Original Article

Antihypertensive Efficacy and Safety of Fixed-Dose Combination Therapy with Losartan plus Hydrochlorothiazide in Japanese Patients with Essential Hypertension

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A randomized, double-blind, placebo-controlled, parallel-group multicenter study was conducted to evaluate the antihypertensive efficacy and safety of 8-week treatment with one of three fixed-dose combinations—losartan 50 mg plus hydrochlorothiazide 12.5 mg, losartan 50 mg plus hydrochlorothiazide 6.25 mg, or losartan 25 mg plus hydrochlorothiazide 6.25 mg—in comparison with those of hydrochlorothiazide 12.5 mg alone, losartan 50 mg alone, or placebo in Japanese patients with essential hypertension. Significant reductions in sitting diastolic blood pressure (DBP) and systolic blood pressure (SBP) were seen in all three combination groups compared with the placebo group (each $p<0.001$). The greatest reductions in DBP and SBP were observed in the losartan 50 mg plus hydrochlorothiazide 12.5 mg group (12.7 and 18.0 mmHg, respectively). The reductions in the losartan 50 mg plus hydrochlorothiazide 12.5 mg group were significantly greater (each $p<0.001$) than those in the placebo group and each of the monotherapy groups. There were no significant differences in the incidences of clinical and laboratory drug-related adverse events between any of the combination groups and the placebo group. All combination groups showed improved hypokalemia and hyperuricemia compared to the hydrochlorothiazide 12.5 mg group. These results demonstrated that once-daily, fixed-dose combination therapy with losartan 50 mg plus hydrochlorothiazide 12.5 mg is well tolerated and more efficacious in lowering DBP and SBP than monotherapy in Japanese hypertensive patients. (*Hypertens Res* 2007; 30: 729–739)

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

Introduction

Hypertension plays a major role in the development of cerebrovascular disease, ischemic heart disease, and cardiac and renal failure. The risk of these events decreases with the magnitude of sustained reduction in blood pressure (*1*, *2*).

Angiotensin II receptor antagonists exert an antihypertensive effect by specifically inhibiting the binding of angiotensin II to the angiotensin II subtype 1 receptor (*3*). Losartan potassium (losartan), an orally active and highly specific nonpeptide competitive angiotensin II subtype 1 receptor antagonist, is the first member of this new class of cardiovascular drugs available for treatment of patients with hypertension

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and potentially useful for other cardiovascular diseases as well (*4*, *5*). A number of clinical trials have demonstrated that losartan given alone lowers blood pressure and is well tolerated in patients with hypertension (*6–9*). Furthermore, losartan has been demonstrated to have benefits on renal diseases and stroke beyond blood pressure reduction (*10*, *11*).

Hydrochlorothiazide, a thiazide diuretic, has been used for the treatment of hypertension over 40 years. Thiazide diuretics affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing the excretion of sodium and chloride. Although hydrochlorothiazide has been demonstrated to have an antihypertensive effect, the mechanism of its action is not fully understood. Since a number of studies have demonstrated that diuretics lower morbidity and mortality in hypertensive patients (*12–14*), the 7th Joint National Committee Report recommends diuretics as one of the first-line drugs for the treatment of hypertension (*15*). The Japanese Society of Hypertension Guidelines for the Management of Hypertension in 2004 also recommend low doses of diuretics as one of the first-line drugs for the treatment of hypertension (*16*).

Despite the widespread use of monotherapies in treating hypertension, only 40% of patients achieve the target blood pressure by these therapies (*17*, *18*). Therefore, the majority of hypertensive patients require concomitant therapy with two or more different classes of drugs to achieve the target blood pressure level (*15*, *19*). A combination of different types of antihypertensive agents is more successful than a single agent in most hypertensive patients, with the added advantage of a better safety profile. The combination of an angiotensin II receptor antagonist and a diuretic such as hydrochlorothiazide is frequently recommended for the treatment of hypertension (*1*, *15*, *16*, *20*) for the following reasons (*21*, *22*): first, angiotensin II receptor antagonists and hydrochlorothiazide have complementary pharmacological mechanisms of action that provide greater reductions in blood pressure than can be achieved by either alone; and second, the lower doses of hydrochlorothiazide used in combination therapy to achieve adequate blood pressure reduction minimize the likelihood of drug-related adverse events. The increased efficacy and safety of combination therapy, and the simplified dosing with a single tablet, may also result in better patient compliance and help patients to remain on this therapy.

A fixed combination of losartan and hydrochlorothiazide has been used safely and effectively to treat more than 10 million patients in 82 countries since it was first introduced into clinical practice in France in 1995. The combination has been shown to produce clinically relevant reductions in blood pressure in male and female, Caucasian and African-American, elderly and non-elderly patients, in patients with varying degrees of hypertension, and in patients complicated with renal impairment (*21–26*). However, no study has been conducted so far to investigate the efficacy and safety of a fixed-dose therapy with losartan and hydrochlorothiazide in Japanese patients with hypertension.

The purpose of this study was to investigate the antihypertensive efficacy and safety of 8-week treatment with one of three fixed-dose combinations—losartan 50 mg plus hydrochlorothiazide 12.5 mg, losartan 50 mg plus hydrochlorothiazide 6.25 mg, or losartan 25 mg plus hydrochlorothiazide 6.25 mg—in comparison with those of hydrochlorothiazide 12.5 mg alone, losartan 50 mg alone, or placebo in Japanese patients with essential hypertension.

Methods

This study was conducted at 101 clinical centers in Japan, the USA, and Peru (76, 21 and 4 clinical centers, respectively). The study protocol was approved by the institutional review board at each clinical center. All patients gave their written informed consent to participate in the study in accordance with the Declaration of Helsinki. The execution and monitoring of the study were conducted in accordance with the requirements of good clinical practice.

Patient Selection

Eligible patients were men and women between 25 and 74 years of age with essential hypertension, which was diagnosed by clinical and laboratory examinations, and were Japanese (by self-report, patients were of Japanese descent with all four biological grandparents born in Japan and of Japanese descent). Patients were excluded from the study if there was any evidence of clinically significant hematologic, renal, hepatic, or gastrointestinal tract problems, known drug hypersensitivities or diseases involving the cerebrovascular, immune, or cardiovascular systems, including myocardial infarction, angina pectoris, congestive heart failure (New York Heart Association [NYHA] class III to IV) or left ventricular dysfunction (ejection fraction $<40\%$), or other concurrent severe diseases. Patients were also excluded from the study if they were concomitantly using other antihypertensive medications or drugs with significant hemodynamic effects, or if they were taking lithium, psychotropic agents, antidepressants, anxiolytic or hypnotic agents, oral corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), COX-II inhibitors or high-dose aspirin (daily use), ephedrine, astemizole, terfenadine, digoxin or any agent that had an effect on blood pressure. Pregnant or lactating women were also excluded.

Study Procedures

This randomized, placebo-controlled, double-blind, parallel–group study consisted of a screening visit (visit 1), 4 to 6 weeks of a placebo run-in period followed by 8 weeks of double-blind treatment during which patients received either losartan 50 mg plus hydrochlorothiazide 12.5 mg, losartan 50 mg plus hydrochlorothiazide 6.25 mg, losartan 25 mg plus hydrochlorothiazide 6.25 mg, losartan 50 mg alone, hydro-

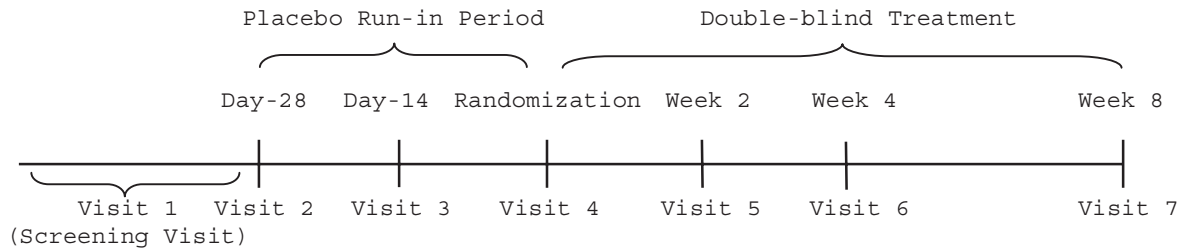

Fig. 1. *Study design.*

chlorothiazide 12.5 mg alone, or placebo (Fig. 1). Patients were seen in the clinic at day −28 (visit 2) and day −14 (visit 3) during the placebo run-in period, at randomization (visit 4), and at weeks 2, 4 and 8 of the double-blind treatment period (visit 5, 6 and 7, respectively). All visits had to be done within ±3 days of the specified time point.

Prior to study entry, patients had a complete medical history review, physical examination and laboratory evaluation. If eligible, patients were given 5 placebo tablets matched to each of losartan 50 mg plus hydrochlorothiazide 12.5 mg, losartan 50 mg plus hydrochlorothiazide 6.25 mg, losartan 25 mg plus hydrochlorothiazide 6.25 mg, losartan 50 mg, and hydrochlorothiazide 12.5 mg once daily for 4 weeks. The mean sitting diastolic blood pressure (DBP) for patients who had no previous antihypertensive therapy had to be 95 to 115 mmHg prior to entering the placebo run-in period. The mean DBP for patients who were under antihypertensive treatment had to be <110 mmHg after withdrawal from antihypertensive therapy (taper/washout), prior to entering the placebo run-in period. All patients who had a mean trough sitting DBP of 95 to 115 mmHg and a mean trough sitting systolic blood pressure (SBP) <210 mmHg at each visit throughout the placebo run-in period up to the day of randomization and those who continued to fulfill the eligibility criteria were randomized into 1 of 6 treatment arms (losartan 50 mg plus hydrochlorothiazide 12.5 mg, losartan 50 mg plus hydrochlorothiazide 6.25 mg, losartan 25 mg plus hydrochlorothiazide 6.25 mg, losartan 50 mg, hydrochlorothiazide 12.5 mg, or placebo). The randomizations were separately performed by region (inside and outside of Japan, respectively). Any patient who had not attained stability (the difference between the mean trough DBP value at visit 3 and that at visit 4 [randomization] was >7 mmHg) after 4 weeks on placebo was continued in the placebo run-in period for an additional 2 weeks, and then the blood pressure was measured again. The study medication (5 blinded tablets) was taken in the morning between the hours of 6 AM and 10 AM after breakfast (except on the day of the clinic visit) once-daily from the starting day of randomization.

Blood pressure criteria for discontinuation from the study during the double-blind period included: mean trough SBP <100 mmHg, mean trough DBP <50 mmHg, mean trough SBP >210 mmHg or mean trough DBP >120 mmHg at any visit, or change in the mean trough DBP or SBP from the baseline (visit 4, randomization) of >15 mmHg or >30 mmHg, respectively. In all patients who met any of the blood pressure discontinuation criteria, the blood pressure was measured again after 1 h. If the blood pressure still met the discontinuation criteria, the patient was discontinued. Except for the screening visit (visit 1), all clinic visits had to be done in the morning before 12 noon to ensure that blood pressure measurements were performed at trough, defined as 24 h (range 22 to 26 h) after the last dose of medication.

Methods of Observation

Trough sitting blood pressure and heart rate were measured at the beginning of every clinic visit. Trough supine and standing blood pressure were measured at visit 4 (randomization) and visit 7. For the sitting and supine blood pressure measurements, the patients were in each position for at least 5 min and blood pressure was recorded. For standing blood pressure readings, the patients were in the standing position for at least 1 min prior to the measurements. DBP and SBP were determined as the average of three replicate measurements obtained 1 to 2 min apart. None of the three consecutive DBP readings could be >5 mmHg from the calculated average of the three readings; additional readings were made until this was achieved. Only one reading was conducted for the supine and standing blood pressure measurements.

All observed or volunteered adverse events were recorded at each visit and designated by the investigator as definitely drug related, probably drug related, possibly drug related, probably not drug related, or definitely not drug related. Standard fasting laboratory tests were performed at visits 1, 4, 6 and 7. A 12-lead electrocardiogram and body weight were obtained during the placebo run-in period and after 8 weeks of double-blind therapy.

Statistical Analysis

The data analysis was carried out based on a "Full Analysis Set" (FAS), which was defined as all of the enrolled patients except the following: patients who committed serious good clinical practice (GCP) violations; patients who did not take at least one dose of study medication; patients who lacked any

Table 1. Patient Demographics and Baseline Characteristics

	L50/H12.5 (n=154)	L50/H6.25 (n=159)	L25/H6.25 (n=153)	L50 (n=157)	H12.5 (n=162)	Placebo (n=157)
Gender (No. (%))						
Male	88 (57.1)	102 (64.2)	91 (59.5)	97 (61.8)	91 (56.2)	86 (54.8)
Female	66 (42.9)	57 (35.8)	62 (40.5)	60 (38.2)	71 (43.8)	71 (45.2)
Age (years)*	54.7±9.9	56.1±8.9	54.9±10.3	55.5±9.9	55.7±9.4	54.8±10.5
Any medical history† (yes (%))	63 (40.9)	66 (41.5)	69 (45.1)	74 (47.1)	64 (39.5)	60 (38.2)
Any concomitant therapy (yes (%))	124 (80.5)	123 (77.4)	124 (81.0)	121 (77.1)	134 (82.7)	130 (82.8)
Prior antihypertensive therapy (yes (%))	84 (54.5)	86 (54.1)	97 (63.4)	94 (59.9)	91 (56.2)	95 (60.5)
Baseline DBP (mmHg)*	100.7±5.1	100.6±5.4	100.7±4.8	100.8±5.3	99.8±4.8	100.2±4.9
Baseline SBP (mmHg)*	154.3±13.8	155.3±13.3	154.7±14.6	154.4±15.1	155.3±15.3	153.4±12.8
Place of residence (No.(%))						
Japan	130 (84.4)	132 (83.0)	129 (84.3)	131 (83.4)	133 (82.1)	128 (81.5)
USA	7 (4.5)	8 (5.0)	9 (5.9)	9 (5.7)	11 (6.8)	9 (5.7)
Peru	17 (11.0)	19 (11.9)	15 (9.8)	17 (10.8)	18 (11.1)	20 (12.7)

*Values are mean±SD. †Any medical history in the past 5 years except hypertension. L50, losartan 50 mg; H12.5, hydrochlorothiazide 12.5 mg; H6.25, hydrochlorothiazide 6.25 mg; L25, losartan 25 mg; DBP, sitting diastolic blood pressure; SBP, sitting systolic blood pressure. There were no significant differences among the treatment groups.

data of trough DBP postrandomization; patients who withdrew consent during the study and declined use of any data obtained before the withdrawal; patients who did not satisfy the major entry criteria (*i.e.*, violations of the inclusion criteria of blood pressures). The last measurements of the withdrawn patients in the double-blind period were carried forward to subsequent time points. For the safety evaluation, patients who had taken the study medication at least once were included in the analysis.

The primary and secondary hypotheses in this study were that the combinations of losartan and hydrochlorothiazide would be more effective in lowering mean trough DBP and SBP, respectively, than placebo, hydrochlorothiazide monotherapy or losartan monotherapy. All analyses described below were pre-specified in a Data Analysis Plan prior to unblinding the data except for the analysis of laboratory values. As the primary efficacy analysis, the changes in mean trough DBP from baseline (visit 4, randomization) at week 8 were evaluated using an analysis of covariance model, which included factors for the treatment group and patient's place of residence (inside or outside of Japan) with the baseline blood pressure as a covariate. In the comparison among treatment groups, the statistical superiority of each of the three combinations of losartan plus hydrochlorothiazide compared to placebo, hydrochlorothiazide 12.5 mg, or losartan 50 mg was examined by following a hierarchy of conditions (step-down procedures). First, losartan 50 mg plus hydrochlorothiazide 12.5 mg was compared with placebo, hydrochlorothiazide 12.5 mg and losartan 50 mg, respectively, using the 95% confidence intervals (CIs) for the difference of the least square means of the change from baseline between the treatment groups. Only if losartan 50 mg plus hydrochlorothiazide 12.5 mg was superior to placebo, hydrochlorothiazide 12.5 mg and losartan 50 mg, would the second set of analyses be performed. In the second set, losartan 50 mg plus hydrochlorothiazide 6.25 mg was compared with placebo, hydrochlorothiazide 12.5 mg and losartan 50 mg, respectively, in the same manner as in the first step. Only if losartan 50 mg plus hydrochlorothiazide 6.25 mg was superior to placebo, hydrochlorothiazide 12.5 mg and losartan 50 mg, would the third step, the analyses of losartan 25 mg plus hydrochlorothiazide 6.25 mg, be performed in the same manner. The data was analyzed in this step-wise fashion, so that no adjustment for multiplicity was required. Nominal 95% CIs were included in the output for all comparisons. An analysis of covariance model with the interaction between treatment and region as an additional factor was used to assess the effect of this factor on the primary analysis. As a secondary efficacy analysis, the change in mean trough SBP was evaluated by the same procedures as used for the primary efficacy.

Homogeneity of patient demographic characteristics among treatment groups was examined using an analysis of variance for continuous variables and Pearson's χ^2 test for categorical variables. The incidences of all adverse events were compared between the treatment groups using Fisher's exact test. The difference of the change in blood pressure on postural change from a supine position to a standing position from baseline to week 8 was compared in a pair-wise fashion among the treatment groups using the same analysis of covariance model as used for the primary variable. For laboratory values, the changes in each parameter at the end of the treatment period from baseline were compared between the three combinations of losartan plus hydrochlorothiazide and each of placebo, hydrochlorothiazide 12.5 mg and losartan 50 mg using the analysis of variance (not pre-specified).

A significance level of 15% on a two-tailed test was used

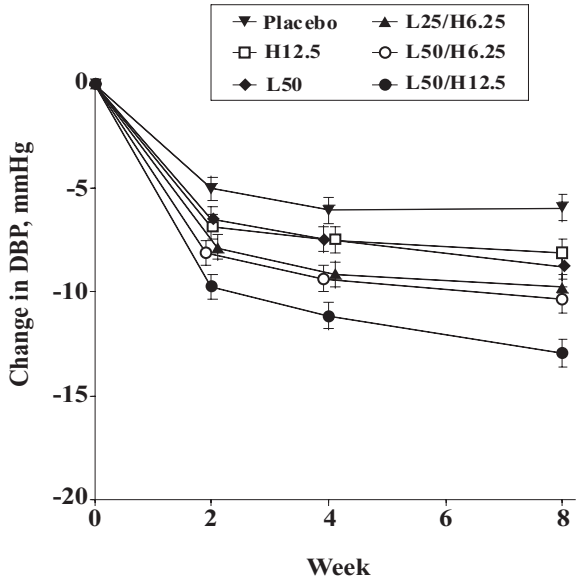

Fig. 2. *Mean change (mean±SEM) in trough sitting diastolic blood pressure during double-blind treatment from baseline in patients with essential hypertension. L50, losartan 50 mg; H12.5, hydrochlorothiazide 12.5 mg; H6.25, hydrochlorothiazide 6.25 mg; L25, losartan 25 mg; DBP, diastolic blood pressure.*

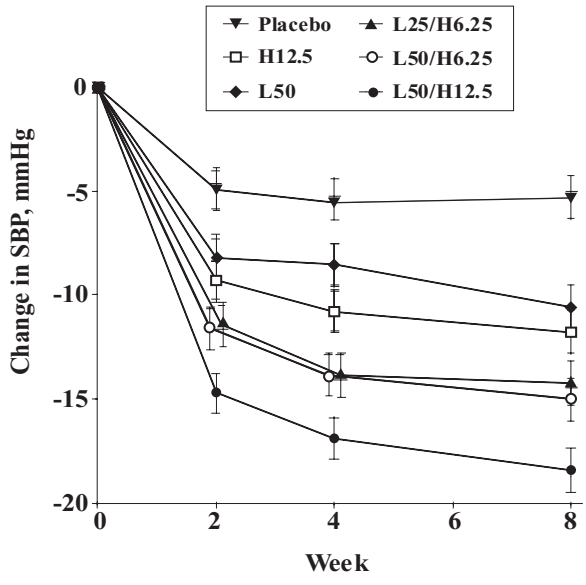

Fig. 3. *Mean change (mean±SEM) in trough sitting systolic blood pressure during double-blind treatment from baseline in patients with essential hypertension. L50, losartan 50 mg; H12.5, hydrochlorothiazide 12.5 mg; H6.25, hydrochlorothiazide 6.25 mg; L25, losartan 25 mg; SBP, systolic blood pressure.*

for analysis of baseline comparability among the treatment groups, a significance level of 2.5% (one-tailed) was used for verification of superiority, and a significance level of 10% (two-tailed) was used for the test of interaction. For all other analyses, a significance level of 5% (two-tailed) was used.

Results

Patient Characteristics

A total of 961 patients were randomized and entered the double-blind phase of this study. Among them, 942 patients were available for FAS, and 954 patients for safety analysis. Seven patients in whom previous medication for essential hypertension was discontinued or tapered before obtaining written consent were excluded from all analyses. Eleven patients who did not meet the major entry criteria and one patient who lacked any postrandomization data were excluded from FAS. The baseline patient demographic characteristics used in the efficacy FAS are summarized in Table 1. There were no statistically significant differences among the patient groups with respect to gender, age, significant medical history in the past 5 years other than hypertension, concomitant therapy or prior antihypertensive therapy. The baseline trough DBP and SBP were also similar among the treatment groups, ranging from 99.8 to 100.8 mmHg and from 153.4 to 155.3 mmHg, respectively. More than 80% of patients lived in Japan, but no geographical biases were observed in any treatment group in any country.

Mean Change in Blood Pressure

Trough blood pressure was measured at baseline and at weeks 2, 4 and 8 of the double-blind treatment period. Figures 2 and 3 display the mean change in trough DBP and SBP from baseline for each treatment group, respectively. The reductions of both DBP and SBP were apparent at the first measurement (after 2 weeks of daily treatment) in all treatment groups, and were maintained or continued to decrease throughout the remainder of the 8-week treatment period. The losartan 50 mg plus hydrochlorothiazide 12.5 mg group showed the maximum reduction of both DBP and SBP throughout the 8-week treatment.

Mean changes and least square mean changes from baseline after 8-week treatment for trough DBP and SBP are displayed in Table 2. Significant reductions in trough DBP and SBP were observed in all treatment groups (each $p<0.001$), with the greatest reductions occurring in the losartan 50 mg plus hydrochlorothiazide 12.5 mg group (12.7 and 18.0 mmHg, respectively). In regard to the reduction of DBP, the losartan 50 mg plus hydrochlorothiazide 12.5 mg group was significantly superior to the placebo, hydrochlorothiazide 12.5 mg monotherapy, and losartan 50 mg monotherapy groups (Table 2). The losartan 50 mg plus hydrochlorothiazide 6.25 mg group was superior to the placebo and hydrochlorothiazide

Table 2. Mean Changes in Trough Sitting Blood Pressure from Baseline after 8 Weeks of Treatment

Treatment group	Baseline* (mmHg)	Week 8* (mmHg)	Mean change* (mmHg)	LS-mean change† (mmHg)	95% CI (LS-mean change)	Comparison (*p*)		
						vs. L50	*vs*. H12.5	*vs*. placebo
Diastolic								
L50/H12.5	100.7±5.1	88.0±9.3	−12.7±8.2	−12.9±0.7	−14.2 to −11.7	<0.001	<0.001	<0.001
L50/H6.25	100.6±5.4	90.5±9.8	−10.1±7.9	−10.4±0.6	−11.6 to −9.1	0.061	0.008	<0.001
L25/H6.25	100.7±4.8	91.2±8.2	−9.5±6.6	−9.8±0.7	−11.1 to −8.5	0.241	0.051	<0.001
L50	100.8±5.3	92.3±8.3	−8.5±7.6	−8.8±0.6	−10.0 to −7.5	—	—	—
H12.5	99.8±4.8	91.9±8.8	−7.8±6.6	−8.1±0.6	−9.3 to −6.9	—	—	—
Placebo	100.2±4.9	94.5±9.8	−5.7±8.3	−5.9±0.6	−7.2 to −4.7	—	—	—
Systolic								
L50/H12.5	154.3±13.8	136.3±17.2	−18.0±14.3	−18.4±1.0	−20.5 to −16.4	<0.001	<0.001	<0.001
L50/H6.25	155.3±13.3	140.4±15.2	−14.9±14.2	−15.0±1.0	−17.0 to −13.1	0.001	0.018	<0.001
L25/H6.25	154.7±14.6	140.8±15.0	−13.9±11.8	−14.2±1.1	−16.3 to −12.1	0.009	0.078	<0.001
L50	154.4±15.1	144.2±16.7	−10.2±13.1	−10.6±1.0	−12.6 to −8.5	—	—	—
H12.5	155.3±15.3	143.6±14.6	−11.7±11.9	−11.8±1.0	−13.8 to −9.8	—	—	—
Placebo	153.4±12.8	148.7±16.0	−4.7±11.5	−5.3±1.0	−7.3 to −3.3	—	—	—

*Values are mean±SD. †Values are least square mean (LS-mean) ±SEM. L50, losartan 50 mg; H12.5, hydrochlorothiazide 12.5 mg; H6.25, hydrochlorothiazide 6.25 mg; L25, losartan 25 mg; CI, confidence interval. There were significant differences of the mean change in trough sitting blood pressure between baseline and Week 8 in all treatment groups (each $p<0.001$).

12.5 mg, but not to the losartan 50 mg group. The losartan 25 mg plus hydrochlorothiazide 6.25 mg group was superior to the placebo, but not to the hydrochlorothiazide 12.5 mg monotherapy or losartan 50 mg monotherapy group. An analysis of covariance model with treatment-by-region interaction as an additional factor was used to evaluate the influences on the primary analysis of the primary endpoint. No significant difference was seen with the interaction between treatment group and region ($p=0.603$).

The reduction in SBP in the losartan 50 mg plus hydrochlorothiazide 12.5 mg group was significantly greater than those in the placebo, hydrochlorothiazide 12.5 mg monotherapy, and losartan 50 mg monotherapy groups (Table 2). The reduction in the losartan 50 mg plus hydrochlorothiazide 6.25 mg group was also significantly greater than those in the placebo, hydrochlorothiazide 12.5 mg monotherapy, and losartan 50 mg monotherapy groups. The reduction in the losartan 25 mg plus hydrochlorothiazide 6.25 mg group was significantly greater than that in the placebo group.

The subgroup analysis for the primary endpoint was performed by age (≤64 years, ≥65 years) and by severity of hypertension, as measured by mean trough DBP at the time of randomization (≤105 mmHg, ≥106 mmHg). In all subgroup analyses, the losartan 50 mg plus hydrochlorothiazide 12.5 mg group demonstrated the greatest reduction in DBP among the treatment groups, and the efficacy in each of the subgroups was generally similar to the overall efficacy (data not shown).

Safety

Clinical and laboratory adverse events are summarized in Table 3. The percentages of patients having a clinical adverse event or clinical drug-related adverse event (as assessed by the investigators) were generally similar in each treatment group. There were no significant differences in the incidences of clinical drug-related adverse events among the treatment groups. The percentage of patients having a laboratory adverse event or laboratory drug-related adverse event were also similar in each treatment group. No significant differences in the incidences of laboratory adverse events and laboratory drug-related adverse events were observed among the combination groups (losartan 50 mg plus hydrochlorothiazide 12.5 mg, losartan 50 mg plus hydrochlorothiazide 6.25 mg, losartan 25 mg plus hydrochlorothiazide 6.25 mg) and the placebo group. There were no deaths in this study and 9 patients had serious adverse events, which were all considered by the investigators to be definitely not or probably not drug-related. The rates of discontinuation due to adverse events during the double-blind period were not significantly different among the treatment groups.

Of the 9 patients for whom dizziness was reported as an adverse event in the losartan 50 mg plus hydrochlorothiazide 12.5 mg group, 5 cases were considered to be drug-related by the investigators; these 5 cases were all mild and did not require any treatment, and none of these patients were discontinued from the study due to dizziness. The other 4 cases were considered to be not drug-related by the investigators. The incidence of pollakisuria reported as an adverse event was less

Table 3. Clinical and Laboratory Adverse Event (AE) Summary

	L50/H12.5 (n=155)	L50/H6.25 (n=162)	L25/H6.25 (n=155)	L50 (n=160)	H12.5 (n=163)	Placebo (n=159)
Clinical AE	80 (51.6)	70 (43.2)	59 (38.1)	68 (42.5)	69 (42.3)	71 (44.7)
Clinical drug-related AE	14 (9.0)	11 (6.8)	6 (3.9)	10 (6.3)	13 (8.0)	7 (4.4)
Laboratory AE	36 (23.2)	27 (16.7)	36 (23.2)	24 (15.0)	38 (23.3)	32 (20.1)
Laboratory drug-related AE	22 (14.2)	15 (9.3)	19 (12.3)	10 (6.3)	28 (17.2)	21 (13.2)
Discontinuations due to AE	1 (0.6)	6 (3.7)	1 (0.6)	2 (1.3)	4 (2.5)	1 (0.6)
Most common clinical AEs (patient incidence ≥2% in any treatment group)						
Nausea	6 (3.9) [2]	0 (0.0)	2 (1.3) [0]	1 (0.6) [0]	1 (0.6) [0]	2 (1.3) [0]
Headache	5 (3.2) [1]	5 (3.1) [1]	11 (7.1) [1]	9 (5.6) [1]	4 (2.5) [0]	10 (6.3) [1]
Dizziness	9 (5.8) [5]	2 (1.2) [0]	3 (1.9) [0]	4 (2.5) [2]	5 (3.1) [2]	3 (1.9) [0]
Malaise	3 (1.9) [0]	2 (1.2) [0]	2 (1.3) [1]	2 (1.3) [0]	5 (3.1) [1]	1 (0.6) [0]
Arthralgia	2 (1.3) [0]	1 (0.6) [0]	5 (3.2) [0]	0 (0.0)	1 (0.6) [0]	1 (0.6) [0]
Nasopharyngitis	23 (14.8) [0]	19 (11.7) [0]	15 (9.7) [0]	20 (12.5)[0]	22 (13.5)[0]	26 (16.4) [0]
Most common laboratory AEs (patient incidence ≥4% in any treatment group)						
Aspartate aminotransferase increased	3 (2.0) [2]	2 (1.3) [0]	7 (4.5) [6]	1 (0.6) [0]	4 (2.5) [4]	6 (3.8) [3]
Alanine aminotransferase increased	4 (2.6) [3]	2 (1.3) [1]	5 (3.2) [4]	2 (1.3) [1]	7 (4.3) [7]	5 (3.1) [2]
Blood creatine phosphokinase increased	4 (2.6) [3]	2 (1.3) [0]	9 (5.8) [0]	2 (1.3) [1]	3 (1.9) [2]	4 (2.5) [2]
Blood uric acid increased	10 (6.6) [8]	2 (1.3) [2]	7 (4.5) [6]	0 (0.0)	13 (8.1) [11]	8 (5.0) [6]
Red blood cells in urine: positive	1 (0.7) [0]	1 (0.6) [0]	1 (0.6) [0]	3 (1.9) [0]	7 (4.4) [5]	0 (0.0)

Values are number (%) of patients. Numbers in brackets indicate numbers of adverse events considered by the investigator to be possibly, probably, or definitely study drug-related. L50, losartan 50 mg; H12.5, hydrochlorothiazide 12.5 mg; H6.25, hydrochlorothiazide 6.25 mg; L25, losartan 25 mg.

than 2% in each treatment group. The incidence of increased blood uric acid in the hydrochlorothiazide 12.5 mg group (8.1%) was the highest rate for any laboratory adverse event among the treatment groups. There were no laboratory adverse events which were not seen in the monotherapy groups but were characteristically seen in the combination groups.

Mean changes from baseline for various laboratory measurements were evaluated and no clinically significant trends were evident in the combination groups after 8 weeks of treatment. As reported previously, monotherapy with hydrochlorothiazide 12.5 mg increased the mean blood uric acid level from baseline after the 8 weeks of treatment (+35 μmol/L, Table 4), while monotherapy with losartan 50 mg decreased it (−14 μmol/L). The combination of losartan 50 mg plus hydrochlorothiazide 12.5 mg induced a slight increase (+12 μmol/L), but the increase was significantly smaller than the increase by hydrochlorothiazide 12.5 mg (p<0.001). Combination therapy with losartan 50 mg plus hydrochlorothiazide 6.25 mg did not change the mean blood uric acid level. Monotherapy with hydrochlorothiazide 12.5 mg slightly lowered the blood potassium level after the 8 weeks of treatment (−0.17 mmol/L). A similar change was observed in the group treated with losartan 50 mg plus hydrochlorothiazide 12.5 mg (−0.09 mmol/L), but the decrease was significantly smaller than that by hydrochlorothiazide 12.5 mg alone (p=0.040). No clinically significant change of mean casual blood glucose level was observed in any treatment group.

There were no statistically significant differences in the mean changes from baseline after 8-weeks of treatment for heart rate, body weight and blood pressure on postural change in any of the treatment groups. There were also no differences observed for electrocardiographic measurements. The incidences of clinical and laboratory adverse events in the age subgroups (≤64 years, ≥65 years) and in the subgroups formed according to severity of hypertension, as measured by mean trough DBP at the time of randomization (≤105 mmHg, ≥106 mmHg) were also examined, and they were generally similar to the overall incidences of adverse events (data not shown).

Discussion

This study examined the antihypertensive efficacy of 8-week treatment with three different fixed-dose combinations of losartan plus hydrochlorothiazide in Japanese patients with essential hypertension. The greatest reductions in DBP and SBP were achieved by the combination of losartan 50 mg plus hydrochlorothiazide 12.5 mg (12.7 and 18.0 mmHg, respectively). In a similar clinical study in the USA, MacKay *et al*. (*22*) reported that the greatest reductions in DBP and SBP from baseline after 12-week treatment were observed in the losartan 50 mg plus hydrochlorothiazide 12.5 mg group (13.2 and 17.2 mmHg, respectively) compared with the placebo (4.1 and 2.0 mmHg, respectively), hydrochlorothiazide 12.5

Table 4. Mean Changes of Blood Uric Acid, Potassium and Glucose from Baseline after 8 Weeks of Treatment

Parameter and treatment group	No.	Baseline*	Week 8*	Change*	Comparison (*p*)		
					vs. L50	*vs*. H12.5	*vs*. placebo
Serum uric acid (μmol/L[a])							
L50/H12.5	152	350±81	362±85	12±48	<0.001	<0.001	0.007
L50/H6.25	160	347±77	346±77	−1±47	0.019	<0.001	0.744
L25/H6.25	154	353±83	358±79	5±52	0.001	<0.001	0.170
L50	160	346±79	333±77	−14±40	—	—	—
H12.5	161	345±89	380±102	35±51	—		—
Placebo	159	333±88	330±90	−3±51	—	—	—
Serum potassium (mmol/L)							
L50/H12.5	154	4.20±0.33	4.11±0.34	−0.09±0.36	0.011	0.040	0.099
L50/H6.25	160	4.24±0.36	4.17±0.39	−0.07±0.40	0.040	0.009	0.257
L25/H6.25	154	4.26±0.33	4.15±0.30	−0.11±0.29	0.002	0.140	0.025
L50	160	4.22±0.35	4.24±0.38	0.01±0.38	—	—	—
H12.5	162	4.24±0.39	4.07±0.32	−0.17±0.34	—	—	—
Placebo	159	4.23±0.38	4.21±0.40	−0.02±0.34	—	—	—
Casual blood glucose (mmol/L[b])							
L50/H12.5	151	5.59±1.37	5.71±1.47	0.12±1.21	0.342	0.520	0.717
L50/H6.25	160	5.51±1.13	5.72±1.18	0.21±0.89	0.122	0.216	0.831
L25/H6.25	154	5.78±1.49	5.82±1.74	0.04±1.47	0.711	0.951	0.344
L50	160	5.58±1.25	5.56±1.74	−0.02±1.55	—	—	—
H12.5	161	5.83±1.70	5.86±1.90	0.03±1.06	—	—	—
Placebo	158	5.61±1.26	5.78±1.63	0.18±1.42	—	—	—

*Values are mean±SD. L50, losartan 50 mg; H12.5, hydrochlorothiazide 12.5 mg; H6.25, hydrochlorothiazide 6.25 mg; L25, losartan 25 mg. [a]To convert values to mg/dL, divide by 59.48. [b]To convert values to mg/dL, divide by 0.05551.

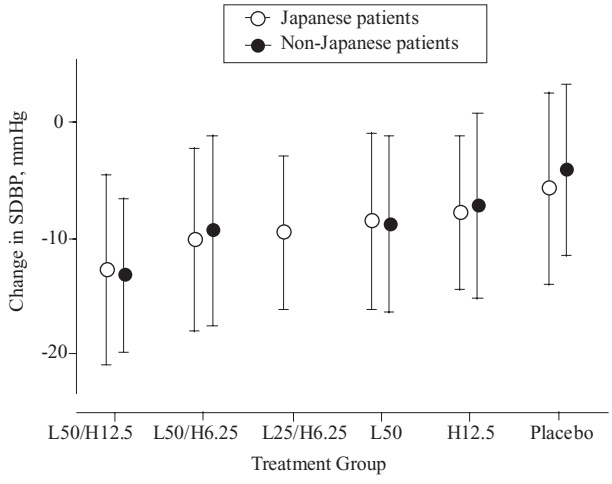

Fig. 4. *Mean change (mean±SD) in trough sitting diastolic blood pressure from baseline after 8 weeks treatment in Japanese patients and after 12 weeks treatment in non-Japanese patients with essential hypertension. L50, losartan 50 mg; H12.5, hydrochlorothiazide 12.5 mg; H6.25, hydrochlorothiazide 6.25 mg; L25, losartan 25 mg; DBP, diastolic blood pressure.*

mg (7.2 and 9.2 mmHg, respectively) and losartan 50 mg (8.8 and 10.7 mmHg, respectively) groups in patients with hypertension (86% Caucasian, 12% African-American, 2% others). Figure 4 shows the reduction in trough DBP from baseline for each treatment group of the Japanese cohort in the current study and of non-Japanese patients in the USA study. There was no difference in the blood pressure response to any of these medications between Japanese and non-Japanese patients. Furthermore, no differences in the efficacy profiles of the combinations were observed according to the patient's place of residence (inside or outside of Japan) as well as by age or severity of hypertension, indicating that our hypertensive patients showed the same response to the medications irrespective of whether they lived inside or outside Japan.

Hydrochlorothiazide monotherapy was approved in Japan at the manufacturer's recommended dose of 25 to 100 mg/day, which has been proven efficacious in controlling blood pressure. Furthermore, several studies have demonstrated that hydrochlorothiazide 12.5 mg, which is less than the approved dose in Japan, has antihypertensive efficacy with minimal drug-related adverse events (*15*, *27*). A number of clinical studies have shown enhanced blood pressure–lowering effects when different doses of losartan were added to a fixed dose of hydrochlorothiazide or when different doses of hydrochlorothiazide were added to a fixed dose of losartan (*21*, *22*, *28*, *29*). In a study outside of Japan, Ruilope *et al*. (*29*)

reported that losartan 50 mg plus hydrochlorothiazide 12.5 mg produced clinically beneficial reductions in blood pressure with a metabolic safety profile generally similar to losartan alone, and concluded that hydrochlorothiazide 12.5 mg was the optimal dose of diuretic when added to losartan 50 mg, which was consistent with the current study in Japanese patients.

The incidence of all clinical and laboratory adverse events was generally similar in each treatment group. Nine patients had serious adverse events, but all cases were considered to be not drug-related by the investigators. There were no statistically significant differences in the rate of discontinuation due to adverse events among the treatment groups. These results indicated that the safety profile of the three combinations of losartan plus hydrochlorothiazide was comparable with that of placebo. When used as monotherapy, hydrochlorothiazide causes adverse events (hypokalemia, hyperuricemia, hyperglycemia, hyperlipidemia, sexual dysfunction, dizziness, *etc*.) in a dose-dependent manner. However, if the dose of diuretic in a fixed combination product is kept low, the potential adverse events of the diuretic are minimized (*15*). One of the advantages of the combination of angiotensin II receptor antagonists with low-doses of hydrochlorothiazide is the potential reduction of hydrochlorothiazide-induced metabolic disorders such as hypokalemia. In particular, when losartan is used as the angiotensin II receptor antagonist, the combination with hydrochlorothiazide can have attractive benefits for cases of hyperuricemia. That is, losartan, unlike the other angiotensin II receptor antagonists, has been shown to have a uricosuric action (*28*, *30*). Recently, Enomoto *et al*. identified a renal urate-anion exchanger that regulates blood urate levels (*31*). They reported that losartan inhibited the urate uptake, and the IC_{50} of losartan tended to be the same as that of probenecid, consistent with the uricosuric property of losartan. In the present study, the increase in blood uric acid and decrease in blood potassium induced by hydrochlorothiazide were lessened by the co-administration of losartan. This finding could represent an additional benefit of the combination of losartan and low-doses of hydrochlorothiazide for Japanese hypertensive patients with elevated blood uric acid levels.

Though the current study employed an 8-week treatment period, several clinical studies on the long-term use of losartan plus hydrochlorothiazide in patients with hypertension have revealed that the antihypertensive efficacy of this regimen was maintained for at least 12 months and that the safety profile of losartan alone or in combination with hydrochlorothiazide was essentially the same as that observed in the short-term studies and in patients receiving placebo (*21*, *32*). After the 8-week treatment in the current study, the combination of losartan 50 mg plus hydrochlorothiazide 12.5 mg was administered for the following 52 weeks to some of our patients. There were no significant differences in the safety profiles between the initial 8-week and the following 52-week treatments (unpublished data).

The goal of antihypertensive treatment is to reduce cardiovascular and cerebrovascular events associated with high blood pressure (*1*, *15*). If conventional monotherapy fails, the control of blood pressure could be attempted by a progressive increase in the dose of the single drug, a switch to other monotherapy, or by combination therapy. Combinations of antihypertensive drugs with complementary actions represent a logical approach that is likely to achieve target blood pressure control, and may minimize adverse events and reduce clinical outcomes by improving blood pressure control and organ protection. Current trends in hypertension management emphasize multidrug regimens rather than monotherapy; the HOT study (the Hypertension Optimal Trial) demonstrated that the vast majority of patients require two or more antihypertensive agents in order to achieve blood pressure control (*33*). The INVEST study (the International Verapamil-Trandolapril Study) indicated that lower targets for blood pressure control can be achieved in most hypertensive patients with coronary artery disease using a multidrug strategy (*34*).

Although the current study does not provide information on the percentage of patients for whom monotherapy failed, it demonstrated that the fixed-dose combination therapy with losartan 50 mg plus hydrochlorothiazide 12.5 mg once-daily was well tolerated and more efficacious in lowering DBP and SBP than monotherapy in Japanese hypertensive patients. Furthermore, this simplified treatment regimen with a single tablet may also result in improved compliance.

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