Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 57, No. 5, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.07.053

Antihypertensive Efficacy of Hydrochlorothiazide as Evaluated by Ambulatory Blood Pressure Monitoring

A Meta-Analysis of Randomized Trials

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Objectives The purpose of this study was to evaluate the antihypertensive efficacy of hydrochlorothiazide (HCTZ) by ambulatory blood pressure (BP) monitoring.

Background HCTZ is the most commonly prescribed antihypertensive drug worldwide. More than 97% of all HCTZ prescriptions are for 12.5 to 25 mg per day. The antihypertensive efficacy of HCTZ by ambulatory BP monitoring is less well defined.

Methods A systematic review was made using Medline, Cochrane, and Embase for all the randomized trials that assessed 24-h BP with HCTZ in comparison with other antihypertensive drugs.

Results Fourteen studies of HCTZ dose 12.5 to 25 mg with 1,234 patients and 5 studies of HCTZ dose 50 mg with 229 patients fulfilled the inclusion criteria. The decrease in 24-h BP with HCTZ dose 12.5 to 25 mg was systolic 6.5 mm Hg (95% confidence interval: 5.3 to 7.7 mm Hg) and diastolic 4.5 mm Hg (95% confidence interval: 3.1 to 6.0 mm Hg) and was inferior compared with the 24-h BP reduction of angiotensin-converting enzyme inhibitors (mean BP reduction 12.9/7.7 mm Hg; $p < 0.003$), angiotensin-receptor blockers (mean BP reduction 13.3/7.8 mm Hg; $p < 0.001$), beta-blockers (mean BP reduction 11.2/8.5 mm Hg; $p < 0.00001$), and calcium antagonists (mean BP reduction 11.0/8.1 mm Hg; $p < 0.05$). There was no significant difference in both systolic ($p = 0.30$) and diastolic ($p = 0.15$) 24-h BP reduction between HCTZ 12.5 mg (5.7/3.3 mm Hg) and HCTZ 25 mg (7.6/5.4 mm Hg). However, with HCTZ 50 mg, the reduction in 24-h BP was significantly higher (12.0/5.4 mm Hg) and was comparable to that of other agents.

Conclusions The antihypertensive efficacy of HCTZ in its daily dose of 12.5 to 25 mg as measured in head-to-head studies by ambulatory BP measurement is consistently inferior to that of all other drug classes. Because outcome data at this dose are lacking, HCTZ is an inappropriate first-line drug for the treatment of hypertension. (J Am Coll Cardiol 2011;57:590–600) © 2011 by the American College of Cardiology Foundation

Hydrochlorothiazide (HCTZ) has been available for half a century and remains the most commonly prescribed antihypertensive drug worldwide. In the U.S. alone, >134.1 million prescriptions of HCTZ were written in the year 2008 (1). For comparison, the second most commonly prescribed drug was atenolol, with 44 million prescriptions (1). More than a third of the HCTZ prescriptions (47.5 million) were written for monotherapy and the remainder in fixed combination, mostly with blockers of the renin-angiotensin system. The dose of HCTZ prescribed was almost exclusively (>97%) 12.5 to 25 mg/day, and hypertension remains, by far, the most common indication. Over the past 30 years, this persistent prescription pattern of HCTZ has been heavily influenced by reports of the Joint National Committee for Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, all 7 of which recommended "thiazides" or "thiazide-like drugs" or "thiazide-type diuretics" as first-line or as preferred therapy for hypertension. In an attempt to promote the use of thiazide-type diuretics, the National Heart, Lung, and Blood Institute sponsored the ALLHAT/JNC7 (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial/Joint National Committee Seventh Report) dissemination project, which reached

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Manuscript received April 7, 2010; revised manuscript received June 29, 2010, accepted July 5, 2010.

18,524 physicians in 1,698 venues through 147 physician educators (2). This effort resulted in a small increase in thiazide-type diuretics use that almost exclusively consisted of HCTZ. However, despite the extensive use, little evidence is available regarding the efficacy and safety of HCTZ for the treatment of essential hypertension, particularly at the dose of 12.5 to 25 mg. In the following paper, we scrutinize antihypertensive efficacy of HCTZ as assessed by 24-h ambulatory blood pressure (ABP) monitoring and the evidence for morbidity and mortality reduction available in the extensive literature on this drug.

Abbreviations and Acronyms

ABP = ambulatory blood pressure
ACE = angiotensin-converting enzyme
ARB = angiotensin-receptor blocker
BP = blood pressure
HCTZ = hydrochlorothiazide

Methods

Search strategy. We searched PubMed, Embase, and Cochrane Central Register of Clinical Trials (Cochrane Library, Issue 2, 2009) using the terms "HCTZ," "hydrochlorothiazide," "ABP," "ambulatory blood pressure," and "hypertension." We limited our search to randomized trials in human subjects and in peer-reviewed journals from 1966 to March 2010. No language restriction was applied. The reference lists of identified articles and bibliographies of original articles were also reviewed. Trials in the abstract form without a manuscript published were excluded for this analysis.

Selection criteria. To be included in the analysis, a trial had to fulfill the following criteria: 1) randomized trials involving patients with hypertension that assessed the antihypertensive efficacy by 24-h ABP monitoring comparing HCTZ with other antihypertensive drug classes; 2) use of HCTZ as a monotherapy in the trial; and 3) trial duration of at least 4 weeks.

Data extraction. Two reviewers (J.R. and C.A.) extracted the data independently and in duplicate. Data were extracted using standardized protocol and reporting form. Disagreements were resolved by arbitration (H.M. or A.B.), and consensus was reached after discussion. We extracted characteristics of each trial, duration of intervention and methods, baseline demographics, and 24-h ABP and office BP at baseline and after the intervention for our analysis. Authors of the papers were individually contacted in case the data were unclear.

Outcomes assessed. The main outcome of the present analysis was BP (systolic/diastolic) reduction from baseline to follow-up.

Quality assessment. The criteria used for quality assessment were sequence generation of allocation, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias (3). We classified studies with high or unclear risk for bias for any of the first 3 components as low quality.

Statistical analysis. The statistical analysis was done in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines (4) using Review Manager (RevMan) version 5.0.23 (Copenhagen, Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

Heterogeneity was assessed using the I^2 statistics. The I^2 statistic is the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error (chance), and we considered I^2 <25% as low and I^2 >75% as high. The random-effects model of DerSimonian and Laird (5) was used to calculate the effect sizes if I^2 >25% and/or $p < 0.05$. Analysis was performed on an intention-to-treat basis. Data from changes in baseline BP were combined using the weighted mean difference method. Publication bias was estimated visually by funnel plots, and/or using Begg's test and the weighted regression test of Egger (6). For trials that did not provide complete information about variance for net change in BP, the information was obtained from confidence intervals (CIs), p value, or *t* statistics. Variance was estimated from pre-test–post-test (parallel group and factorial design) and crossover designs, as suggested by Follmann et al. (7)

Sensitivity analysis. Sensitivity analysis was performed for BP reduction in HCTZ dose 12.5 to 25 mg based on the quality of study, study design, and type of blinding in the study. We estimated difference between subgroups according to the tests of interaction (8).

Results

Study selection. We identified 2,440 articles, out of which 86 abstracts were retrieved and reviewed for possible inclusion (Fig. 1). Nineteen studies (Table 1) enrolling 1,463 patients (mean age 58 years; 54% men) fulfilled the inclusion criteria and were included in the analysis.

Baseline characteristics. Of the 19 studies, 14 studies (9–22) enrolling 1,234 patients evaluated HCTZ dose 12.5 to 25 mg, and 5 studies (23–27) with 229 patients evaluated HCTZ dose 50 mg. Of the 14 studies of HCTZ dose of 12.5 to 25 mg, 4 studies evaluated HCTZ 12.5 mg dose, 1 evaluated HCTZ 12.5 to 25 mg dose, and the majority (9 studies) evaluated HCTZ 25 mg dose. Fifteen studies (28–42) were excluded because they did not meet the inclusion criteria: 5 had inadequate data, 3 were nonrandomized studies, 2 had HCTZ combined with other drugs in case of inadequate response, 2 were duplicate studies, 1 had HCTZ compared with placebo, and 1 had HCTZ compared with exercise.

Quality assessment. Of the 14 studies with HCTZ dose 12.5 to 25 mg, 4 studies reported adequate generation of allocation sequence and adequate allocation concealment, and 10 reported adequate masking of participants, personnel, and outcome assessors. On the basis of quality assess-

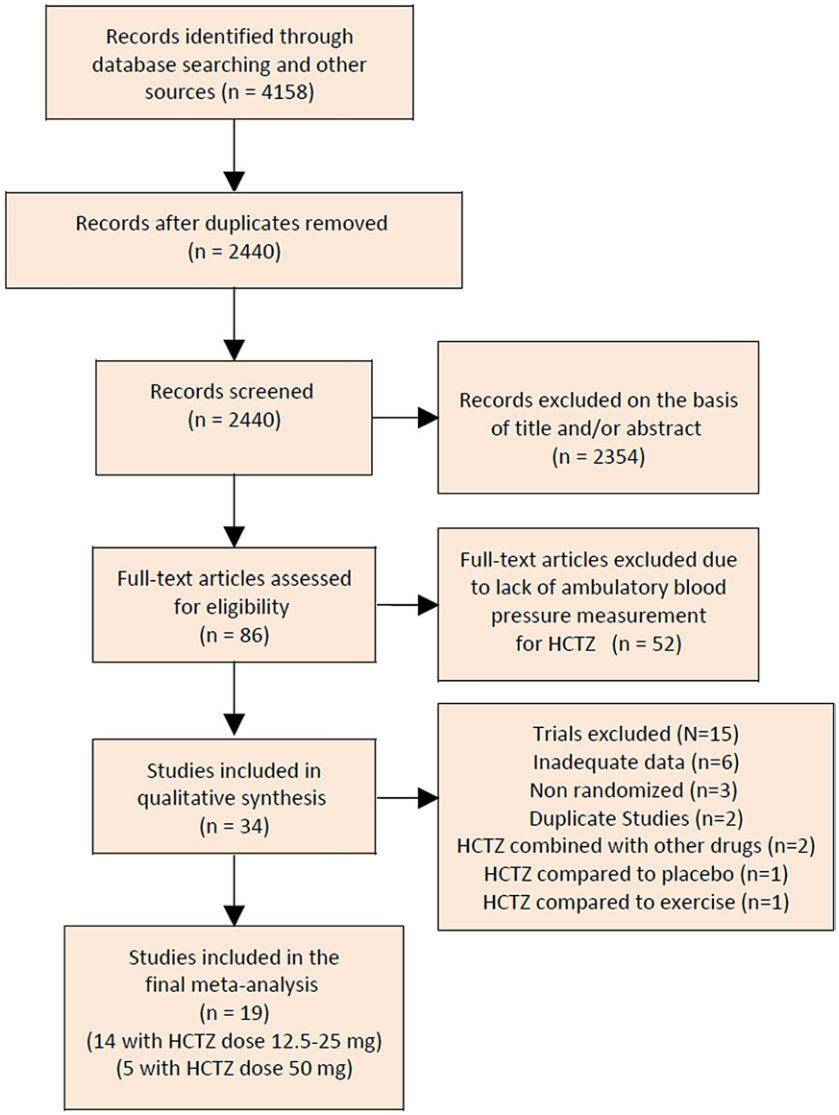

Figure 1 **Selection of Studies**

HCTZ = hydrochlorothiazide.

ment, 4 were deemed as low bias risk trials and the rest as high bias risk.

Antihypertensive efficacy. The antihypertensive efficacy of HCTZ in the dose of 12.5 to 25 mg was assessed from 14 randomized controlled trials. The mean baseline BP in these studies was 148 ± 7.5/92 ± 5.6 mm Hg. After treatment with HCTZ for a mean duration of 17 weeks, systolic ABP decreased by 6.5 mm Hg (95% CI: 5.3 to 7.7 mm Hg) and diastolic ABP by 4.5 mm Hg (95% CI: 3.1 to 6.0 mm Hg) (Figs. 2 and 3). Other antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta-blockers, and calcium antagonists were significantly more efficacious than HCTZ in the dose of 12.5 to 25 mg as shown in Figure 2.

Head-to-head comparisons. In head-to-head comparisons with other antihypertensive drug classes, HCTZ in the usual dose of 12.5 to 25 mg lowered systolic ABP less well than ACE inhibitors by 4.5 mm Hg ($p = 0.001$), ARBs by 5.1 mm Hg ($p = 0.003$), beta-blockers by 6.2 mm Hg ($p < 0.00001$), and calcium antagonists by 4.5 mm Hg ($p = 0.02$). HCTZ lowered diastolic ABP less well than ACE inhibitors by 4.0 mm Hg ($p < 0.0001$), ARBs by 2.9 mm Hg ($p = 0.002$), beta-blockers by 6.7 mm Hg ($p < 0.00001$), and calcium antagonists by 4.2 mm Hg ($p = 0.0001$) (Figs. 4 and 5).

Office versus ambulatory pressure. Both office BP and ABP readings were available in 8 studies with HCTZ in the commonly used dose of 12.5 to 25 mg evaluating 488

Table 1 Baseline Characteristics of Studies Included in the Meta-Analysis

First Author (Ref #)	Study Design	Inclusion Criteria	n	Follow-Up (Weeks)	Age (yrs)	Men (%)	HCTZ Dose (mg)	Comparison Drug (mg)	Baseline ABP (mm Hg)
HCTZ dose 12.5 to 25 mg									
Damasceno et al. (9) 1999	P, DB, CO, R, PC	Black hypertensive patients	12	4	NR	NR	25	Nifedipine 30	148/99
Falconnet et al. (10) 2004	P, SB, RC, CO	Hypertensive patients of East African descent	61	4	49	56	25	Lisinopril 20	139/92
Galzerano et al. (11) 2004	P, DB, RC	Mild to moderate essential hypertension	69	52	54	55	25	Telmisartan 80	154/95
Kraiczi et al. (12) 2000	P, DB, CO, RC	Hypertensive patients with obstructive sleep apnea	40	12	57	100	25	Amlodipine 5, atenolol 50, enalapril 20, losartan 50	145/92
Lacourcière et al. (14) 1995	P, DB, R, PC	Mild to moderate primary hypertension	42	32	69	60	12.5–25	Amlodipine 5–10	154/89
Lacourcière et al. (13) 2003	P, OL, PG, RC	Uncomplicated systolic hypertension	120	6	61	55	12.5	Losartan 50	150/86
Pelttari et al. (15) 1998	P, DB, CO, RC	Hypertensive patients with obstructive sleep apnea	18	8	52	NR	25	Atenolol 50, isradipine 2.5, spirapril 6	152/105
Suonsyrjä et al. (16) 2008	P, DB, CO, R, PC	Finnish men with moderate hypertension	233	4	51	100	25	Amlodipine 5, bisoprolol 5, losartan 50	135/93
Tedesco et al. (17) 1998	P, DB, RC	Mild to moderate hypertension	77	95	54	53	25	Losartan 50	156/96
Ubaid-Girioli et al. (18) 2007	P, OL, PG, RC	Mild to moderate hypertension	63	12	49	46	25	Irbesartan 150, quinapril 20	136/88
White et al. (19) 2008	P, MC, DB, RC	Stage II hypertension	354	8	51	55	25	Ramipril 20	148/92
Wing et al. (20) 2003	P, DB, CO, R, PC	Elderly with hypertension	19	6	68	58	12.5	Candesartan 8–16	161/85
Abate et al. (21) 1998	P, MC, DM, DB, RC	Mild to moderate hypertension	84	8	78	46	12.5	Pinacidil 25	148/85
Radevski et al. (22) 2002	P, OL, R, PC	Black patients with mild to moderate hypertension	42	12	57	33	12.5	Indapamide 2.5	147/94
HCTZ dose 50 mg									
Lacourcière et al. (23) 1989	P, DB, PG, RC	Mild to moderate hypertension	38	12	57	42	25–50	Zofenopril 30–60	150/94
Morgan et al. (24) 2003	P, DB, CO, R, PC	Elderly hypertensive patients	24	8	77	75	50	Atenolol 50, felodipine 10, perindopril 8	157/85
Silagy et al. (25) 1992	P, DB, RC	Elderly patients with isolated systolic hypertension	24	6	72	38	25–50	Atenolol 50–100, enalapril 10–20, isradipine 2.5–5	156/76
Weir et al. (26) 1998	P, MC, DB, PG, RC	Obese patients with hypertension	124	12	51	62	12.5–50	Lisinopril 10–40	145/89
Wing et al. (27) 1997	P, DB, CO, RC	Elderly patients with isolated systolic hypertension	19	4	71	26	25-50	Lacidipine 2–4	160/84

ABP = ambulatory blood pressure; BP = blood pressure; CO = crossover; DB = double blind; DBP = diastolic blood pressure; DM = double masked; FT = forced-titrated; HCTZ = hydrochlorothiazide; HTN = hypertension; MC = multicenter; NR = not reported; OL = open label; P = prospective; PG = parallel group; R = randomized; RC = randomized controlled; SB = single blind; SBP = systolic blood pressure.

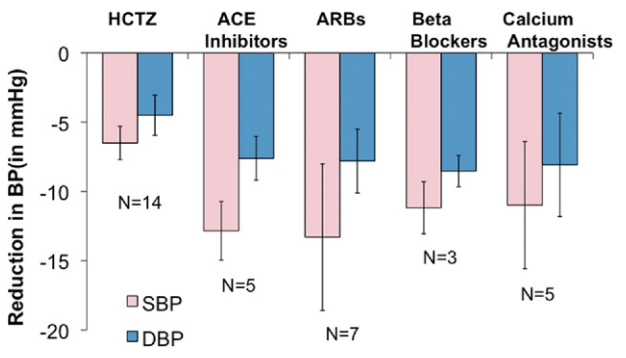

Figure 2 **Antihypertensive HCTZ Efficacy as Assessed by 24-h ABP Monitoring**

Compared with hydrochlorothiazide (HCTZ) dose 12.5 to 25 mg, $p < 0.001$ for other antihypertensive drugs, as assessed by 24-h ambulatory blood pressure (ABP) monitoring. **Bars** represent 95% confidence intervals; N indicates number of studies. ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; DBP = diastolic blood pressure **(blue bars)**; SBP = systolic blood pressure **(pink bars)**.

patients followed up for a mean of 8 weeks. The mean baseline office BP was 163 ± 7.5/98 ± 6.5 mm Hg and the mean ABP was 149 ± 7.4/89 ± 3.6 mm Hg. In these 8 studies, office BP reduction by HCTZ was systolic 12.4 mm Hg (95% CI: 8.1 to 16.6 mm Hg) and diastolic 6.5 mm Hg (95% CI: 3.9 to 9.2 mm Hg). HCTZ lowered mean office systolic BP by 4.9 mm Hg (95% CI: 0.8 to 9.0 mm Hg) better than by ABP monitoring ($p = 0.02$). Average office diastolic BP was lowered by 2.5 mm Hg (95% CI: 0.9 to 4.1 mm Hg) better than by ABP monitoring ($p = 0.002$) (Fig. 6).

The mean office systolic and diastolic BP reduction with HCTZ 12.5 to 25 mg of 12.4/6.5 mm Hg was not significantly different from the mean office BP reduction with ACE inhibitors of 11.8/7.4 mm Hg ($p = 0.65$), with ARBs of 13.3/6.7 mm Hg ($p = 0.66$), with beta-blockers of 12.9/9.9 mm Hg ($p = 0.71$), and with calcium antagonists of 12.0/9.7 mm Hg ($p = 0.36$).

Dose response. The ABP was not significantly different when compared between the HCTZ 12.5 dose and the HCTZ 25 mg dose. However, with the HCTZ dose of 50 mg, the reduction in systolic ABP was 12.0 (95% CI: 8.2 to 15.9), and the reduction in diastolic ABP was 5.4 (95% CI: 3.2 to 7.7). Thus, there was a significant difference in the systolic ABP ($p = 0.04$), but not diastolic ABP ($p = 0.97$) (Fig. 7), when compared with the 25 mg dose.

Significant heterogeneity was found to be present in the ABP reduction with HCTZ (Fig. 3), head-to-head comparison of HCTZ with ACE inhibitors, ARBs, and calcium antagonists (Figs. 4 and 5), comparison of office BP with ABP monitoring of HCTZ (Fig. 6), office BP reduction with HCTZ, and BP reduction with different doses of HCTZ (Fig. 7). There was no evidence of publication bias for any of our analyses. Sensitivity analyses for various subgroups based on the study design, blinding, and the risk of bias did not make any noticeable difference to these outcomes (data not shown).

Discussion

The principal findings of our study are that the most commonly prescribed HCTZ dose of 12.5 to 25 mg has clinically significant inferior antihypertensive efficacy compared with other drug classes used to treat hypertension. Our analysis was based on 24-h ABP monitoring, which is the most thorough and objective way to assess antihypertensive efficacy. In contrast, the reduction of office BP by HCTZ (12.4/6.5 mm Hg) was similar to the reduction of office BP by ACE inhibitors, ARBs, beta-blockers, and calcium-channel blockers.

The office BP reduction with ACE inhibitors (11.4/6.4 mm Hg) and ARBs (11.6/6.5 mm Hg) obtained from Cochrane meta-analysis (43,44) was similar to that obtained from our analysis. Thus, when HCTZ is assessed by outpatient BP measurement, the antihypertensive efficacy seems comparable to that of other antihypertensive drug classes. This finding would indicate that HCTZ lowers BP well during daytime when patients are seen in the physician's office but has less effect during the night and early morning hours. Indeed, Finkielman et al. (28) documented that the antihypertensive response to HCTZ is overestimated by using office BP measures. In their patient population of 228 subjects treated with HCTZ 25 mg daily, the difference between office BP and 24-h ABP was 4.8/2.1 mm Hg ($p < 0.01$). This difference is very similar to that found in our present analysis (4.9/2.5 mm Hg). Thus, assessing the antihypertensive efficacy of HCTZ by office BP measurements only is deceptive and is prone to provide to physicians and patients a false sense of security.

Not surprisingly, at a daily dose of 50 mg and above, HCTZ's antihypertensive efficacy seems to be similar to most other drug classes. However, all biochemical adverse effects such as hypokalemia, hyponatremia, hyperuricemia, insulin resistance, and visceral fat accumulation are dose dependent and become clinically more significant with daily doses exceeding 25 mg (45). Thus, biochemical adverse effects of HCTZ may prohibit the prescription of higher doses in many patients. An additional concern is the risk of sudden cardiac death that has been shown to increase in a dose dependant fashion with HCTZ doses exceeding 25 mg daily (46). A recent meta-analysis also showed that the chlorthalidone reduces systolic BP significantly better than the HCTZ at equivalent doses of both drugs without increase in the risk of hypokalemia (47).

What then is the evidence that HCTZ reduces morbidity and mortality in hypertension? A thorough scrutiny of the literature reveals that outcome evidence for low-dose HCTZ is lacking. All outcome studies were done with higher doses than the currently used 12.5 to 25 mg or with other thiazides such as chlorthalidone or indapamide.

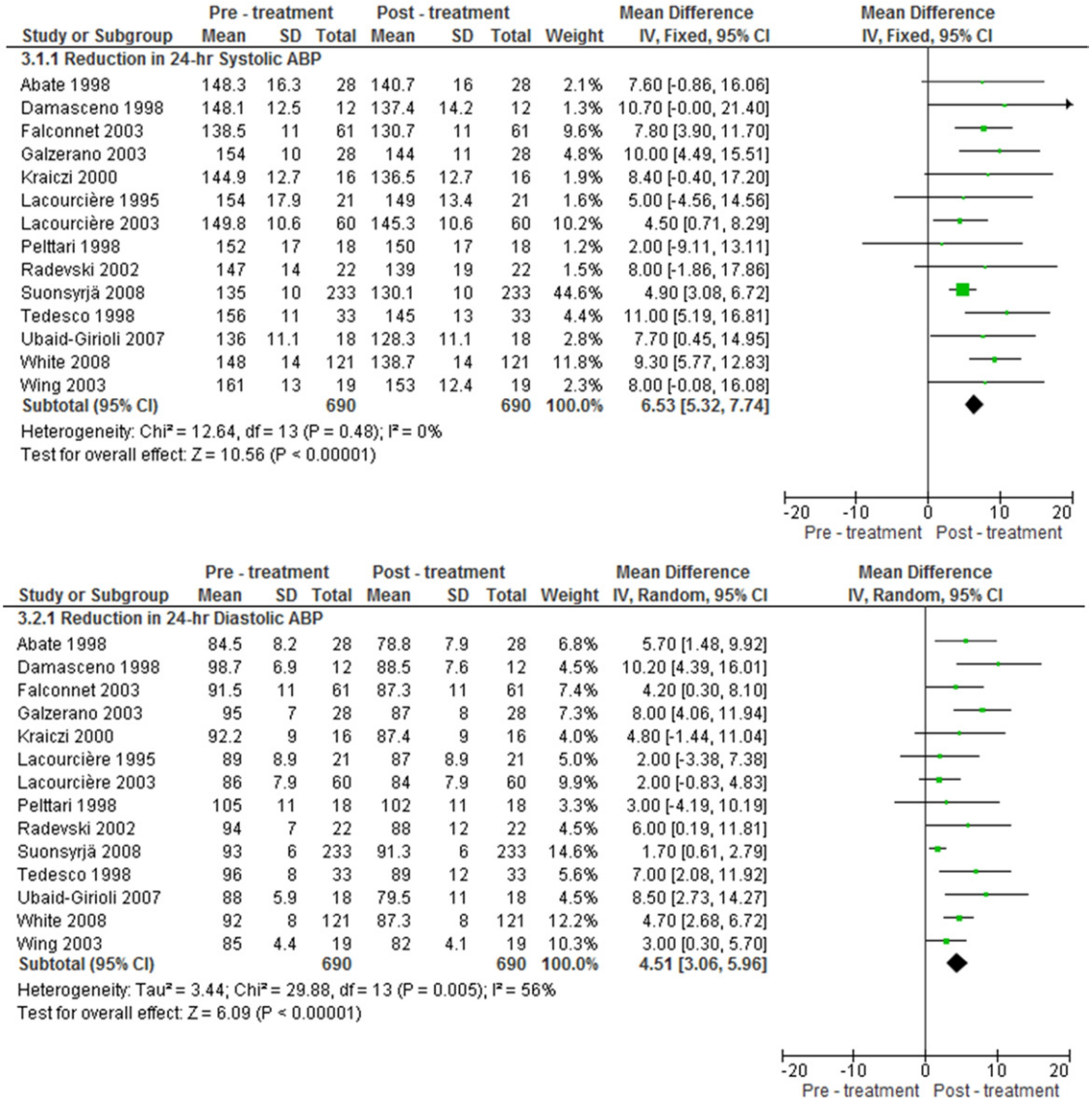

Figure 3 **Reduction in 24-h ABP With HCTZ 12.5 and 25 mg**

Reduction in systolic **(top)** and diastolic **(bottom)** 24-h ambulatory blood pressure (ABP) with hydrochlorothiazide (HCTZ) dose 12.5 to 25 mg. Trial references as in Table 1. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CCB = calcium-channel blocker; CI = confidence interval; df = degrees of freedom; IV = instrumental variables.

HCTZ was compared with and found to be inferior to enalapril in the large Australian National Blood Pressure 2 study (48), although the exact dose was not specified. In the MRFIT (Multiple Risk Factor Intervention Trial) study (49), both HCTZ and chlorthalidone were used, and the highest mortality rates were found in a subset of hypertensive patients treated with HCTZ, with death most likely from lethal arrhythmias due to hypokalemia. In 9 clinics whose staff prescribed HCTZ, the trend of mortality was unfavorable whereas it was favorable in the 6 clinics whose staff primarily used chlorthalidone (50). The investigators decided to switch everybody to chlorthalidone, and concluded that the more favorable mortality trend was due to "a change in the diuretic treatment protocol about 5 years after randomization which involved replacement of HCTZ with chlorthalidone" (50). On the basis of these data, we have to conclude that, for the most prescribed antihypertensive drug in the U.S., outcome evidence is lacking. In its commonly used dose of 12.5 to 25 mg once a day, there has been no evidence that HCTZ reduces myocardial infarction, stroke, or death. This lack of outcome data together with the poor antihypertensive efficacy should strongly motivate physicians to refrain from prescribing HCTZ as initial therapy in hypertension.

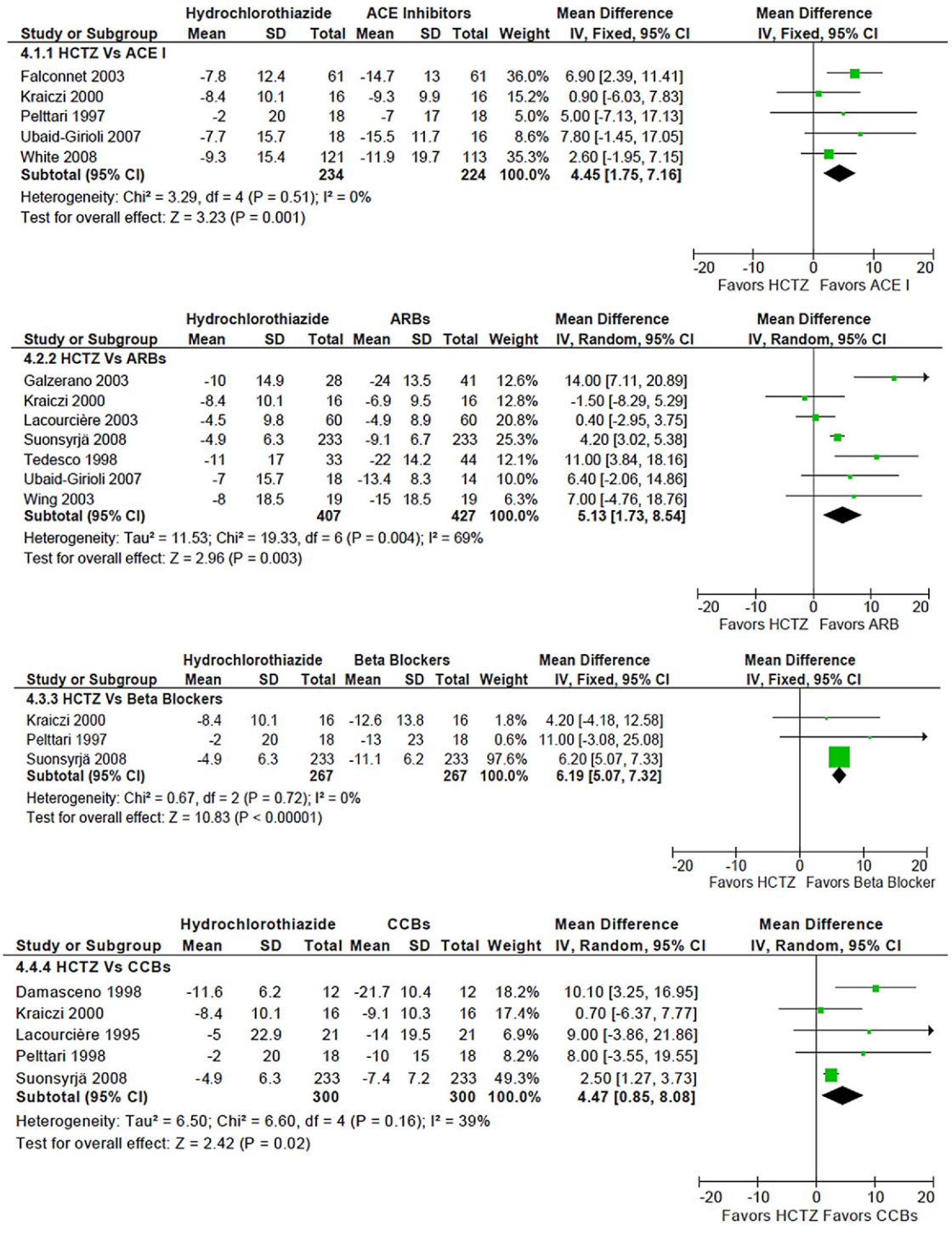

Figure 4 **Systolic 24-h ABP Reduction by HCTZ at 12.5 to 25 mg Compared With Other Antihypertensive Drugs**

Head-to-head comparison of systolic 24-h ambulatory blood pressure (ABP) reduction with hydrochlorothiazide (HCTZ) at the dose of 12.5 to 25 mg with other classes of antihypertensive drugs. Trial references as in Table 1; abbreviations as in Figure 3.

The fact that our data indicate that HCTZ in its commonly used dose is a suboptimal antihypertensive drug should not prevent it from it being useful in combination with a blocker of the renin-angiotensin system such as an ACE inhibitor, an ARB, or even a direct renin inhibitor. Numerous, mostly factorial design studies have shown that when combined with these drug classes, HCTZ, even at low doses, elicits a distinct incremental fall in BP. That would

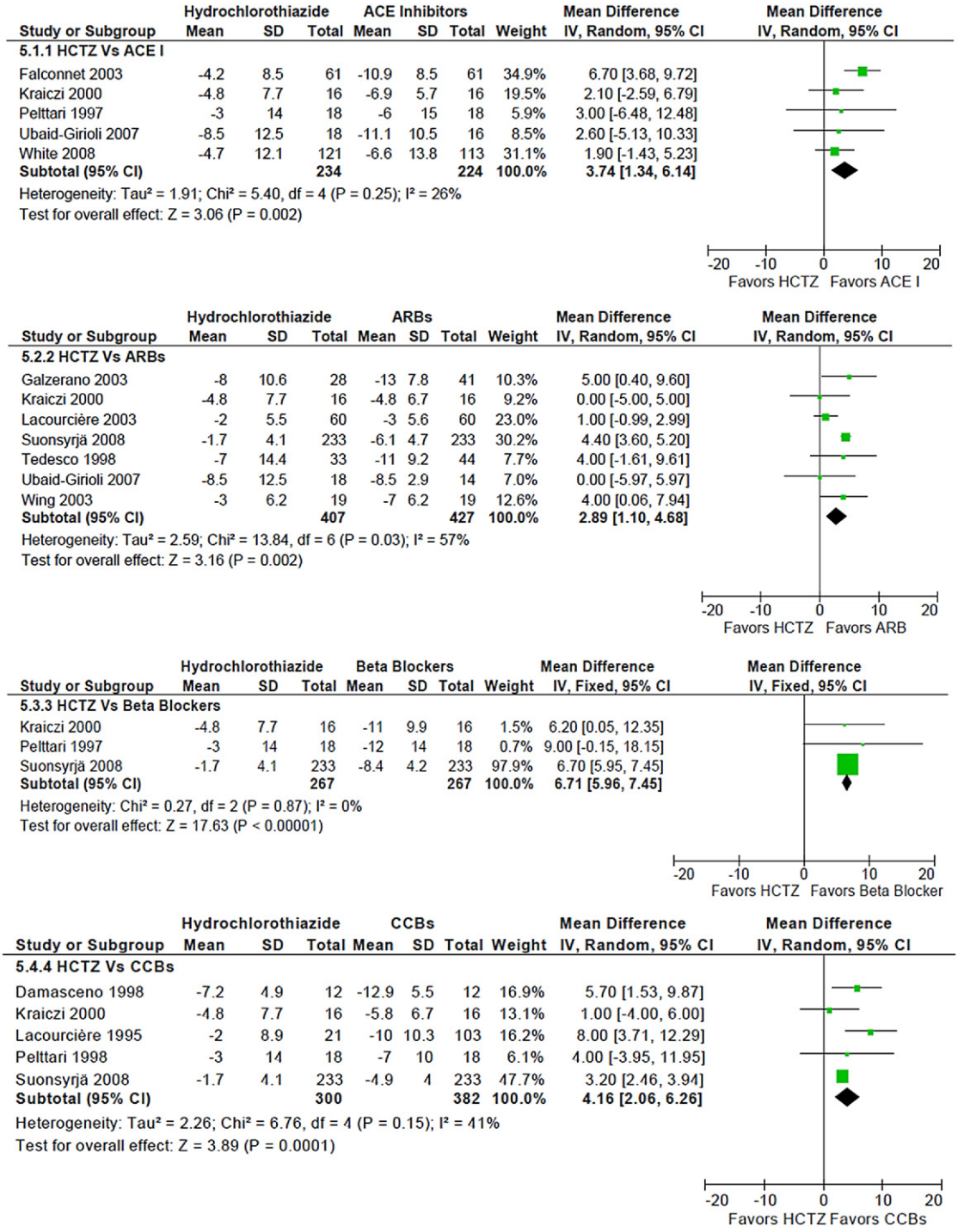

Figure 5 **Diastolic 24-h ABP Reduction by HCTZ at 12.5 to 25 mg Compared With Other Antihypertensive Drugs**

Head-to-head comparison of diastolic 24-h ambulatory blood pressure (ABP) reduction with hydrochlorothiazide (HCTZ) at the dose of 12.5 to 25 mg with other classes of antihypertensive drugs. Trial references as in Table 1; abbreviations as in Figure 3.

indicate that HCTZ is more useful as an "enhancer" or "sensitizer" for the antihypertensive effect of renin-angiotensin system blockers than as a monotherapeutic agent. However, even when combined with a renin-angiotensin system blocker, outcome data suggest that HCTZ is inferior to amlodipine, as was reported in the recent ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension) study (51).

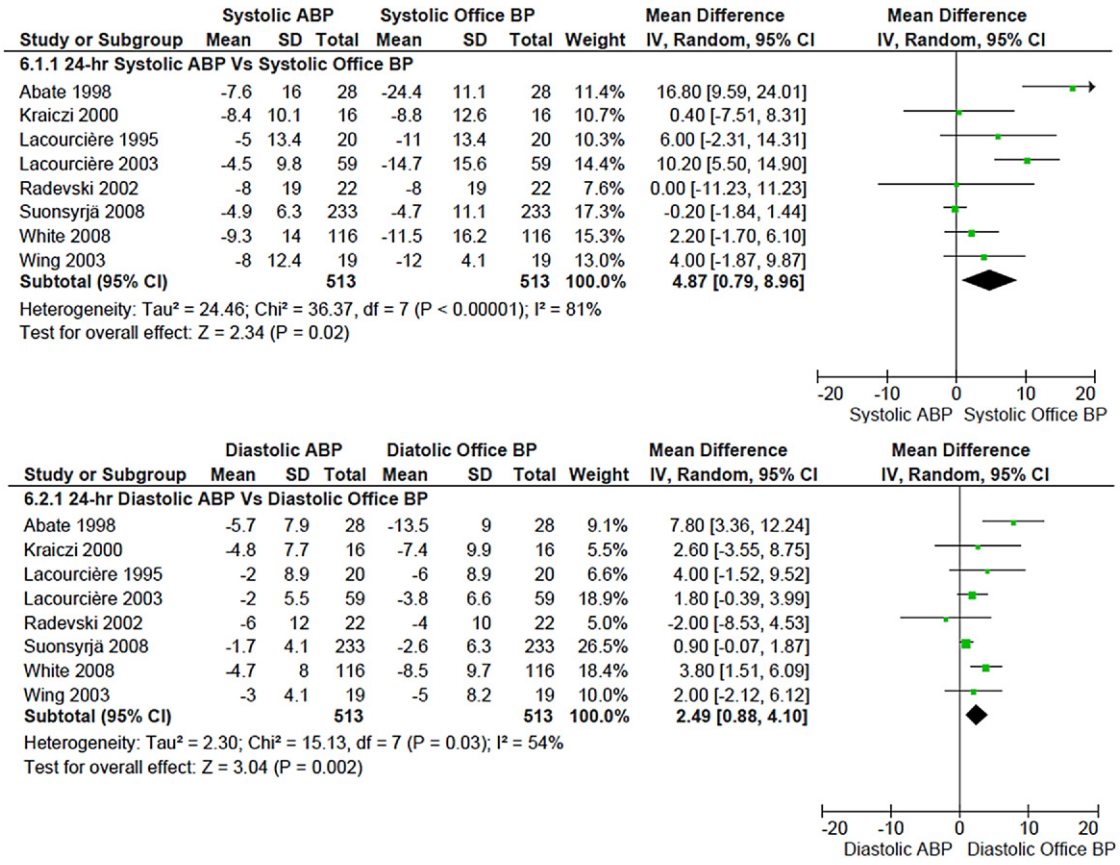

Figure 6 **Systolic and Diastolic 24-h ABP Reduction Compared With Office BP Reduction**

Comparison of systolic **(top)** and diastolic **(bottom)** 24-h ambulatory blood pressure (ABP) reduction with office BP reduction with hydrochlorothiazide (HCTZ) dose 12.5 to 25 mg. Trial references as in Table 1; other abbreviations as in Figure 3.

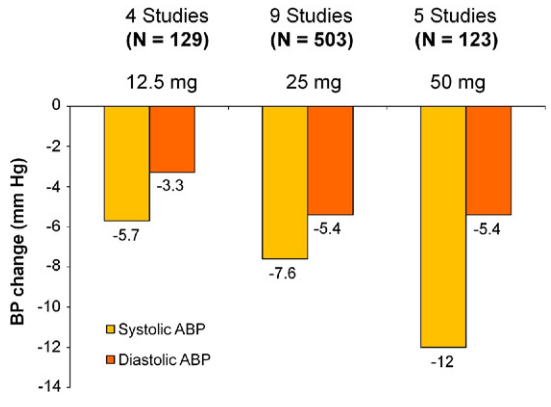

Figure 7 **Dose Response Curve With Hydrochlorothiazide**

Systolic ambulatory blood pressure (ABP) is indicated by **yellow bars**; diastolic ABP is indicated by **red bars**. Compared with HCTZ 25 mg ABP: p = NS versus 12.5 mg (both systolic and diastolic), p = 0.0001 versus 50 mg systolic, and p = NS versus 50 mg diastolic. N indicates number of patients. HCTZ = hydrochlorothiazide; NS = not significant.

Clinical implications. HCTZ still remains the most commonly prescribed antihypertensive drug in the U.S. and worldwide. The National Heart, Lung and Blood Institute continues to advocate (2) the use of "thiazide-type diuretics," which, for practicing physicians, simply means HCTZ in a daily dose of 12.5 to 25 mg. However, because the BP-lowering effect of HCTZ is inferior to that of every other drug class and outcome data at commonly used doses are nonexistent, its use as a first-line antihypertensive agent is ill advised. On a milligram-per-milligram basis using pooled data, chlorthalidone, for which solid outcome data are available, produced greater reductions in systolic BP than HCTZ did, while mean changes in potassium were found to be equivalent (47). Thus, if a clinical indication calls for a thiazide-type diuretic, chlorthalidone or indapamide remain the drugs of choice.

Study limitations. As in other meta-analyses, given the lack of data in each trial, we did not adjust our analyses for compliance to assigned therapy. Also, the results are subject to limitations inherent to any meta-analysis based on pooling of data from different trials with different designs, different duration, and different patient groups. The trials

did not report cardiovascular outcomes, and hence, the superiority of ABP monitoring over office BP measurement for prevention of cardiovascular outcomes cannot be derived from our study. However, there are solid data establishing ABP monitoring as a better surrogate end point than office BP measurement (52). There is also evidence that thiazides are primarily or only effective for patients with low renin, salt-volume hypertension, so monotherapy limited to this group might have shown different results; however, the design of the meta-analysis precluded examining such a possibility (53). Although no clear dose range was established for other antihypertensive drugs when used for comparison with HCTZ in this meta-analysis, most of these drugs were used in one-half the maximal dose.

Conclusions

HCTZ in its commonly used dose of 12.5 to 25 mg daily lowers BP significantly less well than do all other drug classes as measured in head-to-head studies by ABP monitoring. Because of such paltry antihypertensive efficacy and the lack of outcome data at these doses, physicians should refrain from prescribing HCTZ as initial antihypertensive therapy.

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Key Words: ambulatory blood pressure ■ hydrochlorothiazide ■ hypertension ■ meta-analysis.