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Review Article

Effects of chlorthalidone and hydrochlorothiazide on blood pressure and serum potassium levels: a systematic review and meta-analysis

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Abstract: Background: Whether chlorthalidone (CTDN) is more potent than hydrochlorothiazide (HCTZ) in the management of hypertension is controversial. Although CTDN has been used as an alternative treatment to HCTZ for lowering blood pressure, HCTZ is still used far more frequently than CTDN. Objectives: Trials comparing the antihypertensive potency and potassium effects of HCTZ with those of CTDN and direct systematic reviews and meta-analyses of such trials are scarce; therefore, our objective was to further examine the controversy regarding the potency of these two drugs. Methods: Pubmed, Embase, and CENTRAL databases were searched for randomized controlled trials that directly compared the antihypertensive potencies of HCTZ and CTDN; a manual search of the reference lists of relevant articles was also conducted to identify additional eligible articles. Weighted mean differences (WMD) with 95% confidence intervals (CI) were pooled by using a fixed-effect model or a random-effect model. Results: Six randomized controlled trials with a total of 366 participants were included in this meta-analysis. The results indicated that a dose of HCTZ double to that of CTDN has the same efficacy for lowering SBP and DBP (WMD=-3.22 mmHG, 95% CI: -6.48 to 0.04, I^2=0%, WMD=-0.67 mmHG, 95% CI: -2.60 to 1.26, I^2=0%; respectively); But CTDN caused a greater reduction than HCTZ in 24-hour ambulatory blood pressure (WMD=-5.03 mmHG, 95% CI: -9.22 to -0.84, I^2=0%), ambulatory nighttime mean SBP (WMD=-6.70 mmHG, 95% CI: -11.10 to -2.30, I^2=0%); Moreover, there was no detectable difference in serum potassium levels between the CTDN and HCTZ groups (WMD=0.07, 95% CI: -0.14 to 0.28, I^2=71.3%). Conclusions: CTDN may be more effective for the management of mild-to-moderate hypertension without causing greater serum potassium loss than HCTZ.

Keywords: Chlorthalidone, hydrochlorothiazide, hypertension, randomized controlled trials

Introduction

Hypertension is the most common cardiovascular disease and also the greatest risk factor for mortality and morbidity, more than 9 million people have been reported to die of hypertension annually worldwide [1]. Therefore, more timely and appropriate treatment for hypertension is crucial. An increasing number of hypertension guidelines recommend thiazide diuretics and thiazide-like diuretics for first-line treatment [2-4]. In fact, a guideline published as early as 2003 gave that recommendation, but it did not specify which drug was more effective [5]. Hydrochlorothiazide (HCTZ) had been used for over fifty years, in recent years, the number of prescriptions for HCTZ has been increasing quickly. Approximately 12% of USA adults were administered HCTZ in 2012, which is an increase of 1.4 times the rate of administration in 1999 [6]. In the USA, approximately 50 million prescriptions for HCTZ were written in 2013, increasing it to the 12th most commonly prescribed drug [7].

However, the thiazide-like diuretic chlorthalidone (CTDN) has attracted increasing attention. Although HCTZ and CTDN have very similar structures, they have very different pharmacological profiles; compared to HCTZ, CTDN has a longer half-life and is more effective for lowering blood pressure [8]. Furthermore, many stud-

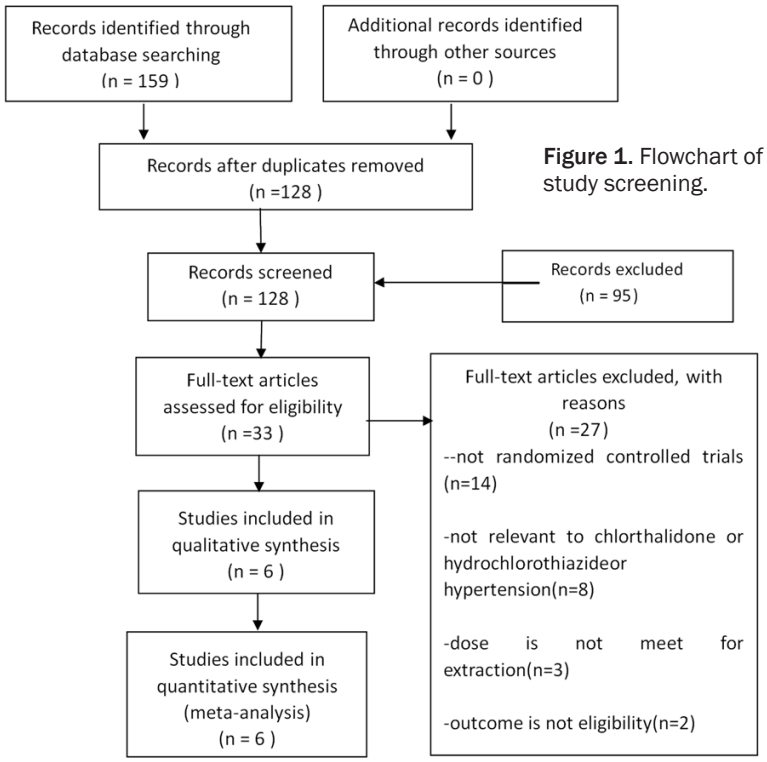

Figure 1. Flowchart of study screening.

ies have demonstrated that low-dose CTDN (12.5-25 mg/day) can reduce the incidence of cardiovascular events [9, 10] and left ventricular hypertrophy [11]. Thus, in the past 10 years, scholars have advocated for CTDN as an alternative to HCTZ for the treatment of hypertension [12-14].

Despite this, randomized controlled trials and meta-analyses directly comparing these two drugs are scarce. Therefore, we performed this systematic review and meta-analysis to determine which drug is more effective for lowering blood pressure.

Methods

Search strategy

Our review and meta-analysis strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. We searched PubMed, Embase, and CENTRAL (the Cochrane Central Register of Controlled Trials) databases for articles published in English in peer-reviewed scientific journals through June 2016. In addition, the references of relevant articles were manually searched to identify additional eligible articles. Our search strategy involved a combination of the following relevant medical subject headings (MeSH) and keywords: hypertension (Blood Pressure High OR Blood Pressures, High OR High Blood Pressure OR High Blood Pressures); chlorthalidone (Chlorthalidone OR Phthalamudine OR Chlorphthalidolone OR Oxodoline OR Hygroton OR Thalitone); and Hydrochlorothiazide (Dihydrochlorothiazide OR HCTZ OR Dichlothiazide OR Hydrodiuril OR Oretic OR Sectrazide OR Esidrix OR Esidrex OR Hypothiazide). The search identified six studies eligible for inclusion in this meta-analysis.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) patients with hypertension (systolic blood pressure ≥140 mmHG or diastolic blood pressure ≥90 mmHg; (2) clinical trials comparing HCTZ and CTDN; (3) examination of at least one of the following outcomes: systolic BP (SBP), diastolic BP (DBP), 24-hour ambulatory blood pressure monitoring (24-h ABPM), ambulatory nighttime mean SBP, and serum potassium; and (4) for clinical trials: randomized controlled study design, follow-up ≥4 weeks, sitting BP superior to supine BP, and wash-out period ≥2 weeks. The following exclusion criteria were used: (1) for patients: SBP >180 mmHG or DBP >110 mmHG and diagnosis of secondary hypertension and (2) for studies: insufficient data and animal rather than human research subjects.

Data extraction and quality assessment

Data extraction was carried out by two reviewers (Jie Chen and Chao Deng) independently, a special standardized form was used to record the following data: author's name, sample size, weight, country, gender, age, follow-up time, dose, baseline SBP, and baseline comorbidities. Controversies regarding the eligibility of a study were resolved by a third reviewer, and the

Table 1. Basic characteristics of the included studies

Study	Study design	BP Measure position	BP Measure time	Number (case/control)	Country	Gender (case/control)	Age, years (case/control)	Weight (kg)	Baseline SBP (mmHG)	HCTZ and CTDN Dose (mg)	Baseline Comorbidities	Follow-up
Lund Johansen (1970)	RCT	Sitting	Casual	9/15	Norway	Males (9/15)	48/43	70.80/77.0	178	100 and 50	no	1 year
Pareek (2009)	RCT	Sitting	In morning prior to taking medications	65/65	India	Males (29/26)	50/52	59.91/60.75	157	12.5 and 6.25	no	3 months
Pareek (2009)	RCT	Sitting	In morning prior to taking medications	60/60	India	Males (30/30)	48/51	62.30/59.24	154	12.5 and 6.25	no	4 weeks
Ernst (2006)	RCT	Sitting	23 to 26 hours after taking medications	14/16	America	Males (7/9)	46/49	80.00/90.10	142	50 and 25	no	8 weeks
Kwon (2013)	RCT	Sitting	In morning prior to taking medications	13/15	Korea	Males (NR)	NR	NR	152	25 and 12.5	no	8 weeks
Pareek (2016)	RCT	Sitting	In morning prior to taking medications	16/18	India	Males (9/8)	41/47	NR	149	12.5 and 6.25	no	12 weeks

SBP, systolic blood pressure; HCTZ, hydrochlorothiazide; CTDN, chlorthalidone; NR, no reported. RCT: randomized controlled trials.

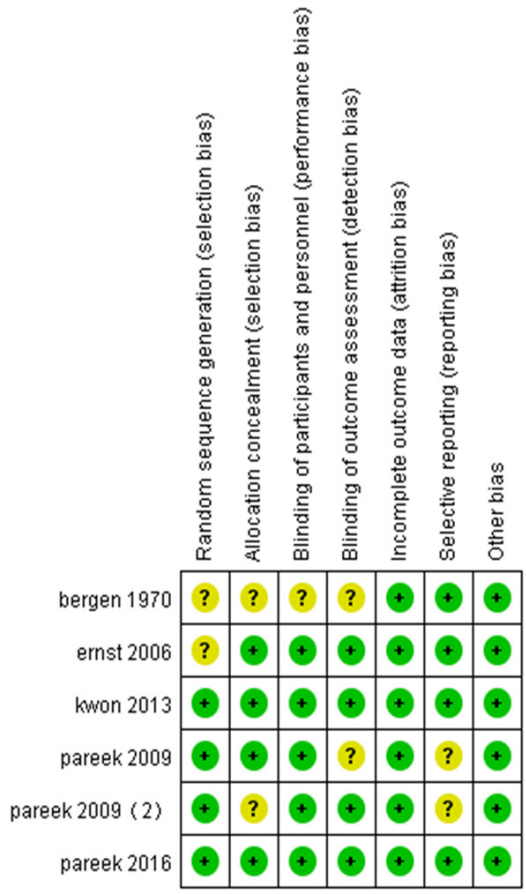

Figure 2. Risk of bias summary for all included studies. Green, low risk of bias; Yellow, unclear risk of bias; Red, high risk of bias.

authors of the articles were contacted if the original data were not included in the publication. For BP and serum potassium level, the mean changes from baseline to end-of-study were extracted; however, for cross-over trials, only data from the first active treatment period were considered. The qualities of the included studies were evaluated using the Cochrane risk-of-bias tool, which contains the following seven assessment domains: namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias [16].

Statistical analysis

The data and charts of the included studies were obtained for the meta-analysis. The pooled effect of the intervention was calculated using weighted mean differences (WMDs) with 95% confidence intervals (95% CIs). Heterogeneity was determined using the Q test and I^2 statistic, with $P<0.1$ or $I^2>50\%$ was considered representative of significant heterogeneity. When heterogeneity was present, the inverse variance randomized-effect model was used; otherwise, the inverse variance fixed-effect model was used. Sensitivity analyses were performed by omitting one study at a time and recalculating the pooled WMD to explore sources of heterogeneity. publication bias were tested by Egger's test. All data analyses were conducted using Stata 12.0 (StataCorp LP) and RevMan 5.3 (Nordic Cochrane Centre).

Results

Article screening

A total of 159 potentially eligible studies were identified using the search strategy described above. **Figure 1** presents the study screening process. First, 31 duplicate reports were excluded. The titles and abstracts of the remaining articles were reviewed, and 95 were excluded because they were not relevant to our objective. Further screening of the full-texts of the remaining 33 articles resulted in the exclusion of 14 articles that were not randomized trials; 8 articles that did not examine CTDN, HCTZ or hypertension; 3 articles with medication doses that did not meet our criteria; and 2 articles with outcomes that did not meet our criteria. Finally, six articles were included in our meta-analysis [17-22].

Study characteristics

The baseline information of the included studies is shown in **Table 1**. Three studies were completed in India, and one was completed in each of the following countries: America, Norway and Korea. The sample size ranged from 24 to 130, and the percentage of male subjects ranged from 42% to 100%. The follow-up period ranged from 4 weeks to 1 year. The maximum approved dose was used in one study, and the rest of the studies used the common dose. No baseline comorbidities were present in any of the study populations.

Risk of bias in included studies

Figure 2 shows the risk of bias for each included study. For the method of randomization, four of the six studies had a low risk of bias, and the

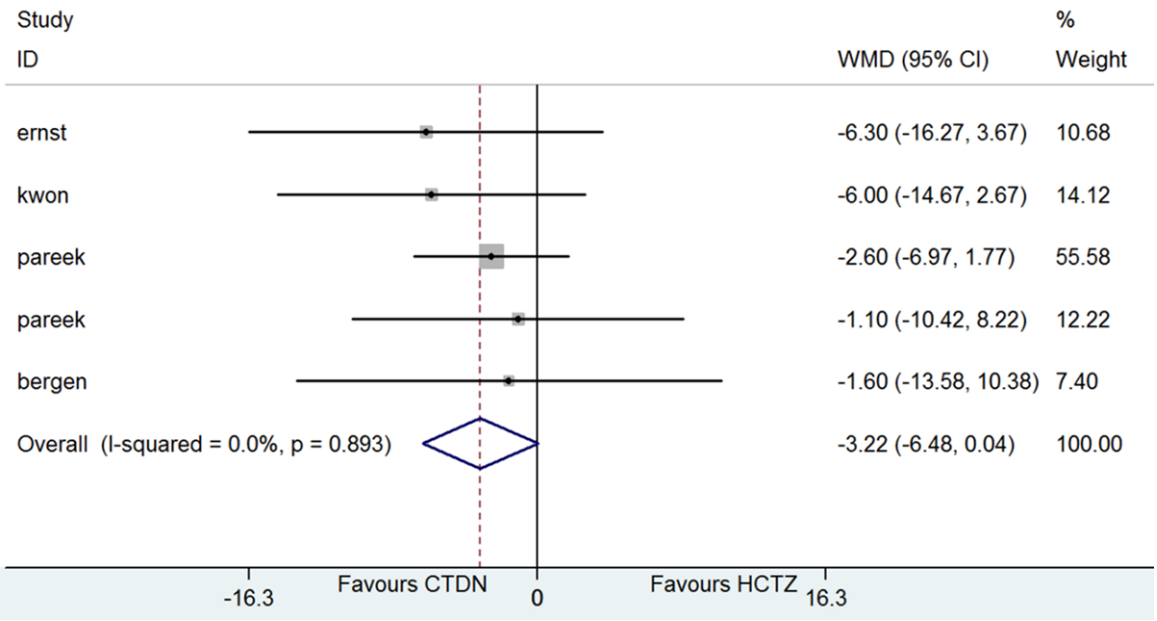

Figure 3. Comparison of the effect of CTDN on office SBP to that of HCTZ. SBP = systolic blood pressure, CTDN = chlorthalidone, HCTZ = hydrochlorothiazide, WMD = weighted mean difference, CI = confidence interval.

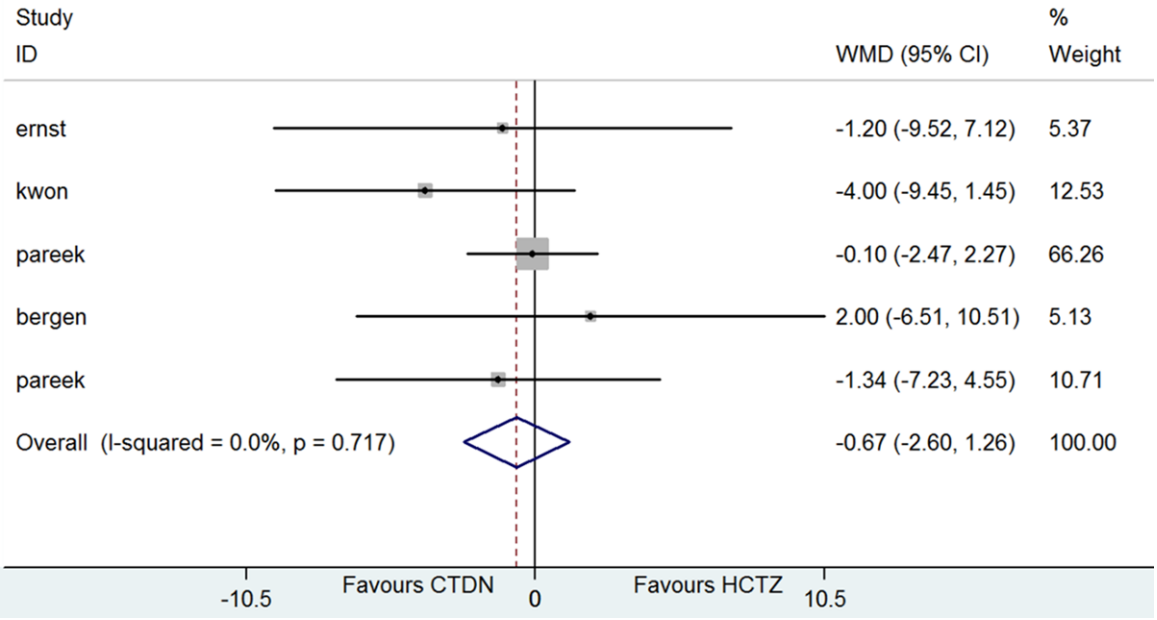

Figure 4. Comparison of the effect of CTDN on office DBP to that of HCTZ. DBP = diastolic blood pressure, CTDN = chlorthalidone, HCTZ = hydrochlorothiazide, WMD = weighted mean difference, CI = confidence interval.

remaining two studies had an unclear risk. Allocation concealment, detection and reporting biases had the same results. Five of the six studies had a low risk of performance bias. Although some studies were single-blind, the outcomes of interest could not have been influenced by that study design. All studies had a low risk of other bias and attrition bias. In summary, two studies were considered to have a low risk of bias [21, 22], and four studies were considered to have an unclear risk of bias [17-20].

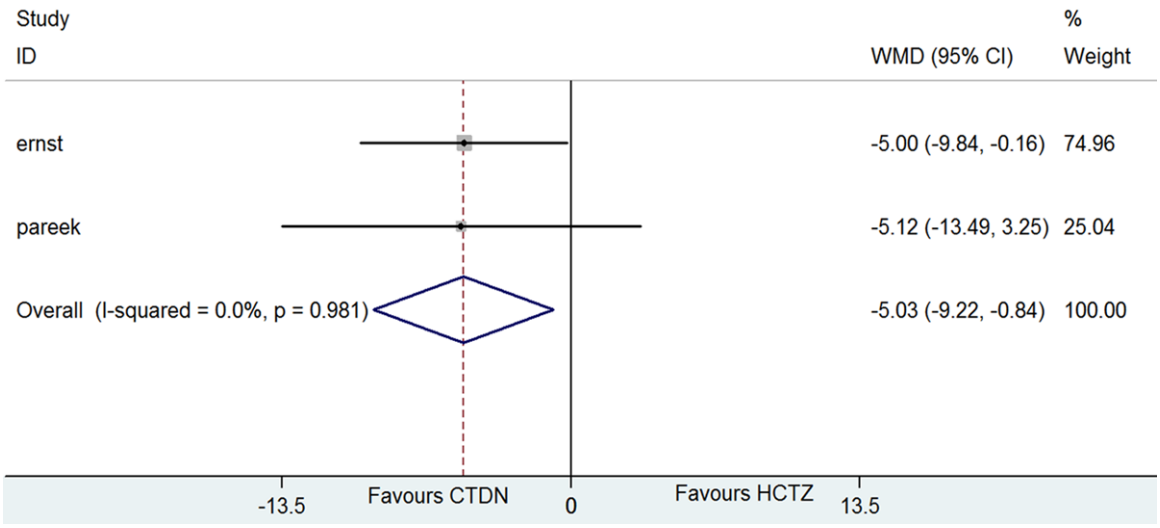

Figure 5. Comparison of the effect of CTDN on 24-h ABPM to that of HCTZ. 24-h ABPM = 24-hour ambulatory blood pressure monitoring, CTDN = chlorthalidone, HCTZ = hydrochlorothiazide, WMD = weighted mean difference, CI = confidence interval.

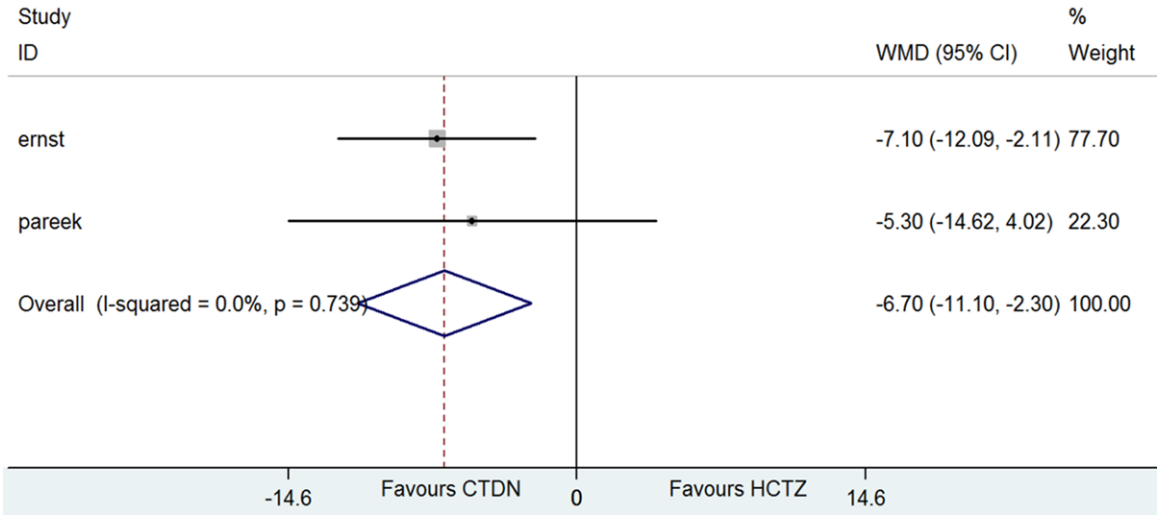

Figure 6. Comparison of the effect of CTDN on ambulatory nighttime mean SBP to that of HCTZ. SBP = systolic blood pressure, CTDN = chlorthalidone, HCTZ = hydrochlorothiazide, WMD = weighted mean difference, CI = confidence interval.

Effects of interventions

Office BP: Five studies compared office SBP and DBP between CTDN and HCTZ study groups [17, 18, 20-22]. The pooled results of our meta-analysis showed that a dose of HCTZ double to that of CTDN has the same efficacy for lowering SBP and DBP as follows: -3.22 mmHG (95% CI, -6.48 to 0.04; **Figure 3**) and -0.67 mmHG (95% CI, -2.60 to 1.26; **Figure 4**); however, there was a trend toward a greater reduction of office SBP in patients with CTDN treatment. The data were analyzed using the Fixed-effect model according to the test of heterogeneity (P=0.893, I^2=0% and P=0.717, I^2=0% for SBP and DBP, respectively), and there were not publication bias were detected for office SBP (P=0.301) and office DBP (P=0.897) in Egger's test. (see Figures S1 and S2).

Ambulatory BPS

Two studies compared the effectiveness of HCTZ on 24-h ABP monitoring (ABPM) and ambulatory nighttime mean SBP to that of CTDN [20, 22]. The pooled effect showed a sig-

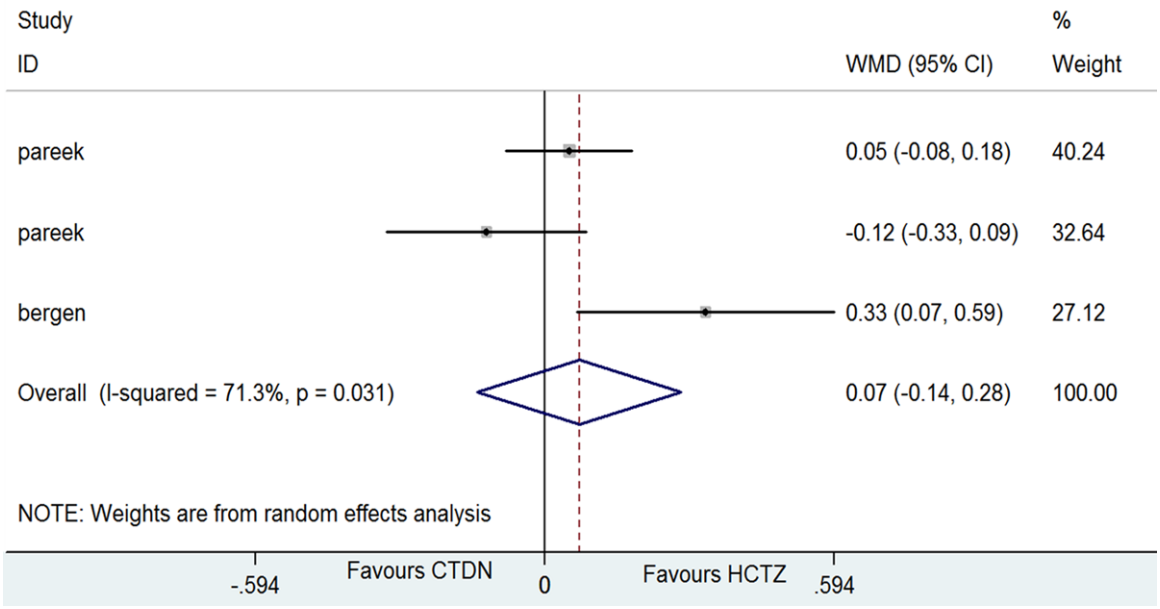

Figure 7. Comparison of the effect of CTDN on serum potassium to that of HCTZ. CTDN = chlorthalidone, HCTZ = hydrochlorothiazide, WMD = weighted mean difference, CI = confidence interval.

nificant reduction in both 24-h ABPM and ambulatory nighttime mean SBP with CTDN treatment compared to HCTZ treatment (ABPM: WMD=-5.03 mmHG; 95% CI, -9.22 to -0.84; **Figure 5**) and (ambulatory nighttime mean SBP: WMD=-6.70 mmHG; 95% CI, -11.10 to -2.30; **Figure 6**), respectively. The fixed-effect model was adopted based on the heterogeneity test results (P=0.981, I^2=0% and P=0.739, I^2=0%).

Serum potassium

Three studies measured serum potassium level to assess the safety of HCTZ and CTDN in hypertensive patients [17-19]. The pooled results showed no statistically significant difference in serum potassium level between the HCTZ and CTDN groups (WMD=0.07, 95% CI: -0.14 to 0.28; I^2=71.3%, P=0.03; **Figure 7**). Because statistical heterogeneity (I^2=71.3%) was found, the sensitivity analyses was used to examine its source. We found that the heterogeneity was reduced to I^2=47.1% without changing the pooled effect (WMD=-0.02, 95% CI: -0.18 to 0.15) with the exclusion of one study [18].

Sensitivity analyses and publications bias

To determine whether our primary results were robust, we conducted a sensitivity analysis by omitting one study at a time, and no changes to the results were observed.

Discussion

In the present meta-analysis, which included 6 randomized controlled trials with a total of 366 participants, we demonstrated that CTDN has greater potency than HCTZ in lowering office SBP and DBP, 24-h ABMP and ambulatory nighttime mean SBP. Of particular interest, there was no significant evidence of a greater reduction in serum potassium level with CTDN than with HCTZ.

Our meta-analysis shows that a dose of HCTZ double to that of CTDN has the same efficacy for lowering SBP and DBP. The results of this meta-analysis are consistent with those of previous studies as follows: a few small direct comparative trials confirmed that CTDN is 1.5-2.0 times as potent as HCTZ [23, 24]. The difference in the potency of these two drugs may be explained by the result of an animal experiment: the affinity of CTDN for NaCl cotransporters was approximately 2 times greater than that of HCTZ [25]. The longer half-life of CTDN may also explain its increased potency compared to that of HCTZ. The results of our meta-analysis are supported by those of other systematic reviews. In 2003, a meta-analysis that

compared the effects of equivalent doses of HCTZ and CTDN on blood pressure showed that systolic BP was reduced by 4.4 and 8.8 mmHG, respectively [26]. The results of two indirect meta-analyses also supported our findings [27, 28]; however, in contrast to our study, they both described the dose-response relationship for HCTZ and CTDN in regards to blood pressure, with dose ranges greater than those in the studies analyzed here. Nevertheless, they both drew the same conclusion that the efficacy of CTDN in lowering SBP was greater than that of HCTZ in the commonly used dose range (12.5-25 mg). However, those two meta-analyses did not show a specific relationship between the two drugs, as they included some studies that were not RCTs; whereas, the present meta-analysis only included RCTs.

Although the results of the most recent meta-analysis to directly compare HCTZ to CTDN supported those of our study, it only included three trials (70 patients) [7]. Therefore, the current meta-analysis used more detailed and wider inclusion criteria, resulting in a greater sample size (366 patients). Another distinguishing characteristic of our meta-analysis from previous ones is that our study examined more clinical outcomes, particularly 24-h ABPM and ambulatory nighttime mean SBP, which are better evaluators of cardiovascular events [29]. Our study showed that CTDN produces a greater reduction in 24-h ABPM and ambulatory nighttime mean SBP than HCTZ at half the HCTZ dose. It is well known that HCTZ has less than a 24-hour duration of action; in fact, the effect of HCTZ starts to decline at 8 hours after administration [30], resulting in failure to control nighttime BP. In contrast to HCTZ, CTDN has a 48- or 72-hour duration of action [31], which insures that nocturnal BP can be reduced in parallel with daytime BP. This characteristic of CTDN is noteworthy because the reduction of nighttime BP is extremely important for 24-h BP management [32], multiple studies have shown that lowering nighttime BP reduces the risk of cardiovascular events more than lowering daytime BP [33-35].

While CTDN was shown to be more effective than HCTZ at lowering blood pressure, it was not shown to decrease serum potassium level more than HCTZ, especially when comparing low doses of HCTZ and CTDN. This finding is consistent with the results of previous meta-analyses [27, 28]; however, our meta-analysis was found to have significant heterogeneity (I^2=71.3%). Sensitivity analyses suggested that the sources of the observed heterogeneity [18] were the large drug dose and long follow-up duration. Studies of hypertension treatment have shown that high doses (>50 mg) of CTDN produce a greater degree of hypokalemia than high doses of HCTZ [36]; however, no RCT directly comparing the effects of these two drugs on serum potassium has been conducted.

In the past 10 years, an increasing number of scholars have begun recommending CTDN over HCTZ for the treatment of hypertension. In addition to the benefits of CTDN in hypertension management, is has also been demonstrated to be more effective at preventing cardiovascular events [10]. Furthermore, concerns about hypokalemia and hyperglycemia seem to be unfounded when administering a low dose of CTDN [37, 38]. Despite the large amount of evidence that CTDN is superior to HCTZ, HCTZ is prescribed far more frequently than CTDN. Many clinicians avoid using CTDN in the USA. In Germany, the frequency of CTDN prescription was reported to be only 1/20 of that of HCTZ [39]. The low frequency of CTDN prescription may be due to the limited number of dosage forms and drug combinations of CTDN in comparison to HCTZ [40] in addition to concerns about hypokalemia with the administration of CTDN.

Our meta-analysis had some limitations. Firstly, although all included studies were RCTs, we could not adjust the data for all baseline characteristics. Secondly, the number of participants and included studies were small, which decreases the generalizability of our findings and prevented us from conducting subgroup analyses for race, dose, and follow-up time. Finally, the included studies did not evaluate the outcome of cardiovascular events; 24-h ABPM and ambulatory nighttime mean SBP were measured, but they are only predictors of cardiovascular events.

In conclusion, the results of the current meta-analysis indicated that CTDN may be more effective at lowering blood pressure, 24-h ABPM and ambulatory nighttime mean SBP than HCTZ, and there was no significant evidence of a greater reduction in serum potassi-

um level. Further large-scale RCTs are necessary to confirm these findings.

Disclosure of conflict of interest

None.

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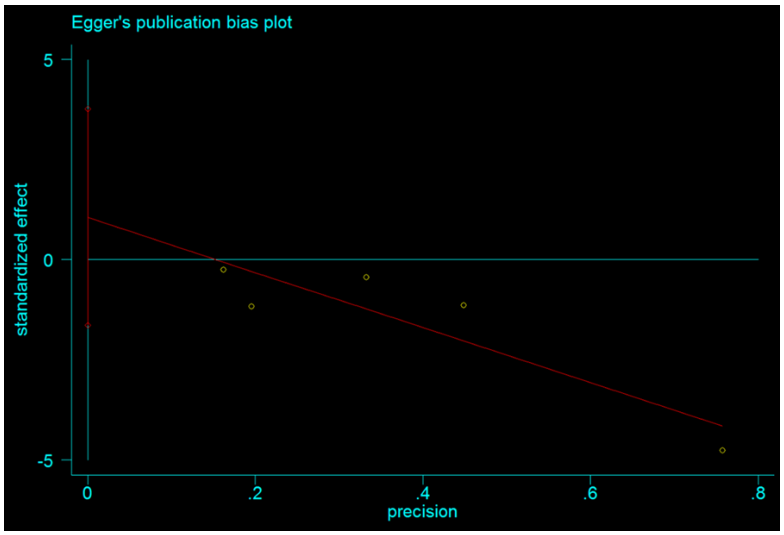

Figure S1. Egger's publication bias plot for SBP.

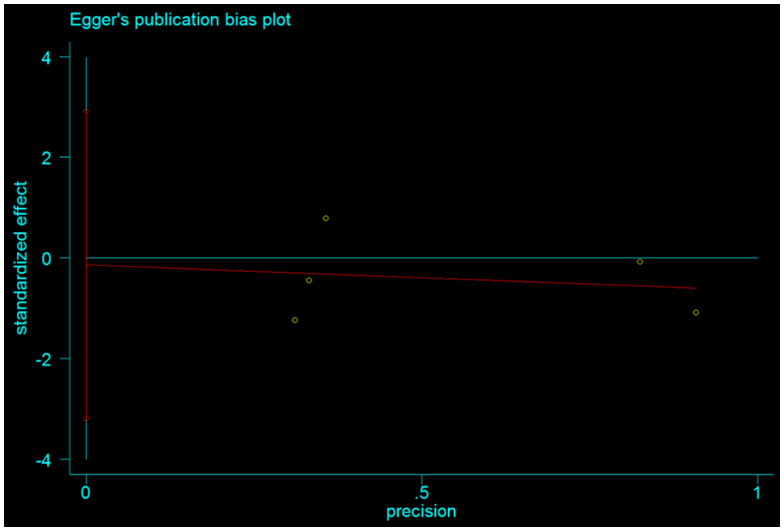

Figure S2. Egger's publication bias plot for DBP.