Original Article

Telmisartan/Hydrochlorothiazide in Comparison with Losartan/Hydrochlorothiazide in Managing Patients with Mild-to-Moderate Hypertension

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Hypertension is risk factor for cardiovascular morbidity and mortality, and stroke. A critical surge in blood pressure occurs during the early morning hours coincident with increased incidences of myocardial infarction, unstable angina, stroke and sudden cardiac death. This suggests that, in patients with hypertension, it may be important to maintain the efficacy of antihypertensive medication over the 24-h dosing interval, especially in the risky early morning hours. In order to evaluate the antihypertensive efficacies of fixed-dose combinations of angiotensin II receptor blockers with hydrochlorothiazide (HCTZ) 12.5 mg, a multicenter, randomized, prospective, open-label, blinded-endpoint study was performed in 805 patients with mild-to-moderate hypertension randomized to once-daily treatment with telmisartan 40 mg plus HCTZ (T40/H12.5), losartan 50 mg plus HCTZ (L50/H12.5), or telmisartan 80 mg plus HCTZ (T80/H12.5), with the primary objective of comparing T40/H12.5 with L50/H12.5 and evaluating the additional response of T80/H12.5. Efficacy was assessed by ambulatory blood pressure monitoring (ABPM), clinic seated cuff sphygmomanometry and calculated responder rates after 6 weeks' active treatment. The primary endpoint was reduction from baseline in the last 6-h mean (relative to dosing) diastolic blood pressure (DBP) measured using 24-h ABPM. Compared with the L50/H12.5 group, the mean reductions in the last 6-h mean DBP for the T40/H12.5 and T80/H12.5 groups were significantly greater: −2.0 mmHg (p=0.0031) and −2.8 mmHg (p=0.0003), respectively. We conclude that T40/H12.5 provided clinically and statistically significantly superior blood pressure reductions compared with L50/H12.5 during the last 6 h of the 24-h dosing interval, which corresponds to the high-risk early-morning hours, and that T80/H12.5 provided additional blood pressure reductions. (*Hypertens Res* 2005; 28: 555–563)

***Key Words*: hypertension, telmisartan, losartan, hydrochlorothiazide, combination therapy**

Introduction

Hypertension, an important and independent risk factor for cardiovascular disease, is best managed by maintaining blood pressure below 140/90 mmHg (*1*, *2*). Individuals with persistent resting diastolic blood pressure (DBP) ≥90 mmHg and/or systolic blood pressure (SBP) ≥140 mmHg are at increased risk of cardiovascular morbidity and mortality (*1*). It has been estimated that a 5–6-mmHg reduction in DBP and 10-mmHg reduction in SBP lowers the risk of stroke by approximately 33% and of coronary events by approximately 17% (*3*). Lewington *et al*. (*4*) demonstrated a doubling in the risk of cardiovascular disease for each 20/10-mmHg increase in SBP/DBP

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in subjects aged 40–69 years.

A circadian pattern in blood pressure has been noted in both normotensive and hypertensive individuals, with blood pressure being highest during the day, declining at night, and reaching a low between midnight and 3:00 AM. In the early-morning hours, a surge in blood pressure is noted, coinciding with awakening from overnight sleep (*5*). Incidences of myocardial infarction, angina, sudden cardiac death and stroke have also been shown to increase between 4:00 AM and 6:00 AM, peaking between 8:00 AM and 9:00 AM (*6–8*). Other potentially deleterious factors, such as increases in pulse rate, fibrinolytic activity, platelet aggregation and circulating catecholamines, demonstrate peak adverse modifications during the morning hours (*9*, *10*). Cross-sectional and longitudinal studies support the hypothesis that adverse outcomes are directly related to the inability to maintain 24-h mean blood pressure in the normal range (*9*). Theoretically, therefore, greater cardiovascular benefits may be attainable if the blood pressure-lowering activity of antihypertensive drugs is maintained throughout the 24-h dosing interval, including the critical early-morning hours.

The angiotensin II receptor blockers (ARBs) are a relatively recently developed class of antihypertensive agents that target the renin–angiotensin–aldosterone system and prevent binding of angiotensin II to type 1 receptors (*11*). In addition to their proven clinical efficacy when given once daily as monotherapy, ARBs are notable for their placebo-like tolerability (*12*). Telmisartan and losartan are two ARBs with different half-lives: the terminal plasma elimination half-life of telmisartan is approximately 24 h (*13*), compared with approximately 2 h for losartan and 6–9 h for its active metabolite, EXP3174 (*14*). Despite the relatively short half-life of losartan, a pharmacodynamic study in healthy volunteers showed that blocking of the pressor response to exogenous angiotensin II was apparent 24 h after losartan administration (*15*). A study of similar design demonstrated that the inhibitory effect of telmisartan on angiotensin II challenge was still apparent 48 h after dosing (*16*). In hypertensive patients, losartan given once daily has been reported to provide effective blood pressure control that persists throughout the 24-h dosing interval and is comparable to enalapril, atenolol and felodipine extended release (*17*). Telmisartan monotherapy has recently been shown to be effective in reducing morning home blood pressure, as well as improving arterial wall stiffness (*18*).

Blood pressure-lowering activity may be enhanced when two classes of antihypertensive agents are co-administered. To achieve the recommended blood pressure targets, it is now acknowledged that many patients require a combination of antihypertensive agents (*2*, *19*). The combination of an ARB and a low dose of a diuretic increases the antihypertensive efficacy, but not at the expense of tolerability, compared with the individual components administered alone (*20*). Both telmisartan and losartan are available in fixed-dose combinations with low-dose hydrochlorothiazide (HCTZ). The primary purpose of this study was to compare the efficacy of a low-dose telmisartan/HCTZ fixed-dose combination with a low-dose losartan/HCTZ fixed-dose combination, and to determine the additional response obtained with the higher-dose telmisartan/HCTZ fixed-dose combination, in the management of mild-to-moderate hypertension measured using 24-h ambulatory blood pressure monitoring (ABPM).

Methods

Study Subjects

The study population comprised adult (≥18 years) male and female patients with mild-to-moderate hypertension, defined as mean seated DBP 95–109 mmHg. In addition, patients were required to have a 24-h ABPM mean DBP ≥85 mmHg at baseline. Patients were excluded from the trial for any of the following reasons: mean seated SBP ≥180 mmHg or mean seated DBP ≥110 mmHg; known or suspected secondary hypertension; significant cardiac, hepatic, or renal disease; or poorly controlled type 1 diabetes mellitus. A history of angioedema, drug or alcohol dependency, receipt of concomitant medications known to affect blood pressure, or known allergies to any component of the study drugs were further exclusion criteria. Nightshift workers who worked between midnight and 4:00 AM and women who were pregnant or nursing were also excluded. Ethical approval was obtained from the Institutional Review Board at each center.

Study Design

This was a multicenter, prospective, randomized, open-label, blinded-endpoint (PROBE), parallel-group study. An independent principal investigator at each study center was responsible for assuring the proper conduct of the study. The PROBE design allows a head-to-head comparison of treatment groups, with a blinded evaluation of ambulatory blood pressure to reduce the possibility of bias (*21*). Patients underwent clinical evaluation that included medical history, 12-lead electrocardiography, clinical laboratory assessment and physical examination before a placebo run-in period lasting 2–4 weeks. At the end of the run-in period, seated blood pressure (mean of three measurements taken 2 min apart using a manual mercury cuff sphygmomanometer, according to the American Society of Hypertension guidelines (*22*)) was measured and 24-h ABPM was performed using a Spacelabs Model 90207 device (Spacelabs Medical Data, Issaquah, USA), with the device being programmed to collect measurements at 20-min intervals throughout the 24-h monitoring period. Patients reported to the clinic at the end of the monitoring period for the removal of the device and the downloading of the data by the investigator to the independent ABPM vendor (Spacelabs Medical Data). Eligible patients were randomly assigned to 6 weeks' treatment with one of the following fixed-dose combinations in a 2:2:1 ratio: telmisartan 40

Table 1. Demographics and Baseline Characteristics of Study Patients

	T40/H12.5 (*n*=318)	L50/H12.5 (*n*=320)	T80/H12.5 (*n*=167)
Males (*n* [%])	211 (66.4)	212 (66.3)	100 (59.9)
Age (years)*	52.1±10.2	52.6±9.6	53.2±10.2
<65 years (*n* [%])	283 (89.0)	284 (88.8)	150 (89.8)
≥65 years (*n* [%])	35 (11.0)	36 (11.3)	17 (10.2)
Race (*n* [%])			
Caucasian or white	221 (69.5)	212 (66.3)	111 (66.5)
African-American	86 (27.0)	99 (30.9)	53 (31.7)
Asian	11 (3.5)	9 (2.8)	3 (1.8)
Hypertension duration (years)*	9.2	9.1	8.4
Body mass index (kg/m^2)*	31.1	30.9	30.74
Smoking history (*n* [%])			
Never smoked	151 (47.5)	150 (46.9)	85 (50.9)
Ex-smoker	91 (28.6)	91 (28.4)	43 (25.7)
Smoker	76 (23.9)	79 (24.7)	39 (23.4)
Average alcohol consumption (*n* [%])	183 (57.5)	193 (60.3)	87 (52.1)
Clinic seated trough			
SBP (mmHg)*	153.9±11.5	153.8±11.1	154.8±12.7
DBP (mmHg)*	99.8±4.1	99.5±4.2	100.0±4.1
Pulse rate (beats/min)	75.3±9.2	74.5±9.8	74.1±8.7
24-hour ambulatory			
SBP (mmHg)*	150.5±12.4	150.4±11.2	151.3±12.6
DBP (mmHg)*	93.8±6.9	93.8±6.6	94.0±7.2
Morning ambulatory			
SBP (mmHg)*	155.0±13.5	154.8±11.9	156.5±12.8
DBP (mmHg)*	98.3±7.2	98.5±7.3	99.2±7.5
Daytime ambulatory			
SBP (mmHg)*	155.4±12.6	154.8±11.4	156.3±12.4
DBP (mmHg)*	97.7±6.7	97.7±6.8	98.1±7.1
Nighttime ambulatory			
SBP (mmHg)*	141.1±15.1	141.0±13.9	141.9±16.0
DBP (mmHg)*	85.4±9.3	85.8±9.1	85.8±9.9
Pulse rate (beats/min)*	79.7±10.7	79.6±11.3	80.2±10.1

T40 (80)/H12.5, telmisartan 40 (80) mg plus hydrochlorothiazide (HCTZ) 12.5 mg; L50/H12.5, losartan 50 mg plus HCTZ 12.5 mg; SPB, systolic blood pressure; DBP, diastolic blood pressure. *Mean values.

mg plus HCTZ 12.5 mg (T40/H12.5); losartan 50 mg plus HCTZ 12.5 mg (L50/H12.5); or telmisartan 80 mg plus HCTZ 12.5 mg (T80/H12.5). Patients were instructed to take the assigned study medication once daily with water at approximately the same time each morning. Each clinic visit was scheduled for the same time of the day. During these visits, the study medication was administered at the clinic after determining the seated blood pressure and/or fitting the ambulatory blood pressure monitor. Adverse events and the results of concomitant medication monitoring were also recorded at each visit.

Efficacy Endpoints

The primary endpoint was the reduction from baseline in the last 6-h (relative to dosing time) mean DBP at the end of the 6 weeks' active treatment, comparing T40/H12.5 with L50/H12.5 and then T80/H12.5. Secondary efficacy endpoints included reduction from baseline in the last 6-h mean SBP, changes from baseline in the 24-h mean DBP and SBP, changes from baseline in the mean DBP and SBP (relative to clock time) at different periods during the 24-h dosing interval (morning [6:00 AM–11:59 AM], daytime [6:00 AM–9:59 PM], and nighttime [10:00 PM–5:59 AM]), reductions from baseline in SBP and DBP load during the 24-h dosing interval and reduction from baseline in mean seated trough DBP and SBP. Responder and control rates based on both the 24-h ABPM mean blood pressures and the in-clinic trough measurements were among the other secondary endpoints measured.

Statistical Analyses

Data management was performed by an independent clinical research organization, who also conducted the day-to-day running of the study. Statistical analysis was performed by a Boehringer Ingelheim statistician. All data were available to the authors. The primary analysis—the effect of treatments on the reduction from baseline in the last 6-h mean DBP—was based on the full analysis set created according to the intent-to-treat principle. Analysis of covariance was performed with treatment regimen and center as the main effects and baseline as the covariate. The primary endpoint was tested using a "closed testing procedure," whereby individual comparisons between either of the treatments with the two telmisartan/HCTZ doses and treatment with the losartan/HCTZ dose were made if an overall difference was found among the three treatment groups. Global testing and subsequent treatment comparisons were performed at the same α-level (0.05). A sensitivity analysis of the primary endpoint was performed to rule out any interaction between treatment and center. Subgroup analyses were performed on the primary endpoint; subgroups evaluated were age, gender and race. Secondary endpoints of changes from baseline in blood pressure were evaluated using the same model as in the primary analysis. Response rates were evaluated using the Mantel-Haenszel test adjusted for center.

A sample size of 288 patients for both the T40/H12.5 and L50/H12.5 groups and a size of 144 patients for the T80/H12.5 group would have 90% power at the 5% (two-sided) level of significance to reject the overall null hypothesis of no treatment differences, if treatment differences truly existed. Once having rejected the overall null hypothesis, these samples would have 84% and 86% power to detect differences

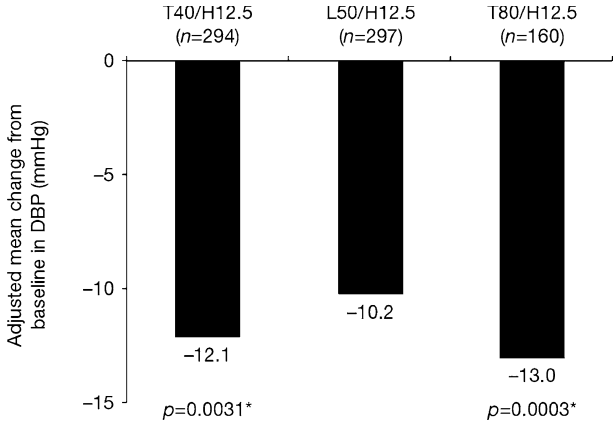

Fig. 1. *Adjusted mean reductions from baseline in the last 6-h (relative to dosing) mean DBP with T40/H12.5, L50/H12.5 and T80/H12.5. *Compared with L50/H12.5.*

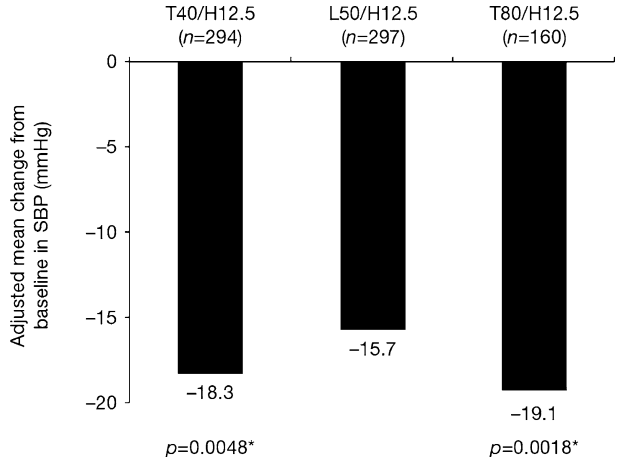

Fig. 2. *Adjusted mean reductions from baseline in the last 6-h (relative to dosing) mean SBP with T40/H12.5, L50/H12.5 and T80/H12.5. *Compared with L50/H12.5.*

between T40/H12.5 and L50/H12.5, and between T80/H12.5 and L50/H12.5, respectively, each at a 5% (two-sided) level of significance. The following assumptions were made: a SD of 8 mmHg for change from baseline in last 6-h mean DBP expected difference between treatment effects; T40/H12.5 and L50/H12.5 having a reduction that is 2.0 mmHg greater for the former; T80/H12.5 and L50/H12.5 having a reduction that is 2.5 mmHg greater for the former; and 10% premature discontinuation rates.

Results

A total of 805 patients were randomized at 67 centers. The three treatment groups were comparable with regard to demographics and baseline characteristics (Table 1). After 6 weeks' active treatment, there was a statistically significant ($p=0.0004$) difference in the last 6-h mean DBP between the three treatment groups. T40/H12.5 produced significantly greater reductions in the last 6-h mean DBP compared with L50/H12.5 (−12.1 mmHg *vs.* −10.2 mmHg, $p=0.0031$, Fig. 1). This resulted in a mean difference (adjusted for baseline and center effects) from L50/H12.5 of −2.0 mmHg in favor of T40/H12.5 (95% confidence intervals [CI]: −3.2 to −0.7). T80/H12.5 also brought about significantly greater reductions in the last 6-h mean DBP compared with L50/H12.5 (−13.0 mmHg *vs.* −10.2 mmHg, $p=0.0003$), resulting in an adjusted mean difference from L50/H12.5 of −2.8 mmHg in favor of T80/H12.5 (95% CI: −4.4 to −1.3, Fig. 1). No significant treatment-by-center interaction was found for either of these comparisons. There were no significant differences in the last 6-h mean DBP with respect to age (*i.e.*, <65 years *vs.* ≥65 years), gender or race.

Telmisartan fixed-dose combinations also produced statistically significant ($p=0.004$) mean reductions in the last 6-h mean SBP. The mean reductions, adjusted for baseline and center effects, were −18.3, −15.7 and −19.1 mmHg for T40/H12.5, L50/H12.5 and T80/H12.5, respectively; the adjusted mean differences of −2.6 mmHg (95% CI: −4.5 to −0.8, $p=0.0048$) and −3.5 mmHg (95% CI: −5.6 to −1.3, $p=0.0018$) were in favor of T40/H12.5 and T80/H12.5, respectively (Fig. 2).

The observed mean profiles of changes from baseline for the DBP hourly means show that treatment with T40/H12.5 resulted in DBP reductions that were consistently greater compared with those by treatment with L50/H12.5 not only for each of the last 6 h of the 24-h dosing interval, but also for the last 15 h (Fig. 3a). T80/H12.5 was also consistently superior to L50/H12.5. Similar changes from baseline were also observed for the mean profiles of SBP hourly means over 24 h (Fig. 3b).

The summary statistics reported in Table 2 show that, for each of the secondary ABPM endpoints of 24-h mean, morning mean, nighttime mean and blood pressure load, T40/H12.5 produced significantly greater ($p<0.05$) adjusted mean reductions in DBP and SBP than L50/H12.5, as did T80/H12.5 ($p<0.01$). During the daytime period, T40/H12.5 produced significantly greater adjusted mean reductions in DBP than L50/H12.5 ($p=0.0452$), and T80/H12.5 brought about significantly greater mean reductions in DBP ($p=0.0001$) and SBP ($p=0.0032$) than L50/H12.5.

Clinic trough seated blood pressure endpoints for the change from baseline were also significantly greater for both T40/H12.5 (−12.5 mmHg, $p=0.0007$) and T80/H12.5 (−14.1 mmHg, $p<0.0001$) compared with L50/H12.5 (−10.3 mmHg). Similar observations were made when the adjusted mean changes from baseline in trough seated SBP for T40/H12.5 (−18.5 mmHg, $p=0.0043$) and T80/H12.5 (−20.5 mmHg, $p=0.0001$) were compared with L50/H12.5 (−15.6 mmHg).

After 6 weeks' active treatment, the response rates of 24-h mean ambulatory blood pressure were higher for T40/H12.5

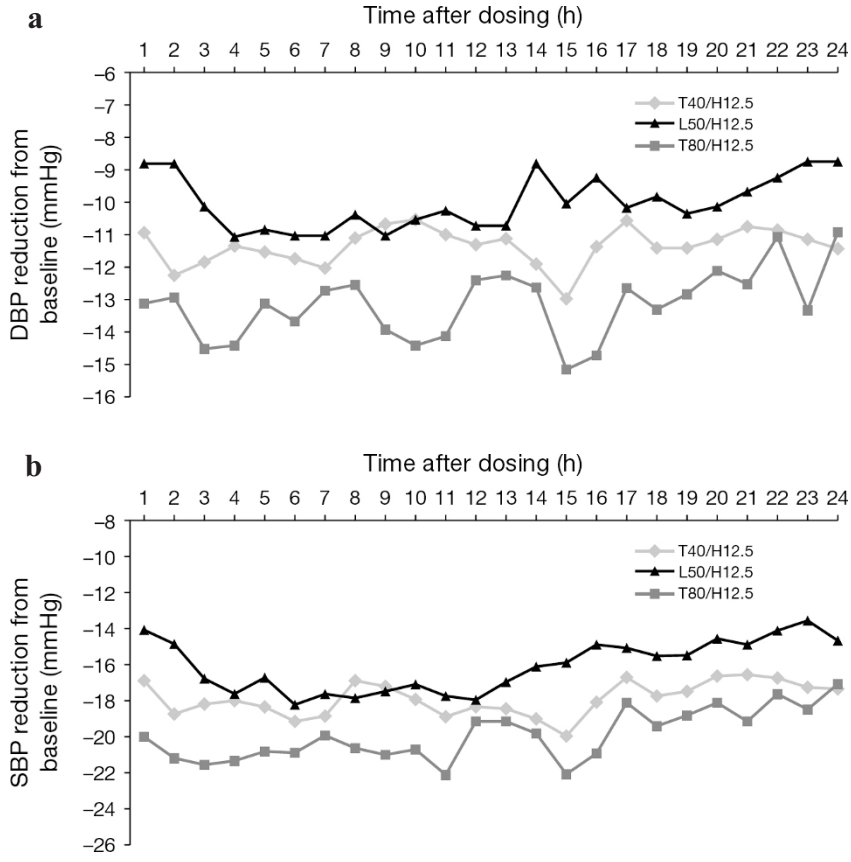

Fig. 3. *Observed mean hourly reductions measured using ABPM (a) diastolic blood pressure (DBP) and (b) systolic blood pressure (SBP) with T40/H12.5, L50/H12.5 and T80/H12.5.*

Table 2. Change from Baseline in the Secondary Ambulatory Blood Pressure Endpoints

Endpoint	Difference (T40/H12.5 − L50/H12.5)		Difference (T80/H12.5 − L50/H12.5)	
	Adjusted mean* (mmHg)	*p* value	Adjusted mean* (mmHg)	*p* value
24-h mean				
SBP	−1.7	0.0431	−3.5	0.0006
DBP	−1.4	0.0161	−3.0	<0.0001
Morning (6:00 AM–11:59 AM) mean				
SBP	−2.8	0.0037	−4.0	0.0004
DBP	−2.4	0.0001	−3.6	<0.0001
Daytime (6:00 AM–9:59 PM) mean				
SBP	−1.4	0.1272	−3.2	0.0032
DBP	−1.2	0.0452	−3.0	0.0001
Nighttime (10:00 PM–5:59 AM) mean				
SBP	−2.6	0.0046	−4.1	0.0002
DBP	−1.9	0.0040	−3.4	< 0.0001
Blood pressure load				
SBP	−4.3	0.0334	−9.1	0.0002
DBP	−3.8	0.0256	−8.3	< 0.0001

T40 (80)/H12.5, telmisartan 40 (80) mg plus hydrochlorothiazide (HCTZ) 12.5 mg; L50/H12.5, losartan 50 mg plus HCTZ 12.5 mg; DBP, diastolic blood pressure; SBP, systolic blood pressure. *Adjusted for baseline and center effects.

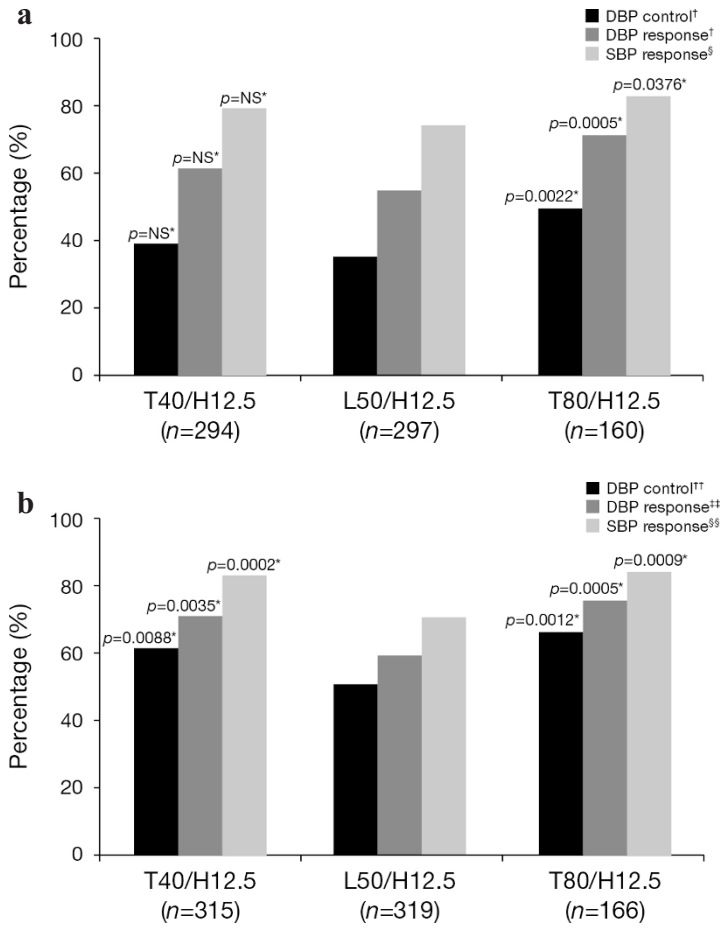

Fig. 4. *Response and control rates for T40/H12.5, L50/H12.5 and T80/H12.5 (a) ambulatory blood pressure and (b) clinic trough seated blood pressure in the full analysis set. Compared with *L50/H12.5; †24-h mean DBP < 80 mmHg; ‡24-h DBP < 80 mmHg and/or reduction from baseline of ≥10 mmHg; §24-h mean SBP < 130 mmHg and/or reduction from baseline of ≥10 mmHg; ††trough seated DBP < 90 mmHg; ‡‡trough seated DBP < 90 mmHg and/or reduction from baseline of ≥10 mmHg; §§trough seated SBP < 140 mmHg and/or reduction from baseline of ≥10 mmHg. NS, non-significant.*

than for L50/H12.5, although this difference did not reach the level of statistical significance (Fig. 4a). For the T80/H12.5 treatment group, 24-h mean ambulatory blood pressure showed significantly greater DBP control and higher DBP and SBP response rates compared with the L50/H12.5 treatment group. Response and control rates based on clinic trough seated measurements were also significantly higher for both T40/H12.5 and T80/H12.5 than for L50/H12.5 (Fig. 4b).

The study drugs were well tolerated. The discontinuation rates due to adverse events were low in all three treatment groups (2.5%, 0.9% and 0.6% for T40/H12.5, L50/H12.5 and T80/H12.5, respectively). Discontinuations were due to worsening of hypertension or concomitant disease in only one patient in the T40/H12.5 group and two in the L50/H12.5 group. The incidences of drug-related adverse events were also similar across all treatment groups (4.4%, 2.8% and 6.0%, respectively). Eleven patients experienced adverse events of severe intensity (two with T40/H12.5, seven with L50/H12.5 and two with T80/H12.5). The number of adverse events occurring in ≥2% of patients was low across all treatment groups and included headache, fatigue, dizziness and upper respiratory tract infection (Table 3).

Discussion

The results from this 6-week active-treatment study demonstrate that for patients with mild-to-moderate hypertension, the T40/H12.5 fixed-dose combination produced significantly greater mean reductions in the last 6-h mean DBP than L50/H12.5. The additional antihypertensive efficacy of T80/HCTZ 12.5 observed in our study confirms the clear dose–response effect of telmisartan. In previous studies evaluating monotherapy, the benefit of increasing the dose from 40 mg to 80 mg has been clearly demonstrated (*23*). The benefits of telmisartan may extend beyond that of blood pressure lowering. A study by Uchida *et al*. (*18*) found that telmisartan

Table 3. Adverse Events Occurring in ≥2% of Patients

Adverse event	T40/H12.5 (*n* [%])	L50/H12.5 (*n* [%])	T80/H12.5 (*n* [%])
Fatigue	4 (1.3)	4 (1.3)	5 (3.0)
Upper RTI	4 (1.3)	7 (2.2)	3 (1.8)
Dizziness	5 (1.6)	9 (2.8)	6 (3.6)
Headache	10 (3.1)	14 (4.4)	4 (2.4)

T40 (80)/H12.5, telmisartan 40 (80) mg plus hydrochlorothiazide (HCTZ) 12.5 mg; L50/H12.5, losartan 50 mg plus HCTZ 12.5 mg; RTI, respiratory tract infection.

improved arterial wall stiffness and thus may be important in improving cerebrocardiovascular mortality, while Derosa *et al*. (*24*) showed that, in addition to providing superior DBP control compared with eprosartan, telmisartan significantly improved lipid profiles.

The clinical use of ARBs in fixed-dose combinations is increasing, since treatment guidelines now recommend that they should be used not only as second-line therapy, but also for treatment-naïve patients whose blood pressure is 20/10 mmHg above the target (*2*, *19*). For this reason, it is important to have comprehensive evaluations of the clinical efficacies provided by the different commercially available combinations. Telmisartan 40 mg and losartan 50 mg are the starting doses of these two ARBs when given as monotherapy, with telmisartan 40 mg having been shown to provide superior blood pressure control compared with losartan 50 mg (*25*). Nevertheless, there are few studies that have compared them in fixed-dose combination with HCTZ 12.5 mg in order to assess whether or not differences exist between the two ARBs. One previous multicenter, PROBE study performed by Lacourcière *et al*. (*26*) has shown that T40/H 12.5 is superior to L50/H12.5 in patients with mild-to-moderate essential hypertension.

It is acknowledged that a drawback of our study is the lack of comparison of T80/H12.5 with an equipotent fixed-dose combination of losartan/HCTZ (*i.e.*, losartan 100 mg plus HCTZ 12.5 mg); however, no such fixed-dose combination is available for clinical use. It may be argued that increasing the dose of losartan to 100 mg may provide better blood pressure control when combined with HCTZ, but previous studies have not clearly defined a dose–response relationship for different losartan doses up to 150 mg (*27*, *28*). Gradman *et al*. (*28*), for example, reported that once-daily losartan doses above 50 mg did not result in additional blood pressure reductions. An ABPM study comparing once-daily telmisartan with once-daily losartan demonstrated that telmisartan produced sustained 24-h blood pressure control that compared favorably with that of the losartan monotherapy (*26*). This finding led Messerli to propose that twice-daily dosing of losartan may be more appropriate to ensure good blood pressure control in the last 6 h of a 24-h dosing period (*29*). Nevertheless, once-daily administration remains the normal dosing regimen.

The results of our study argue that the addition of HCTZ to each of the two ARBs did not act as a universal equalizer, and the efficacy differential between telmisartan and losartan monotherapy (*25*) is maintained despite the addition of the diuretic. The finding that T40/H12.5 provided greater blood pressure control than L50/H12.5 is probably related to the well-documented pharmacokinetic differences between telmisartan and losartan (*30*). The lower-dose fixed-dose combination of telmisartan/HCTZ (T40/H12.5) was superior to the L50/H12.5 fixed-dose combination in achieving blood pressure control at the end of the dosing interval. If combination therapy is considered appropriate initially, administration of T40/H12.5 rather than L50/H12.5 is likely to confer superior blood pressure and thus avoid the inconvenience of dose titration in a portion of patients.

The superior blood pressure control provided by T40/H12.5 compared with L50/H12.5 over the 24-h dosing interval and, most notably, at the end of the dosing interval may confer a significant long-term clinical benefit for the patient. For the majority of patients, morning dosing is most convenient; hence, the end of the dosing interval coincides with the time of day that correlates with a high prevalence of cardiovascular events (*6*–*8*). Clement *et al*. (*31*) recently concluded that higher values for ambulatory DBP or SBP predict cardiovascular events. After adjusting for clinic blood pressure, their study showed that increases in 24-h, daytime (8:00 AM– 8:00 PM) and nighttime (8:00 PM–8:00 AM) ambulatory blood pressure were associated with an increased risk for cardiovascular events, myocardial infarction or stroke. Furthermore, patients with a 24-h mean SBP ≥135 mmHg had an increased risk of cardiovascular events (relative risk: 1.74; 95% CI: 1.15 to 2.63) (*31*). Additionally, Kario *et al*. (*32*) noted that in older patients with hypertension, 78% of stroke events in those with the highest morning surge occur between the hours of 6:00 AM and midday. These observations suggest a correlation between the higher prevalence of cardiovascular events in the waking hours and a surge in morning blood pressure in people with hypertension. However, there is a currently a lack of definitive studies directly linking cardiovascular events with an early morning surge in blood pressure.

In summary, this study demonstrated that fixed-dose combinations of telmisartan/HCTZ and losartan/HCTZ were effective in lowering blood pressure and were well tolerated. However, T40/H12.5 offered sustained blood pressure control over the 24-h dosing interval and was better suited than L50/H12.5 for maintaining blood pressure reductions, with T80/H12.5 conferring additional blood pressure control. The superior antihypertensive activity of telmisartan/HCTZ was particularly notable in the last 6 h of the 24-h dosing cycle. This coincides with the early morning surge of blood pressure, indicating a true 24-h efficacy with telmisartan, a drug with an extremely long half-life, when combined with HCTZ.

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Appendix

Investigators Participated in This Trial

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