Original Paper

Effects of the Angiotensin II Receptor Blockers Telmisartan vs Valsartan in Combination With Hydrochlorothiazide 25 mg Once Daily for the Treatment of Hypertension

William B. White, MD;[1] Henry A. Punzi, MD;[2] Debra Murwin, BS;[3] Stephen E. Koval, MS;[3] Giora Davidai, MD;[3] Joel M. Neutel, MD[4]

To attain recent goals of blood pressure (BP) control, multiple drug therapy combinations are required, including higher doses of thiazide diuretics in combination with other classes of antihypertensive drug therapy. Thus, the authors evaluated the antihypertensive effects of telmisartan vs valsartan when combined with hydrochlorothiazide (HCTZ) 25 mg in a large (N=1066), placebo-controlled trial in patients with stage 1 or 2 hypertension. The primary end points were the changes from baseline in seated diastolic and systolic BP at the end of the 8-week treatment period. Safety end points included adverse events, changes in laboratory parameters, and pulse rate. Changes from baseline in BP following telmisartan-HCTZ (–24.0/–17.6 mm Hg) were significantly greater than both placebo (–4.4/–6.8 mm Hg) and valsartan-HCTZ (–21.2/–16.1 mm Hg) (vs placebo, P<.001 for systolic and diastolic BP; vs valsartan-HCTZ, P=.004 for systolic BP and P=.019 for diastolic BP). The total number of patients with at least 1 adverse event reported were similar among the 3 treatment groups (placebo, 49%; telmisartan-HCTZ, 43%; and valsartan-HCTZ, 38%). In conclusion, telmisartan-HCTZ at doses of 80/25 mg lowered both systolic and diastolic BP to a greater extent than valsartan-HCTZ at doses of 160/25 mg. These data support using a higher dose of a thiazide diuretic (25 mg) with a long-acting angiotensin receptor blocker as a useful strategy for improving hypertension control. (J Clin Hypertens. 2006;8:626–633) ©2006 Le Jacq

From the Division of Hypertension and Clinical Pharmacology, Pat and Jim Calhoun Cardiology Center, University of Connecticut School of Medicine, Farmington, CT;[1] Trinity Hypertension Research Institute and Texas Women's University, Dallas, TX;[2] Medical Department and Biostatistics, Boehringer-Ingelheim Pharmaceuticals, Inc., Ridgefield, CT;[3] and Orange Research Center and University of California, Irvine, Irvine, CA[4]
Address for correspondence:
William B. White, MD, Professor of Medicine and Chief, Section of Hypertension and Clinical Pharmacology, Pat and Jim Calhoun Cardiology Center, University of Connecticut School of Medicine, 263 Farmington Avenue, Farmington, CT 06030-3940
E-mail: wwhite@nso1.uchc.edu
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There is substantial evidence that tight control of blood pressure (BP) in patients with hypertension is required to produce the maximum reduction in clinical cardiovascular end points,[1,2] and published hypertension guidelines now advocate a target BP below 140/90 mm Hg in patients with uncomplicated hypertension and below 130/80 mm Hg in patients with complicated hypertension who have any form of cardiovascular or kidney disease.[3,4] While several drug classes effectively treat hypertension, there has been a growing trend toward the use of angiotensin receptor blockers (ARBs), alone or in fixed combination with

Table I. Characteristics of the Study Patients at Baseline

Parameter	Telmisartan-HCTZ	Valsartan-HCTZ	Placebo
Number	485	498	126
Men/women	270/215 (56/44)	305/193 (61/39)	69/57 (55/45)
Age, y	54±11	53±10	53±11
Race			
White	352 (72)	368 (74)	90 (72)
Black	120 (25)	122 (24)	33 (26)
Asian	13 (3)	8 (2)	3 (2)
Body mass index, kg/m^2	32±7	31±6	32±6
Systolic BP, mm Hg	155±12	154±12	155±13
Diastolic BP, mm Hg	102±4	102±4	102±4
Pulse rate, bpm	75±9	75±10	75±10

Data are presented as n (%) or mean ± SD. HCTZ indicates hydrochlorothiazide; BP, blood pressure.

low-dose (12.5 mg) hydrochlorothiazide (HCTZ). ARBs have demonstrated increased utility for treating hypertension because these agents are not only effective in reducing BP, but demonstrate tolerability profiles that are similar to placebo in clinical trials.[5,6] More importantly, clinical outcome studies have demonstrated that ARBs reduce cardiovascular and cerebrovascular events, reduce the proportion of hypertensive patients who develop type 2 diabetes mellitus, and prolong survival in such conditions as high-risk hypertension,[7,8] heart failure,[9] and diabetic nephropathy.[10,11]

Since the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[12] and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), trends in hypertension management have been to use higher doses of thiazide diuretics in combination with other antihypertensive drugs to improve BP control.[13] Accordingly, it is relevant to study fixed-dose combinations of ARBs with 25 mg of HCTZ to determine the benefits and side effects of these increasingly used therapies. To that end, we performed a large comparative clinical trial evaluating 2 fixed-dose combination therapies: telmisartan 80 mg plus HCTZ 25 mg (telmisartan-HCTZ 80/25) and valsartan 160 mg plus HCTZ 25 mg (valsartan-HCTZ 160/25) in patients with stage 1 or 2 hypertension.

METHODS

Study Design

This trial was a multicenter, double-blind, double-dummy, randomized, parallel group study that compared the efficacy and safety of telmisartan-HCTZ 80/25 vs valsartan-HCTZ 160/25 and telmisartan-HCTZ 80/25 vs placebo. The study was conducted at 105 clinical sites in the United States. The purpose of the study was to determine whether telmisartan-HCTZ 80/25 mg administered once daily was superior to placebo once daily and noninferior and possibly superior to valsartan-HCTZ 160/25 once daily for the control of seated clinic BP following 8 weeks of treatment.

Following a 3–4 week run-in period that included a 1-week washout period for patients who were currently receiving antihypertensive therapy, followed by a 2–3 week single-blind placebo period to establish baseline BP values, eligible patients were randomized to double-blind treatment of telmisartan 80 mg, valsartan 160 mg, or placebo in a ratio of 4:4:1, respectively. After 2 weeks, patients were brought back to the clinic for up-titration to telmisartan-HCTZ 80/25, valsartan-HCTZ 160/25, or placebo, depending on their initial randomized treatment arm. Starting at the up-titration visit and at 2-week intervals thereafter for a total of an additional 6 weeks, study patients were examined in the clinic between 7 AM and 10 AM for clinical evaluation (typically 23–26 hours postdose). At every visit, adverse events were assessed by nonleading questions.

Patient Population

Men and women with systemic hypertension were included in the study if their average seated diastolic BP (DBP) was ≥95 mm Hg at the end of the single-blind placebo treatment period. Patients with stroke or myocardial infarction within the past 6 months, congestive heart failure, known or suspected secondary hypertension, poorly controlled diabetes mellitus, and chronic kidney failure were excluded from the study.

Measurements of Efficacy and Safety Parameters

The office BP was measured by mercury column or aneroid manometry in the seated position at

Table II. Seated Clinic Trough Blood Pressures (BPs) and Changes From Baseline by Treatment Group

BP Measurements, mm Hg	Telmisartan-HCTZ 80/25 mg (n=467)	Valsartan-HCTZ 160/25 mg (n=479)	Placebo (n=120)
Systolic			
Observed, mean (SD)			
Baseline	154.6 (11.5)	154.3 (11.9)	154.6 (13.1)
Final	130.5 (16.0)	133.2 (15.6)	150.1 (16.0)
Change from baseline	–24.0 (14.7)	–21.2 (15.4)	–4.4 (13.8)
Adjusted* change from baseline, mean (SE)	–23.6 (0.70)	–20.9 (0.70)	–3.9 (1.3)
Comparison to telmisartan-HCTZ, difference (95% CI)		–2.8 (–4.6 to –1.0)†	–19.6 (–22.4 to –16.8)‡
Diastolic			
Observed, mean (SD)			
Baseline	101.8 (4.0)	101.9 (4.3)	101.9 (3.9)
Final	84.2 (9.7)	85.8 (9.6)	95.1 (10.2)
Change from baseline	–17.6 (8.9)	–16.1 (9.0)	–6.8 (9.3)
Adjusted* change from baseline, mean (SE)	–17.5 (0.4)	–16.1 (0.4)	–6.7 (0.8)
Comparison to telmisartan-HCTZ, difference (95% CI)		–1.8 (–3.0 to –0.6)§	–10.8 (–12.5 to –9.0)†

HCTZ indicates hydrochlorothiazide; SE, standard error; and CI, confidence interval. *Adjusted for gender and race with both baseline response and age as covariates. †P=.0039; ‡P<.0001; §P=.0190.

all visits. The pulse rate was measured in conjunction with the BP measurements at each visit. Study coordinators recorded times of medication dosing and BP measurements in the case report forms. Safety by the evaluation of adverse events and vital signs at each visit of the study and changes from baseline to the end of the study in laboratory parameters were assessed. All reported adverse events were categorized by body system and preferred term using the *Medical Dictionary for Regulatory Activities* (*MedDRA*).[14] The incidence of treatment-emergent adverse effects in each treatment group was tabulated by severity and relationship to study drug (as ascertained by the site study personnel). Treatment compliance was assessed by a physical count of returned study medications.

Statistical Analyses

The primary end points for assessing efficacy were the changes from baseline to the end-of-study visit in clinic DBP and systolic BP (SBP) measured 23–26 hours after dosing of the study medication. In the case of patients who withdrew from the study before the completion of the 8-week treatment period, last-observation-carried-forward principles were utilized.

To control the experiment-wise error rate (α=.05), testing of multiple treatment comparisons (i.e., telmisartan-HCTZ 80/25 vs placebo and telmisartan-HCTZ 80/25 vs valsartan-HCTZ 160/25) for both primary end points, a hierarchic closed testing procedure was used. All secondary analyses performed on the primary end points and all testing on secondary end points were performed at a 2-sided α=.05. All statistical testing was primarily performed on the full analysis set involving all patients randomized to the study who had at least 1 set of BP measurements following titration to combination therapy.

The primary objective of the study was to show that telmisartan-HCTZ was not inferior to valsartan-HCTZ. Assuming an SD of 9 mm Hg and a noninferiority margin of 2 mm Hg for DBP, a sample size of 400 patients per treatment group would have 88% power to demonstrate at the 5% (2-sided) level of significance that telmisartan-HCTZ is not inferior to valsartan-HCTZ if both combination treatments are equal. Assuming a 7.5% rate of premature discontinuation from the study and a screen failure rate of 30%, approximately 1320 patients were needed to enroll 920 randomized patients. For a superiority comparison with placebo for the active therapies, >99% power to detect a 5-mm Hg difference in the change from baseline in DBP required 70 placebo patients. To be able to assess any center effects, the study was designed to randomize 1 patient per each of the 115 centers. Therefore, a total of 1480 patients was required for enrollment to attain approximately 1035 randomized patients.

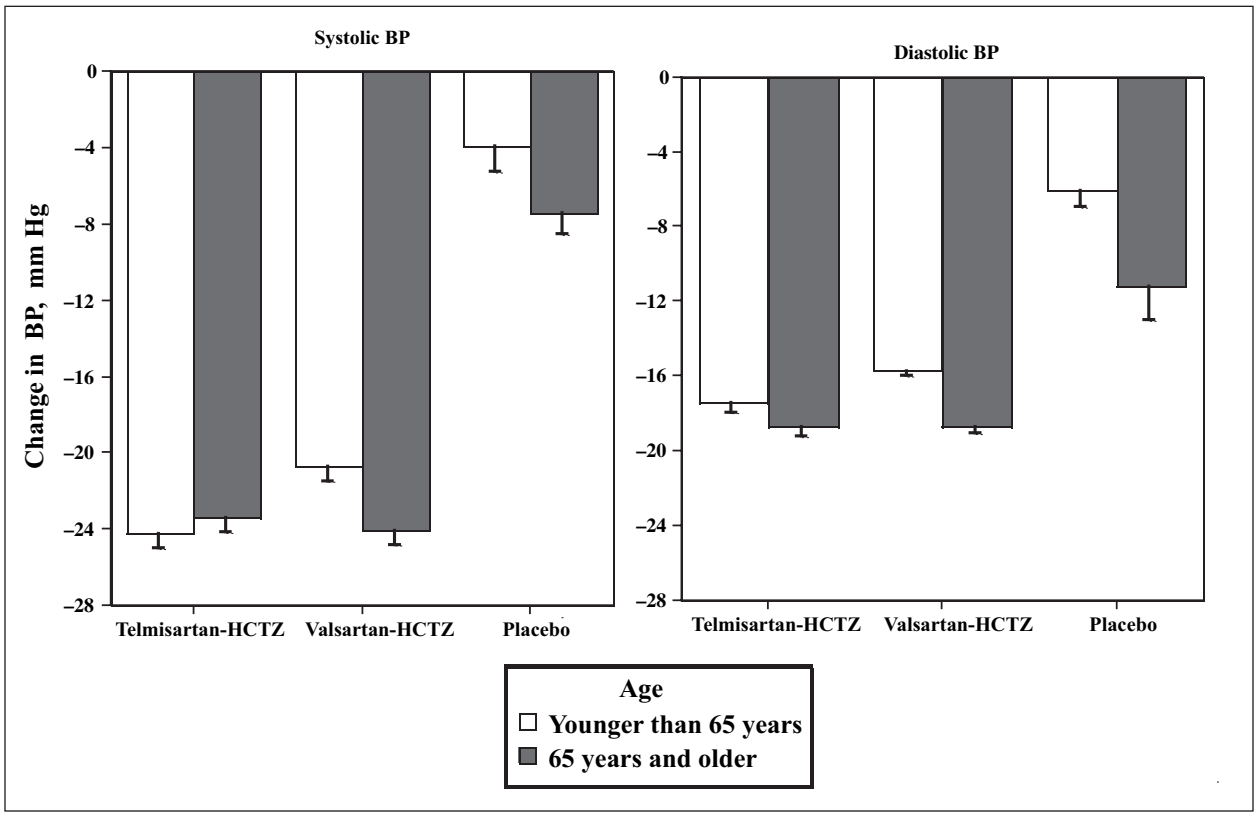

Figure 1. Impact of age group (younger than 65 years vs 65 years and older) on changes from baseline in systolic and diastolic blood pressure (BP) for each of the treatment groups. HCTZ indicates hydrochlorothiazide.

The comparability of patients in the 3 treatment groups was determined from the demographic data and baseline BP values. The primary end points as well as all secondary continuous variables were analyzed using an analysis of covariance model involving treatment groups with baseline values as a covariate. Further adjustments were made for age, gender, and race for comparative effects of the 3 treatments. Treatment group comparisons were based on the least square means obtained via the SAS general linear model procedure (SAS Institute, Inc, Cary, NC; version 8 Open Virtual Memory System [VMS] operating system, Hewlett-Packard, Palo Alto, CA). In addition, effects of age, gender, and race on the primary end points were evaluated in subgroup analyses.

RESULTS

Patient Enrollment and Disposition

A total of 1825 patients were screened for the study, of whom 1109 patients who met the inclusion criteria were randomized to the following treatment arms: 485 patients to telmisartan-HCTZ, 498 patients to valsartan-HCTZ, and 126 to placebo. A total of 1006 of the 1109 randomized patients completed the study as planned (444 [92%] in the telmisartan-HCTZ arm, 461 [93%] in the valsartan-HCTZ arm, and 101[80%] in the placebo arm). The most common reasons for discontinuing the study early were adverse events (57 patients [5.1%]) and withdrawal of consent (17 patients [1.5%]).

Baseline Characteristics of the Study Population

The baseline characteristics of all randomized patients in the 3 treatment arms are shown in Table I. For the entire patient population, the mean age was 53.5 years, with a greater percentage of men (58%), predominantly nonblack (75%), and with a mean baseline BP of 155/102 mm Hg. There was a slightly lower proportion of women in the valsartan-HCTZ arm compared with the other 2 treatment arms. No other differences in baseline characteristics among the 3 treatment arms were noted.

Changes in the Clinic Trough BPs

The effects in the 3 treatment groups on trough clinic BPs are shown in Table II. Compared with placebo, both combination therapies lowered seated BP substantially. For patients treated with telmisartan-HCTZ 80/25, the reductions in trough clinic BPs (–24.0/–17.6 mm Hg) were significantly

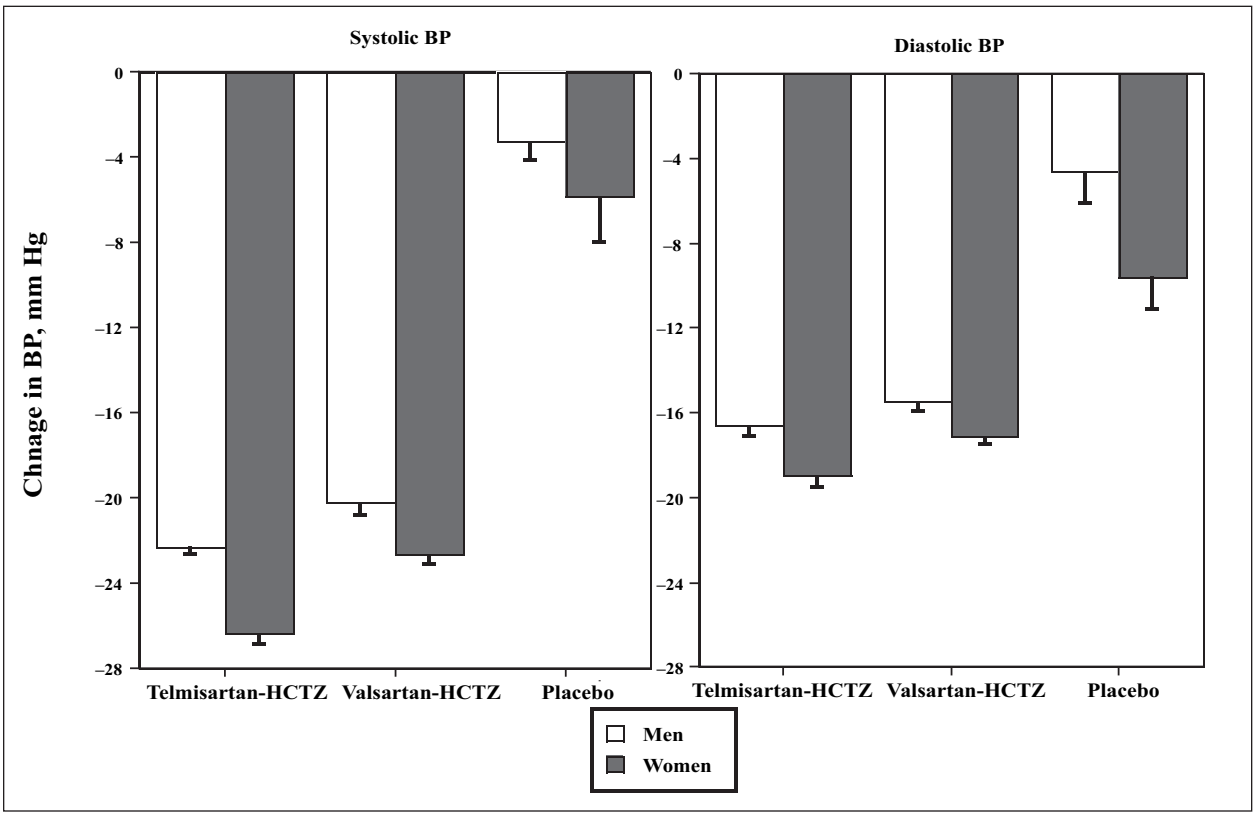

Figure 2. Impact of gender on changes from baseline in systolic and diastolic blood pressure (BP) for each of the treatment groups. HCTZ indicates hydrochlorothiazide.

greater (P<.0001 for both SBP and DBP) than those for patients treated with placebo (–4.4/–6.8 mm Hg). Compared with patients treated with valsartan-HCTZ 160/25 (reductions of –21.2/–16.1 mm Hg), telmisartan-HCTZ 80/25 was found to have significantly greater reductions in both DBP (adjusted mean difference of –1.8 mm Hg; P=.0190) and SBP (adjusted mean difference of –2.8 mm Hg; P=.0039).

The Impact of Age, Gender, and Race on BP

Age. The impact of age group (younger than 65 vs 65 years and older) on reductions in BP for the 3 treatment groups is shown in Figure 1. There was no significant treatment-by-age-group interaction for either DBP (P=.27) or SBP (P=.10). For DBP, there was a significant difference (P=.001) found between the overall adjusted mean changes for patients younger than 65 (–13.1 mm Hg) vs 65 and older (–16.2 mm Hg). However, the overall greater reduction in DBP in the older subgroup might be overestimated, as a result of a relatively large placebo effect (–11.1 mm Hg) in a relatively small number of patients (n=18). As shown in Figure 1, there were significant differences in the individual treatment groups according to age.

Gender. The impact of gender on reductions in BP for the 3 treatment groups is shown in Figure 2. No significant treatment-by-gender interaction was found for either DBP (P=.14) or SBP (P=.46). When comparing the overall effects due to gender, there were significant differences between men and women in the changes from baseline in both DBP and SBP (P<.001 for both). The adjusted mean changes from baseline for women (–18.2/–15.3 mm Hg) were significantly greater than the changes from baseline for men (–15.3/–12.2 mm Hg). These trends occurred similarly for all 3 treatment groups (Figure 2).

Race. The impact of racial group (nonblack vs black) on reductions in BP for the 3 treatment groups is shown in Figure 3. No significant treatment-by-race interaction was found for either DBP (P=.79) or SBP (P=.12). Additionally, there were no significant overall differences found between the adjusted mean changes in DBP for nonblack and black patients (–13.7 vs –13.0 mm Hg, respectively). For SBP, there was a small, but statistically significant (P=.04) difference between the overall adjusted mean change from baseline for nonblack patients (–16.7 mm Hg) and black patients (–15.9 mm Hg). As shown in Figure 3, changes from baseline in BP

Table III. Adverse Events With an Incidence ≥2% in Any Treatment Arm

	Telmisartan-HCTZ 80/25 mg (n=485)		Valsartan-HCTZ 160/25 mg (n=498)		Placebo (n=126)	
Adverse Event*	n	%	n	%	n	%
Diarrhea	9	1.9	12	2.4	5	4.0
Dry mouth	3	0.6	3	0.6	4	3.2
Nausea	11	2.3	9	1.8	1	0.8
Fatigue	10	2.1	7	1.4	3	2.4
Peripheral edema	4	0.8	2	0.4	4	3.2
Sinusitis	5	1.0	17	3.4	3	2.4
Upper respiratory infection	9	1.9	13	2.6	6	4.8
Back pain	14	2.9	8	1.6	1	0.8
Muscle spasm	2	0.4	3	0.6	3	2.4
Dizziness	22	4.5	13	2.6	4	3.2
Headache	18	3.7	31	6.2	15	11.9
Cough	5	1.0	9	1.8	3	2.4
Increased blood pressure	2	0.4	3	0.6	4	3.2

HCTZ indicates hydrochlorothiazide. **Medical Dictionary for Regulatory Activities* (*MedDRA*)[14] preferred term.

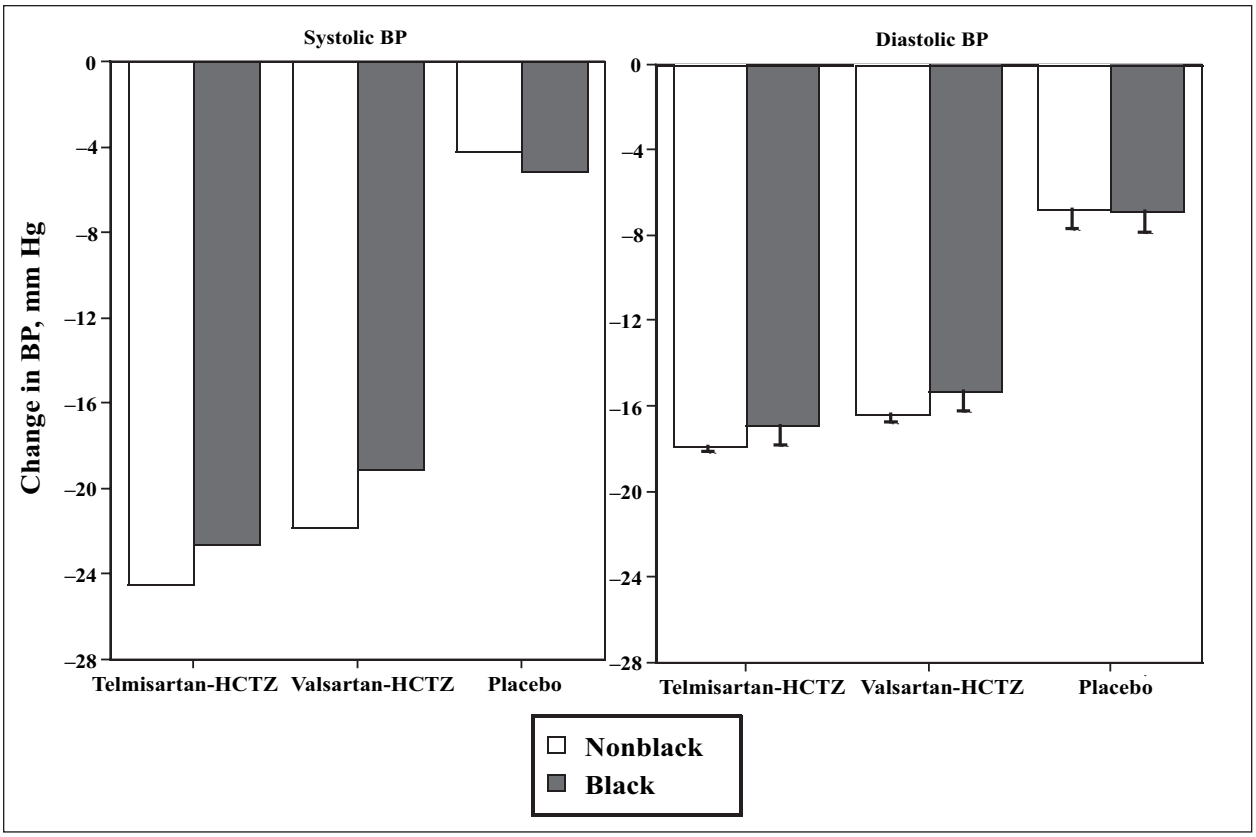

Figure 3. Impact of race (nonblack vs black) on changes from baseline in systolic and diastolic blood pressure (BP) for each of the treatment groups. HCTZ indicates hydrochlorothiazide.

were significantly greater for telmisartan-HCTZ compared with valsartan-HCTZ.

Pulse Rate

There were no significant differences in changes from baseline in pulse rate among the 3 treatment groups (telmisartan-HCTZ 80/25, –0.3 bpm; valsartan-HCTZ 160/25, –0.8 bpm; placebo, 0.8 bpm).

Adverse Experiences

Of the 1109 patients who were randomized to the study, a total of 457 (41%) had at least 1 adverse

event with treatment at onset during the 8-week double-blind treatment period: 207/485 (43%) in the telmisartan arm, 188/498 (38%) in the valsartan arm, and 62/126 (49%) of placebo patients. The most common adverse events during the trial are shown in Table III. Of note, the incidence of headache was greater for placebo (11.9%) than either the telmisartan arm (3.7%) or the valsartan arm (6.2%).

There were no deaths reported during the study. There were 21 patients who had a serious adverse event: 9 during screening or placebo run-in, 10 during the double-blind treatment period, and 2 following completion of the trial. Of the 10 patients with a serious adverse event during the double-blind active treatment phase, all but 2 discontinued prematurely from the trial: 5 patients in the telmisartan arm, 4 in the valsartan arm, and 1 in the placebo arm.

There were few laboratory parameters with any significant changes during the study. A reduction in sodium was observed in 27 (6.2%) and 19 (4.3%) patients in the telmisartan and valsartan arms, respectively, vs 1 (0.9%) of the placebo-treated patients. In contrast, there were just 2 patients (0.5%) in the telmisartan arm and 3 patients (0.7%) in the valsartan arm with clinically significant reductions in serum potassium concentrations. Increases in serum uric acid were more common in the active treatment arms (telmisartan, 10.6%; valsartan, 10.4%) than in the placebo group (2.8%).

DISCUSSION

Principal Findings

This large study was designed to provide a definitive comparison of the BP-lowering effects of these two ARBs administered in combination with a thiazide diuretic. The primary findings demonstrated that telmisartan-HCTZ 80/25 lowered both SBP and DBP to a greater extent than valsartan-HCTZ 160/25 (Table II and Figures 1–3). As expected, both agents lowered BP to a much greater extent than placebo. The findings between the active treatment groups were predictable, in part, considering the pharmacokinetic profile of telmisartan, which is characterized by a longer half-life than valsartan[9,13] and previous pharmacodynamic studies using ambulatory BP monitoring that showed greater BP reductions with telmisartan compared with valsartan without the diuretic component.[13,16,17] The present study adds comprehensive information on the effects of the combination therapy of ARBs plus a higher dose of HCTZ (25 mg), which has become considered an important option in clinical practice.[3,13]

Effects of ARBs in Combination With HCTZ

Several fixed-dose combination therapies of ARBs and diuretics are now available for the treatment of hypertension. Initially, combinations using ARBs were developed with HCTZ at a dose of 12.5 mg; these combinations typically showed additive effects on BP lowering regardless of which ARB was studied.[6,18–21]

More recently, incremental BP-lowering effects have been observed with larger doses of HCTZ, ie, 25 mg, in combination with the ARBs,[6,18] which has led to the development of the fixed-dose combination formulations used in our trial. For example, in the factorial design study by Benz et al,[18] valsartan-HCTZ at a dose of 160/25 mg lowered BP by 22/15 mm Hg compared with 18/14 mm Hg for valsartan-HCTZ at a dose of 160/12.5 mg. These results are quite similar to those of the present trial (Table II), in which valsartan-HCTZ 160/25 lowered BP by 21/16 mm Hg.

In a study by McGill and Reilly,[6] the greatest effects from a large factorial design study with varying doses of telmisartan and HCTZ was seen with telmisartan-HCTZ at 160/25 (a dose not clinically available), which decreased BP by 25/18 mm Hg. As shown in Table II, in the present trial, telmisartan-HCTZ 80/25 lowered BP by 24/18 mm Hg. Of interest is that both of the earlier studies demonstrated that as the dose of the ARBs increased when added to the diuretic,[6,18] reductions in serum potassium induced by HCTZ were attenuated or negated.

Importance of Small Differences in BP Control

Head-to-head comparisons such as those in our large clinical trial are important in establishing differences in the antihypertensive efficacy of the various ARBs.[22] As shown in Table II and Figures 1–3, regardless of age, gender, or race, telmisartan-HCTZ 80/25 had significantly greater reductions in BP compared with valsartan-HCTZ 160/25, by about 3/1.5 mm Hg at the end of the dosing period. In a meta-analysis involving 1 million adults in 61 prospective studies, the relationship between the reduction in BP and cardiovascular morbidity and mortality events was shown to be approximately log-linear, and differences of 20 mm Hg SBP and 10 mm Hg DBP directly correlated to a 50% reduction in stroke mortality and death rates for ischemic heart disease and other vascular deaths. From these data, it could be estimated that a 2-mm Hg reduction in systolic BP would provide about 10% lower stroke mortality and 7% lower mortality from ischemic heart disease or other

vascular death without a BP threshold down to the 115/75 mm Hg level.[1] Another study, by Cook et al,[23] confirmed that a 2-mm Hg DBP reduction was associated with a 9% reduction in the risk of coronary heart disease and a 15% reduction in the risk of stroke. Lastly, as has been demonstrated in both ALLHAT[12] and the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE)[24] trial, greater reductions in BP induced by one pharmacologic regimen vs another may have important clinical implications related to reductions in cardiovascular and cerebrovascular morbidity even during a period of 1 year or less.

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