JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 67, NO. 4, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.10.083

Efficacy of Low-Dose Chlorthalidone and Hydrochlorothiazide as Assessed by 24-h Ambulatory Blood Pressure Monitoring

Anil K. Pareek, MD,[a] Franz H. Messerli, MD,[b,c] Nitin B. Chandurkar, MPharma,[d] Shruti K. Dharmadhikari, MSc,[d] Anil V. Godbole, MD,[e] Prasita P. Kshirsagar, MD,[f] Manish A. Agarwal, MD,[g] Kamal H. Sharma, MD, DNB, DM,[h] Shyam L. Mathur, MD,[i] Mukund M. Kumbla, MD, DM[j]

ABSTRACT

BACKGROUND Thiazide and thiazide-like diuretic agents are being increasingly used at lower doses. Hydrochlorothiazide (HCTZ) in the 12.5-mg dose remains the most commonly prescribed antihypertensive agent in the United States.

OBJECTIVES This study compared chlorthalidone, 6.25 mg daily, with HCTZ, 12.5 mg daily, by 24-h ambulatory blood pressure (ABP) monitoring and evaluated efficacy. Because HCTZ has been perceived as a short-acting drug, a third comparison with an extended-release formulation (HCTZ-controlled release [CR]) was added.

METHODS This 12-week comparative, double-blind, outpatient study randomized 54 patients with stage 1 hypertension to receive either chlorthalidone, 6.25 mg, (n = 16); HCTZ 12.5 mg (n = 18); or HCTZ-CR 12.5 mg (n = 20). ABP monitoring was performed at baseline and after 4 and 12 weeks of therapy.

RESULTS All 3 treatments significantly ($p < 0.01$) lowered office BP at weeks 4 and 12 from baseline. At weeks 4 and 12, significant reductions in systolic and diastolic 24-h ambulatory and nighttime BP ($p < 0.01$) were observed with chlorthalidone but not with HCTZ. At weeks 4 ($p = 0.015$) and 12 ($p = 0.020$), nighttime systolic ABP was significantly lower in the chlorthalidone group than in the the HCTZ group. With HCTZ therapy, sustained hypertension was converted into masked hypertension. In contrast to the HCTZ group, the HCTZ-CR group also showed a significant ($p < 0.01$) reduction in 24-h ABP. All 3 treatments were generally safe and well tolerated.

CONCLUSIONS Treatment with low-dose chlorthalidone, 6.25 mg daily, significantly reduced mean 24-h ABP as well as daytime and nighttime BP. Due to its short duration of action, no significant 24-h ABP reduction was seen with HCTZ, 12.5 mg daily, which merely converted sustained hypertension into masked hypertension. Thus, low-dose chlorthalidone, 6.25 mg, could be used as monotherapy for treatment of essential hypertension, whereas low-dose HCTZ monotherapy is not an appropriate antihypertensive drug. (Comparative Evaluation of Safety and Efficacy of Hydrochlorothiazide CR with Hydrochlorothiazide and Chlorthalidone in Patients With Stage I Essential Hypertension; CTRI/2013/07/003793) (J Am Coll Cardiol 2016;67:379–89) © 2016 by the American College of Cardiology Foundation.

From the [a]Medical Affairs and Clinical Research, Ipca Laboratories Limited, Mumbai, India; [b]Department of Cardiology, Mount Sinai Health Medical Center, Icahn School of Medicine, New York, New York; [c]Department of Cardiology University Hospital, Bern, Switzerland; [d]Clinical Research and Development, Ipca Laboratories Limited, Mumbai, India; [e]Department of Medicine, King Edward Memorial Hospital, Pune, India; [f]Department of Medicine, Rajiv Gandhi Medical College and Chhatrapati Shivaji Maharaj Hospital, Kalwa, Thane, India; [g]Medilink Hospital and Research Centre, Ahmadabad, India; [h]Dr. Kamal Sharma Cardiology Clinic, Ahmadabad, India; [i]Department of Medicine, Dr. Sampurnanand Medical College and Mathura Das Mathur Hospital, Jodhpur, India; and the [j]Omega Hospital, Mangalore, India. This study was supported by Ipca Laboratories Ltd. Dr. Messerli is a consultant for or has consultant/advisory relationships with Daiichi-Sankyo, Pfizer, Takeda, Abbott, AbbVie, Servier, Medtronic, Ipca Laboratories, and Menarini. Dr. Pareek, Mr. Chandurkar, and Ms. Dharmadhikari are employees of Ipca Laboratories Ltd. Drs. Godbole, Kshirsagar, Agarwal, Sharma, Mathur, and Kumbla (study investigators) have received honoraria for executing the study at their respective sites. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. George Bakris, MD, served as Guest Editor for this paper.

Manuscript received October 1, 2015; revised manuscript received October 23, 2015, accepted October 27, 2015.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ABBREVIATIONS AND ACRONYMS

ABPM = ambulatory blood pressure monitoring

BP = blood pressure

CR = controlled release

DBP = diastolic blood pressure

HCTZ = hydrochlorothiazide

SBP = systolic blood pressure

12.5 mg of hydrochlorothiazide per day has no significant antihypertensive effect
—P.F. Magee, E.D. Freis (1)

Hydrochlorothiazide (HCTZ) has been available for more than one-half a century and remains the most commonly prescribed antihypertensive drug worldwide. In the United States alone, >134.1 million prescriptions of HCTZ were written in 2008 (2). More than one third of HCTZ prescriptions (i.e., 48 million) were written for monotherapy. Over more than 3 decades, the prescription pattern of HCTZ has been heavily influenced by the 8 reports of the Joint National Committee (JNC) for Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, all of which recommended "thiazides" or "thiazide-like drugs" or "thiazide-type diuretics" as first-line or preferred therapy for hypertension. For most practicing physicians, the term "thiazide" simply means HCTZ (3). The more recent JNC reports also increasingly have recommended low-dose thiazide and thiazide-like diuretics as initial therapy in hypertensive patients. Although a clinical study 30 years ago showed that a dose of 12.5 mg of HCTZ per day had

SEE PAGE 390

no significant antihypertensive effect (1), this dose remains the one most frequently prescribed in monotherapy, and hypertension remains, by far, its most common indication (2). However, despite its widespread use, and in contrast to chlorthalidone, little if any evidence is available regarding the efficacy and safety of HCTZ for the treatment of essential hypertension, particularly at the dose of 12.5 mg (4-6). Almost a decade ago, Carter et al. (7) found significant pharmacokinetic and pharmacodynamic differences between HCTZ and chlorthalidone. Chlorthalidone was found to be approximately 1.5× to 2.0× as potent as HCTZ and to have a much longer duration of action. Subsequently, Ernst et al. (8) compared effects of HCTZ with those of chlorthalidone in the daily doses of 25 mg (forced titrated to 50 mg) and 12.5 mg (force titrated to 25 mg), respectively, on ambulatory blood pressure (ABP) and office blood pressure (BP). In the present study, we scrutinized the antihypertensive efficacy of HCTZ, 12.5 mg daily, as assessed by 24-h ABP monitoring (ABPM), and compared it with low-dose (6.25 mg) chlorthalidone in patients with stage 1 essential hypertension. Because the antihypertensive efficacy of HCTZ may be hampered by its short half-life, a third arm, with an extended-release formulation (HCTZ-controlled release [CR]), was added.

METHODS

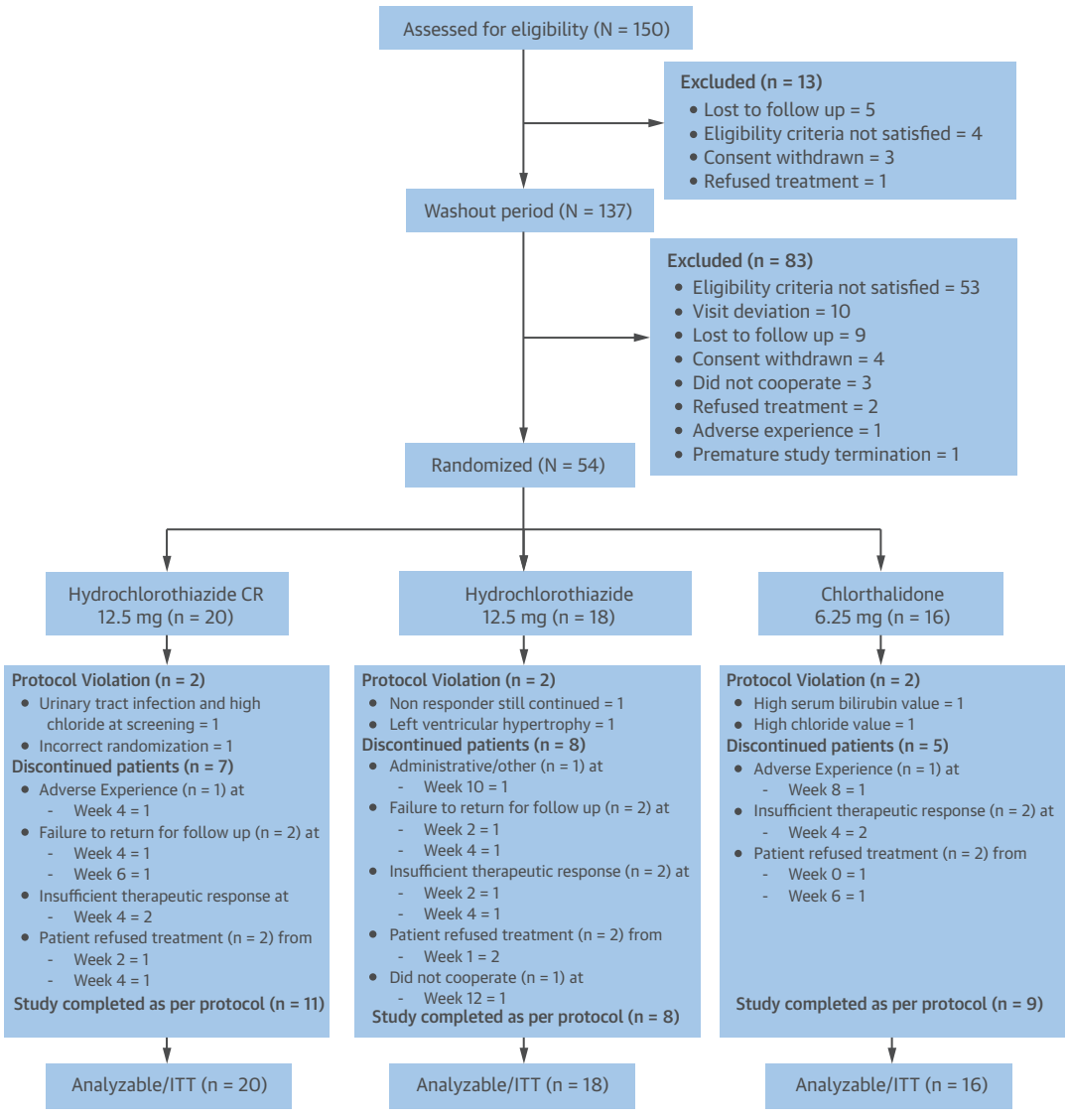
TRIAL DESIGN. This was a double-blind, double-dummy, randomized, parallel group, comparative, multicentric study conducted in Indian patients. The study was initially planned in 213 patients with stage 1 hypertension randomized in a 1:1:1 ratio to receive chlorthalidone, 6.25 mg tablets, or HCTZ-CR, 12.5 mg, tablets, or conventional HCTZ, 12.5-mg tablets. Between December 2012 and February 2015, only 54 patients were enrolled in the study. The reason for this slow recruitment was difficulty in getting patients with stage 1 hypertension at tertiary centers.

The study was carried out according to Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by the ethics committee at each of the participating centers, namely, KEM Hospital Research Centre, Ethic Committee (Pune, India); Institutional Clinical Ethics Committee at Rajiv Gandhi Medical College and Chhatrapati Shivaji Maharaj Hospital (Thane, India); Medilink Ethics Committee (Ahmadabad, India); Aadhya Independent Ethics Committee (Ahmadabad, India); Office of the Principal and Controller, Institutional Ethics Committee at Dr. S.N Medical College (Jodhpur, India); and Omega Ethical Committee (Mangalore, India). The Drug Controller General of India also approved the study protocol. All patients were provided with an oral explanation of the nature of the study and study drugs by the investigator at each center. The patient information sheet was provided in a language understood by the patient, and patients who provided written consent to participate were screened for the study.

SELECTION CRITERIA. Male and female patients between 18 and 65 years of age were eligible if they had stage 1 essential hypertension (office systolic blood pressure [SBP] between 140 and 159 mm Hg and diastolic blood pressure [DBP] between 90 and 99 mm Hg). As recommended in European Society of Hypertension/European Society of Cardiology hypertension guidelines (9) and 2 other guidelines (10,11), the hypertension was diagnosed on the basis of office BP and confirmed by 24-h ABPM measurements.

Exclusion criteria (among others) were secondary hypertension; diabetes; hyperuricemia; gout; chronic kidney disease; parathyroid diseases; recent cardiovascular disease or cardiovascular accident; abnormal renal function (serum creatinine: >1.5 mg/dl; blood urea nitrogen [BUN]: >20 mg/dl), abnormal liver function (aspartate aminotransferase [AST], alanine

FIGURE 1 Disposition of Study Participants



CR = controlled release; ITT = intention-to-treat.

aminotransferase [ALT], total bilirubin, or alkaline phosphatase >2.5× the upper limit of normal values); electrolyte imbalance; hypercalcemia; and hypophosphatemia. Women who were pregnant, lactating, or of childbearing potential and not practicing contraception were also excluded from the study, as were alcoholics or patients who had participated in a clinical trial within 30 days prior to enrollment.

TREATMENT AND STUDY PROCEDURES. Patients with stage 1 essential hypertension were subjected to a 2-week placebo washout period. Post completion of the washout period, 24-h ABPM was performed at the baseline visit. A 24-h ABP machine (Bravo model monitor; Suntech Medical, Raleigh, North Carolina) was used to perform 24-h ABP measurements. Eligible patients were randomized to receive treatment with a once-daily dose of chlorthalidone, 6.25 mg, or HCTZ-CR, 12.5 mg, or conventional HCTZ, 12.5-mg tablets for 12 weeks. Patients were instructed to take the study medicines in the morning.

Evaluations comparing efficacy were performed at baseline and weeks 4 and 12 for 24-h ABPM and at baseline and weeks 2, 4, 8, and 12 for office BP

TABLE 1 Demographic and Baseline Disease Characteristics of Enrolled Patients

	Hydrochlorothiazide-CR (n = 20)	Hydrochlorothiazide (n = 18)	Chlorthalidone (n = 16)	Total (N = 54)	p Value
Sex*					
Male	10 (50.0)	8 (44.44)	9 (56.25)	27 (50.0)	0.915
Female	10 (50.0)	10 (50.0)	7 (43.75)	27 (50.0)	
Age, yrs†	46.8 ± 11.77	47.72 ± 10.37	41.13 ± 13.40	45.44 ± 11.96	0.348
BMI, kg/m^2†	26.89 ± 3.75	27.81 ± 5.08	26.61 ± 4.12	27.14 ± 4.31	0.613
Waist circumference, m†	0.81 ± 0.27	0.89 ± 0.22	0.90 ± 0.18	0.87 ± 0.23	0.508
SBP, mm Hg†	148.82 ± 5.73	149.87 ± 4.50	147.38 ± 4.59	148.74 ± 5.02	0.437
DBP, mm Hg†	92.03 ± 2.48	93.39 ± 2.45	93.94 ± 2.84	93.05 ± 2.66	0.062
Smoking status*					
Current smoker	1 (5.0)	2 (11.11)	1 (6.25)	4 (7.41)	0.775
Former smoker	1 (5.0)	-	2 (12.50)	3 (5.56)	0.598
Never smoked	18 (90.00)	16 (88.89)	13 (81.25)	47 (87.04)	0.612

Values are n (%) or mean ± SD. *Chi-square test or Fisher exact test was used for comparison, as appropriate. †Kruskal-Wallis test was used for comparison.
BMI = body mass index; CR = controlled release; DBP = diastolic blood pressure; SBP = systolic blood pressure.

measurements. At each visit, physical examination and safety assessment were performed; and vital signs, details of concomitant medications, and compliance to study drug were recorded. The investigator instructed and educated the patient on diet and exercise at all visits.

BLINDING AND RANDOMIZATION TECHNIQUES. Patients were randomized to 1 of the 3 treatment arms according to the randomization chart provided by the sponsor. Randomization codes were generated using block randomization technique. The number of blocks was calculated on the basis of block size and number of patients assigned to each center.

To eliminate evaluation bias, the study used a double-blind, double-dummy design. All patients received an active drug along with placebos matching the other 2 drugs. Each site was provided with a sealed envelope that contained individual, patient-specific envelopes with details of the treatment assigned to that particular patient. Investigators were instructed to open this envelope only in case of an emergency or serious adverse events.

TABLE 2 Change in Mean Systolic and Diastolic Ambulatory Blood Pressure Levels

Outcome	Hydrochlorothiazide-CR (n = 20)	Hydrochlorothiazide (n = 18)	Chlorthalidone (n = 16)
Ambulatory SBP			
Change at week 4*	−11.05 ± 11.91	−2.95 ± 10.24	−7.49 ± 10.24
p value†	0.001	0.426	0.001
Change at week 12*	−10.27 ± 11.78	−6.02 ± 12.46	−11.14 ± 12.41
p value†	0.002	0.104	<0.001
Ambulatory DBP			
Change at week 4*	−7.73 ± 9.05	−2.83 ± 8.02	−5.82 ± 8.29
p value†	0.001	0.104	0.003
Change at week 12*	−8.21 ± 9.79	−4.17 ± 8.15	−7.78 ± 9.74
P value†	0.002	0.058	0.007

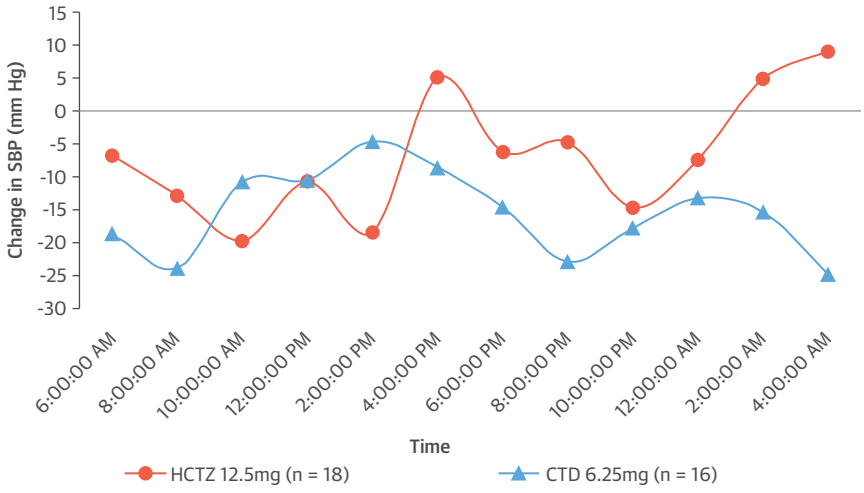
Values are mean ± SD. *Kruskal-Wallis test used with Dunn's test for multiple comparisons; all change values are calculated from baseline values. †Comparison between baseline and Wilcoxon signed rank test results. Mean 24-h SBP was significantly lower for the chlorthalidone group than for the hydrochlorothiazide group at week 4 (125.52 vs. 139.71 mm Hg, respectively, p = 0.019) and week 12 (121.87 vs. 136.64 mm Hg, respectively, p = 0.013). This analysis was performed in an intention-to-treat population that included all patients randomized in the study.
Abbreviations as in Table 1.

EFFICACY. The primary efficacy parameter was the change in mean 24-h ambulatory SBP and DBP from baseline to weeks 4 and 12. Secondary efficacy parameters were changes in mean office SBP and DBP and changes in mean ambulatory daytime and nighttime SBP and DBP from baseline to weeks 4 and 12.

Office BP measurements were performed according to standard guidelines for measurement of BP by sphygmomanometer. For 24-h ABPM, BP was recorded every 15 min during the day (i.e., 6 AM to 10 PM) and every 30 min during the night (i.e., from 10 PM to 6 AM). For ABP readings to be considered evaluable, at least 2 readings per hour during the daytime and at least 1 reading per hour during the nighttime were required. At week 4, patients were evaluated for response to their treatment. Patients with BP >140/90 mm Hg after 4 weeks of therapy were considered nonresponders. Nonresponders were considered treatment failures and were excluded from the study.

SAFETY. Patients who provided written consent for participation were evaluable for safety assessment. At baseline and at the end-of-therapy visit, tests for routine hematology (hemoglobin, platelet count, red blood cell count, white blood cell count, differential count, erythrocyte sedimentation rate, packed cell volume, mean corpuscular volume), biochemistry (AST, ALT, alkaline phosphatase, bilirubin, albumin, globulin, total proteins, BUN, serum creatinine,

FIGURE 2 Mean Change From Baseline to Week 12 in Average Ambulatory SBP



CTD = chlorthalidone; HCTZ = hydrochlorothiazide; SBP = systolic blood pressure.

serum potassium, uric acid, calcium, phosphorous, sodium, chloride), lipid profile (high-density lipoprotein, low-density lipoprotein [LDL], very low-density lipoprotein, triglycerides, total cholesterol), random blood glucose, and routine urinalysis were performed. Electrocardiograms were recorded at screening, baseline and at weeks 4 and 12. Urine pregnancy tests were performed at the screening visit, the baseline visit, and the end-of-therapy visit for all female patients of childbearing potential.

STATISTICAL METHODS. A sample size of 71 patients per group was estimated to show the difference of at least 5 mm Hg in mean fall of SBP among groups to demonstrate HCTZ-CR was superior to HCTZ and noninferior to chlorthalidone, with a power of 80% at the 5% level of significance and considering 20% dropouts.

Data were analyzed on the basis of an intention-to-treat (ITT) population that included all subjects who were randomized according to the randomization schedule provided by the sponsor. The approach of last observation carried forward was used to impute missing assessments.

Descriptive statistics were used to compare demographic and baseline disease characteristics. All patients were compared at baseline for homogeneity using the Kruskal-Wallis test for continuous variables and the chi-square test or Fisher exact test, as appropriate, for categorical variables.

Data were not normal due to the small sample size. Hence, nonparametric tests were used for analysis. The primary endpoint was the comparative change in mean 24-h ambulatory SBP and DBP values from baseline to weeks 4 and 12. Secondary endpoints were comparative changes in mean office SBP and DBP values at weeks 4 and 12 from baseline and in mean ambulatory daytime and nighttime SBP and DBP values from baseline to weeks 4 and 12.

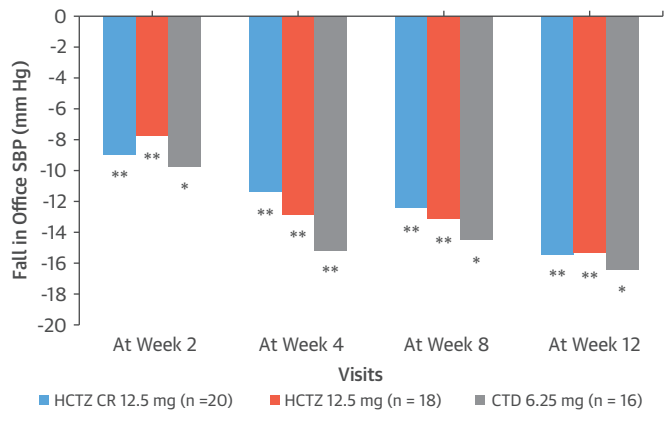
TABLE 3 Change in Mean Office SBP and DBP Between Weeks 4 and 12 From Baseline

Outcome	Hydrochlorothiazide-CR (n = 20)	Hydrochlorothiazide (n = 18)	Chlorthalidone (n = 16)
Office SBP			
Week 0*	148.82 ± 5.73	149.87 ± 4.50	147.38 ± 4.59
Week 4*	137.48 ± 11.10	137.00 ± 10.40	132.19 ± 9.98
Change at week 4*	−11.34 ± 11.34	−12.87 ± 9.96	−15.19 ± 10.14
p value†	<0.001	<0.001	<0.001
Week 12*	133.38 ± 15.16	134.57 ± 12.36	130.98 ± 14.94
Change at week 12*	−15.43 ± 14.49	−15.30 ± 11.87	−16.40 ± 15.38
p value†	<0.001	<0.001	0.002
Office DBP			
Week 0*	92.03 ± 2.48	93.39 ± 2.45	93.94 ± 2.84
Week 4*	85.38 ± 7.75	85.39 ± 6.42	84.18 ± 8.23
Change at week 4*	−6.65 ± 7.33	−8.00 ± 6.12	−9.76 ± 8.48
p value†	0.001	<0.001	<0.001
Week 12*	86.18 ± 8.50	85.23 ± 6.85	84.44 ± 9.47
Change at week 12*	−5.85 ± 8.44	−8.16 ± 6.42	−9.50 ± 10.39
p value†	0.006	<0.001	0.005

Values are mean ± SD. *Kruskal-Wallis test was used with Dunn's test for multiple comparisons; all changes were calculated from baseline values. †Comparison with baseline, and Wilcoxon signed rank test was used for comparison. Analysis was performed in an intent-to-treat population that included all patients randomized in the study.

Abbreviations as in Table 1.

FIGURE 3 Visit-to-Visit Fall in Office SBP

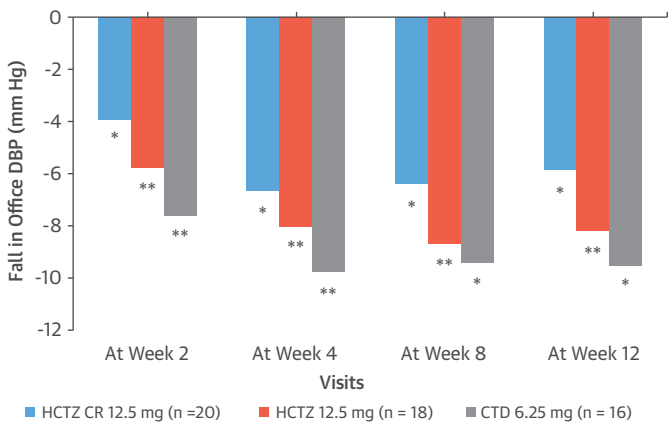


**p < 0.001; *p < 0.01; Wilcoxon signed rank test was used for comparisons. HCTZ CR = hydrochlorothiazide controlled release; other abbreviations as in Figure 2.

All previously mentioned continuous parameters were assessed using the Kruskal-Wallis test with Dunn's multiple comparison. The Wilcoxon signed rank sum test was used for within-group comparisons. All categorical parameters were assessed using the chi-square test or Fisher exact test, as appropriate.

The safety population consisted of all patients who provided written informed consent for participation in the study. Safety parameters consisted of adverse events and changes in laboratory parameters from baseline to end-of-therapy visit. Percentages of patients who reported an adverse event were compared using the chi-square test or Fisher exact test, as appropriate. Changes in laboratory parameters were assessed by Wilcoxon signed rank sum tests for within-group comparison and Kruskal-Wallis tests for between-group comparisons. For all statistical tests, the significance level was 0.05. All analyses were performed using SAS version 9.3 software (SAS Institute, Inc., Cary, North Carolina).

FIGURE 4 Visit-to-Visit Fall in Office DBP



**p < 0.001; *p < 0.01; Wilcoxon signed rank test was used for comparisons. DBP = diastolic blood pressure; other abbreviations as in Figures 2 and 3.

RESULTS

PATIENTS. Of the 150 patients screened, 137 patients satisfying the eligibility criteria were put on placebo washout for 2 weeks (Figure 1). After completion of washout period, 54 eligible patients were enrolled in the study and randomized to receive either chlorthalidone, 6.25 mg (n = 16), HCTZ-CR, 12.5 mg (n = 20), or HCTZ, 12.5 mg (n = 18). Demographic and baseline disease characteristics were generally matched and were not significantly different among treatment groups (Table 1).

EFFICACY. Primary efficacy parameter. Changes in mean 24-h ambulatory SBP and DBP values are shown in Table 2 and Figure 2. Patients treated with chlorthalidone and HCTZ-CR showed a significant reduction in 24-h ambulatory SBP and DBP values from baseline ($p < 0.01$). At weeks 4 and 12, this reduction was not statistically significant for patients treated with conventional HCTZ. At weeks 4 ($p = 0.019$) and 12 ($p = 0.013$), the 24-h ambulatory SBP was significantly lower in patients treated with chlorthalidone than those treated with conventional HCTZ.

Secondary efficacy parameters. Changes in mean office SBP and DBP are shown in Table 3 and Figures 3 to 5. At weeks 4 and 12, all 3 treatments showed a significant reduction in mean office SBP (HCTZ: $p < 0.001$; HCTZ-CR: $p < 0.001$; chlorthalidone: $p = 0.002$) and DBP (HCTZ: $p = 0.006$; HCTZ-CR: $p < 0.001$; chlorthalidone: $p = 0.005$). There were no significant differences in changes in office SBP and DBP from baseline at weeks 4 and 12 among treatment groups, despite the numerically greater fall in BP in chlorthalidone-treated patients.

A total of 6 patients (2 from each group) were withdrawn from the study because of insufficient therapeutic response ($p = 0.999$). The proportion of patients who met BP goal levels (BP <140/90 mm Hg) did not differ significantly among treatment groups (chlorthalidone: 62.5% vs. HCTZ-CR: 55% vs. conventional HCTZ: 55.56%; $p = 0.847$). Tighter BP control (BP: <130/80 mm Hg) was attained by 25.0% of patients from the chlorthalidone group, 11.11% from the conventional HCTZ group, and 15% from the HCTZ-CR group. For all 3 treatments, significantly

lower office SBP was observed at week 4 and maintained through week 12 (Figure 5).

CHANGE IN AMBULATORY DAYTIME BP. At week 12, patients from all 3 treatment groups showed a significant reduction from baseline in ambulatory daytime SBP (Table 4), whereas only patients from the chlorthalidone and HCTZ-CR groups showed a significant reduction in ambulatory daytime DBP. The reduction in mean ambulatory daytime SBP and DBP values was not significantly different among treatment groups. At week 12, the mean ambulatory daytime SBP was significantly lower for patients treated with chlorthalidone than for those treated with conventional HCTZ ($p = 0.018$).

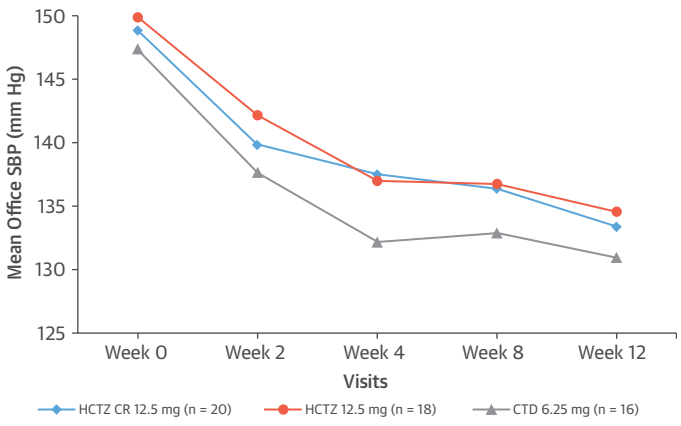
CHANGE IN AMBULATORY NIGHTTIME BP. At week 12, patients from the chlorthalidone and HCTZ-CR groups showed a significant reduction from baseline in ambulatory nighttime SBP (chlorthalidone: $p = 0.002$; HCTZ-CR: $p < 0.001$) and DBP (chlorthalidone: $p = 0.001$; HCTZ-CR: $p = 0.001$) (Table 5). However, this change was not significant in patients treated with conventional HCTZ. At weeks 4 ($p = 0.015$) and 12 ($p = 0.020$), ambulatory nighttime SBP was significantly lower in patients treated with chlorthalidone than in those treated with HCTZ.

SAFETY. All treatments were generally safe and well tolerated. During the washout period, 2 patients reported 3 adverse events; and during the treatment period, 26 patients reported a total of 48 adverse events (Table 6). All adverse events reported during the washout period were of mild intensity, and in the investigator's opinion, most were unlikely related to study drug. A total of 4 patients (2 from the HCTZ-CR group, 1 from the conventional HCTZ group, and 1 from the chlorthalidone group) experienced borderline hypokalemia (defined as <3.5 mmol/l). No patient experienced hyponatremia. One patient from the HCTZ-CR group was found to have increased blood glucose levels. Nine patients (3 from the HCTZ-CR group, 4 from the conventional HCTZ group, and 2 from the chlorthalidone group) showed increased uric acid levels. At the end of the study, no significant changes were observed in total cholesterol, triglycerides, or LDL-cholesterol levels.

DISCUSSION

Previous studies have evaluated the antihypertensive efficacy of chlorthalidone, 6.25 mg, on office BP, as monotherapy (12), as well as in combination with losartan (13) and metoprolol (14). However, no previous studies had evaluated and compared the 24-h BP-lowering efficacy of chlorthalidone at a dose of 6.25 mg.

FIGURE 5 Visit-to-Visit Mean Office SBP



Abbreviations as in Figures 2 and 3.

OFFICE BP VERSUS 24-H ABP. The principal findings of the present study are that the most commonly prescribed antihypertensive drug, namely HCTZ, at the dose of 12.5 mg daily failed to significantly lower 24-h ABP after 12 weeks of monotherapy (Central Illustration). In contrast, chlorthalidone in the very low daily dose of 6.25 mg lowered 24-h ABP by 11.1/7.8 mm Hg (Central Illustration). Thus, whenever the antihypertensive efficacy of HCTZ is assessed by office BP measurement, it seems comparable to that of chlorthalidone and other drug classes. This

TABLE 4 Changes in Ambulatory Daytime Mean SBP and DBP

Outcome	Hydrochlorothiazide-CR (n = 20)	Hydrochlorothiazide (n = 18)	Chlorthalidone (n = 16)
Ambulatory SBP			
Change at week 4*	−9.15 ± 13.70	−3.55 ± 10.64	−6.74 ± 9.62
p value†	0.014	0.191	0.005
Change at week 12*	−7.88 ± 13.45	−7.16 ± 11.75	−12.11 ± 12.29
p value†	0.034	0.017	0.001
Ambulatory DBP			
Change at week 4*	−6.73 ± 9.94	−2.71 ± 9.22	−5.73 ± 8.43
p value†	0.012	0.217	0.013
Change at week 12*	−6.32 ± 10.08	−4.73 ± 8.89	−8.74 ± 10.45
p value†	0.014	0.058	0.002

Values are mean ± SD. *Kruskal-Wallis test used with Dunn's test for multiple comparisons; all change values were calculated from baseline values. †Comparison with baseline and Wilcoxon signed rank tests were used for comparison. Mean 24-h SBP was significantly lower for the chlorthalidone group than for the hydrochlorothiazide group at week 12 (127.57 mm Hg vs. 141.90 mm Hg, respectively, p value = 0.018). This analysis was performed in an intent-to-treat population that included all patients randomized in the study.

Abbreviations as in Table 1.

TABLE 5 Changes in Ambulatory Nighttime Mean SBP and DBP

Outcome	Hydrochlorothiazide-CR (n = 20)	Hydrochlorothiazide (n = 18)	Chlorthalidone (n = 16)
Ambulatory SBP			
Change at week 4*	−12.94 ± 13.25‡	−2.35 ± 11.58	−8.24 ± 12.14
p value†	<0.001	0.326	0.001
Change at week 12*	−12.66 ± 12.63	−4.87 ± 14.12	−10.17 ± 13.59
p value†	<0.001	0.268	0.002
Ambulatory DBP			
Change at week 4*	−8.73 ± 10.72	−2.96 ± 8.88	−5.92 ± 8.73
p value†	0.001	0.173	0.002
Change at week 12*	−10.10 ± 11.03	−3.62 ± 9.34	−6.82 ± 9.62
p value†	0.001	0.135	0.001

Values are mean ± SD. *Kruskal-Wallis test was used with Dunn's test for multiple comparisons; all change values were calculated from baseline values. †Comparison with baseline, and Wilcoxon signed rank test was used for comparison. ‡p = 0.034 vs. hydrochlorothiazide group. Mean 24-h SBP was significantly lower for the chlorthalidone group than for the hydrochlorothiazide group at week 4 (118.10 vs. 133.90 mm Hg, respectively, p value = 0.015) and week 12 (116.17 vs. 131.38 mm Hg, respectively, p value = 0.020). This analysis was performed in an intent-to-treat population that included all patients randomized in the study.

Abbreviations as in Table 1.

discrepancy between ABPM and office BP indicates that HCTZ lowers BP appropriately during daytime, when patients are seen in the physician's office but has little if any effect during the night and early morning hours.

The consistent overestimation of the antihypertensive response to HCTZ by office BP measurements has been shown in 3 previous studies. In the patient population in the study by Finkielman et al. (15), the difference between office BP and 24-h ABP was 4.8/2.1 mm Hg ($p < 0.01$) in 228 subjects treated with HCTZ, 25 mg daily. This difference is very similar to that found in our previous analysis (4.9/2.5 mm Hg) in more than 16,000 patients (16). In the present study, HCTZ lowered office BP by 9.3/4.0 mm Hg more than that of 24-h ABPM. In the study by Ernst et al. (8), the reduction in SBP during nighttime hours was −13.5 ± 1.9 mm Hg for chlorthalidone versus −6.4 ± 1.7 mm Hg for HCTZ ($p > 0.01$). Thus, 4 independent

TABLE 6 Adverse Events Reported During Treatment

Adverse Event	Hydrochlorothiazide-CR (n = 20)	Hydrochlorothiazide (n = 18)	Chlorthalidone (n = 16)	Total (N = 54)
Clinical adverse events				
Abdominal pain	-	1	1	2
Abdominal pain, upper	1	-	-	1
Arthralgia	1	-	-	1
Asthenia	-	1	-	1
Back pain	-	1	1	2
Constipation	1	-	-	1
Diarrhea	-	1	-	1
Dyspnea	-	-	1	1
Dyspnea, paroxysmal nocturnal	-	-	1	1
Dysuria	-	-	1	1
Ear pain	1	-	-	1
Fatigue	-	1	-	1
Gastritis	1	-	-	1
Headache	5	1	1	7
Insomnia	1	-	-	1
Nausea	2	-	-	2
Esophageal pain	1	-	-	1
Paresthesia	1	-	-	1
Restlessness	1	-	-	1
Tooth abscess	-	-	1	1
Toothache	-	-	1	1
Vomiting	1	-	-	1
Laboratory adverse events				
Serum potassium decreased	2	1	1	4
Blood glucose increased	1	-	-	1
Blood uric acid increased	3	4	2	9
Pyuria	1	-	-	1
Urinary tract infection	2	-	-	2
Total	26	11	11	48
Number of patients*	12 (60.00)	8 (44.44)	6 (37.50)	26 (48.15)

*Values are n or n (%). p = 0.686 using the chi-square test.

CR = controlled release.

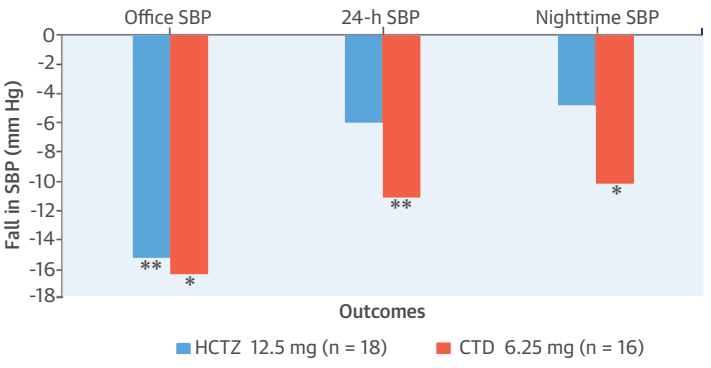
studies have now documented the fact that assessing the antihypertensive efficacy of HCTZ by office BP measurements only is deceptive and prone to lull physicians and patients into a false sense of security. With HCTZ therapy, sustained hypertension merely will be converted into masked hypertension. BP seems to be well controlled during daytime, when patients are seen in the office. However, as shown in **Figure 2**, late night-to-early morning BP remains poorly controlled by HCTZ. Importantly, this time period has been identified as the most critical in the diurnal cycle because it coincides with the highest risk of stroke and other cardiovascular events (17–19).

Over the past decades, JNC reports have increasingly recommended low-dose thiazide diuretic agents as initial therapy in hypertensive patients. For most physicians, a "thiazide" is synonymous with HCTZ (3). The National Heart, Lung, and Blood Institute has continued to deceptively promote low-dose thiazides on the basis of chlorthalidone data, although tacitly aware that such promotion will only motivate physicians to treat more and more patients with HCTZ (20). The calamity of millions of patients being exposed to an inefficacious drug could have been avoided if the advice of Maggie and Freis had been heeded, approximately 3 decades ago (1). Many of us still consider Dr. Freis to be the father of HCTZ.

In contrast to conventional HCTZ, chlorthalidone (and HCTZ-CR) provides smooth BP control throughout the diurnal cycle. Chlorthalidone possesses a distinct pharmacokinetic profile, and its longer and smoother duration of action may be due to its wider volume of distribution, with partitioning into red blood cells (21,22). The resulting sustained antihypertensive effects, particularly throughout the night and in the early morning hours, may be the reason for chlorthalidone's well-documented benefits for reduced cardiovascular morbidity and mortality (23–25). Thus, it is not surprising that when higher-dose-outcome data were compared, chlorthalidone proved superior to HCTZ (26,27). No outcome data are available for HCTZ in doses of 12.5 to 25 mg/day (4,5). Although our study did not evaluate the antihypertensive efficacy of indapamide, low-dose indapamide has been found effective in treatment of patients with hypertension alone and in those with comorbidities, such as renal insufficiency or diabetes (28,29).

With chronic kidney disease, thiazide diuretics have been shown to be efficacious in patients with a glomerular filtration rate of approximately 40 to 50 ml/min. Importantly, in a recent pilot study, Agarwal et al. (30) documented the fact that chlorthalidone improved BP control, even in patients with moderately advanced chronic kidney disease, as defined by glomerular filtration rates between 20 and 45 ml/min/1.73 m^2 (30).

CENTRAL ILLUSTRATION Low-Dose Thiazides in Hypertension: 24-h and Nighttime Ambulatory BP After 12 Weeks of Therapy



Pareek, A.K. et al. J Am Coll Cardiol. 2016; 67(4):379–89.

A significant decrease of both 24-h and nighttime ambulatory BP with chlorthalidone, 6.25 mg/day, was observed. There was no significant decrease with HCTZ, 12.5 mg/day. **p < 0.001; *p < 0.01; Wilcoxon signed rank tests were used for comparison. CTD = chlorthalidone; HCTZ = hydrochlorothiazide; SBP = systolic blood pressure.

SAFETY OF LOW-DOSE DIURETICS. Almost all adverse effects of thiazide and thiazide-like diuretics are dose-dependent (31,32). It is therefore not surprising that, in the present study with low doses, few if any adverse effects were seen. In an earlier 8-week study by Ernst et al. (8), the incidence of hypokalemia (potassium <3.5 mmol/l) was 50% with HCTZ, 25 mg, and 46% with chlorthalidone, 12.5 mg. In our study, the incidence was merely 10% (2 of 20 patients) with HCTZ-CR, 12.5 mg; 5.6% (1 of 18 patients) with conventional HCTZ 12.5 mg; and 6.3% (1 of 16 patients) with chlorthalidone, 6.25 mg.

STUDY LIMITATIONS. This is a relatively small study with a limited number of patients. Although the decrease in ambulatory blood pressure differs among the 3 drugs, no conclusion regarding outcome should be drawn from these data. Outcome data have been put forward in randomized controlled trials for chlorthalidone (and indapamide) but not for low-dose hydrochlorothiazide.

CONCLUSIONS

The present data show that because of its short duration of action, HCTZ, one of the most widely prescribed antihypertensive drugs, failed to lower 24-h ABP in its most common dose of 12.5 mg, thereby

converting sustained hypertension into masked hypertension. In contrast, chlorthalidone, in the very low dose of 6.25 mg daily, provided smooth BP control throughout the diurnal cycle. Thus, low-dose chlorthalidone, 6.25 mg, can be used as monotherapy, whereas low-dose HCTZ should no longer be considered an acceptable option for treatment of essential hypertension.

ACKNOWLEDGMENTS The authors thank Ipca Laboratories Ltd. employees Ravikiran Payghan and Amruta Bhor for their support in execution; Kumar Naidu, Uma Sargar, and Tushar Nikumbh for statistical analysis and data management; and Tushar Jadhao for managing clinical trial supplies. The authors also thank Drs. Suman Rathod, Aparna More, and Swapnali Kadam, co-investigators at Rajiv Gandhi Medical College and Chhatrapati Shivaji Maharaj Hospital, Thane, India.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Franz H. Messerli, Division of Cardiology, Mount Sinai Health Medical Center, Icahn School of Medicine, 1 Gustave L. Levy Pl, New York, New York 10029. E-mail: messerli.f@gmail.com.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Treatment with low-dose chlorthalidone, 6.25 mg daily, is more effective than hydrochlorothiazide, 12.5 mg daily, in reducing daytime, nighttime, and mean 24-h ambulatory blood pressure over 4 to 12 weeks and can be prescribed as initial therapy for treatment of hypertension, whereas low-dose HCTZ should no longer be used.

TRANSLATIONAL OUTLOOK: The mere fact that hydrochlorothiazide has been available for over one-half a century and was prescribed to millions of patients is not an acceptable document of its efficacy. Large, longer-term studies are needed to compare the efficacy and safety of low-dose chlorthalidone to that of other thiazide diuretic agents.

REFERENCES

1. Magee PF, Freis ED. Is low-dose hydrochlorothiazide effective? Hypertension 1986;8:II135–9.

2. IMS Health. National Prescription Audit Plus, Year 2008.

3. Kurtz TW. Chlorthalidone: don't call it "thiazide-like" anymore. Hypertension 2010;56:335–7.

4. Messerli FH, Bangalore S. Half a century of hydrochlorothiazide: facts, fads, fiction, and follies. Am J Med 2011;124:896–9.

5. Argulian E, Grossman E, Messerli FH. Misconceptions and facts about treating hypertension. Am J Med 2015;128:450–5.

6. Roush GC, Buddharaju V, Ernst ME, et al. Chlorthalidone: mechanisms of action and effect on cardiovascular events. Curr Hypertens Rep 2013;15:514–21.

7. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. Hypertension 2004;43:4–9.

8. Ernst ME, Carter BL, Goerdt CJ, et al. Comparative anti-hypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension 2006;47:352–8.

9. Mancia G, Fagard R, Narkiewicz K, et al., for the Task Force Members. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertension 2013;31:1281–357.

10. Hermida RC, Smolensky MH, Ayala DE, et al. [2013 Ambulatory blood pressure monitoring recommendations for the diagnosis of adult hypertension, assessment of cardiovascular and other hypertension-associated risk, and attainment of therapeutic goals (summary). Joint recommendations from the International Society for Chronobiology (ISC), American Association of Medical Chronobiology and Chronotherapeutics (AAMCC), Spanish Society of Applied Chronobiology, Chronotherapy, and Vascular Risk (SECAC), Spanish Society of Atherosclerosis (SEA), and Romanian Society of Internal Medicine (RSIM)] [article in Spanish]. Clin Investig Arterioscler 2013;25:74–82.

11. Dasgupta K, Quinn RR, Zarnke KB, et al. Canadian Hypertension Education Program. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2014;30:485–501.

12. Pareek A, Karnik N, Salagre SB, et al. Clinical effectiveness of low-dose chlorthalidone (6.25 mg) + atenolol combination in stage I hypertensive patients: a multicenter, randomized, controlled study. Curr Med Res Opin 2008;24:1771–9.

13. Pareek A, Basavanagowdappa H, Zawar S, et al. A randomized, comparative study evaluating the efficacy and tolerability of losartan-low dose chlorthalidone (6.25 mg) combination with losartan-hydrochlorothiazide (12.5 mg) combination in Indian patients with mild-to-moderate essential hypertension. Expert Opin Pharmacother 2009;10:1529–36.

14. Pareek A, Zawar SD, Salagre SB, et al. Antihypertensive efficacy of metoprolol XL/low dose chlorthalidone (6.25 mg) combination: a randomized, comparative study in Indian patients with mild-to-moderate essential hypertension. Eur J Med Res 2009;14:297–303.

15. Finkielman JD, Schwartz GL, Chapman AB, et al. Lack of agreement between office and ambulatory blood pressure responses to hydrochlorothiazide. Am J Hypertens 2005;18:398–402.

16. Messerli F, Makani H, Benjo A, et al. Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory blood pressure monitoring: a meta-analysis of randomized trials. J Am Coll Cardiol 2011;57:590–600.

17. Kario K, Pickering TG, Umeda Y, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation 2003;107:1401–6.

18. Sheppard JP, Hodgkinson J, Riley R, et al. Prognostic significance of the morning blood pressure surge in clinical practice: a systematic review. Am J Hypertens 2015;28:30–41.

19. Kario K, Saito I, Kushiro T, et al. LB01.02: morning home blood pressure is a strong predictor of coronary artery disease events as well as stroke events in hypertensive patients on antihypertensive treatment. The HONEST study. J Hypertens 2015;33 Suppl 1:e45 (abstr).

20. Stafford RS, Bartholomew LK, Cushman WC, et al., for the ALLHAT Collaborative Research Group. Impact of the ALLHAT/JNC7 dissemination project on thiazide-type diuretic use. Arch Intern Med 2010;170:851–8.

21. Sica DA. Chlorthalidone: has it always been the best thiazide-type diuretic? Hypertension 2006;47:321–2.

22. Sica DA. Chlorthalidone—a renaissance in use? Expert Opin Pharmacother 2009;10:2037–9.

23. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA 1991;265:3255–64.

24. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981–97.

25. National Heart, Lung and Blood Institute, NIH. Systolic Blood Pressure Intervention Trial (SPRINT) Overview. 2015. Available at: http://www.nhlbi.nih.gov/news/spotlight/fact-sheet/systolic-blood-pressure-intervention-trial-sprint-overview. Accessed November 17, 2015.

26. Dorsch MP, Gillespie BW, Erickson SR, et al. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. Hypertension 2011;57:689–94.

27. Mortality after 10 1/2 years for hypertensive participants in the Multiple Risk Factor Intervention Trial. Circulation 1990;82:1616–28.

28. Madkour H, Gadallah M, Riveline B, et al. Indapamide is superior to thiazide in the preservation of renal function in patients with renal insufficiency and systemic hypertension. Am J Cardiol 1996;77:23B–5B.

29. Madkour H, Ali K, Nosrati S, et al. Efficacious response with low-dose indapamide therapy in the treatment of type II diabetic patients with normal renal function or moderate renal insufficiency and moderate hypertension. Am J Nephrol 2002;22:2–5.

30. Agarwal R, Sinha AD, Pappas MK, et al. Chlorthalidone for poorly controlled hypertension in chronic kidney disease: an interventional pilot study. Am J Nephrol 2014;39:171–82.

31. 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;101:83S–92S.

32. Roush GC, Ernst ME, Kostis JB, et al. Head-to-head comparisons of hydrochlorothiazide with indapamide and chlorthalidone: antihypertensive and metabolic effects. Hypertension 2015;65:1041–6.

KEY WORDS hypertension, low-dose diuretic agent, thiazide