Effects of the angiotensin II receptor blockers telmisartan versus valsartan in combination with hydrochlorothiazide: a large, confirmatory trial

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In 2004–2005, the antihypertensive effects of telmisartan 80 mg versus valsartan 160 mg combined with hydrochlorothiazide 25 mg were assessed in a large placebo-controlled trial in patients with stages 1 and 2 hypertension and demonstrated that both agents were highly effective in lowering blood pressure (BP) compared with placebo and that telmisartan lowered BP significantly greater than valsartan. To confirm this finding according to Food and Drug Administration guidelines, we performed a second large trial using the same design in an entirely separate patient population. The trial was double-blind with a 4:4:1 randomization scheme to compare once daily telmisartan 80 mg plus hydrochlorothiazide 25 mg versus once daily valsartan 160 mg plus hydrochlorothiazide 25 mg versus once daily placebo on reductions in seated clinic BP in patients with stages 1 and 2 hypertension. The primary endpoints were the changes from baseline in seated diastolic and systolic BP at the end of the 8-week treatment period. Safety endpoints included adverse events, changes in laboratory parameters and pulse rate. In total, 1185 patients were randomized (of which 1181 were treated and included in the primary analysis: 528 in the telmisartan-hydrochlorothiazide group, 523 in the valsartan-hydrochlorothiazide group, and 130 in the placebo group), changes from baseline in BP following telmisartan-hydrochlorothiazide (–24.6/–18.2 mmHg) were significantly greater than both placebo (–4.1/–6.1 mmHg) and valsartan-hydrochlorothiazide (–22.5/–17.0 mmHg) (versus placebo, \(P<0.0001\) for systolic and diastolic BP; versus valsartan-hydrochlorothiazide, \(P=0.017\) for systolic BP and \(P=0.025\) for diastolic BP). The total number of patients with at least one adverse event reported was similar among the three treatment groups (placebo, 42%; telmisartan-hydrochlorothiazide, 36%; and valsartan-hydrochlorothiazide, 37%). Thus, this large, second trial confirms that telmisartan-hydrochlorothiazide at doses of 80/25 mg lowered both systolic and diastolic BP to a greater extent than valsartan-hydrochlorothiazide at doses of 160/25 mg in stages 1–2 hypertension. Although these are not the highest doses of these agents at present, at the time that the studies were conducted, they were the maximally approved dosages. Both studies support the strategy of using angiotensin receptor blockers with a higher dose of a thiazide diuretic (25 mg) for enhancing the control of hypertension. *Blood Press Monit* 13:21–27 @ 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.


Keywords: confirmatory antihypertensive clinical trial, fixed-dose combination therapy, telmisartan, thiazide diuretics, valsartan

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Introduction

Improved control of blood pressure in patients with hypertension is necessary to produce the maximum reduction in clinical cardiovascular endpoints [1,2] and expert consensus guidelines advocate blood pressure levels <140/90 mmHg in patients lacking target organ involvement and <130/80 mmHg in patients with diabetes or kidney disease [3,4]. During the past decade, the use of angiotensin receptor blockers alone or in fixed combinations with low-dose (12.5 mg) hydrochlorothiazide has become a popular strategy in the management of hypertension. This is not surprising as angiotensin receptor blockers are not only effective in reducing blood pressure, but clinical trial results demonstrate tolerability profiles that are similar to placebo [5,6]. Furthermore, clinical trials have shown that the angiotensin receptor blockers reduce cardiovascular events (especially stroke), 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].

Use of higher doses of thiazide diuretics (i.e. 25 mg total daily dose) in combination with other antihypertensive drugs has become recognized as a safe and effective strategy to improve BP control [12]. Therefore, it is
appropriate to evaluate fixed-dose combinations of angiotensin receptor blockers with 25 mg of hydrochlorothiazide to determine the benefits and side effects of these increasingly used therapies. In our first study [13], we performed a large (n = 1066), comparative clinical trial evaluating two fixed-dose combination therapies: telmisartan 80 mg plus hydrochlorothiazide 25 mg (telmisartan-HCT 80/25) and valsartan 160 mg plus hydrochlorothiazide 25 mg (valsartan-HCT 160/25) in patients with stages 1 or 2 hypertension, the maximum approved doses of these fixed-dose combination agents at the time of the study. This study demonstrated that both therapies were highly effective in lowering both systolic and diastolic BP and that telmisartan-HCT lowered through BP to a greater extent than valsartan-HCT. The current study was performed to determine whether these results could be confirmed using the identical study design and treatment regimens in an entirely different patient population.

**Methods**

**Study design**

This trial was a multicenter, double-blind, double-dummy, randomized, parallel group study that compared the efficacy and safety of telmisartan-HCT 80/25 versus valsartan-HCT 80/25 and telmisartan-HCT 80/25 versus placebo. The study was conducted at 117 clinical centers in the United States. The objective of the study was to determine whether telmisartan-HCT 80/25 mg administered once daily was superior to placebo once daily and noninferior and possibly superior to valsartan-HCT 160/25 once daily for the control of the clinic BP following 8 weeks of treatment.

Following a 3 to 4 week run-in period that included a 1-week washout period for patients who were currently receiving antihypertensive therapy followed by a 2 to 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 returned to the clinic and uptitrated to telmisartan-HCT 80/25, valsartan-HCT 160/25, or placebo depending upon their initial randomized treatment arm. Starting at the uptitration visit and at 2-week intervals thereafter for a total of an additional 6 weeks, study patients were examined in the clinic between 7.00 and 10.00 h for clinical evaluation (typically 23–26 h postdosing). At every visit, adverse events were also assessed by nonleading questions.

**Patient population**

Men and women with systemic hypertension were included in the study if their average seated diastolic BP was ≥ 95 mmHg to < 120 mmHg 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 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 was assessed 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. All reported adverse events were categorized by body system and preferred term using the Medical Dictionary for Regulatory Activities [14]. The incidence of treatment-emergent adverse effects in each treatment group was tabulated by severity and by 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 endpoints for assessing efficacy were the changes from baseline to the end-of-study visit in clinic diastolic blood pressure (DBP) and systolic blood pressure (SBP) measured 23–26 h after dosing of study medication. In the case of patients withdrawing 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 = 0.05), testing of multiple treatment comparisons (i.e., telmisartan-HCT 80/25 versus placebo and telmisartan-HCT 80/25 vs. valsartan-HCT 160/25) for both of the primary endpoints, a hierarchical closed testing procedure was used. All secondary analyses were performed on the primary endpoints and all testing on secondary endpoints was performed at a two-sided α = 0.05. All statistical testing was primarily performed on the full analysis set involving all patients randomized to the study, who had at least one set of BP measurements following titration to combination therapy.

The primary objective of the study was to show that telmisartan HCT was not inferior to valsartan HCT. Assuming a standard deviation of 9 mmHg and a noninferiority margin of 2 mmHg for diastolic BP, a sample size of 400 completed patients per treatment group would have 88% power to demonstrate at the 5% (two-sided) level of significance that telmisartan HCT is not inferior to valsartan HCT if both combination treatments are equal. Assuming a 7.5% rate of premature discontinuation from the study and a screening failure rate of 30%, approximately 1320 patients were needed to enroll.
920 randomized patients. For a superiority comparison with placebo for the active therapies, greater than 99% power to detect a 5-mmHg difference in the change from baseline in diastolic BP required 70 placebo patients. To be able to assess any center effects, the study was designed to randomize nine patients per each of the 117 centers.

The comparability of patients in the three treatment groups was determined from the demographic data and baseline BP values. The primary endpoints as well as all secondary continuous variables were analyzed using an analysis of covariance model involving treatment group with baseline value as a covariate. Further adjustments were made for age, sex, and ethnicity for comparative effects of the three treatments. Treatment group comparisons were based on the least square means obtained via the SAS general linear model procedure (SAS version 8.2, Cary, North Carolina, USA). In addition, effects of age, sex, race, and ethnicity on the primary endpoints were evaluated in subgroup analyses.

**Results**

**Patient enrollment and disposition**

A total of 2322 patients were screened for the study. Of the 1185 patients who met the inclusion criteria and were randomized, 1181 received treatment and were randomized to the following treatment arms: 528 patients to telmisartan-HCT, 523 patients to valsartan-HCT, and 130 to placebo. A total of 1036 of the 1185 randomized patients completed the study as planned: [469 (89%) in the telmisartan-HCT arm, 470 (90%) in the valsartan-HCT arm, and 97 (75%) in the placebo arm]. The most common reasons for discontinuing the study early were adverse events [55 patients (4.7%)] and withdrawal of consent [37 patients (3.1%)].

**Baseline characteristics of the study population**

The baseline characteristics of all randomized and treated patients in the three treatment arms are shown in Table 1. For the entire patient population the mean age was 53 years, with a greater percentage of males (55%), was predominantly non-black (73%) and with baseline BPs of 155/102 mmHg. No significant differences in baseline characteristics among the three treatment arms were observed.

**Changes in the clinic trough (24-h postdose) blood pressures**

The effects of the three treatment groups on trough clinic BPs are shown in Table 2. Compared with placebo, both combination therapies lowered seated BP substantially. For patients treated with telmisartan-HCT 80/25, the reductions in trough clinic BPs (–24.6/–18.2 mmHg) were significantly greater (P < 0.0001 for both SBP and DBP) than those for patients treated with placebo (–3.1/–6.0 mmHg). Compared with patients treated with valsartan-HCT 160/25 (reductions of –22.5/–17.0 mmHg), telmisartan-HCT 80/25 was found to have significantly greater reductions in both DBP (adjusted mean difference of –1.2 mmHg; P = 0.025) and SBP (adjusted mean difference of –2.1 mmHg; P = 0.017). The percentages of patients achieving a BP of less than 140/90 mmHg were 19.3% in the placebo group, 65.3% in the telmisartan-HCT group and 59.9% in the valsartan-HCT group.

**The impact of age, sex, and ethnicity on blood pressure**

**Age**

The impact of age group (< 65 or ≥ 65 years old) on reductions in BP for the three treatment groups is shown

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**Table 1** Characteristics of the study patients at baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Telmisartan-HCT</th>
<th>Valsartan-HCT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>528</td>
<td>523</td>
<td>130</td>
</tr>
<tr>
<td>Male/female</td>
<td>285/243 (54/46)</td>
<td>288/236 (55/45)</td>
<td>75/55 (58/42)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53±10</td>
<td>53±10</td>
<td>54±10</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td>White 381 (72)</td>
<td>356 (68) 91 (70)</td>
<td>Black 135 (26) 156 (30) 33 (25)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32±2.6</td>
<td>32±7</td>
<td>32±7</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>154±13</td>
<td>155±13</td>
<td>153±12</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>102±4</td>
<td>102±4</td>
<td>102±4</td>
</tr>
</tbody>
</table>

**Table 2** Seated clinic trough blood pressures and changes from baseline by treatment group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Telmisartan-HCT 80/25</th>
<th>Valsartan-HCT 160/25</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>Observed mean (SD)</td>
<td>Baseline 154.1 (12.6)</td>
<td>154.9 (12.5)</td>
</tr>
<tr>
<td></td>
<td>Final 129.5 (14.8)</td>
<td>132.1 (15.8)</td>
<td>149.1 (15.6)</td>
</tr>
<tr>
<td></td>
<td>Change from baseline – 24.6 (15.7)</td>
<td>– 22.9 (15.4)</td>
<td>– 3.1 (12.7)</td>
</tr>
<tr>
<td></td>
<td>Adjusted mean (SE) – 24.6 (0.63)</td>
<td>– 22.5 (0.63)</td>
<td>– 4.1 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Comparison with – 2.1 (– 3.9, – 0.4)</td>
<td>– 20.6 (– 23.4, – 17.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Telmisartan-HCT 80/25 Difference (95% CI)</td>
<td>0.0174</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>Observed mean (SD)</td>
<td>Baseline 101.8 (4.2)</td>
<td>101.6 (4.3)</td>
</tr>
<tr>
<td></td>
<td>Final 83.5 (8.9)</td>
<td>84.9 (9.6)</td>
<td>95.3 (9.9)</td>
</tr>
<tr>
<td></td>
<td>Change from baseline – 18.3 (8.8)</td>
<td>– 17.0 (8.8)</td>
<td>– 6.0 (8.9)</td>
</tr>
<tr>
<td></td>
<td>Adjusted mean (SE) – 18.2 (0.4)</td>
<td>– 17.0 (0.4)</td>
<td>– 6.1 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Comparison with – 1.2 (– 2.3, – 0.2)</td>
<td>– 12.1 (– 13.9, – 10.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Telmisartan-HCT 80/25 Difference (95% CI)</td>
<td>0.0254</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for sex and race group with both baseline response and age as covariates.
in Fig. 1. Overall, there were no significant treatment-by-age group interactions for either diastolic BP \((P = 0.40)\) or systolic BP \((P = 0.60)\). For diastolic BP there was a significant difference \((P = 0.004)\) found between the overall adjusted mean changes for patients less than 65 years old \((-13.6\, \text{mmHg})\) and \(\geq 65\) years old \((-15.2\, \text{mmHg})\). No significant differences were observed between age groups for the systolic BP.

**Ethnicity group**
The impact of ethnicity group (non-black and black) on reductions in BP for the three treatment groups is shown in Fig. 2. A significant treatment-by-race group interaction was found for diastolic BP \((P = 0.003)\) but not for systolic BP \((P = 0.28)\). Additionally, there were small, but significant overall differences found between the adjusted mean changes in systolic BP for non-black and black patients \((-16.5\) versus \(-17.3\, \text{mmHg})\, \text{respectively,} \, P = 0.04)\).

**Sex**
The impact of sex on reductions in BP for the three treatment groups is shown in Fig. 3. A significant treatment-by-sex interaction was found for systolic BP \((P = 0.02)\).
When comparing the overall effects owing to sex there were significant differences between men and women in the change from baseline in both diastolic BP and systolic BP ($P < 0.01$ for both). The adjusted mean changes from baseline for women ($–17.8/–14.6$ mmHg) were significantly greater than the changes from baseline for men ($–16.4/–13.1$ mmHg). These trends occurred in both active treatment groups (Fig. 3).

### Adverse events

Of the 1181 patients who were randomized to the study and received at least one dose of study drug, a total of 438 (37%) had at least one adverse event with treatment at onset during the 8-week double-blind treatment period; 192 (36%) in the telmisartan arm, 191 (37%) in the valsartan arm, and 55 (42%) of placebo patients. The most common adverse events during the trial are shown in Table 3.

Two deaths were reported during the study. One death (sudden death) occurred on the first day of placebo run-in; the cause of the 2nd death was not determined and this occurred in a patient 1 week after completion of the trial (patient had been randomized to the telmisartan arm). Twenty-three patients had a serious adverse event; 10 during screening or placebo run-in, 10 during the double-blind treatment period, and three following completion of the trial. Of the 10 patients with a serious adverse event during the double-blind active treatment phase, all but three discontinued prematurely from the trial; no events were determined to be drug-related.

Few laboratory parameters with any significant changes during the study were observed. No clinically important differences in plasma sodium or potassium among the three treatment groups were present. The percentages of patients who had any increase in serum uric acid were larger in the active treatment arms (telmisartan-HCT: 11.2%, valsartan-HCT: 10.3%) than in the placebo group (1.9%). Similarly, the proportion of patients who had any increase in blood urea nitrogen was more common in the active treatment arms (telmisartan-HCT: 40%, valsartan-HCT: 39%) than in the placebo group (17%).

### Discussion

#### Principal findings

This large clinical trial provided confirmation of our first assessment of the BP lowering effects of telmisartan and valsartan administered in combination with a thiazide diuretic [13]. The primary findings demonstrated that telmisartan-HCT 80/25 lowered both the systolic and diastolic BP to a greater extent than valsartan-HCT

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**Table 3** Adverse events with an incidence $\geq 2\%$ in any treatment arm

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Telmisartan-HCT ($n=528$)</th>
<th>Valsartan-HCT ($n=523$)</th>
<th>Placebo ($n=130$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Back pain</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Increased BP</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2</td>
<td>0.4</td>
<td>4</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>14</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>

*MedDRA preferred term [17]. BP, blood pressure; HCT, hydrochlorothiazide.
160/25 (Table 2 and Figs 1–3). Not surprisingly, both fixed-dose combination 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 [9,12] and previous pharmacodynamic studies using ambulatory BP monitoring that showed greater BP reductions on telmisartan compared with valsartan without the diuretic component [15–17]. Thus, the current study confirms what has already been demonstrated comprehensively regarding the combination therapies for the angiotensin II receptor blockers that utilize a higher dose of hydrochlorothiazide (25 mg) [13], an option that has been shown to be increasingly useful in clinical hypertension management [3,12].

Effects of angiotensin receptor blockers in combination with hydrochlorothiazide

Several fixed-dose combination therapies of angiotensin receptor blocking agents and diuretics are available for the treatment of hypertension. All combinations with the angiotensin receptor blockers were developed with hydrochlorothiazide at a dose of 12.5 mg; these combinations typically show additive effects on blood pressure lowering regardless of which angiotensin receptor blocker was studied [6,18–23].

More recently, incremental BP-lowering effects have been observed with larger doses of hydrochlorothiazide, that is, 25 mg, in combination with the angiotensin receptor blockers [6,18], which has led to the development of the fixed-dose combination formulations used in our trial. In an earlier study by Benz et al. [18], valsartan-HCT at a dose of 160/25 mg lowered the BP by 22/15 mmHg compared with 18/14 mmHg for valsartan-HCT at a dose of 160/12.5 mg. These results are quite similar to those of the current trial (Table 2) in which valsartan-HCT 160/25 lowered the BP by 23/17 mmHg. In our first trial [13], BP reductions were strikingly similar to the second study. For example, in this study, telmisartan-HCT lowered the trough BP by 24.6/18.3 mmHg whereas in the first trial, telmisartan-HCT lowered the BP by 24.0/17.6 mmHg, a difference of just 0.6/0.7 mmHg. The baseline BP levels in both treatment groups and demographics of the study population for the two studies were also nearly identical. Thus, despite the potential for ‘equalizing’ BP reductions by using hydrochlorothiazide at 25 mg daily, the differences in BP lowering between the two angiotensin receptor blockers were preserved and account for the differences between the combination therapies. Of note, one small study involving 70 patients by Calvo et al. [24] showed a substantially larger reduction in 24-h BP on valsartan 160 mg monotherapy compared with telmisartan 80 mg monotherapy. The reason for this rather large difference (nearly 8/4 mmHg) is not clear.

Importance of small differences in blood pressure control

Confirmation of combination therapies from our two large clinical trials are important in establishing differences in the antihypertensive efficacy of angiotensin receptors blockers [13,23]. As shown in Table 2 and Figs 1–3, regardless of age, sex, or ethnicity, telmisartan-HCT 80/25 induced greater reductions in BP compared with valsartan-HCT 160/25 by about 2.1/1.2 mmHg at the end of the dosing period. In analyses involving one million adults in 60 prospective studies, the relationship between the reduction in BP and cardiovascular morbidity and mortality events support that a 2-mmHg 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 mmHg level [1]. Cook et al. [25] showed that a 1-mmHg diastolic BP reduction was associated with a 5% reduction in the risk of coronary heart disease and an 8% reduction in the risk of stroke. Lastly, as has been demonstrated in both the ALLHAT [26] and VALUE [27] trials, greater reductions in BP induced by one pharmacologic regimen versus another may have important clinical implications related to reductions in cardiovascular and cerebrovascular morbidity even during a period of less than 1 year.

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References


