domain.

For Office SBP, Equipotent-dose studies reported a reduction of -5.00 mmHg (95% CI: -6.73 to -3.27) favouring chlorthalidone, while equal-dose studies showed -4.08 mmHg (95% CI: -6.22 to -1.95), which was not statistically significant (Supplementary Fig. 3).

For office DBP, equipotent-dose studies showed a mean reduction of -1.55 mmHg (95% CI: -2.88 to -0.22) favouring chlorthalidone, while equal-dose studies showed a non-significant change of -0.77 mmHg (95% CI: -7.28 to 5.74) (Supplementary Fig. 3).

For hypokalaemia, equipotent-dose studies showed no significant difference (RR = 1.24; 95% CI: 0.67–2.30), and a single equal-dose study reported RR = 4.95 (95% CI: 0.58–42.10) with wide uncertainty (Supplementary Fig. 4).

Sensitivity analysis: Moderate heterogeneity was observed for 24-h ambulatory and office diastolic BP. Sensitivity analyses, excluding trials with extreme opposing results and small sample sizes (<100 per group), reduced heterogeneity for most endpoints, except for office diastolic BP in the analysis excluding trials with opposite effects. Effect estimates remained consistent in both magnitude and direction with the primary analysis, supporting the robustness of findings (Supplementary Tables IV and V; Supplementary Figs. 5 and 6).

Risk of bias: Four studies raised concerns regarding randomization, while the remaining studies demonstrated a low risk across all domains. Overall, only four studies raised some concerns, while the others had a low risk. Quality assessments are shown in the summary plot (Fig. 3) and traffic-light plot (Supplementary Fig. 7).

GRADE assessment: High-certainty evidence supports a strong recommendation for change in 24-h ambulatory BP with chlorthalidone *versus* hydrochlorothiazide. Moderate-certainty evidence supports recommendations for clinic BP changes and hypokalaemia incidence, downgraded due to risk-of-bias concerns (Table II).

Discussion

A thorough search identified randomised controlled trials meeting the inclusion criteria for this systematic review and meta-analysis. Chlorthalidone provided superior blood pressure control compared to hydrochlorothiazide without a significant increase in the risk of hypokalaemia. These findings support guideline recommendations favouring chlorthalidone, though its clinical use remains limited. Subgroup analyses indicate that chlorthalidone achieved superior blood pressure reduction even at lower doses than higher doses of hydrochlorothiazide, supporting its preferential use for both effective blood pressure control and improved clinical outcomes.

Chlorthalidone achieved an additional 4–5 mmHg Systolic blood pressure reduction *versus* hydrochlorothiazide in both ambulatory and office measurements, a clinically meaningful difference. The blood pressure lowering treatment trialists' collaboration demonstrated that every 5-mmHg systolic blood pressure reduction lowers cardiovascular event risk by about 10 per cent²⁷. Thus, chlorthalidone's incremental benefit is likely to translate into a reduction in cardiovascular morbidity and mortality. This emphasizes that even modest blood pressure improvements have important clinical implications and should guide selection of the optimal thiazide

Table II. Summary of findings. Synthesizes effects of chlorthalidone versus hydrochlorothiazide on blood pressure. Includes number of studies, patients, risk-of-bias assessment, effect estimates (absolute and relative), 95 per cent confidence intervals, certainty of evidence, and clinical importance

Certainty assessment		No. of patients		Effect		Certainty		Importance				
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chlorthalidone	hydrochlorothiazide	Relative (95% CI)	Absolute (95% CI)		
Change in 24-h SBP by AMBP												
4	Randomised trials	Not Serious	Not serious	Not serious	Not serious	None	290	299	-	MD 4.21 lower (4.37 lower to 4.05 lower)	⊕⊕⊕High	CRITICAL
Change in 24-h DBP by AMBP												
4	Randomised trials	Not Serious	Not serious	Not serious	Not serious	None	290	299	-	MD 2.23 lower (3.13 lower to 1.32 lower)	⊕⊕⊕High	CRITICAL
Change in clinic SBP												
9	Randomised trials	Serious ^a	Not serious	Not serious	Not serious	None	517	530	-	MD 4.1 lower (6.11 lower to 2.08 lower)	⊕⊕○Moderate ^a	IMPORTANT
Change in clinic DBP												
9	Randomised trials	Serious ^a	Not serious	Not serious	Not serious	None	517	530	-	MD 1.7 lower (3.4 lower to 0)	⊕⊕○Moderate ^a	IMPORTANT
Incidence of hypokalaemia												
4	Randomised trials	Serious ^b	Not serious	Not serious	Not serious	None	21/358 (5.9%)	14/357 (3.9%)	RR 1.51 (0.83 to 2.72)	20 more per 1,000 (from 7 fewer to 67 more)	⊕⊕○Moderate ^b	IMPORTANT

^aFour clinical trials were having open label design; ^bone clinical trials had open label design. CI, confidence interval; MD, mean difference; RR, risk ratio; SBP, systolic blood pressure; AMBP, ambulatory blood pressure

diuretic. Thiazide diuretics are widely prescribed for hypertension, yet debate persists regarding the interchangeability of hydrochlorothiazide and chlorthalidone²⁸. A 2020 network meta-analysis by Dineva *et al*⁷ also preferred chlorthalidone for blood pressure control. However, hydrochlorothiazide remains more commonly prescribed worldwide. Our analysis found no significant increase in hypokalaemia risk with chlorthalidone, which is at odds with the results of previous meta-analyses that combined Randomised controlled trials with observational studies, possibly inflating adverse event estimates^{6,29}. Using only randomised controlled trials likely reduced bias and yielded more conservative results.

A 2012 network meta-analysis reported chlorthalidone's superiority in preventing cardiovascular events, showing 21 per cent and 23 per cent risk reductions for total events and heart failure, respectively⁵. However, the diuretic comparison project, involving 13,523 veterans, reported no significant difference in major cardiovascular outcomes, though hypokalaemia occurred more frequently with chlorthalidone³⁰. The ALLHAT trial supported chlorthalidone's cardiovascular benefits and its superiority in preventing heart failure compared with other anti-hypertensive agents³¹. Conversely, observational studies have found no significant difference in cardiovascular outcomes between the two drugs^{6,32}. While blood pressure reduction is key, it may not always translate into improved cardiovascular outcomes. Variability in study design, population characteristics, and follow up duration likely explains the conflicting evidence. Given the current evidence, both chlorthalidone and hydrochlorothiazide remain viable treatment options, and patient-specific factors should guide the choice between them. A large, long-term trial is needed to compare cardiovascular efficacy.

Our findings align with landmark chlorthalidone trials. SPRINT analysis compared chlorthalidone with amlodipine and reported higher treatment failure rates with chlorthalidone, mainly due to investigator treatment decisions rather than lack of blood pressure control³³. The PREVER trial showed that a low-dose chlorthalidone/amiloride reduced the incidence of hypertension and left ventricular mass progression versus placebo in pre-hypertensive individuals³⁴. TOMHS showed chlorthalidone significantly lowered blood pressure and improved cardiovascular risk factors³⁵. The long-term follow up of the SHEP trial showed that chlorthalidone-based therapy reduced cardiovascular morbidity and extended survival in

elderly patients³⁶. The MRFIT study highlighted that chlorthalidone responses can vary by patient subgroup, emphasizing the need for individualized therapy³⁷. Collectively, these trials reinforce the robustness of evidence for chlorthalidone in hypertension management.

Beyond hydrochlorothiazide and chlorthalidone, other diuretics have a narrower role in hypertension management. Loop diuretics (*e.g.*, furosemide) are used in heart failure or chronic kidney disease, while potassium-sparing agents (*e.g.*, spironolactone) serve as add-on therapy for resistant hypertension. Thiazide diuretics remain the preferred first-line option for blood pressure control. In comparative trials, chlorthalidone was typically administered at roughly half the hydrochlorothiazide dose (*e.g.*, chlorthalidone 12.5 mg vs. hydrochlorothiazide 25 mg; chlorthalidone 6.25 mg vs. hydrochlorothiazide 12.5 mg) yet produced equal or superior blood pressure reductions. Even very low-dose chlorthalidone (6.25–12.5 mg) matched or exceeded double-dose hydrochlorothiazide effects. Follow up durations ranged from 6 to 12 wk, sufficient to capture meaningful blood pressure changes. These findings confirm that low-dose chlorthalidone is more potent than full-dose hydrochlorothiazide, reinforcing its clinical advantage while potentially reducing dose-related side effects.

Our study prioritized ambulatory blood pressure monitoring as the primary endpoint, providing a more accurate and reliable measure of 24-h blood pressure control than office blood pressure, which is subject to variability and observer bias. This strengthens the validity of the study. GRADE pro assessment rated evidence certainty for chlorthalidone's greater 24-h blood pressure reduction as high and for clinic-based blood pressure and hypokalaemia as moderate. Hence, conclusions apply separately to each outcome rather than to an overall treatment effect. Study limitations include the small number of head-to-head randomised controlled trials assessing cardiovascular outcomes, limited ambulatory blood pressure monitoring -based trials, and inclusion of studies using combination therapy, which could confound blood pressure and safety effects. Long-duration head-to-head randomised controlled trials are warranted to validate efficacy and safety across diverse populations.

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Conflicts of Interest: None.

Use of Artificial Intelligence (AI)-Assisted Technology for manuscript preparation: The authors confirm that there was no use of AI-assisted technology for assisting in the writing of the manuscript and no images were manipulated using AI.

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