ORIGINAL ARTICLE

Losartan/hydrochlorothiazide combination vs. high-dose losartan in patients with morning hypertension—a prospective, randomized, open-labeled, parallel-group, multicenter trial

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The treatment of morning hypertension has not been established. We compared the efficacy and safety of a losartan/hydrochlorothiazide (HCTZ) combination and high-dose losartan in patients with morning hypertension. A prospective, randomized, open-labeled, parallel-group, multicenter trial enrolled 216 treated outpatients with morning hypertension evaluated by home blood pressure (BP) self-measurement. Patients were randomly assigned to receive a combination therapy of 50 mg losartan and 12.5 mg HCTZ ($n=109$) or a high-dose therapy with 100 mg losartan ($n=107$), each of which were administered once every morning. Primary efficacy end points were morning systolic BP (SBP) level and target BP achievement rate after 3 months of treatment. At baseline, BP levels were similar between the two therapy groups. Morning SBP was reduced from 150.3 ± 10.1 to 131.5 ± 11.5 mm Hg by combination therapy ($P<0.001$) and from 151.0 ± 9.3 to 142.5 ± 13.6 mm Hg by high-dose therapy ($P<0.001$). The morning SBP reduction was greater in the combination therapy group than in the high-dose therapy group ($P<0.001$). Combination therapy decreased evening SBP from 141.6 ± 13.3 to 125.3 ± 13.1 mm Hg ($P<0.001$), and high-dose therapy decreased evening SBP from 138.9 ± 9.9 to 131.4 ± 13.2 mm Hg ($P<0.01$). Although both therapies improved target BP achievement rates in the morning and evening ($P<0.001$ for both), combination therapy increased the achievement rates more than high-dose therapy ($P<0.001$ and $P<0.05$, respectively). In clinic measurements, combination therapy was superior to high-dose therapy in reducing SBP and improving the achievement rate ($P<0.001$ and $P<0.01$, respectively). Combination therapy decreased urine albumin excretion ($P<0.05$) whereas high-dose therapy reduced serum uric acid. Both therapies indicated strong adherence and few adverse effects ($P<0.001$). In conclusion, losartan/HCTZ combination therapy was more effective for controlling morning hypertension and reducing urine albumin than high-dose losartan.

Hypertension Research (2012) 35, 708–714; doi:10.1038/hr.2012.27; published online 8 March 2012

Keywords: Ang II receptor blockers; antihypertensive therapy; clinical trial; diuretics; home blood pressure measurement

INTRODUCTION

Cardiovascular events, such as stroke and myocardial infarction, occur most frequently in the morning.^{1,2} Elevation of blood pressure (BP) in the early morning (morning hypertension) is a risk factor for cardiovascular events in the morning.^{3–6} A recent study using home-based BP self-measurement revealed that morning hypertension exists in ~65% of patients receiving antihypertensive medications.⁷ Currently, the treatment of morning hypertension has not been established.

Current guidelines for the management of hypertension recommend a combination therapy of antihypertensive agents when an antihypertensive monotherapy cannot achieve target BP levels.^{8,9}

Among various combinations, an angiotensin II type-1 receptor blocker (ARB) combined with a small dose of thiazide diuretic is desirable because the two drugs have complementary mechanisms of action, effectively reduce BP, and are generally well tolerated.^{10,11} A high-dose regimen of ARB is another treatment option. At present, however, little or no information is available on the efficacy of the ARB/thiazide diuretic combination for controlling morning hypertension.

Therefore, we conducted a prospective, randomized, open-labeled, multicenter trial to determine the efficacy and safety of a fixed-dose combination of losartan and hydrochlorothiazide (HCTZ) and a high dose of losartan in the treatment of patients with morning hypertension. For this purpose, outpatients experiencing morning hypertension

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This study was presented in the 'Late-Breaking Clinical Trials session' at the 34th Annual Scientific Meeting of the Japanese Society of Hypertension on 20 October 2011.

Received 15 September 2011; revised 8 November 2011; accepted 20 December 2011; published online 8 March 2012

despite antihypertensive medications were randomly assigned to receive a 'combination therapy' with a combination of 50 mg losartan and 12.5 mg HCTZ or a 'high-dose therapy' with 100 mg losartan. The primary efficacy end points were morning systolic BP (SBP) level and target BP achievement rate after 3 months of treatment on the basis of home BP self-measurement.

METHODS

The design of this study was a 3-month prospective, randomized, open-labeled, parallel-group, multicenter trial, with a blinded end-point assessment. This study was performed by the Morning Hypertension and Angiotensin Receptor Blocker/Hydrochlorothiazide Combination Therapy Study investigators in Japan (listed in Supplementary Data). The Institutional Review Boards or Ethics Committees of all participating institutions approved the study protocol. All patients provided written informed consent.

Study population

Outpatients who had morning hypertension despite antihypertensive medications were enrolled in the study. Morning hypertension was defined as a morning SBP ≥ 135 mm Hg, diastolic BP (DBP) ≥ 85 mm Hg or both⁹ on 7 different days of home BP self-measurements during the run-in period (at least 1 month). Exclusion criteria included secondary hypertension, malignant hypertension or uncontrolled hypertension (for example, DBP ≥ 120 mm Hg), uncontrolled diabetes mellitus with HbA1c $\geq 9.0\%$, a history of gout or serum uric acid ≥ 8.0 mg dl⁻¹, serum creatinine ≥ 2.0 mg dl⁻¹, serum potassium ≥ 5.5 mmol l⁻¹, liver damage (for example, alanine aminotransferase or γ -GTP level $>3\times$ the upper normal limit), administration of a thiazide diuretic, administration of an ARB or angiotensin-converting enzyme inhibitor (ACEI) exceeding the standard doses approved in Japan, and the presence of contraindications for thiazides or ARBs.

Study design

Patients were randomly assigned to receive a combination of 50 mg losartan and 12.5 mg HCTZ (combination therapy) or 100 mg losartan (high-dose therapy), each of which were administered once every morning. A 50-mg losartan/12.5-mg HCTZ combination tablet was used for the combination therapy. The envelope method was used for randomization. If patients had been administered an ARB or ACEI, the ARB or ACEI was switched to the losartan/HCTZ combination or 100 mg losartan. If an ARB or ACEI had not been prescribed, one of the prescribed antihypertensives was changed to either of the test drugs. There was no washout period before the randomization. The prescription of antihypertensive agents was not changed during the observation period.

On the day of the randomization, the initial evaluation (that is, medical history, medications) and laboratory tests were performed after written informed consent was obtained. Clinic BP values, adherence and information about adverse events were routinely recorded at each hospital visit every 4 weeks. After the 3-month treatment, the follow-up evaluation and laboratory tests were repeated. Adherence was semi-quantitatively evaluated: 1, 80% or more; 2, 50–80%; 3, $<50\%$. The adverse events included intractable high BP (for example, DBP >120 mm Hg), intractable hypotension symptoms (for example, fainting or dizziness), hyperkalemia (potassium >6.0 mmol l⁻¹), laboratory data abnormalities (for example, doubling increase of serum creatinine or transaminases) and any other conditions that the attending physicians considered to be medically necessary to protect the patients' best interests.

Measurements

Patients were instructed to perform BP self-measurements at home in the early morning (within 1 h after waking up, after urination, before dosing in the morning, before breakfast and after resting for 1–2 min in a sitting position) and in the evening (before bedtime, after resting for 1–2 min in a sitting position) every day, according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension 2009 (JSH2009 guidelines).⁹ Cuff oscillometry was applied using electronic upper arm-cuff devices. The type of devices is unknown, but the devices used were certified to comply with the

Association for the Advancement of Medical Instrumentation standards. Each patient used the same type of home BP monitoring device throughout the study. The values of the first measurements taken each morning and evening were recorded. The measurements of the last 7 days preceding each clinic visit were averaged for the morning and evening BP values. BP was measured in the clinic using a sphygmomanometer after 5 min resting in a seated position at 1- to 2-min intervals. At least two measurements were averaged for the clinic BP values.⁹

Circulating biochemical parameters and urinary albumin excretion were measured in the morning in a fasting state at baseline and after 3 months of treatment. All assays were performed using a commercially available laboratory. Estimated glomerular filtration rates (eGFR) were calculated with the Cockcroft-Gault equation.¹² Urine albumin levels were determined from a spot urine sample using a turbidimetric immunoassay and expressed as the urine albumin/creatinine ratio (urine albumin/creatinine ratio (UACR), mg g⁻¹ creatinine).¹³

Study outcomes

The primary efficacy end points were morning SBP level and target BP achievement rate in the morning (SBP <135 mm Hg and DBP <85 mm Hg) after the 3-month-treatment period. The secondary efficacy end points included (1) evening SBP level and the achievement rate of evening target BP (SBP <135 mm Hg and DBP <85 mm Hg), (2) clinic SBP level and target BP achievement ratio in the clinic (SBP <140 mm Hg and DBP <90 mm Hg) and (3) changes in serum potassium, uric acid, plasma type-B natriuretic peptide, eGFR and urinary albumin secretion after the 3-month-treatment period. The safety end points were adherence to medications and the prevalence of adverse events during the 3-month-treatment period.

Statistical analysis

Statistical analysis was performed using commercially available software (IBM SPSS Statistics 18.0J, IBM, Tokyo, Japan). Data are expressed as mean $\pm$ s.d. Because of skewed distributions, natural logarithmic transformations were performed for triglycerides, B-type natriuretic peptide and UACR before the data analyses. Paired Student's *t*-test and the χ^2 test were applied to determine the significance of differences between baseline and post-treatment values. Unpaired Student's *t*-test and the χ^2 test were used for detecting the significance of differences between the two treatment groups. A repeated measures analysis of variance followed by the Bonferroni/Dunn test was performed to evaluate the differences in the time-dependent changes between the two therapy groups. Differences were considered statistically significant at $P<0.05$. To detect a 5-mm Hg between-group BP difference with a power of 90% and a minimum significance level of $P<0.05$, given a s.d. of 10 mm Hg, 86 patients per group were necessary.

RESULTS

Baseline characteristics and demographics

A total of 216 patients were randomly assigned to the combination therapy ($n=107$) and high-dose therapy ($n=109$) groups (Table 1). The mean age of participants was 67.8 years (ranging from 37 to 92 years; 50% male). Morning BP was significantly higher than evening BP ($P<0.001$). At baseline, BP levels and target BP achievement rates were similar between the combination therapy and high-dose therapy groups. The groups had similar characteristics, with the exception of male gender prevalence, low-density lipoprotein cholesterol level and β -blocker use, which were slightly greater in the combination therapy group. During the run-in period, the average number of antihypertensive medications was 1.63 ± 0.81 and 1.57 ± 0.67 per patient in the combination therapy and high-dose therapy groups, respectively (no significance (NS)). An ACEI or ARB was prescribed to 93.6% in combination therapy and 94.4% in high-dose therapy (NS).

Follow-up and safety end points

During the follow-up period, 53.2% of patients in the combination therapy group and 52.3% of patients in the high-dose therapy group had no co-administered antihypertensive drugs (NS; Table 1).

Table 1 Baseline characteristics and demographics

	Total	Combination	High dose	P-value
Number, <i>n</i>	216	109	107	—
Age, year	67.8 ± 10.8	67.9 ± 11.3	67.8 ± 10.4	NS
Male, <i>n</i> (%)	108 (50.0)	63 (57.8)	45 (42.1)	0.021
BMI, kg m ⁻²	24.1 ± 3.1	24.1 ± 3.2	24.1 ± 3.0	NS
<i>Morning BP</i>				
Systolic BP, mm Hg	151.1 ± 9.7	150.1 ± 10.8	151.0 ± 9.9	NS
Diastolic BP, mm Hg	84.2 ± 9.3	83.9 ± 10.1	84.6 ± 9.5	NS
Target BP achievement, %	0.0	0.0	0.0	NS
<i>Evening BP</i>				
Systolic BP, mm Hg	139.9 ± 11.8	140.8 ± 13.3	139.0 ± 11.1	NS
Diastolic BP, mm Hg	76.5 ± 9.2	76.7 ± 10.4	76.2 ± 9.0	NS
Target BP achievement, %	26.1	25.0	27.1	NS
<i>Clinic BP</i>				
Systolic BP, mm Hg	148.4 ± 14.0	148.4 ± 14.5	148.4 ± 13.4	NS
Diastolic BP, mm Hg	80.6 ± 11.0	80.4 ± 12.0	79.5 ± 9.9	NS
Target BP achievement, %	24.9	27.2	23.5	NS
eGFR, ml per min per 1.73m ²	65.1 ± 12.3	63.6 ± 10.4	66.6 ± 13.9	NS
K, mmol l ⁻¹	4.3 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	NS
Uric acid, mg dl ⁻¹	5.8 ± 1.5	5.8 ± 1.7	5.7 ± 1.5	NS
LDL cholesterol, mg dl ⁻¹	112.5 ± 29.4	107.5 ± 28.8	117.7 ± 29.3	0.020
HDL cholesterol, mg dl ⁻¹	57.6 ± 14.5	58.0 ± 14.0	57.2 ± 15.1	NS
Triglycerides, mg dl ^{-1a}	131.1 (120.1–142.1)	126.0 (108.0–144.0)	135.4 (118.9–152.0)	NS
HbA1c, %	5.60 ± 0.68	5.61 ± 0.63	5.59 ± 0.74	NS
BNP, pg ml ^{-1a}	49.1 (40.2–58.1)	56.1 (38.9–73.3)	46.5 (30.4–63.7)	NS
UACR, mg g ⁻¹ Cre ^a	72.8 (40.1–104.6)	59.5 (23.1–95.8)	61.8 (34.9–88.7)	NS
<i>Comorbidity n (%)</i>				
Diabetes	36 (16.6)	21 (19.2)	15 (14.0)	NS
Dyslipidemia	88 (40.7)	41 (37.6)	47 (43.9)	NS
CAD	20 (9.3)	11 (10.1)	9 (8.4)	NS
CVD	18 (8.3)	11 (10.1)	7 (6.5)	NS
Smoking	30 (13.9)	11 (10.1)	19 (17.8)	NS
<i>Treatment during the run-in period n (%)</i>				
No. of antihypertensive drugs	1.60 ± 0.74	1.63 ± 0.81	1.57 ± 0.67	NS
ARB	195 (90.3)	99 (90.8)	96 (89.7)	NS
ACEI	8 (3.7)	3 (2.8)	5 (4.7)	NS
ARB or ACEI	203 (94.0)	102 (93.6)	101 (94.4)	NS
ARB or ACEI alone	105 (48.6)	54 (49.5)	51 (47.7)	NS
Ca channel blocker	88 (40.7)	39 (37.4)	49 (45.8)	NS
α-blocker	12 (5.6)	9 (8.3)	3 (2.8)	NS
β-blocker	33 (15.3)	22 (20.2)	11 (10.3)	0.043
Loop diuretics	2 (0.9)	1 (0.9)	1 (0.9)	NS
Aldosterone blocker	2 (0.9)	1 (0.9)	1 (0.9)	NS
Statins	56 (25.9)	24 (22.0)	32 (29.9)	NS
Antidiabetics or insulin	20 (9.3)	10 (9.2)	10 (9.2)	NS
<i>Antihypertensive treatment during the follow-up period n (%)</i>				
No coadministration	114 (52.8)	58 (53.2)	56 (52.3)	NS
Coadministered drug				
Ca channel blocker	80 (37.0)	35 (32.1)	45 (42.1)	NS
α-blocker	11 (5.1)	8 (7.3)	3 (2.8)	NS
β-blocker	30 (13.9)	20 (18.3)	10 (9.3)	NS
Loop diuretics	2 (0.9)	1 (0.9)	1 (0.9)	NS
Aldosterone blocker	1 (0.5)	1 (0.9)	0 (0.0)	NS

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type-1 receptor blocker; BMI, body mass index; BNP, type-B natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration ratio; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, no significance; UACR, urine albumin/creatinine ratio.

^a*P*-values <0.05 were considered significant for the intergroup comparisons.

^aGeometric mean (95% confidence interval) was expressed and log-transformed value was used for statistic analysis because of skewed distribution.

Figure 1 Enrollment and follow-up.**Table 2** Adherence and adverse effects

Adherence	1 month	2 month	3 month
Combination (%)			
80 or more	99.0	97.8	94.6
50–80	1.0	1.1	1.1
<50	0.0	0.0	2.2
High dose (%)			
80 or more	96.5	94.1	93.3
50–80	2.3	2.4	1.1
<50	1.2	1.2	1.1

Adverse effects n (%)	Untractable high BP	Headache	Hot flash	Urticaria or itching	Palpitation	Creatinine elevation	Total
Combination	1 (0.9)	1 (0.9)	0 (0)	1 (0.9)	0 (0)	1 (0.9)	4 (3.7)
High dose	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)	0 (0)	5 (4.6)

Abbreviation: BP, blood pressure.

The frequency of co-administration of Ca channel blockers, α -blockers, β -blockers, loop diuretics and aldosterone blockers was similar between the two groups.

Six (5.5%) patients receiving combination therapy and five (4.7%) patients receiving high-dose therapy were withdrawn or lost to follow-up, primarily because of these patients relocated (NS; Figure 1). Table 2 illustrates that the adherence to medications was high in both groups throughout the observation period. The follow-up was discontinued because of adverse effects in four (3.7%) patients receiving combination therapy and five (4.7%) patients receiving high-dose therapy (NS). However, no serious adverse effects were reported in either group (Table 2).

As shown in Figure 1, 97 patients receiving combination therapy and 99 receiving high-dose therapy completed the 3-month treatment and were included in the efficacy analyses.

Primary efficacy end points

Combination therapy reduced morning SBP from 150.3 ± 10.1 to 131.5 ± 11.5 mm Hg ($P < 0.001$), and high-dose therapy reduced morning SBP from 151.0 ± 9.3 to 142.5 ± 13.6 mm Hg ($P < 0.001$)

after 3 months of treatment (Figure 2a). Post-treatment morning SBP levels were lower in the combination therapy group than in the high-dose therapy group ($P < 0.001$). Combination therapy increased the target achievement rate of morning BP to 58.7%, and high-dose therapy increased it to 27.0% (Figure 3). Combination therapy indicated a twofold greater target BP achievement rate for morning BP than high-dose therapy ($P < 0.001$).

Secondary efficacy end points

Evening SBP was reduced from 141.6 ± 13.3 to 125.3 ± 13.1 mm Hg by combination therapy ($P < 0.001$) and from 138.9 ± 9.9 to 131.4 ± 13.2 mm Hg by high-dose therapy ($P < 0.01$; Figure 2b). Although the achieved SBP levels were similar between the two groups, combination therapy induced a greater evening SBP reduction than high-dose therapy ($P < 0.001$). The target BP achievement rate of evening BP was improved from 24.2 to 79.0% by combination therapy and from 28.3 to 61.7% by high-dose therapy ($P < 0.001$ for both; Figure 3). After treatment, the target BP achievement rate of evening BP was greater in the combination therapy group than in the high-dose therapy group ($P < 0.05$).

Combination therapy reduced clinic SBP from 147.0 ± 14.3 to 128.6 ± 14.7 mm Hg ($P < 0.001$), and high-dose therapy reduced clinic SBP from 147.5 ± 13.8 to 140.0 ± 15.2 mm Hg ($P < 0.05$; Figure 2c). Post-treatment clinic SBP levels were lower from combination therapy than from high-dose therapy ($P < 0.001$). Target BP achievement rates in the clinic were increased from 25.6 to 75.6% by combination therapy and from 22.8 to 51.3% by high-dose therapy ($P < 0.001$ for

both; Figure 3). Combination therapy improved the post-treatment target achievement rates of clinic BP more than high-dose therapy ($P < 0.01$).

Changes in UACR, uric acid, eGFR and HbA1c

UACR was reduced by combination therapy ($P < 0.05$) but was not changed by high-dose therapy after the 3-month-treatment period (Figure 4a). The serum uric acid levels were decreased by high-dose therapy ($P < 0.001$), but it was not changed by combination therapy (Figure 4b). There were no differences in eGFR and HbA1c levels between combination therapy and high-dose therapy groups after the 3-month-treatment period (Figures 4c and d). Neither therapy affected other biochemical parameters, such as serum potassium and B-type natriuretic peptide, after the 3-month-treatment period (Supplementary Table).

DISCUSSION

This study indicated that among patients with morning hypertension undergoing treatment, combination therapy with 50 mg losartan and 12.5 mg HCTZ and high-dose therapy with 100 mg losartan decreased SBP levels and improved target BP achievement rates. Combination therapy reduced morning and clinic SBP more than high-dose therapy, and the improvement of target BP achievement rates in the morning, evening and the clinic were greater with combination therapy than with high-dose therapy. Combination therapy reduced urine albumin excretion whereas high-dose therapy reduced serum uric acid levels. Both therapies were safe and well tolerated. This study provides the first evidence for the efficacy and safety of losartan/HCTZ combination therapy for patients with uncontrolled morning hypertension on the basis of home BP self-measurements.

Home-based BP measurements have been indicated to be superior to office BP measurements in the prediction of hypertensive organ damage and prognosis.^{14–17} Self-measurement of home BP is now popular in clinical practice for hypertension treatment in Japan.^{18,19} A recent study has confirmed that morning BP taken by BP self-measurements at home is similar to that by 24-h ambulatory BP monitoring.²⁰ Thus, the recent Japanese guidelines appreciate its use in the diagnosis and management of hypertension.⁹ In middle-aged and elderly populations, SBP is more closely associated with cardiovascular prognosis than DBP.^{21,22} Of the patients participating in this study, the mean age was 67.8 years, and 98% were >45 years. We therefore primarily evaluated SBP levels. More than 90% of the enrolled patients had been administered an ARB before this study was initiated. Thus, the current observations mostly reflect the switching effects from a standard dose of ARB to the combination therapy with losartan and HCTZ or to a high dose of losartan.

Figure 2 Effects of combination therapy ($n=99$, open column) and high-dose therapy ($n=97$, closed column) on systolic blood pressure (SBP) in the morning (a), evening (b) and clinic (c). Left, absolute values; right, changes. Bar=1 s.d. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ vs. baseline. ### $P < 0.001$ vs. high-dose therapy.

Figure 3 Target blood pressure (BP) achievement rates in the morning, evening and clinic. Open column, combination therapy ($n=99$); closed column, high-dose therapy ($n=97$). *** $P < 0.001$ vs. baseline. # $P < 0.05$, ## $P < 0.01$ and ### $P < 0.001$ vs. high-dose therapy.

Figure 4 Effects of combination therapy (open column) and high-dose therapy (closed column) on urine albumin/creatinine ratio (UACR; **a**), serum uric acid (**b**), estimated glomerular filtration rate (eGFR; **c**) and HbA1c (**d**). Right panels of (**a**, **b**) represent the percent changes in UACR and uric acid, respectively. Bar=1 s.d. *** $P<0.001$ vs. baseline. # $P<0.05$ and ### $P<0.001$ vs. high-dose therapy.

Although combination therapy and high-dose therapy reduced morning SBP and improved the target BP achievement rate, combination therapy was superior in controlling morning hypertension through a greater SBP reduction and a greater improvement of target BP achievement rates (Figures 2 and 3). The superiority of combination therapy to high-dose therapy was also documented for the evening and clinic BP measurements. There are several possible reasons for the superiority of combination therapy. First, the combination of ARB and thiazide diuretic exerts a synergistic BP-lowering effect through complementary mechanisms of action whereas the antihypertensive effect of ARBs is not dose dependent.^{10,11,23} Second, 50 mg of losartan combined with 12.5 mg of HCTZ has a longer duration and a greater trough-to-peak ratio of BP-lowering effect than once daily 100 mg losartan.²⁴ Next, increased salt sensitivity is associated with a non-dipper pattern of circadian BP rhythm.^{25,26} A non-dipper pattern contributes to morning hypertension in some patients.^{27–29} Thiazide diuretics have been indicated to not only improve salt sensitivity but also shift the circadian BP rhythm from non-dipper to dipper in hypertensive patients.^{25,30} Thus, combination therapy has an advantage over high-dose therapy for controlling morning hypertension.

The urinary albumin secretion is an established prognostic risk factor for cardiovascular and renal outcomes.^{31–33} Long-term trials have indicated an antiproteinuric effect of losartan.^{33–36} In this study, the 3-month treatment with 100 mg losartan failed to show a significant UACR reduction in patients with morning hypertension (Figure 4a). This negative result may be explained by the fact that most patients had already been administered a standard dose of ARB

or ACEI before the randomization. In contrast, UACR was significantly reduced by combination therapy (Figure 4a). The use of diuretics may have affected the UACR reduction by reducing the GFR. However, eGFR was not changed by the 3-month treatment with combination therapy (Figure 4c). Thus, the UACR reduction may be attributable to a greater BP-lowering effect by combination therapy.

Serum uric acid elevation is one of the clinical concerns regarding the use of thiazide diuretics because diuretic-induced elevation of uric acid to >1.0 mg dl⁻¹ may be a risk factor for coronary events independent from achieved BP control.³⁷ Note that a high dose of losartan brought a further uric acid reduction in the patients studied, most of whom had received a standard dose of ARB during the run-in period (Figure 4b). This finding supports the notion that losartan is a unique ARB, which reduces serum uric acid levels through the cis-inhibitory effects on the reabsorption of uric acid by the renal uric acid transporter 1.³⁸ In this study, combination therapy did not increase uric acid levels (Figure 4b), suggesting that losartan minimized the HCTZ-induced uric acid elevation in combination therapy. This beneficial effect is a characteristic feature distinguishing losartan from other ARBs.³⁹

In this study, adherence was substantially high in both therapy groups throughout the observation period (Table 2), which is in line with previous studies demonstrating that losartan and a combination of losartan and a small dose of HCTZ were well tolerated in hypertensive patients.^{40–42} In addition, BP self-measurements at home might be useful in raising the adherence to hypertensive medications by improving patient motivation.⁴³

Combination therapy included more male subjects than high-dose therapy (Table 1). Thus, the imbalance of gender may have affected the results of this study. However, as shown in the Supplementary Figure, there were no gender differences in the effects of combination therapy or high-dose therapy on the primary end points (morning SBP levels and target BP achievement rates after the 3-month-treatment period).

Study limitations

From this study, it remains unknown whether combination therapy would provide a greater reduction in future cardiovascular events in patients with morning hypertension than high-dose therapy. A large-scale, long-term, randomized trial is necessary to address this issue. Second, adverse effects of diuretics, such as glucose intolerance, are major concerns in the clinical setting. Therefore, a longer observation period is required to examine adverse metabolic effects, such as electrolyte imbalance, glucose intolerance and hyperuricemia. Next, bedtime administration of antihypertensives was reported to improve BP control more than morning administration.^{44,45} The feasibility of bedtime administration of combination therapy and high-dose therapy for morning hypertension should be determined in future studies.

In conclusion, combination therapy with a standard dose of losartan and a low dose of HCTZ is more effective for controlling morning hypertension and reducing urine albumin excretion than high-dose therapy with losartan. These beneficial effects may be attributable to the consistent and well-maintained BP-lowering effects of the combination therapy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank Mari Shibata, Naoko Shiotani, Motoko Kakehashi and Midori Ikeda for their secretarial assistance. This study was supported in part by a grant from the Science Frontier Research Promotion Centers from the Ministry of Education, Science, Sports and Culture of Japan.

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