# Association of Thiazide-Type Diuretics With Glycemic Changes in Hypertensive Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials

Xiaodan Zhang, MD; Qingyu Zhao, MD

From the Intensive Care Unit, Sun Yat-sen University Cancer Center, Guangzhou, China

Patients receiving thiazide diuretics have a higher risk of impaired glucose tolerance or even incident diabetes, but the change of blood glucose level varies across different trials. The aim of this study was to investigate the glycemic changes in hypertensive patients with thiazide-type diuretics. Twenty-six randomized trials involving 16,162 participants were included. Thiazide-type diuretics were found to increase fasting plasma glucose (FPG) compared with nonthiazide agents or placebo or nontreatment (mean difference [MD], 0.27 mmol/L [4.86 mg/dL]; 95% confidence interval [CI], 0.15–0.39).

Thiazide-type diuretics, which include thiazide diuretics such as hydrochlorothiazide (HCTZ) and thiazide-like diuretics such as chlorthalidone (CTD) and indapamide, are a classic class of antihypertensive medications. Studies over decades have demonstrated a reduction in morbidity and mortality of cardiovascular events in patients who receive thiazide-type diuretics.<sup>1,2</sup> This class has been widely used for more than 40 years and is still recommended as one of the first-line treatments in the latest guidelines for the management of hypertension.<sup>3</sup>

However, despite the strong evidence of benefits, there are some adverse effects of thiazide diuretics that have led to debates over their wide use. Randomized trials and observational studies have demonstrated multiple metabolic abnormalities such as dysglycemia, new-onset diabetes, hypokalemia, hyponatremia, hype-ruricemia, and hyperlipidemia.<sup>4-7</sup> Among these adverse metabolic effects, glycemic dysregulation is the greatest concern. Although there has been agreement that patients receiving thiazide diuretics have a higher risk of impaired glucose tolerance or even incident diabetes, the change of blood glucose level in hypertensive patients varies across different trials. We propose that it is essential to quantify the glycemic effect of thiazide diuretics by reviewing trials that used diverse doses and types of thiazides. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials to assess the effects of thiazide-type diuretics on glycemic metabolism in hypertensive patients.

Patients receiving lower doses of thiazides (hydrochlorothiazide or chlorthalidone  $\leq$ 25 mg daily) had less change in FPG (MD, 0.15 mmol/L [2.7 mg/dL]; 95% Cl, 0.03–0.27) than those receiving higher doses (MD, 0.60 mmol/L [10.8 mg/dL]; 95% Cl, 0.39–0.82), revealed by the subgroup analysis of thiazides vs calcium channel blockers. Thiazide-type diuretics are associated with significant but small adverse glycemic effects in hypertensive patients. Treatment with a lower dose might reduce or avoid glycemic changes. *J Clin Hypertens* (*Greenwich*). 2016;18:342–351. © 2015 Wiley Periodicals, Inc.

## **METHODS**

#### Search Strategy

We searched PubMed and Web of Science for relevant articles until November 2014, using the following search items: ("thiazide" OR "HCTZ") AND ("diabetes" OR "glucose"). Species were limited to humans. We also manually checked the reference lists of eligible studies and relevant reviews for further information. The design and conduction of this review followed the recommendations of the Cochrane Collaboration<sup>8</sup> and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.<sup>9</sup>

#### Study Selection and Data Extraction

Studies were considered eligible if they met the following inclusion criteria: (1) randomized controlled clinical trial in hypertensive patients; (2) comparing thiazide or thiazide-like diuretics with other hypertensive agents or placebo or nontreatment; (3) assessing one or more glycemic parameters, including fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and glycated hemoglobin (HbA<sub>1c</sub>); and (4) reporting data both before and after intervention or values changed with intervention, expressed as mean±standard deviation (SD). Trials in normotensive patients were excluded since they might have different metabolic characteristics from hypertensive patients. In studies with multiple doses or duration of treatment, only data on the largest dose and longest duration were extracted. Trials with a crossover design were also excluded to avoid overestimation of their effects. Trials using thiazides in combination with other types of antihypertensive agents were excluded to prevent possible bias caused by the interaction or synergistic effects. Information including type and dose of thi-

Address for correspondence: Qingyu Zhao, MD, Sun Yat-sen University Cancer Center, 651 Dongfeng East Road, Guangzhou 510060, China E-mail: zhaoqy@sysucc.org.cn

Manuscript received: June 11, 2015; revised: July 14, 2015; accepted: July 16, 2015 July 16, 2015 DOI: 10.1111/jch.12679

diabetes, data of glycemic and other metabolic parameters, and baseline characteristics of participants were extracted independently by two reviewers. Consensus was reached through discussion and repetitive review of the details in cases of discrepancies.

#### Assessment of Risk of Bias

The risk of bias of included studies was assessed according to the recommendations of the Cochrane Handbook of Systematic Reviews of Interventions<sup>8</sup> in the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other bias.

## **Statistical Analysis**

For outcome comparison between two groups, the mean differences (MDs) with SDs measuring the changes from baseline, were pooled across studies using the randomeffects model. In case of a missing SD for the changes, we followed the Cochrane Handbook<sup>8</sup> and the recom-mendations of Musini and colleagues.<sup>10</sup> Heterogeneity was examined by Cochran Q test (considered significant when P<.10) and quantified by  $I^2$  statistic (considered substantial when  $I^2 \ge 50\%$ ). Sensitivity analyses were performed by successively excluding studies. To explore the reasons for heterogeneity, we performed subgroup analyses based on age of patients, type and dose of medication, and duration of treatment. Publication bias was assessed by Begg's funnel plot and Egger's regression test. A P value <.05 was considered statistically significant. Statistical analyses were conducted by Review Manager (RevMan) version 5.2 (The Cochrane Collaboration, Copenhagen, Denmark) and STATA 12.0 (STATA, College Station, TX).

## RESULTS

## Characteristics of Included Studies

The initial literature search retrieved 1369 relevant articles. Of these, 26 studies met the inclusion criteria and were selected in the meta-analysis, which included a total of 16,162 participants (Figure S1). Seven trials contained more than one study group except for thiazide and one trial contained two study groups receiving different kinds of thiazides. We included these outcomes and regarded them as different comparisons in the pooled analysis. The basic characteristics of included studies are shown in the Table. The number of participants ranged from 19 to 7703 across the trials, <sup>11–36</sup> of which only three enrolled obese participants.<sup>12,14,31</sup> The longest duration of treatment was 6 years,<sup>35</sup> but most trials lasted less than half a year. Intervention with HCTZ was the most commonly reported. CTD, bendrofluazide, and indapamide were also included. The

dose of treatment varied across different trials (HCTZ 12.5–100 mg/d, CTD 6.25–50 mg/d, bendrofluazide 2.5–10 mg/d, and indapamide 1.25–2.5 mg/d).

## The Risk of Bias and Publication Bias

We determined the risk of bias in seven domains using the criteria of the Cochrane handbook.<sup>8</sup> Most studies did not report the process of randomization or allocation concealment and we therefore judged them as having an unclear risk of bias (Figure S2 and Figure S3). Funnel plots for FPG suggested asymmetry visually (Figures S4–S6) while Egger's tests did not show sufficient evidence of publication bias (thiazide vs nonthiazide: P=.421; thiazide vs placebo or nontreatment: P=.643; thiazide vs angiotensin-converting enzyme inhibitor or angiotensin receptor blocker: P=.395).

## Outcomes

Fasting Plasma Glucose. All trials reported the changes of FPG. Thiazide or thiazide-like diuretics were found to increase FPG level compared with nonthiazide agents or placebo or nontreatment (MD, 0.27 mmol/L [4.86 mg/dL]; 95% confidence interval [CI], 0.15-0.39 [P<.0001]) (Figure 1). Heterogeneity was substantial in the pooled analysis ( $I^2=97\%$ , P<.00001). Since different kinds of hypertensive agents with different pharmacology were included, we performed subgroup analysis based on types of medication in control groups. In addition, after classifying the studies into five categories including placebo or nontreatment, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACE) inhibitor or angiotensin receptor blocker (ARB),  $\beta$ -blocker, and  $\alpha$ -blocker, we performed further analysis in these groups, respectively. Thiazidetype diuretics did not significantly increase FPG level when compared with placebo or nontreatment or β-blockers (thiazide vs placebo or nontreatment: MD, 0.21 mmol/L [3.78 mg/dL]; 95% CI, 0.00–0.41 [P=.05] and thiazide vs β-blocker: MD, 0.23 mmol/L [4.14 mg/ dL]; 95% CI, -0.14 to 0.59 [P=.22]). However, subgroup analysis did not show a significant difference between different kinds of control groups (Figure S7). Subgroup analysis of the CCB group based on dose of medication significantly reduced heterogeneity and indicated that patients receiving lower doses of thiazides (HCTZ or CTD  $\leq 25$  mg daily, n=5148) had less change in FPG (MD, 0.15 mmol/L [2.7 mg/dL]; 95% CI, 0.03-0.27) compared with patients receiving higher doses (n=130) (MD, 0.60 mmol/L [10.8 mg/dL]; 95% CI, 0.39-0.82) (P=.0003) (Figure 2). Patients with a longer duration of treatment ( $\geq 6$  months, n=221) also had less glycemic change (MD, -0.01 mmol/L [-0.18 mg/dL]; 95% CI, -0.47 to 0.45) than patients with short treatment duration (n=114) (MD, 0.50 mmol/L [9.0 mg/dL]; 95% CI, 0.36-0.64), revealed by the subgroup analysis of thiazide vs  $\beta$ -blocker (P=.04) (Figure 3). Sensitivity analyses did not significantly reduce the heterogeneity.

Group         Patients         Number           s placebo or empty control         Patients with hypertension         84           vit         Placebo         Patients with hypertension         81           i         10 mg/d         moderate hypertension         81           i         10 mg/d         moderate hypertension         81           i         10 mg/d         moderate hypertension         81           i         125 mg/d         Patients with mild to         11           vit         Placebo         moderate hypertension         10           vit         Placebo         moderate hypertension         10           vit         Placebo         moderate hypertension         10           vit         Placebo         moderate hypertension         125           vit         Placebo         moderate hypertension         22           vit         Placebo         moderate hypertension         23           vit         Placebo         moderate hypertension         26           vit         Placebo         moderate hypertension         27           vit         Placebo         moderate hypertension         27           vit         Placebo         Placebo <t< th=""><th></th><th>Daseine Unaracteristics of included frials</th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></t<>		Daseine Unaracteristics of included frials									
Group         Patients         Mmber           Se vs placebo or empty control         Ratents with hypertension         84           Se vs placebo or empty control         Patients with hypertension         84           Seant         HCTZ 25 mg/d         Patients with hypertension         84           Seant         HCTZ 25 mg/d         Patients with hypertension         81           Seant         HCTZ 25 mg/d         Patients with mild to         10           Seant         HCTZ 26 mg/d         Patients with mild to         11           Seant         HCTZ 26 mg/d         Patients with mild to         11           S7 4         Placebo         Patients with mild to         11           S7 4         Placebo         Placebo         Placebo         27           S7 4         Placebo         Placebo         Placebo         27           S7 4         Placebo         Placebo         27         27           S7 4         Placebo         Placebo         27         27           S8 4/P         Placebo         Placebo         27         27           S8 4/P         Placebo         Placebo         28         27         27           S8 4/P         Placebo         Placebo									Changed	Changed	
Patients with hypertension       84         Patients with mild to       51         moderate hypertension       51         moderate hypertension       52         Patients 65 y or older with mild       103         to moderate hypertension       100         Obese patients with mild to       14         moderate hypertension       100         Obese patients with mild to       23         moderate hypertension       23         moderate hypertension       26         Patients with mild to       23         moderate hypertension       27         Patients with mild to       23         moderate hypertension       23         Male patients with mild to       23         moderate hypertension       27         Patients with mild to       27 <th></th> <th>Number</th> <th>Duration</th> <th>Age, y<sup>a</sup></th> <th>Women, %</th> <th>Baseline SBP/DBP, mm Hg<sup>a</sup></th> <th>Diabetic Patients, %</th> <th>BMI, kg/m2<sup>b</sup></th> <th>FPG, mmol/L<sup>b</sup></th> <th>PPG, mmol/L<sup>b</sup></th> <th>Changed HbA1<sub>c</sub>, %<sup>b</sup></th>		Number	Duration	Age, y <sup>a</sup>	Women, %	Baseline SBP/DBP, mm Hg <sup>a</sup>	Diabetic Patients, %	BMI, kg/m2 <sup>b</sup>	FPG, mmol/L <sup>b</sup>	PPG, mmol/L <sup>b</sup>	Changed HbA1 <sub>c</sub> , % <sup>b</sup>
HCTZ 25 mg/d       Patients with hypertension       81         Placebo       Patients with mild to       51         Inmg/d       moderate hypertension       81         Placebo       Patients 65 y or older with mild       52         Indapamide       Patients 65 y or older with mild       103         1.25 mg/d       Patients 65 y or older with mild       100         Placebo       Common enderate hypertension       100         Placebo       Obese patients with mild to       114         Placebo       Obese patients with mild to       114         Placebo       Obese patients with mild to       112         Indapamide       Patients with mild to       277         Placebo       Placebo       Male patients with mild to       277         Placebo       Placebo       Placebo       277         Placebo       Placebo       Placebo       277         Placebo       Placebo       Placebo       279         Placebo       Placebo       Placebo       277         Placebo       Placebo       Placebo       279         Placebo       Placebo       Placebo       279         Placebo       Placebo       Placebo       279	ontrol										
Placebo     Bendrofluezide     Patients with mild to     51       10 mg/d     moderate hypertension     52       Placebo     Patients 65 y or older with mild     103       125 mg/d     ponderate hypertension     100       Placebo     Patients 65 y or older with mild     103       125 mg/d     to moderate hypertension     100       Placebo     Placebo     124       Placebo     Placebo     125       Placebo     Placebo     124       Placebo     Placebo     124       Placebo     Placebo     125       Placebo     Platents with mild to     22       Placebo     Patients with mild to     23       Placebo     Patients with mild to     27       Placebo     Platents wit		84	12 weeks	53	71.8	155/104	0	I	0.5±2.3	I	I
Bendrofluazide         Patients with mild to         51           10 mg/d         moderate hypertension         52           Indapamide         Patients 65 y or older with mild         103           1.25 mg/d         to moderate hypertension         100           Hecebo         Patients 65 y or older with mild         100           H272 100 mg/d         Obese patients with mild to         14           Placebo         Obese patients with mild to         14           Placebo         Patients with mild to         14           Placebo         Patients with mild to         23           Nontreatment         moderate hypertension         27           Nontreatment         mild hypertension         27           Nontreatment         mild hypertension         27           Nontreatment         mild hypertension         27           Placebo         Placebo         HCTZ 10.5.5 mg/d         27		81		53		155/103		I	0.1±2.2	I	I
10 mg/d       moderate hypertension       52         Indapamide       Patients 65 y or older with mild       103         1.25 mg/d       to moderate hypertension       100         HCTZ 100 mg/d       onecate hypertension       10         HCTZ 100 mg/d       Obese patients with mild to       14         Placebo       moderate hypertension       10         HCTZ 100 mg/d       Obese patients with mild to       82         I 125 mg/d       Patients with mild to       83         HCTZ 25 mg/d       Patients with mild to       76         Placebo       Male patients with mild to       76         Nontreatment       Patients with mild to       76         Placebo       Male patients with mild to       76         Placebo       Male patients with mild to       76         Placebo       Placebo       Placebo       90 with         Placebo       HCTZ 50 mg/d       Platents with mild to       76         Placebo       Placebo       Placebo       Platents with mild to       70         <		51	10 weeks	59	45.1	166.9±2.7/103.7±0.8	I	I	0.27±0.15	I	I
Placebo     52       Indapamide     Patients 65 y or older with mild     103       1.25 mg/d     to moderate hypertension     100       HCTZ 100 mg/d     Obese patients with mild to     14       Placebo     moderate hypertension     14       Placebo     moderate hypertension     14       Placebo     moderate hypertension     14       Placebo     moderate hypertension     14       Placebo     Patients with mild to     23       HCTZ 25 mg/d     Patients with mild to     27       Placebo     moderate hypertension     125       MCTZ 25 mg/d     Male patients with mild to     27       Placebo     Male patients with mild to     27       Placebo     Male patients with hypertension     27       Placebo     Placebo     27     27       Nontreatment     Placebo     Placebo     27       Placebo     Placebo     Placebo     25       Placebo     Placents	moderate hypertension										
Indapamide     Patients 65 y or older with mild     10       1.25 mg/d     to moderate hypertension     100       HCTZ 100 mg/d     Coese patients with mild to     14       Placebo     Obsee patients with mild to     14       Placebo     Cobese patients with mild to     14       Placebo     Obsee patients with mild to     14       Placebo     Cobese patients with mild to     23       I .25 mg/d     Patients with mild to     23       Placebo     Patients with mild to     23       Placebo     Patients with mild to     23       Placebo     Male patients with mild to     27       Placebo     Male patients with mild to     27       Nontreatment     Male patients with mild to     27       HCTZ 50 mg/d     Patients with mild to     27       Placebo     Male patients with mild to     27       Placebo     Placebo     Placebo     26       Placebo     Placebo     Placebo     27 <td></td> <td>52</td> <td></td> <td>57</td> <td>55.8</td> <td>161.9±1.9/101.8±0.5</td> <td>Ι</td> <td>I</td> <td><math>-0.08\pm0.09</math></td> <td>I</td> <td>I</td>		52		57	55.8	161.9±1.9/101.8±0.5	Ι	I	$-0.08\pm0.09$	I	I
1.25 mg/d       to moderate hypertension       100         Placebo       1.25 mg/d       Obese patients with mild to       14         Placebo       00 ederate hypertension       14         Placebo       00 ederate hypertension       14         Placebo       00 ederate hypertension       14         Indapamide       Patients with mild to       82         1.25 mg/d       Patients with mild to       82         Placebo       Patients with mild to       23         Placebo       Male patients with mild to       27         Placebo       Male patients with mild to       27         Placebo       Placebo       Placebo       26         Placebo       Placebo       Placebo	Patients 65 y or older with mild		8 weeks	69.4	48	-/98.8	I	I	0.194±1.51	I	I
Placebo     100       HCTZ 100 mg/d     Obese patients with mild to     14       Placebo     moderate hypertension     14       Indapamide     Patients with mild to     82       1.25 mg/d     Patients with mild to     82       1.25 mg/d     Patients with mild to     82       Placebo     Patients with mild to     82       1.25 mg/d     Patients with mild to     82       Placebo     Patients with mild to     82       Placebo     Patients with mild to     70       Placebo     Male patients with mild to     70       Placebo     Male patients with mild to     77       Placebo     Male patients with mild to     77       Placebo     Male patients with hypertension     77       Placebo     Placebo     90       CTD 12.5-25 mg/d     Patients with mild to     76       Placebo     Placebo     76       Placebo     Placebo     76       Placebo     Placebo     76       Placebo     Placebo     70       Placebo     Placebo     76       Placebo     Placebo     76       Placebo     Placebo     76       Placebo     Placebo     76       Placebo     Platents with hypertensio											
HCTZ 100 mg/dObese patients with mild to14Placebomoderate hypertension14IndapamidePatients with mild to821.25 mg/dPatients with mild to82PlaceboPatients with mild to90HCTZ 12.5 mg/dPatients with mild to23PlaceboPatients with mild to23PlaceboPatients with mild to23PlaceboPatients with mild to23PlaceboMale patients with hypertension70PlaceboMale patients with hypertension70PlaceboMale patients with hypertension77PlaceboMale patients with hypertension75PlaceboPlacebo76PlaceboPlacebo76PlaceboPlacebo76PlaceboPlacebo76PlaceboPlacebo76PlaceboPlacebo76PlaceboPlacebo76PlaceboPlacebo76PlaceboPlacebo70PlaceboPlacebo76PlaceboPlacebo76PlaceboPlacebo76PlaceboPlacebo70PlaceboPlacebo70PlaceboPlacebo70PlaceboPlacebo70PlaceboPlacebo70PlaceboPlacebo70PlaceboPlaceboPlaceboPlaceboPlaceboPlaceboPlaceboPlaceboPlacebo<		100		69.7	42	-/99.8	I	I	-0.0556±1.15	I	I
Placebo     moderate hypertension     14       Indapamide     Patients with mild to     82       1.25 mg/d     moderate hypertension     82       Placebo     Patients with mild to     82       Placebo     Patients with mild to     23       Placebo     Patients with mild to     23       Placebo     Patients with mild to     23       Placebo     Patients with hypertension     70       HCTZ 12.5 mg/d     Patients with hypertension     70       Placebo     Male patients with hypertension     77       Nontreatment     mild hypertension     77       Placebo     Male patients with hypertension     76       Placebo     Placebo     Patients with hypertension     76       Placebo     Placebo     Placebo     79     76       Placebo     Hypertensive men aged 35-79     77     76       Placebo     Hypertensive men aged 35-79     76       Placebo     Placebo     25     76       Placebo     Hypertensive men aged 35-79     77       Placebo     Placebo     Placebo     76       Placebo     Placebo     Placebo     76       Placebo     Placebo     Placebo     76       Placebo     Placebo     Placebo <td></td> <td>14</td> <td>1 week</td> <td>50±2</td> <td>I</td> <td>150±2/103±2</td> <td>I</td> <td><b>2</b>9±1</td> <td>0.3±0.2</td> <td>I</td> <td>I</td>		14	1 week	50±2	I	150±2/103±2	I	<b>2</b> 9±1	0.3±0.2	I	I
Indapamide     Patients with mild to     82       1.25 mg/d     moderate hypertension     90       Placebo     Patients with mild to     23       Placebo     Male patients with hypertension     70       Placebo     Male patients with hypertension     70       Placebo     Male patients with hypertension     73       Placebo     Male patients with hypertension     73       Placebo     Desse hypertension     73       Placebo     Placebo     147       Placebo     Hypertensive men aged 35-79 y     74       Placebo     Hypertensive men aged 35-79 y     27       Placebo     Placebo     Placebo     23       CTD 12.5-25 mg/d     Hypertensive men aged 35-79 y     27       Placebo     Placebo     Placebo     23       CTD 25.52 mg/d     Hypertensive men aged 35-79 y     27       Placebo     Placebo     Placebo     25       CTD 25.55 mg/d     Placebo     Placebo     23       Placebo     Placebo     Placebo     25	moderate hypertension	14		50±2	I	148±3/103±2	I	30土1	0.1±0.2	I	I
1.25 mg/d     moderate hypertension     90       Placebo     Patients with mild to     23       Placebo     Patients with mild to     23       HCTZ 12.5 mg/d     Patients with mild to     23       HCTZ 12.5 mg/d     Patients with mild to     23       Placebo     Male patients with hypertension     27       HCTZ 12.5 mg/d     Male patients with hypertension     27       Nontreatment     mild hypertension     27       Nontreatment     mild hypertension     27       HCTZ 12.5 mg/d     Patients with hypertension     27       Nontreatment     mild hypertension     27       HCTZ 12.5 mg/d     Dese hypertension     76       Placebo     Obese hypertension     803       HCTZ 55 mg/d     Patients older than 60 y with     803       HCTZ 50 mg/d     Hypertensive men aged 35-79 y     27       Placebo     Isolated systolic hypertension     803       HCTZ 50 mg/d     Hypertensive men aged 35-79 y     27       Placebo     Isolated systolic hypertension     803       HCTZ 50 mg/d     Hypertensive men aged 35-79 y     27       Placebo     Isolated systolic hypertension     803       Placebo     Placebo     Placebo     27       OTD 25 mg/d     Placebo     Placebo	Patients with mild to	82	8 weeks	I	I	-/100.1	I	I	0.2±1.5	I	I
Placebo     90       HCTZ 25 mg/d     Patients with mild to     23       Placebo     Patients with mild to     23       HCTZ 12.5 mg/d     Patients with mild to     23       Placebo     moderate hypertension     27       HCTZ 12.5 mg/d     Patients with hypertension     27       Placebo     Male patients with hypertension     27       Nontreatment     mild hypertension     27       HCTZ 12.5 mg/d     Patients with hypertension     27       Placebo     Male patients with hypertension     27       Placebo     Obese hypertension     79       Placebo     Isolated systolic hypertension     860       Placebo     Isolated systolic hypertension     67       Placebo     Hypertensive men aged 35.79 y     27       Placebo     Hypertensive men aged 35.79 y     27       Placebo     Hypertensive men 35.79 y     27       Placebo     Placebo     27     27       Placebo     Placebo     Placebo     23       Placebo     Placebo     27     27       Placebo     Placebo     27     27       Placebo     Placebo     26     27       Placebo     Placebo     26     27       Placebo     Hypertensive men 35.											
HCTZ 25 mg/d     Patients with mild to     23       Placebo     moderate hypertension     22       HCTZ 12.5 mg/d     Patients with mild to     23       Placebo     moderate hypertension     23       HCTZ 12.5 mg/d     Patients with hypertension     27       Placebo     Male patients with hypertension     27       Nontreatment     mild hypertension     27       HCTZ 12.5 mg/d     Male patients with hypertension     67       Placebo     mild hypertension     67       Placebo     losee hypertension     60       CTD 12.5-25 mg/d     Patients older than 60 y with     860       Placebo     isolated systolic hypertension     803       HCTZ 50 mg/d     Hypertensive men aged 35-79 y     147       Placebo     Hypertensive men aged 35-79 y     27       CTD 25 mg/d     Hypertensive men 35-79 y     27       Placebo     Hypertensive men 35-79 y     27       Placebo     Placebo     27     27       OTD 25 mg/d     Platents with mild hypertension     803       HCTZ 50 mg/d     Platents with mild hypertension     27       Placebo     Placebo     27     27       OTD 25 mg/d     Platents with mild hypertension     27       Placebo     Placebo     27		06		I	I	-/99.6	I	I	0.2±1.2	I	I
Placebo     moderate hypertension     22       HCTZ 12.5 mg/d     Patients with mild to     69       Placebo     moderate hypertension     70       HCTZ 50 mg/d     Male patients with hypertension     71       HCTZ 12.5 mg/d     Patients with hypertension     77       HCTZ 12.5 mg/d     Patients with hypertension     77       Placebo     Male patients with hypertension     77       Placebo     Obese hypertension     77       Placebo     Disolated systolic hypertension     860       Placebo     isolated systolic hypertension     803       HCTZ 50 mg/d     Patients older than 60 y with     860       Placebo     isolated systolic hypertension     803       HCTZ 50 mg/d     Hypertensive men aged 35-79 y     27       Placebo     Hypertensive men 35-79 y     27       Placebo     Placebo     28       Placebo     Placebo     26       Placebo     Placebo     25-10 mg/d       Placebo     Placebo     295       CTD 25 mg/d     Platients with hypertension     27       Placebo     Placebo     25       CTD 25 mg/d     Placebo     26       Placebo     Placebo     27       CTD 25 mg/d     Placebo     27 <td< td=""><td></td><td>23</td><td>6 weeks</td><td>46.4</td><td>60.9</td><td>147.0/97.6</td><td>I</td><td>I</td><td>-0.14±0.82</td><td>I</td><td>I</td></td<>		23	6 weeks	46.4	60.9	147.0/97.6	I	I	-0.14±0.82	I	I
HCTZ 12.5 mg/dPatients with mild to69Placebomoderate hypertension70HCTZ 50 mg/dMale patients with hypertension125Nontreatmentmild hypertension67HCTZ 12.5 mg/dPatients with hypertension67PlaceboPatients with hypertension67PlaceboDese hypertension67PlaceboObese hypertension67PlaceboDese hypertension803HCTZ 12.5-50 mg/dObese hypertension803HCTZ 12.5-50 mg/dPatients older than 60 y with860Placeboisolated systolic hypertension803HCTZ 50 mg/dHypertensive men aged 35-79 y27PlaceboIth hypertensive men 35-79 y27CTD 50 mg/dHypertension803PlaceboPlacebo257AndolpineNith hypertension803PlaceboPlatents with hypertension <td>moderate hypertension</td> <td>22</td> <td></td> <td>48.5</td> <td>59.1</td> <td>152.5/99.8</td> <td>I</td> <td>I</td> <td><math>-0.03\pm0.50</math></td> <td>I</td> <td>I</td>	moderate hypertension	22		48.5	59.1	152.5/99.8	I	I	$-0.03\pm0.50$	I	I
Placebo     moderate hypertension     70       HCTZ 50 mg/d     Male patients with     125       Nontreatment     mild hypertension     277       HCTZ 12.5 mg/d     Patients with hypertension     67       Placebo     277       HCTZ 12.5.50 mg/d     Dese hypertension     67       Placebo     277       HCTZ 12.5.50 mg/d     Dese hypertension     67       Placebo     0bese hypertension     67       Placebo     12.5-26 mg/d     Dese hypertension     803       HCTZ 12.5.50 mg/d     Patients older than 60 y with     860       Placebo     isolated systolic hypertension     803       HCTZ 50 mg/d     Hypertensive men aged 35-79 y     27       Placebo     Hypertensive men 35-79 y     27       CTD 50 mg/d     Hypertension     803       Placebo     Platents with hypertension     803       Placebo     Platents with hypertension     27       CTD 25 mg/d     Patients with hypertension     295       Placebo     2.5-10 mg/d     Patients with hypertension     295       CTD 25 mg/d     Platents with hypertension     295       Placebo     2.5-10 mg/d     Platents with hypertension     295       CTD 2.5-25 mg/d     Platents with hypertension     297	Pat	69	8 weeks	48.2	36.9	143.5/97.3	I	I	$-0.12\pm0.26$	I	I
HCTZ 50 mg/dMale patients with mild hypertension125Nontreatmentmild hypertension277HCTZ 12.5 mg/dPatients with hypertension57PlaceboDese hypertensive patients76PlaceboDese hypertensive patients76PlaceboDese hypertensive patients76PlaceboDese hypertensive men aged 35-79 y147PlaceboHypertensive men aged 35-79 y27PlaceboHypertensive men 35-79 y27PlaceboPlacebo27PlaceboPlacebo27PlaceboPlacebo27CTD 50 mg/dHypertensive men 35-79 y27PlaceboPlacebo27CTD 55 mg/dPlatents with mild hypertension803PlaceboPlacebo257CTD 25 mg/dPatients with hypertension295Andolpinewith hypertension295Andolpinewith hypertension375-10 mg/dDese patients with mild10AndolpineVith hypertension375-10 mg/dVerapamilto moderate hypertension14160 mg/dUese patients with mild14	moderate hypertension	20		50.7	40.9	142.8/97.6	I	I	-0.02±0.27	I	I
Nontreatment       mild hypertension       277         HCTZ 12.5 mg/d       Patients with hypertension       67         Placebo       57       75         HCTZ 12.5-50 mg/d       Obese hypertensive patients       76         Placebo       0       91       79         CTD 12.5-50 mg/d       Obese hypertension       870         Placebo       12.5-25 mg/d       Patients older than 60 y with       860         Placebo       isolated systolic hypertension       803         HCTZ 50 mg/d       Hypertensive men aged 35-79 y       27         Placebo       Hypertensive men 35-79 y       27         CTD 50 mg/d       Hypertensive men 35-79 y       27         Placebo       Platents with mild hypertension       80         placebo       Patients with hypertension       27         CTD 25 mg/d       Patients with hypertension       265         Alcodoline       With hypertension       295         CTD 25.55 mg/d       Patients with hypertension       295         Alcodoline       With hypertension       295         CTD 25.56 mg/d       Patients with hypertension       295         Alcodoline       With hypertension       295         CTD 25.510 mg/d       Pati		125	5 y	40-49	0	I	I	I	0.18±0.59	I	I
HCTZ 12.5 mg/d       Patients with hypertension       67         Placebo       57         HCTZ 12.5-50 mg/d       Obese hypertensive patients       76         Placebo       0       51         Placebo       0       Patients older than 60 y with       860         Placebo       isolated systolic hypertension       803         HCTZ 50 mg/d       Patients older than 60 y with       860         Placebo       isolated systolic hypertension       803         HCTZ 50 mg/d       Hypertensive men aged 35-79 y       27         Placebo       Hypertensive men 35-79 y       27         CTD 50 mg/d       Hypertensive men 35-79 y       27         Placebo       Platents with mild hypertension       60         placebo       Platents with hypertension       27         CTD 25 mg/d       Patients with hypertension       27         Andolpine       With hypertension       295         Lon mg/d       Patients with hypertension       27         Andolpine       With hypertension       27         LTD 50-100 mg/d       Patients with mild volution       27         LTZ 50-100 mg/d       Patients with hypertension       27         LTZ 50-100 mg/d       Voluter volution       7		277		57	55.8	I	I	I	0.13±0.68	I	I
Placebo       57         HCTZ 12:5-50 mg/d       Obese hypertensive patients       76         Placebo       79       79         CTD 12:5-25 mg/d       Patients older than 60 y with       860         Placebo       isolated systolic hypertension       803         HCTZ 50 mg/d       Hypertensive men aged 35-79 y       147         Placebo       Hypertensive men aged 35-79 y       27         Placebo       Hypertensive men 35-79 y       27         CTD 50 mg/d       Hypertensive men 35-79 y       27         Placebo       Platents with mild hypertension       80         Placebo       Patients with hypertension       60         placebo       Patients with hypertension       27         CTD 25 mg/d       Patients with hypertension       265         Anlodipine       with hypertension       2954         2.5-10 mg/d       Patients with hypertension       76         Andolpine       with hypertension       76         6.10 mg/d       Patients with mild viget than 60 y       100         Andolpine       with hypertension       77         7.10 mg/d       Patients with mild       77         7.10 mg/d       Noderate hypertension       71         7.		67	6 weeks	<b>52.7±10.6</b>	27	153.4±2.2/100.2±0.5	Ι	I	0.35±0.80	I	I
HCTZ 12:5-50 mg/d       Obese hypertensive patients       75         Placebo       79       79         CTD 12:5-25 mg/d       Patients older than 60 y with       860         Placebo       isolated systolic hypertension       803         HCTZ 50 mg/d       Hypertensive men aged 35-79 y       147         Placebo       Hypertensive men aged 35-79 y       27         Placebo       Hypertensive men 35-79 y       27         CTD 50 mg/d       Hypertensive men 35-79 y       27         Placebo       Platents with mild hypertension       60         placebo       Patients with hypertension       60         placebo       Patients with hypertension       23         CTD 25 mg/d       Patients with hypertension       295         Amlodipine       with hypertension       295         2.5-10 mg/d       Patients older than 60 y       100         Amlodipine       with hypertension       37         5-10 mg/d       Patients with mild       100         Amodipine       with hypertension       37         6.10 mg/d       Verapamil       10         6.10 mg/d       Noderate hypertension       14         160 mg/d       Noderate hypertension       14 <td></td> <td>57</td> <td></td> <td><b>53.5±10.5</b></td> <td>40</td> <td>152.9±1.9/99.9±0.5</td> <td>I</td> <td>I</td> <td>0.028±0.66</td> <td>I</td> <td>I</td>		57		<b>53.5±10.5</b>	40	152.9±1.9/99.9±0.5	I	I	0.028±0.66	I	I
Placebo     79       CTD 12.5-25 mg/d     Patients older than 60 y with     860       Placebo     isolated systolic hypertension     803       HCTZ 50 mg/d     Hypertensive men aged 35-79 y     147       Placebo     Hypertensive men aged 35-79 y     27       CTD 50 mg/d     Hypertensive men 35-79 y     27       Placebo     Hypertensive men 35-79 y     27       CTD 50 mg/d     Hypertensive men 35-79 y     27       Placebo     Placebo     27       CTD 25 mg/d     Patients with mild hypertension     60       placebo     Patients with hypertension     60       placebo     25-10 mg/d     Patients with hypertension     4972       Amlodipine     with hypertension     2954       2.5-10 mg/d     Patients older than 60 y     100       Amlodipine     with hypertension     97       5-10 mg/d     Obese patients with mild     14       HCTZ 100 mg/d     Obese patients with mild     14		76	12 weeks	51±10	46.1	148±14/98±5	0	32.5±3.8	0.31±0.99	I	I
CTD 12.5-25 mg/d     Patients older than 60 y with     860       Placebo     isolated systolic hypertension     803       HCTZ 50 mg/d     Hypertensive men aged 35-79 y     147       Placebo     Hypertensive men aged 35-79 y     27       CTD 50 mg/d     Hypertensive men 35-79 y     27       Placebo     Hypertensive men 35-79 y     27       CTD 50 mg/d     Hypertensive men 35-79 y     28       Placebo     Patients with mild hypertension     60       placebo     Patients with hypertension     60       placebo     Patients with hypertension     295       CTD 25 mg/d     Patients with hypertension     295       Amlodipine     with hypertension     295       Andodipine     with hypertension     97       5-10 mg/d     Patients with mild     100       Andolpine     with hypertension     97       6-10 mg/d     Verapanil     10       HCTZ 100 mg/d     Obese patients with mild     14       160 mg/d     Iso moderate hypertension     14		29		49±10	40.5	146±13/96±4	I	32.2±3.8	<b>−0.16±0.90</b>	I	I
Placebo     isolated systolic hypertension     803       HCTZ 50 mg/d     Hypertensive men aged 35-79 y     147       Placebo     Hypertensive men aged 35-79 y     27       CTD 50 mg/d     Hypertensive men 35-79 y     28       Placebo     Hypertensive men 35-79 y     27       CTD 55 mg/d     Hypertensive men 35-79 y     28       Placebo     Patients with mild hypertension     60       placebo     Patients with hypertension     60       placebo     Patients with hypertension     295       CTD 12.5-25 mg/d     Patients with hypertension     4972       Amlodipine     with hypertension     2954       2.5-10 mg/d     Patients older than 60 y     100       Amlodipine     with hypertension     97       5-10 mg/d     Obese patients with mild     14       HCTZ 100 mg/d     Ito moderate hypertension     14		860	3 у	<b>71.6</b> ±6.7	56.3	170.5±9.5/76.7±9.6	10	27.5±4.9	0.51±1.69	I	I
HCTZ 50 mg/d       Hypertensive men aged 35-79 y       147         Placebo       TCD 50 mg/d       Hypertensive men 35-79 y       27         CTD 50 mg/d       Hypertensive men 35-79 y       28         Placebo       Platenbo       27         CTD 25 mg/d       Patients with mild hypertension       60         placebo       Patients with hypertension       60         placebo       Patients with hypertension       295         CTD 12.5-25 mg/d       Patients with hypertension       4972         Amlodipine       with hypertension       2954         2.5-10 mg/d       Patients older than 60 y       100         Amlodipine       with hypertension       97         5-10 mg/d       Dese patients with mild       14         HCTZ 100 mg/d       Obese patients with mild       14         160 mg/d       to moderate hypertension       14				<b>71.5</b> ±6.7	57.4	170.1±9.2/76.5±9.8	10.2	27.5±5.1	0.31±1.42	I	I
Placebo     27       CTD 50 mg/d     Hypertensive men 35-79 y     28       Placebo     27       CTD 25 mg/d     Patients with mild hypertension     60       placebo     59       CTD 25 mg/d     Patients with hypertension     60       placebo     28       CTD 25 mg/d     Patients with hypertension     60       placebo     2954       CTD 12.5-25 mg/d     Patients with hypertension     4972       Amlodipine     with hypertension     2954       2.5-10 mg/d     Patients older than 60 y     100       Amlodipine     with hypertension     97       5-10 mg/d     Obese patients with mild     14       Verapamil     to moderate hypertension     14			2 months	60.8±7.7	0	I	I	27.8±3.9	0.1±0.13	I	I
CTD 50 mg/d     Hypertensive men 35-79 y     28       Placebo     27     27       CTD 25 mg/d     Patients with mild hypertension     60       placebo     59       CTD 12.5-25 mg/d     Patients with hypertension     60       placebo     59       CTD 12.5-25 mg/d     Patients with hypertension     4972       Amlodipine     255-10 mg/d     2954       2.5-10 mg/d     Patients older than 60 y     100       Amlodipine     with hypertension     97       5-10 mg/d     Obese patients with mild     14       HCTZ 100 mg/d     10 moderate hypertension     14       160 mg/d     160     14		27		<b>60.8</b> ±8.5	40.9	I	I	28.0±3.6	0.3±0.14	I	I
Placebo     27       CTD 25 mg/d     Patients with mild hypertension     60       placebo     59       CTD 12.5-25 mg/d     Patients with hypertension     60       Amlodipine     2954       2.5-10 mg/d     Patients older than 60 y     100       HCTZ 50-100 mg/d     with hypertension     97       5-10 mg/d     Obese patients with mild     14       HCTZ 100 mg/d     10 mg/d     14       HCTZ 100 mg/d     16 mg/d     14		28	2 months	<b>61.4</b> ±7.8	0	I	I	28.0±4.7	0.7±0.28	I	I
CTD 25 mg/d     Patients with mild hypertension     60       placebo     59       CTD 12.5-25 mg/d     Patients with hypertension     59       Amlodipine     2954       2.5-10 mg/d     Patients older than 60 y     100       HCTZ 50-100 mg/d     with hypertension     97       5-10 mg/d     Obese patients with mild     14       HCTZ 100 mg/d     Ito moderate hypertension     14		27		<b>60.8±8.5</b>	42	I	Ι	<b>28.0±3.6</b>	0.3±0.14	I	I
placebo 59 CTD 12.5-25 mg/d Patients with hypertension 4972 Amlodipine 25-10 mg/d 2.5-10 mg/d 2.5-10 mg/d 70 HCTZ 50-100 mg/d 97 5-10 mg/d 0bese patients with mild 14 Verapamil to moderate hypertension 14 160 mg/d			12 weeks	21–69	34.2	143.4±1.6/93.7±0.7	0	I	0.61±0.15	I	I
CTD 12.5-25 mg/d     Patients with hypertension     4972       Amlodipine     2954       2.5-10 mg/d     Patients older than 60 y     100       HCTZ 50-100 mg/d     with hypertension     97       5-10 mg/d     Obese patients with mild     14       HCTZ 100 mg/d     It moderate hypertension     14		59				145.7±1.8/93.6±0.7	I	I	0.1±0.13	I	I
<sup>26</sup> Amlodipine     4972 <sup>26</sup> Amlodipine     2954       2.5-10 mg/d     Patients with hypertension     2954       2.5-10 mg/d     Patients older than 60 y     100       Amlodipine     with hypertension     97       5-10 mg/d     Obese patients with mild     14       /or     HCTZ 100 mg/d     to moderate hypertension     14       14     Verapamil     to moderate hypertension     14											
A <sup>26</sup> Amlodipine 2954 2.5-10 mg/d Patients older than 60 y 100 HCTZ 50-100 mg/d with hypertension 97 5-10 mg/d Obese patients with mild 14 avor HCTZ 100 mg/d 14 B1 <sup>4</sup> Verapamil to moderate hypertension 14		4972	4 y	66.9±7.7	47.0	146±16/84±10	36.2	29.7±6.2	0.16±3.09	I	I
2.5-10 mg/d HCTZ 50-100 mg/d Patients older than 60 y 100 MeTZ 50-100 mg/d with hypertension 97 5-10 mg/d Obese patients with mild 14 avor HCTZ 100 mg/d 10 mg/d 14 160 mg/d		2954		66.9±7.7	47.3	146±16/84±10	36.7	29.8±6.3	0.03±3.09	I	I
HCTZ 50-100 mg/d     Patients older than 60 y     100       **     Amlodipine     with hypertension     97       5-10 mg/d     bese patients with mild     14       ayor     HCTZ 100 mg/d     0bese patients with mild     14       B1 <sup>4</sup> Verapamil     to moderate hypertension     14	/d										
Ambdipine         with hypertension         97           5-10 mg/d         with hypertension         14           tyor         HCTZ 100 mg/d         Obese patients with mild         14           3 <sup>14</sup> Verapamil         to moderate hypertension         14		100	8 weeks	67.6±5.9	64	177.8±1.2/87.1±0.7	I	27.4±3.9	0.28±1.22	I	I
5–10 mg/d iyor HCTZ 100 mg/d Obese patients with mild 14 3 <sup>14</sup> Verapamil to moderate hypertension 14 160 mg/d	with hypertension	97		<b>69.0</b> ±6.4	69	178.4±1.3/87.1±0.7	I	27.4±4.3	-0.60±1.22	I	I
<ul> <li>HCTZ 100 mg/d</li> <li>Obese patients with mild</li> <li>Verapamil</li> <li>to moderate hypertension</li> <li>14</li> <li>160 mg/d</li> </ul>	_										
3 <sup>14</sup> Verapamil to moderate hypertension 14 160 mg/d		14	1 week	50±2	I	150±2/103±2	I	29±1	0.3±0.2	I	I
160 mg/d	to moderate hypertension	14		49±2	I	149±2/100±1	I	30土1	-0.3±0.2	I	I
		:			1						
HCTZ 50 mg/d Hypertensive patients	Ну	16	12 weeks 74.9±4.0	74.9±4.0	75	I	I	I	0.3±0.2	I	I
1989 <sup>26</sup> older than 70 y 15	older than 70 y	15		72.3±2.4	73	I	I	I	−0.1±0.5	I	I

										Changed	Changed	
Study	Group	Patients	Number	Number Duration	Age, y <sup>a</sup>	Women, %	Baseline SBP/DBP, mm Hg <sup>a</sup>	Diabetic Patients, %	BMI, kg/m2 <sup>b</sup>	FPG, mmol/L <sup>b</sup>	PPG, mmol/L <sup>b</sup>	Changed HbA1 <sub>c</sub> , % <sup>b</sup>
	Nitrendipine											
	20 mg/d											
Pareek	CTD 6.25 mg/d	Patients with stage	100	4 weeks	46.44±11.79	40.0	$149.43\pm6.99/93.81\pm4.33$	17	I	0.24±2.14	$-0.11 \pm 3.21$	I
2008 A <sup>25</sup>	Amlodipine 2.5 mg/d	I hypertension	102		<b>48.98±10.83</b>	40.2	149.66±7.20/93.50±4.48	16.7	I	$-0.26{\pm}1.52$	$-0.71\pm2.82$	I
Piecha	Indapamide 2.5 mg/d	Patients with mild to	6	6 months	<b>44.8</b> ±12.2	67	154±5/137±10	0	<b>30.8±6.0</b>	0.4±0.9	I	I
2007 A <sup>27</sup>	Amlodipine 5–10 mg/d	moderate hypertension	10		<b>49.6</b> ±11.4	20	161±10/145±13	I	<b>30.0±3.8</b>	0.6±0.5	I	I
Pool	HCTZ 12.5 mg/d	Patients with hypertension	67	6 weeks	<b>52.7±10.6</b>	27	153.4±2.2/100.2±0.5	I	I	0.35±0.80	I	I
1993 B <sup>19</sup>	Diltiazem 120 mg/d		63		<b>55.4</b> ±9.2	36	152.7±1.6/99.4±0.3	I	I	0.18±0.69	Ι	I
Thiazide vs ACE inhibitor/ARB	E inhibitor/ARB											
ALLHAT	CTD 12.5-25 mg/d	Patients with hypertension	4972	4 y	66.9±7.7	47.0	146土16/84土10	36.2	<b>29.7</b> ±6.2	0.16±3.09	I	I
2006 B <sup>26</sup>	Lisinopril 10–40 mg/d		2731		66.9±7.7	46.2	<b>146±16/84±10</b>	35.5	<b>29.8±6.2</b>	$-0.08\pm 2.85$	I	I
Chrysant	HCTZ 25 mg/d	Patients with hypertension	84	12 weeks	53	71.8	155/104	0	I	0.5±2.3	Ι	I
1994 B <sup>11</sup>	Lisinopril 10 mg/d		85		54		154/104		I	0.1±0.8	I	I
Fuenmayor	HCTZ 100 mg/d	Obese patients with mild	14	1 week	50±2	I	150±2/103±2	I	29±1	0.3±0.2	I	I
1997 C <sup>14</sup>	Captopril 100 mg/d	to moderate hypertension	13		49 <b>±</b> 2	I	144±4/100±1	I	30土1	0.4±0.1	I	I
Grassi	HCTZ 25 mg/d	Obese hypertensive patients	59	12 weeks	<b>50.2</b> ±11.2	62.7	146.2±12.6	I	35.1±3.2	0.15±0.82	I	0.13±0.6
2003 <sup>31</sup>	Candesartan		68		<b>51.2±9.5</b>	58.8	<b>98.8</b> ±3.7	I	<b>33.7±2.6</b>	0.13±0.92	I	0.07±0.5
	cilexetil 8 mg/d											
Mersey	HCTZ 12.5 mg/d	Patients with mild to	69	8 weeks	48.2	36.9	143.5/97.3	I	I	$-0.120\pm0.256$	I	I
1993 B <sup>21</sup>	Captopril 25 mg/d	moderate hypertension	68		52.0	49.2	146.6/96.7	I	I	0.0367±0.264	I	I
Piecha	Indapamide 2.5 mg/d	Patients with mild to	6	6 months	<b>44.8</b> ±12.2	67	154±5/137±10	0	30.8±6.0	0.4±0.9	I	I
2007 B <sup>27</sup>	Enalapril 10–20 mg/d	moderate hypertension	10		<b>50.0±9.9</b>	60	163±10/98±9		27.9±2.1	0.7±0.6	I	I
Pollare	HCTZ 40±12 mg/d	Patients with hypertension	50	18 weeks	58 <b>±</b> 10	34.6	$166{\pm}16/101{\pm}4$	2.0	27±4	0.6±1.4	I	0.7±1.5
1989 <sup>29</sup>	Captopril 81±24 mg/d		48		58±12	29.2	$165{\pm}14/101{\pm}4$		28土4	-0.2±1.1	I	0.1±0.7
Reisin	HCTZ 12.5-50 mg/d	Obese hypertensive patients	76	12 weeks	<b>51</b> ±10	46.1	148±14/98±5	0	32.5±3.8	0.31±0.99	I	I
1997 B <sup>12</sup>	Lisinopril 10–40 mg/d		77		51±11	48.1	147±25/98±6	I	32.3±3.7	$-0.21 \pm 0.71$	I	I
Stimpel	HCTZ 25 mg/d	Postmenopausal women	41	12 weeks	62±5	100	158.8±12.7/100.5±3.9	I	I	0.61±0.23	I	I
1998 <sup>33</sup>	Moexipril 15 mg/d	with mild to moderate	43		61±8	100	159.0±13.7/100.5±4.7	I	I	-0.13±0.11-	I	I
		hypertension										
Weinberger	HCTZ 37.5 mg/d	Patients with hypertension	67	6 weeks	I	I	146.1±2.6/97.7±0.9	I	I	0.55±0.17	I	I
1985 <sup>30</sup>			69		I	I	149.5±2.7/99.6±0.9	I	I	-0.06±0.17	I	I
Zappe 2008 <sup>32</sup>		Hypertensive patients with	158	16 weeks	<b>48.8</b> ±11	58	141.7±9/91.4±5	I	37.4±7	0.22±0.9	I	<b>0.2</b> ±0.6
	Valsartan 320 mg/d	cardiometabolic syndrome	164		50.0土11	62	143.5±9/91.5±5	I	36.2±7	0.17±0.9	I	<b>0.1</b> ±0.5
Thiazide vs $\beta$ -blocker	locker											
Berglund	Bendrofluazide	Middle-aged men with	38	6 y	47–54	0	I	I	I	0.0±1.0	I	I
1981 <sup>35</sup>	2.5-5 mg/d	mild to moderate										
	Propanolol	hypertension	37		48.49±12.98	43.9	1	I	I	0.4±1.6	I	I
	160 mg-320 mg/d											
Fuenmayor	HCTZ 100 mg/d	Obese patients with	14	1 week	50土2	I	150±2/103±2		29土1	0.3±0.2	I	I
1997 D <sup>14</sup>	Atenolol 100 mg/d	mild to moderate	14		50±2	I	140±2/99±1		30土1	$-0.2\pm0.2$	I	I
		hypertension										
Pareek	CTD 6.25 mg/d	Patients with stage	100	4 weeks	46.44±11.79	40.0	149.43±6.99/93.81±4.33	17.0	I	0.24±2.14	-0.11±3.21	I
2008 B <sup>25</sup>	Atenolol 25 mg/d	I hypertension	98		48.49±12.98	43.9	149.47±7.69/93.23±3.62	14.3	I	-0.26±1.05	<b>−0.48±1.80</b>	I
	Indapamide 2.5 mg/d		6	6 months	<b>44.8</b> ±12.2	67	154±5/137±10	0	<b>30.8±6.0</b>	<b>0.4±0.9</b>	I	I

Dysglycemia Associated With Thiazides   Zhang and Zh
------------------------------------------------------

TABLE.	TABLE. Baseline Characteristics of Included	stics of Included Trial	Trials (Continued)	(panu								
Study	Group	Patients	Number	Number Duration	Age, y <sup>a</sup>	Women, %	Baseline SBP/DBP, mm Hg <sup>a</sup>	Diabetic Patients, %	BMI, kg/m2 <sup>b</sup>	Changed FPG, mmol/L <sup>b</sup>	Changed PPG, mmol/L <sup>b</sup>	Changed HbA1 <sub>6</sub> , % <sup>b</sup>
Piecha	Metoprolol 50-200 mg/d	Patients with mild to	1		<b>50.3</b> ±10.5	54	157±9/140±13	0	<b>28.1</b> ±3.0	-0.2±0.6	I	I
2007 C <sup>27</sup>		moderate hypertension										
Veterans	HCTZ 50-200 mg/d	Hypertensive men	174	1 y	<b>49.8</b> ±9.9	0	146.5±15.8/101.3±4.5	I	I	0.26±1.61	1.44±4.12	I
1985 <sup>34</sup>	Propranolol 80–640 mg/d		119		<b>49.6</b> ±9.8		146.0±14.4/101.6±4.6	I	I	0.36±1.02	1.01±2.27	I
Thiazide vs $\alpha$ -blocker	blocker											
Alderman	HCTZ 25-50 mg/d	Patients with	6	1 y	<b>53.4±8.8</b>	23.3	150.8±14.2/107.6±8.5	I	I	0.49±0.82	I	I
1986 <sup>36</sup>	Prazosin 1–2 mg/d	hypertension	10		<b>51.4±9.8</b>	15.6	152.2±13.8/105.8±5.2	I	I	-0.17±0.64	I	I
Fuenmayor	HCTZ 100 mg/d	Obese patients with	14	1 week	50土2	I	150±2/103±2	I	<b>2</b> 9±1	0.3±0.2	I	I
1997 E <sup>14</sup>	Prazosin 6 mg/d	mild to moderate	13		<b>4</b> 9±2	I	142±2/100±1	I	30土0.4	0.0±0.1	I	I
		hypertension										
Abbreviation indev: BD h	rs: ACE, angiotensin-con	Abbreviations: ACE, angiotensin-converting enzyme; ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; ARB, angiotensin receptor blocker; BMI, body mass index RD, blond messure: CCB, caloium channel blocker: CTD, chlordbalidone: DRD, diastolic blood messure: FDG, fasting plasma durose: HbA., clurated hemoclobin: HCTZ	tihypertens	ive and Li	ipid Lowerin diastolic bl	g Treatmen	t to Prevent Heart Attac	sk Trial; ARB, ducose: Hb⊿	angiotensi	n receptor blo d hemodlohin	ocker; BMI, b	ody mass
hydrochlorot	thiazide; PPG, postprandi	hydrochlorothiazide; PPG, postprandial plasma glucose; SBP, systolic blood pressure; SHEP, Systolic Hypertension in the Elderly Program; – data unavailable. <sup>a</sup> Mean or mean±standard deviation	tolic blood	pressure;	SHEP, Syst	olic Hyperte	nsion in the Elderly Proc	gram; – data u	inavailable.	<sup>a</sup> Mean or me	an±standard	deviation
or range. <sup>b</sup> M	or range. <sup>b</sup> Mean±standard deviation.											

**Postprandial Plasma Glucose.** Only three studies reported PPG changes, thus the sample size was relatively small (thiazide: n=245, nonthiazide: n=234). Change in PPG was not significantly different between patients receiving thiazides and patients receiving other treatments (MD, 0.46 mmol/L [8.28 mg/dL]; 95% CI, -0.05 to 0.97 [P=.07]) (Figure 4). There was no evidence of heterogeneity ( $I^2=0\%$ , P=.92).

*Glycated Hemoglobin.* The comparison only included three studies, involving 547 hypertensive patients (thiazide: n=267, nonthiazide: n=280). No significant increase in HbA<sub>1c</sub> level was observed in patients receiving thiazides compared with other patients (MD, 0.15%; 95% CI, -0.04 to 0.34 [*P*=.12]) (Figure 5). Heterogeneity was substantial among the studies ( $I^2$ =57%, *P*=.10). Exclusion of the study by Pollare and colleagues<sup>30</sup> reduced  $I^2$  to 0, which might be explained by the largest dose of HCTZ in this study.

Moreover, we found decreasing trends in metabolic parameters including high-density lipoprotein cholesterol, potassium, and sodium. On the other hand, uric acid and major lipid parameters except high-density lipoprotein cholesterol showed a tendency to increase. We generated pooled estimates for the aforementioned metabolic changes, but the level of heterogeneity was statistically significant and could not be explained through subgroup or sensitivity analyses. Therefore, we did not present these outcomes.

## DISCUSSION

The present study reveals an increase in FPG level in patients receiving thiazide-type diuretics, which is consistent with findings from previous studies.<sup>4</sup> Adverse glycemic effects of thiazides have been reported since the application of these medications. Significantly greater concern was generated when thiazides were found to be associated with significantly higher risk of incident diabetes as compared with other antihypertensive medications.<sup>5,37</sup> However, since the glycemic change was small in most included studies and in the pooled outcome (FPG 0.27 mmol/L [4.86 mg/ dL]) and no significant changes in PPG or HbA<sub>1c</sub> were found in the meta-analysis, we wonder how these small changes are able to translate into a higher incidence of new-onset diabetes. In fact, it remains undefined whether the small glycemic changes or the incident diabetes during thiazide therapy has a strong impact on cardiovascular or other major outcomes. Some researchers compared the 4-year cumulative incidence of new-onset diabetes in patients assigned to CTD and those assigned to amlodipine in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and argued that 85% of cases of diabetes associated with a thiazide diuretic was not induced by the diuretic itself.<sup>38</sup> Moreover, diabetes diagnosed during thiazide therapy was not found to be related to an increase in cardiovascular outcomes or mortality.<sup>39</sup>

The mechanism of the adverse glycemic effect of thiazide diuretics has not yet been fully elucidated. Several hypotheses exist. Hypokalemia is a classic hypothesis most frequently mentioned by researchers. The inverse relationship between potassium and glucose was confirmed and potassium supplementation was correlated with a smaller increase in serum glucose.<sup>40</sup> Abdominal obesity and impaired insulin release were found to be involved in this process. Thiazide-induced hyperuricemia may also be responsible for some adverse metabolic effects and may be associated with increased cardiovascular risk and renal injury. Other possible mechanisms related to dysglycemia include visceral fat accumulation, changes in renin-angiotensin-aldosterone system (RAAS) activity, hepatic insulin resistance, and genetic variations.<sup>41</sup>

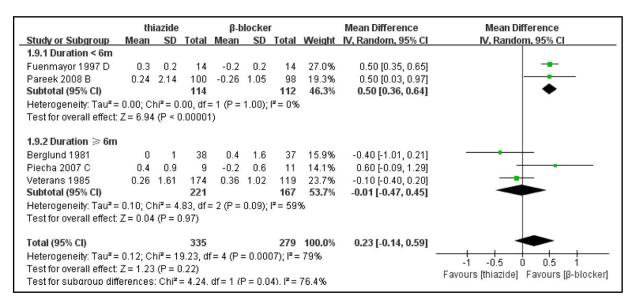
It seems that thiazide diuretics influence glucose metabolism in a dose-dependent manner. Lower doses of thiazides have therefore been recommended by international guidelines to reduce adverse effects.<sup>42</sup> In this meta-analysis, we found that serum glucose levels were significantly lower in patients receiving low doses of thiazides (HCTZ or CTD  $\leq 25$  mg daily) than in those receiving high doses. Similar results were presented in previous studies.<sup>43</sup> Apart from the relatively favorable metabolic outcomes, low-dose thiazides are also effective in controlling blood pressure and preventing cardiovascular events.<sup>10,44</sup> A recent systematic review demonstrated that low-dose HCTZ could effectively lower blood pressure. For thiazide diuretics other than HCTZ, the lowest doses could lower blood pressure maximally and higher doses did not exhibit increased

	t	hiazide		non	thiazide			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Alderman 1986	0.49	0.82	9	-0.17	0.64	10	1.6%	0.66 [-0.01, 1.33]	
ALLHAT 2006 A	0.16	3.09	4972	0.03	3.09	2954	3.0%	0.13 [-0.01, 0.27]	-
ALLHAT 2006 B	0.16	3.09	4972	-0.08	2.85	2731	3.0%	0.24 [0.10, 0.38]	
Berglund 1981	0	1	38	0.4	1.6	37	1.7%	-0.40 [-1.01, 0.21]	
Calvo 2000	0.28	1.22	100	-0.6	1.22	97	2.5%	0.88 [0.54, 1.22]	
Carlsen 1990 A	0.27	0.15	52	-0.08	0.09	52	3.1%	0.35 [0.30, 0.40]	-
Chrysant 1994 A	0.5	2.3	84	0.1	2.2	81	1.5%	0.40 [-0.29, 1.09]	
Chrysant 1994 B	0.5	2.3	84	0.1	0.8	85	2.0%	0.40 [-0.12, 0.92]	<u> </u>
Fiddes 1997	0.194	1.51	103	-0.0556	1.15	100	2.4%	0.25 [-0.12, 0.62]	
Fuenmayor 1997 A	0.3	0.2	14	0.1	0.2	14	3.0%	0.20 [0.05, 0.35]	
Fuenmayor 1997 B	0.3	0.2	14	-0.3	0.2	14	3.0%	0.60 [0.45, 0.75]	
Fuenmayor 1997 C	0.3	0.2	14	0.4	0.1	13	3.0%	-0.10 [-0.22, 0.02]	
Fuenmayor 1997 D	0.3	0.2	14	-0.2	0.2	14	3.0%	0.50 [0.35, 0.65]	
Fuenmayor 1997 E	0.3	0.2	14	0	0.1	13	3.0%	0.30 [0.18, 0.42]	
Grassi 2003	0.15	0.82	59	0.13	0.92	68	2.6%	0.02 [-0.28, 0.32]	
Hall 1994	0.2	1.5	82	0.2	1.2	90	2.3%	0.00 [-0.41, 0.41]	
Jansen 1989	0.3	0.16	16	-0.1	0.5	15	2.7%	0.40 [0.14, 0.66]	——
Jounela 1994	-0.14	0.82	23	-0.03	0.5	22	2.3%	-0.11 [-0.50, 0.28]	
Mersey 1993 A	-0.12	0.26	69	-0.02	0.27	70	3.1%	-0.10 [-0.19, -0.01]	
Mersey 1993 B	-0.12	0.256	69	0.0367		68	3.1%	-0.16 [-0.24, -0.07]	-
Oslo 1984	0.18	0.59	125	0.13	0.68	277	3.0%	0.05 [-0.08, 0.18]	
Pareek 2008 A	0.24	2.14	100	-0.26	1.52	102	2.0%	0.50 [-0.01, 1.01]	
Pareek 2008 B	0.24	2.14	100	-0.26	1.05	98	2.1%	0.50 [0.03, 0.97]	
Piecha 2007 A	0.4	0.9	9	0.6	0.5	10	1.6%	-0.20 [-0.86, 0.46]	
Piecha 2007 B	0.4	0.9	9	0.7	0.6	10	1.5%	-0.30 [-1.00, 0.40]	
Piecha 2007 C	0.4	0.9	9	-0.2	0.6	11	1.5%	0.60 [-0.09, 1.29]	
Pollare 1989	0.6	1.4	50	-0.2	1.1	48	2.0%	0.80 [0.30, 1.30]	
Pool 1993 A	0.35	0.8	67	0.028	0.66	57	2.7%	0.32 [0.06, 0.58]	
Pool 1993 B	0.35	0.8	67	0.18	0.69	63	2.7%	0.17 [-0.09, 0.43]	+
Reisin 1997 A	0.31	0.99	76	-0.16	0.9	79	2.6%	0.47 [0.17, 0.77]	
Reisin 1997 B	0.31	0.99	76	-0.21	0.71	77	2.7%	0.52 [0.25, 0.79]	
SHEP 1998	0.51	1.69	860	0.31	1.42	803	3.0%	0.20 [0.05, 0.35]	
Siegel 1994 A	0.1	0.13	147	0.3	0.14	27	3.1%	-0.20 [-0.26, -0.14]	-
Siegel 1994 B	0.7	0.28	28	0.3	0.14	27	3.0%	0.40 [0.28, 0.52]	
Stimpel 1998	0.61	0.23	41	-0.13	0.11	43	3.1%	0.74 [0.66, 0.82]	-
Vardan 1987	0.61	0.15	60	-0.1	0.13	59	3.1%	0.71 [0.66, 0.76]	-
Veterans 1985	0.26	1.61	174	0.36	1.02	119	2.6%	-0.10 [-0.40, 0.20]	
Weinberger 1985	0.55	0.17	67	-0.06	0.17	69	3.1%	0.61 [0.55, 0.67]	-
Zappe 2008	0.22	0.9	158	0.17	0.9	167	2.9%	0.05 [-0.15, 0.25]	+
Total (95% CI)			13025			8694	100.0%	0.27 [0.15, 0.39]	•
Heterogeneity: Tau <sup>2</sup> =	: 0.12; C	hi <sup>z</sup> = 112		= 38 (P <	0.0000			5.27 [0.15, 0.55]	
Test for overall effect				,		11.			-1 -0.5 0 0.5 1
									Favours [thiazide] Favours [nonthiazide

FIGURE 1. Forest plot for the mean difference (MD) of the change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with nonthiazide medications or placebo or nontreatment. MDs from the individual studies are presented by squares and the size of the square represents the statistical weight of the study in the summary estimate. The horizontal line indicates the 95% confidence interval (CI) of the study.

	th	iazide		1	ССВ			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.2.1 low dose									
ALLHAT 2006 A	0.16	3.09	4972	0.03	3.09	2954	18.4%	0.13 [-0.01, 0.27]	
Pareek 2008 A	0.24	2.14	100	-0.26	1.52	102	10.1%	0.50 [-0.01, 1.01]	
Piecha 2007 A	0.4	0.9	9	0.6	0.5	10	7.6%	-0.20 [-0.86, 0.46]	
Pool 1993 B	0.35	0.8	67	0.18	0.69	63	15.9%	0.17 [-0.09, 0.43]	+
Subtotal (95% CI)			5148			3129	52.1%	0.15 [0.03, 0.27]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; CI	hi <b>=</b> 2.	.95, df=	= 3 (P =	0.40);	l <sup>z</sup> = 0%			
Test for overall effect:	Z = 2.45	6 (P = 0	).01)						
1.2.2 high dose									
Calvo 2000	0.28	1.22	100	-0.6	1.22	97	13.9%	0.88 [0.54, 1.22]	
Fuenmayor 1997 B	0.3	0.2	14	-0.3	0.2	14	18.3%	0.60 [0.45, 0.75]	
Jansen 1989	0.3	0.16	16	-0.1	0.5	15	15.7%	0.40 [0.14, 0.66]	
Subtotal (95% CI)			130			126	47.9%	0.60 [0.39, 0.82]	•
Heterogeneity: Tau <sup>2</sup> =	0.02; CI	hi² = 4.	77, df=	= 2 (P =	0.09);	I <sup>2</sup> = 589	%		
Test for overall effect:	Z = 5.47	'(P < 0	0.00001	)					
Total (95% CI)			5278			3255	100.0%	0.38 [0.15, 0.61]	•
Heterogeneity: Tau <sup>2</sup> =	0.07; CI	hi <b>=</b> 3	4.49, di	f= 6 (P -	< 0.00	001); I <sup>z</sup>	= 83%		-1 -0.5 0 0.5 1
Test for overall effect:	Z = 3.21	(P = 0	).001)						Favours (thiazide) Favours (CCB)
Test for subaroup diff	erences	: Chi <sup>z</sup> ∶	= 13.19	8. df = 1	(P = 0.	.0003).	I <sup>z</sup> = 92.49	6	

FIGURE 2. Forest plot for subgroup analysis of change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with calcium channel blockers (CCBs) based on dose of treatment. Mean differences (MDs) from the individual studies are presented by squares and the size of the square represents the statistical weight of the study in the summary estimate. The horizontal line indicates the 95% confidence interval (CI) of the study.



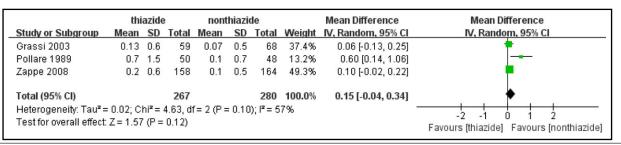
**FIGURE 3.** Forest plot for subgroup analysis of change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with  $\beta$ -blockers based on duration of treatment. Mean differences (MDs) from the individual studies are presented by squares and the size of the square represents the statistical weight of the study in the summary estimate. The horizontal line indicates the 95% confidence interval (CI) of the study.

effects on blood pressure.<sup>10</sup> Low-dose thiazide treatment has been proven to be well-tolerated and could significantly reduce cardiovascular outcomes for hypertensive patients.<sup>44</sup> Another finding of our meta-analysis is that patients with longer duration of treatment had less glycemic change compared with patients with shortterm treatment. However, this result should be cau-

tiously interpreted given the specific comparative agent ( $\beta$ -blocker) and the few number of studies and participants included. For patients with hypertension, blood glucose levels tend to increase over time. According to the results of randomized trials, changes in blood glucose were most evident in the first 1 or 2 years in patients receiving thiazides. This disparity in blood

	th	iazide		non	thiazid	le		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Pareek 2008 A	-0.11	3.21	100	-0.71	2.82	102	37.4%	0.60 [-0.23, 1.43]	
Pareek 2008 B	-0.11	3.21	100	-0.48	1.8	98	49.8%	0.37 [-0.35, 1.09]	
Veterans 1985	1.44	4.12	45	1.01	2.27	34	12.8%	0.43 [-1.00, 1.86]	
Total (95% CI)			245			234	100.0%	0.46 [-0.05, 0.97]	◆
Heterogeneity: Tau² =	0.00; CI	hi² = 0.	17, df=	= 2 (P =	0.92);	$ ^2 = 0\%$			
Test for overall effect:	Z=1.78	(P = 0	).07)						-2 -1 U 1 2 Favours [thiazide] Favours [nonthiazide]

FIGURE 4. Forest plot for the mean difference (MD) of the change in postprandial plasma glucose (PPG) comparing thiazide-type diuretics with other treatments. MDs from the individual studies are presented by squares and the size of the square represents the statistical weight of the study in the summary estimate. The horizontal line indicates the 95% confidence interval (CI) of the study.



**FIGURE 5.** Forest plot for the mean difference (MD) of the change in glycated hemoglobin (HbA<sub>1c</sub>) comparing thiazide-type diuretics with other treatments. MDs from the individual studies are presented by squares and the size of the square represents the statistical weight of the study in the summary estimate. The horizontal line indicates the 95% confidence interval (CI) of the study.

glucose between patients receiving thiazides and patients receiving other treatments appeared to wane over time.<sup>16,26</sup> Nevertheless, an observational study published recently indicated that prolonged duration of thiazide treatment was associated with increased fasting glucose.<sup>45</sup> Long-term randomized clinical trials are needed for more accurate comparisons regarding treatment duration.

Diabetic patients receiving thiazides were shown to have a moderate increase in serum glucose. A recent meta-analysis<sup>46</sup> reported a higher increase in FPG (MD, 1.69 mmol/L [30.42 mg/dL]; 95% CI, 0.69–2.69) in diabetic patients taking thiazide diuretics compared with that in our study. Considering the impaired glucose metabolism of existing diabetes, it can be assumed that the use of thiazides in diabetic patients needs to be more cautiously monitored.

Similar to thiazide diuretics, ACE inhibitors and ARBs are medications widely used and also recommended as first-line antihypertensive medications. These classes showed beneficial effects on glucose metabolism in contrast to thiazide diuretics,<sup>5</sup> probably because of their inhibition of RAAS. The combinations of low-dose thiazides and ACE inhibitors or ARBs were demonstrated to be effective and well-tolerated in hypertensive patients without apparent adverse effects on glucose and lipid profiles,<sup>47</sup> suggesting complementary impacts of these drugs. Based on the neutral or less-adverse glycemic effects, these combinations might be considered for patients with impaired glucose metabolism. On the

contrary,  $\beta$ -blockers were not recommended to be used in combination with thiazide-type diuretics. Because of the negative impacts of both classes on glucose metabolism, patients at increased risk for diabetes should avoid using these combination regimens.

A meta-analysis by Mukete and Rosendorff<sup>48</sup> investigated the glycemic effects of thiazide diuretics and showed that low-dose thiazide diuretics were associated with significantly increased FPG.<sup>48</sup> However, only 10 studies were included and no comparison based on doses of thiazides was shown in this study. Although the total sample size was larger than our study, some nonrandomized trials and some trials using combination therapies containing thiazides were included.

## STUDY LIMITATIONS

There are some limitations to our study. First, except for seven trials,<sup>15,16,22,23,26,32,34</sup> the other included studies were small, with fewer than 200 participants. Second, most studies measured only the changes of FPG without referring to other glycemic parameters, which led to a small sample size in the pooled analysis of PPG and HbA<sub>1c</sub>. In addition, despite the positive findings in subgroup analyses, the sample sizes of the high-dose thiazide subgroup and both subgroups in the analysis based on duration of treatment are relatively small. Third, most studies did not clearly report the process of randomization, which might increase the risk of bias. Finally, since glycemic outcome was not the major endpoint in some trials and most trials lasted less than a

year, further randomized controlled trials with longer duration and larger populations are needed for more conclusive results. In fact, some recommendations have been released by a national working group of the United States to encourage more research on thiazide-induced dysglycemia.<sup>49</sup> Previous evidence suggests that there may be no increased cardiovascular risk in patients with dysglycemia or incident diabetes during thiazide ther-However, a study with a 15-year follow-up apv.3 reported that diabetes associated with diuretic use was linked to significant cardiovascular risk. In addition, patients with incident diabetes receiving antihypertensive treatment that included diuretics were shown to have higher cardiac morbidity rates than those without diabetes.<sup>50</sup> Since antihypertensive treatment is usually a persistent or even lifelong process, further studies are needed to evaluate long-term consequences of the glycemic effects of thiazides, especially their impact on major cardiovascular outcomes.

#### CONCLUSIONS

This meta-analysis demonstrated a significant but small magnitude of glycemic abnormalities associated with thiazide-type diuretics in hypertensive patients. Treatment with lower doses might reduce or avoid adverse effects. Further investigations are needed to clarify whether these metabolic changes are of clinical significance.

Acknowledgments: This research received no specific financial support.

Disclosure: The authors declare no conflict of interest.

#### References

- 1. Multiple Risk Factor Intervention Trial Research Group. Mortality after 10 1/2 years for hypertensive participants in the Multiple Risk Factor Intervention Trial. *Circulation*. 1990;82:1616–1628.
- Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet*. 2000;356:366–372.
- 3. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507–520.
- Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007;369:201– 207.
- 5. Rastogi D, Pelter MA, Deamer RL. Evaluations of hospitalizations associated with thiazide-associated hyponatremia. *J Clin Hypertens* (*Greenwich*). 2012;14:158–164.
- Vandell AG, McDonough CW, Gong Y, et al. Hydrochlorothiazideinduced hyperuricaemia in the pharmacogenomic evaluation of antihypertensive responses study. J Intern Med. 2014;276:486–497.
- Deshmukh M, Lee HW, McFarlane SI, et al. Antihypertensive medications and their effects on lipid metabolism. *Curr Diab Rep.* 2008;8:214–220.
- Higgins J, Green S. Cochrane handbook for systematic reviews of intervention 5.1.0 (2011) Cochrane Collaboration. http://handbook.cochrane.org. Accessed October 16, 2014.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
- Musini VM, Nazer M, Bassett K, et al. Blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension. *Cochrane Database Syst Rev* 2014;5:CD003824.
- Chrysant SG. Antihypertensive effectiveness of low-dose lisinoprilhydrochlorothiazide combination. A large multicenter study. Lisino-

pril-Hydrochlorothiazide Group. Arch Intern Med. 1994;154:737-743.

- Reisin E, Weir MR, Falkner B, et al. Lisinopril versus hydrochlorothiazide in obese hypertensive patients: a multicenter placebocontrolled trial. Treatment in Obese Patients With Hypertension (TROPHY) Study Group. *Hypertension*. 1997;30:140–145.
- Jounela AJ, Lilja M, Lumme J, et al. Relation between low dose of hydrochlorothiazide, antihypertensive effect and adverse effects. Blood Press. 1994;3:231–235.
- Fuenmayor NT, Moreira E, de los Rios V, et al. Relations between fasting serum insulin, glucose, and dihydroepiandrosterone-sulfate concentrations in obese patients with hypertension: short-term effects of antihypertensive drugs. J Cardiovasc Pharmacol 1997;30:523–527.
- Helgeland A, Leren P, Foss OP, et al. Serum glucose levels during long-term observation of treated and untreated men with mild hypertension. The Oslo study. *Am J Med.* 1984;76:802–805.
   Savage PJ, Pressel SL, Curb JD, et al. Influence of long-term, low-dose,
- Savage PJ, Pressel SL, Curb JD, et al. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: the Systolic Hypertension in the Elderly Program. SHEP Cooperative Research Group. Arch Intern Med. 1998;158:741–751.
- 17. Vardan S, Mehrotra KG, Mookherjee S, et al. Efficacy and reduced metabolic side effects of a 15-mg chlorthalidone formulation in the treatment of mild hypertension. A multicenter study. *JAMA*. 1987;258:484–488.
- Carlsen JE, Køber L, Torp-Pedersen C, et al. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. *BMJ*. 1990;300:975–978.
- Pool PE, Applegate WB, Woehler T, et al. A randomized, controlled trial comparing diltiazem, hydrochlorothiazide, and their combination in the therapy of essential hypertension. *Pharmacotherapy*. 1993;13:487–493.
- Siegel D, Saliba P, Haffner S. Glucose and insulin levels during diuretic therapy in hypertensive men. *Hypertension*. 1994;23:688–694.
- Mersey J, D'Hemecourt P, Blaze K. Once-daily fixed combination of captopril and hydrochlorothiazide as first line therapy for mild to moderate hypertension. *Curr Ther Res Clin Exp.* 1993;53:502–512.
- 22. Fiddes R, Blumenthal J, Dawson JE, et al. Evaluation of indapamide 1.25 mg once daily in elderly patients with mild to moderate hypertension. J Hum Hypertens. 1997;11:239-244.
- Hall WD, Weber MA, Ferdinand K, et al. Lower dose diuretic therapy in the treatment of patients with mild to moderate hypertension. J Hum Hypertens. 1994;8:571–575.
- 24. Calvo C, Gude F, Abellan J, et al. A comparative evaluation of amlodipine and hydrochlorothiazide as monotherapy in the treatment of isolated systolic hypertension in the elderly. *Clin Drug Invest.* 2000;19:317–326.
- Pareek A, Karnik N, Salagre SB, et al. Clinical effectiveness of lowdose chlorthalidone (6.25 mg) + atenolol combination in stage I hypertensive patients: a multicenter, randomized, controlled study. *Curr Med Res Opin*. 2008;24:1771–1779.
- 26. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The antihypertensive and lipid-lowering treatment to prevent heart attack trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipidlowering treatment to prevent heart attack trial (ALLHAT). *JAMA*. 2002;288:2981–2997.
- Piecha G, Adamczak M, Chudek J, et al. Indapamide decreases plasma adiponectin concentration in patients with essential hypertension. *Kidney Blood Press Res*. 2007;30:187–194.
- Jansen RW, Van Lier HJ, Hoefnagels WH. Nitrendipine versus hydrochlorothiazide in hypertensive patients over 70 years of age. *Clin Pharmacol Ther*. 1989;45:291–298.
   Pollare T, Lithell H, Berne C. A comparison of the effects of under the standard standard
- 29. Pollare T, Lithell H, Berne C. A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med.* 1989;321:868–873.
- Weinberger MH. Blood pressure and metabolic responses to hydrochlorothiazide, captopril, and the combination in black and white mild-to-moderate hypertensive patients. J Cardiovasc Pharmacol. 1985;7(Suppl 1):S52–S55.
- Grassi G, Seravalle G, Dell'Oro R, et al. Comparative effects of candesartan and hydrochlorothiazide on blood pressure, insulin sensitivity, and sympathetic drive in obese hypertensive individuals: results of the CROSS study. J Hypertens. 2003;21:1761–1769.
   Zappe DH, Sowers JR, Hsueh WA, et al. Metabolic and antihy-
- 32. Zappe DH, Sowers JR, Hsueh WA, et al. Metabolic and antihypertensive effects of combined angiotensin receptor blocker and diuretic therapy in prediabetic hypertensive patients with the cardiometabolic syndrome. J Clin Hypertens (Greenwich). 2008;10:894–903.

- 33. Stimpel M, Koch B, Oparil S. Antihypertensive treatment in postmenopausal women: results from a prospective, randomized, doubleblind, controlled study comparing an ACE inhibitor (moexipril) with a diuretic (hydrochlorothiazide). *Cardiology*. 1998;89:271–276.
- Veterans Administration Cooperative Study Group on Antihypertensive Agents. Propranolol or hydrochlorothiazide alone for the initial treatment of hypertension. IV. Effect on plasma glucose and glucose tolerance. *Hypertension*. 1985;7:1008–1016.
- Berglund G, Andersson O. Beta-blockers or diuretics in hypertension? A 6 year follow-up of blood pressure and metabolic side effects. *Lancet.* 1981;1:744–747.
- Alderman MH, Davis TK, Carroll L. Initial antihypertensive therapy. Comparison of prazosin and hydrochlorothiazide. *Am J Med.* 1986;80:120–125.
- Verdecchia P, Angeli F, Reboldi GP, et al. New-onset diabetes in treated hypertensive patients. *Curr Hypertens Rep.* 2005;7:174–179.
   Barzilay JI, Davis BR, Whelton PK. The glycemic effects of antihy-
- 38. Barzilay JI, Davis BR, Whelton PK. The glycemic effects of antihypertensive medications. *Curr Hypertens Rep.* 2014;16:410.
- Kostis JB, Wilson AC, Freudenberger RS, et al. Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. *Am J Cardiol.* 2005;95:29–35.
- Zillich AJ, Garg J, Basu S, et al. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension*. 2006;48:219–224.
- 41. Eriksson JW, Jansson PA, Carlberg B, et al. Hydrochlorothiazide, but not candesartan, aggravates insulin resistance and causes visceral and hepatic fat accumulation: the mechanisms for the diabetes preventing effect of candesartan (MEDICA) study. *Hypertension*. 2008;52:1030– 1037.
- Guidelines Subcommittee. 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. J Hypertens. 1999;17:151–183.
- Harper R, Ennis CN, Sheridan B, et al. Effects of low dose versus conventional dose thiazide diuretic on insulin action in essential hypertension. *BMJ*. 1994;309:226–230.
- Weir MR, Flack JM, Applegate WB. Tolerability, safety, and quality of life and hypertensive therapy: the case for low-dose diuretics. *Am J Med.* 1996;101:838–925.
- Karnes JH, Gong Y, Arwood MJ, et al. Alteration in fasting glucose after prolong treatment with a thiazide diuretic. *Diabetes Res Clin Pract.* 2014;104:363–369.
- 46. Hirst JA, Farmer AJ, Feakins BG, et al. Quantifying the effects of diuretics and beta-blockers on glycaemic control in diabetes mellitus – a systematic review and meta-analysis. Br J Clin Pharmacol. 2015;79:733–743.
- 47. Fujiwara W, Izawa H, Ukai G, et al. Low dose of hydrochlorothiazide, in combination with angiotensin receptor blocker, reduces blood pressure effectively without adverse effect on glucose and lipid profiles. *Heart Vessels*. 2013;28:316–322.

- Mukete BN, Rosendorff C. Effects of low-dose thiazide diuretics on fasting plasma glucose and serum potassium – a meta-analysis. J Am Soc Hypertens. 2013;7:454–466.
- Carter BL, Einhorn PT, Brands M, et al. Thiazide-induced dysglycemia: call for research from a working group from the National Heart, Lung, and Blood Institute. *Hypertension*. 2008;52:30–36.
- Aksnes TA, Kjeldsen SE, Rostrup M, et al. Impact of new-onset diabetes mellitus on cardiac outcomes in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial population. *Hypertension*. 2007;50:467–473.

#### Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flowchart of literature search and selection.

Figure S2. Risk of bias of included studies.

Figure S3. Risk of bias summary.

Figure S4. Begg's funnel plot for the mean difference of the change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with nonthiazide medications or placebo or nontreatment.

**Figure S5.** Begg's funnel plot for the mean difference of the change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with calcium channel blockers (CCBs).

Figure S6. Begg's funnel plot for the mean difference of the change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Figure S7. Forest plot for subgroup analysis of change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with nonthiazide medications or placebo or nontreatment based on types of medication in control groups. Mean differences (MDs) from the individual studies are presented by squares and the size of the square represents the statistical weight of the study in the summary estimate. The horizontal line indicates the 95% confidence interval of the study.