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Original Article

Losartan/Hydrochlorothiazide Combination Therapy Surpasses High-dose Angiotensin Receptor Blocker in the Reduction of Morning Home Blood Pressure in Patients with Morning Hypertension

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Angiotensin receptor blockers (ARBs) are the first-line antihypertensive agents. In clinical practice, it is often difficult to achieve the recommended blood pressure level by ARBs in their ordinal dosages alone. This study examined the practical efficacy of a combination therapy of ARB with thiazide diuretics for lowering morning home blood pressure (MHBP) in comparison to high-dose ARB therapy in patients with morning hypertension administered an ordinal dosage of ARB. This study was performed in a prospective, randomized, open-labeled and blind-endpoint fashion. Patients were considered to have morning hypertension when their self-measured systolic MHBPs were 135 mmHg or higher, irrespective of their diastolic MHBP and office blood pressures (OBPs). Forty-eight outpatients with morning hypertension receiving the ordinal dosage of ARB were given either losartan/hydrochlorothiazide (n = 26) or high-dose ARB (n = 22) in place of their previously prescribed ARB. No change in any medication was permitted during this period. Decreases of both systolic and diastolic MHBP after 3 months of treatment were significantly greater in the losartan/hydrochlorothiazide group than in the high-dose ARB group ($p < 0.05$, respectively). The ratio of adverse events was somewhat high (23.1% in the losartan/hydrochlorothiazide group, 9.1% in the high-dose ARB group, respectively). However, there were no significant differences in any particular adverse event between groups. This study suggested losartan/hydrochlorothiazide might be superior to high-dose ARB for reducing morning home blood pressure.

Key words: losartan, hydrochlorothiazide, morning blood pressure, angiotensin II, hyperuricemia

Hypertension is a risk factor for mortality and morbidity by cardiovascular diseases [1–4], and thus reduction of blood pressure is very important to reduce cardiovascular diseases-associated mortality and morbidity [5–8]. Angiotensin receptor blockers (ARBs) are the first-line antihypertensive agents. However, hypertensive patients treated with a single antihypertensive agent often fail to achieve the target blood pressure level, and thus most hypertensive patients need 2 or more antihypertensive agents [9, 10]. Consequently, many guidelines have discussed which combinations of antihypertensive agents are most favorable [5, 9, 10]. The ARB/thiazide combination therapy has been highlighted, in part because ARBs counterbalance the hypokalemia induced by thiazide diuretics. Another reason for the favorability

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of this combination is that the natriuretic action of thiazide diuretics increases rennin-angiotensin system (RAS) activity, which in turn enhances the efficacy of RAS inhibitors. Indeed, several studies have reported the efficacy of ARB/thiazide combination therapy for reducing blood pressure in uncontrolled hypertensive patients [11]. On the other hand, high-dose ARB therapy is also important. In order to inhibit not only systemic RAS activity but also local RAS activity, high-dose ARB therapy is required in some cases. Studies have reported that high-dose ARBs conferred effective organ protection [12, 13].

Elevated morning home blood pressure (MHBP) is a causative factor of mortality and morbidity by cardiovascular disease [14–17]. Although it remains unclear whether a reduction of MHBP can improve the mortality and morbidity by cardiovascular disease, it is reasonable to consider that the management of MHBP is as important as that of casual BP. Indeed, many clinicians use MHBP as an index of the efficacy of hypertension treatment in clinical practice. However, no clear guidelines have been published for the management of MHBP.

We hypothesized that ARB/thiazide combination therapy would be superior for reducing MHBP compared to high-dose ARB therapy in hypertensive patients treated with an ordinal dosage of ARB. In the present study, therefore, we compared the practical efficacy of ARB/thiazide combination therapy to that of high-dose ARB therapy in reducing MHBP in patients with morning hypertension.

Materials and Methods

Study objective. The objective of this study was to compare the levels of MHBP reduction between combination therapy with losartan/hydrochlorothiazide (HCTZ) and high-dose ARB therapy in patients with morning hypertension. Morning hypertension was defined as systolic MHBP of 135 mmHg or over. The primary endpoints were decreases of systolic and diastolic MHBP. The secondary endpoints were decreases of systolic and diastolic office blood pressure (OBP).

Subjects. Participants were recruited between January 2008 and March 2010. We enrolled outpatients with hypertension who were administered an ordinal dosage of ARBs and whose average systolic MHBPs were 135 mmHg or over (Table 1).

Patients who met any of the following criteria were excluded: inability to perform self-blood pressure measurement; age under 20 years or over 80 years; severe hypertension (diastolic MHBP 120 mmHg or over); severe diabetes mellitus (hemoglobin A_1c (HbA_1c) level over 8.0%); acute myocardial infarction, stroke or other vascular disease over the preceding 3

Table 1 Inclusion and exclusion criteria

Inclusion Criteria
Age of 20 to 79 years
Ability to perform self-blood pressure measurement at home
Outpatient status
Morning home systolic blood pressures of 135 mmHg or over
Provision of informed consent
Exclusion Criteria
Uncontrolled blood pressures: diastolic morning home blood pressure of 120 mmHg or over
Diabetes mellitus with uncontrolled plasma glucose levels: hemoglobin A_1c of 8.0% or over
Acute myocardial infarction, stroke or other vascular disease within 3 months
Heart failure of New York Heart Association functional class III or IV
Gout or hyperuricemia: serum uric acid level of 8.0 mg/dl or over
Renal failure: serum creatinine level of 2.0 mg/dl or over
Liver injury: aspartate aminotransferase or alanine aminotransferase level elevated to more than three times the upper limit of normal
Bilateral renal arterial stenosis, malignant hypertension or endocrine secondary hypertension
Use of thiazide diuretics
Pregnancy
Disqualification for other reasons at the discretion of the physician in charge

months; heart failure of New York Heart Association functional class III or IV; gout or serum uric acid (UA) level of 8.0 mg/dl or over; renal failure (serum creatinine (Cr) level of 2.0 mg/dl or over); liver injury (aspartate amino transferase (AST) or alanine transaminase (ALT) level 3 times higher than the upper limit of normal); bilateral renal arterial stenosis; malignant hypertension; secondary hypertension; treatment with thiazide diuretics; pregnant; allergy to the drugs used in this study; and any other conditions rendering them inappropriate for participation based on the assessment of their attending physicians.

Study design. This study was a multi-center (5 hospitals and 5 clinics), prospective, randomized and open-labeled study with a 3-month, 2-arm parallel treatment group comparison and a fixed-dose scheme (Fig. 1). The patients were assigned to 1 of 2 groups, the Losartan/HCTZ group or the High-dose ARB group. Patients in the Losartan/HCTZ group were administered losartan/HCTZ in place of the previously prescribed ARB, while patients in the High-dose ARB group were administered the maximum dosage of previous ARBs approved in Japan: losartan, 100 mg; candesartan, 12 mg; valsartan, 160 mg; telmisartan, 80 mg; olmesartan, 40 mg; or irbesartan, 200 mg. The sample size was determined on the basis of the estimated BP reduction reported in a recent study which showed the superiority of combination therapy with losartan 50 mg plus HCTZ 12.5 mg compared to losartan 100 mg after 8 weeks of treatment in

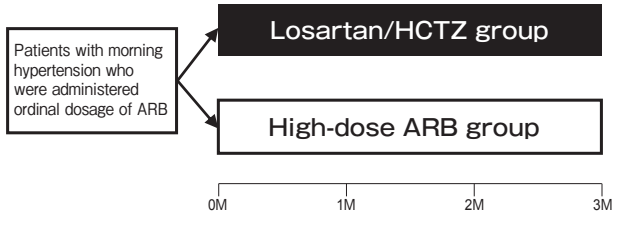

Fig. 1 Outline of this study. Hypertensive patients whose morning home systolic blood pressure was 135 mmHg or over with an ordinal dosage of ARB were enrolled. They were assigned to two groups, the Losartan/HCTZ group or the High-dose ARB group. Patients assigned to the Losartan/HCTZ group were administered losartan/hydrochlorothiazide (losartan/HCTZ), while patients assigned to the High-dose ARB group were administered the maximum dosage of ARB approved in Japan: 100 mg losartan; 12 mg candesartan; 160 mg valsartan; 80 mg telmisartan; 40 mg olmesartan; 200 mg irbesartan.

reduction of systolic OBP (−16.8 mmHg vs. −6.4 mmHg, $p < 0.01$) [18]. We assumed that the mean reduction of systolic MHBP was 10.4 mmHg and the standard deviation (SD) was 10.0 mmHg. For using a 2-sided test for differences, a minimal sample size of 16 patients was required in each group to detect statistical differences in reduction of systolic MHBP with a power of 80% and an α-type error of 5% in the statistical analysis. The results are expressed as the means ± SD.

Blood pressure measurement. The method of self-blood pressure measurement followed the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) [5]. In brief, MHBP was measured using a cuff-oscillometric automated sphygmomanometer within an hour after waking, after urination, before morning dosing, before breakfast and after 1 to 2 min of rest in a sitting position. Blood pressure and pulse rate data were recorded on recording sheets and marked on a data sheet by the patients themselves. The average levels of systolic and diastolic MHBP and morning pulse rate before the enrollment and 3 months after treatment were determined as the average values of all data within a month just before the enrollment and the last month, respectively.

OBP measurement was conducted at every visit. OBP was measured in a sitting position using an automated sphygmomanometer or mercury column sphygmomanometer by each physician.

Parameters. Background medical information was obtained at the time of enrollment, and included age, gender, body mass index (BMI), past medical history (including information on ischemic heart disease, stroke, diabetes mellitus, dyslipidemia and chronic kidney disease), current smoking and current alcohol drinking.

Laboratory data, AST, ALT, Cr, estimated glomerular filtration rate (eGFR), UA, potassium, HbA_1c, low density lipoprotein cholesterol (LDL-Cho), high density lipoprotein cholesterol (HDL-Cho) and triglyceride (TG) were examined before enrollment and at the end of the study. The eGFR of each participant was calculated using the Japanese eGFR equation recently determined by the Japanese Society of Nephrology: $\text{eGFR (ml/min/1.73 m}^2) = 194 \times \text{age}^{-0.287} \times \text{Cr}^{-1.094} \times (0.739 \text{ if female})$ [19].

Ethics. The study protocol was approved by the

Okayama University Institutional Review Board (accredited ISO9001/2000) and by the local ethic committees at the respective institutes where available. It was undertaken in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies in Japan. All patients enrolled in this study provided fully informed written consent. Participants who suffered from adverse events were immediately excluded from this study and given the appropriate treatment and medical care.

Statistical analysis. Data are presented the mean ± standard deviation. Numerical data qualified F-test and normality test were analyzed using Student's *t*-test, and other numerical data were analyzed using Mann-Whitney's U-test. Categorical data were analyzed using Fisher's exact probability test. The statistical analysis was performed using the statistical software packages, Stat View 5.0 and SigmaStat 3.5 (SPSS Inc.).

Results

Enrollment. A total of 48 patients were enrolled. Twenty-six patients were assigned to the Losartan/HCTZ group, and 8 of those patients dropped out (Fig. 2). Twenty-two patients were assigned to the High-dose ARB group, and 5 patients dropped out. Total of 35 patients thus completed the study.

Patient characteristics at baseline. Each parameter at baseline is shown in Table 2. There were no statistically significant differences in any of the parameters between the groups.

Morning home blood pressure. The decrease of systolic MHBP in the Losartan/HCTZ group was significantly greater than that in the High-dose ARB group (16 ± 5 mmHg vs. 6 ± 10 mmHg, $p = 0.0217$, Fig. 3A). Both groups tended to have a gradually decreasing systolic MHBP level (Fig. 3C). The final systolic MHBP level 3 months after treatment in the Losartan/HCTZ group was significantly lower than that in the High-dose ARB group (127 ± 7 mmHg vs. 138 ± 14 mmHg, $p = 0.0416$). The decrease of diastolic MHBP in the Losartan/HCTZ group was significantly greater than that in the High-dose ARB group (7.8 ± 5.2 mmHg vs. 2.9 ± 4.4 mmHg, $p = 0.0075$, Fig. 3B). There was no significant difference between the diastolic MHBP level of the Losartan/HCTZ group and that of the High-dose ARB group either enrollment or after treatment (Fig. 3C). The ratio of subjects with systolic MHBP under 135 mmHg after treatment in the Losartan/HCTZ group was significantly higher than that in the High-dose ARB group (72% vs. 35%, $p = 0.0437$).

Office blood pressure. There were no significant differences in the magnitude of decrease of systolic and diastolic OBP between the Losartan/HCTZ group and the High-dose ARB group (Fig. 4A and B). In addition, there were no significant differences between the Losartan/HCTZ group and the High-dose ARB group in the systolic or diastolic OBP level (Fig. 4C).

Changes of laboratory data. The changes of laboratory data between the baseline and after treatment measurements were evaluated (Table 3). The Change of Cr in the Losartan/HCTZ group was greater than that in the High-dose ARB group (0.06 ± 0.07 mg/dl vs. 0.00 ± 0.07 mg/dl, $p = 0.0393$). However, there was no significant difference in the changes of eGFR or serum potassium level in either group. UA was elevated more in the Losartan/HCTZ group than in the High-dose ARB group (0.6 ± 0.7 mg/dl vs. 0.0 ± 0.7 mg/dl, $p = 0.0369$). In the Losartan/HCTZ group, 1 patient had hyperuricemia at baseline, while

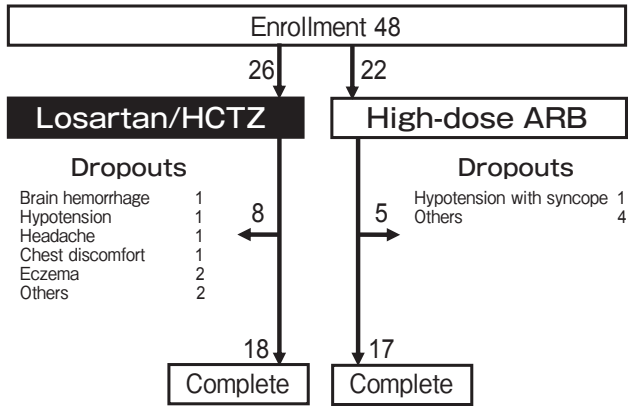

Fig. 2 Enrollment. Forty-eight patients with morning hypertension were assigned to one of two groups, the Losartan/HCTZ group or the High-dose ARB group. Eight patients in the Losartan/HCTZ group dropped out due to brain hemorrhage, hypotension, headache, chest discomfort, eczema or other reasons. Five patients in the High-dose ARB group dropped out due to hypotension with syncope and other reasons. A total of 18 and 17 patients thus completed the study in the Losartan/HCTZ group or the High-dose ARB group, respectively.

Table 2 Patients' characteristics at baseline

	Losartan/HCTZ group ($n = 26$)	High-dose ARB group ($n = 22$)	P value
Age (years)	65 ± 9	64 ± 11	0.6342
Gender (male/female)	13/13	9/13	0.5729
BMI (kg/m^2)	25.0 ± 3.7	24.4 ± 3.7	0.5708
Systolic MHBP (mmHg)	146 ± 12	148 ± 10	0.7142
Diastolic MHBP (mmHg)	87 ± 9	81 ± 10	0.0672
MHPR (beats per minute)	70 ± 13	64 ± 9	0.1394
Systolic OBP (mmHg)	141 ± 17	139 ± 17	0.6837
Diastolic OBP (mmHg)	80 ± 12	77 ± 11	0.3238
OPR (beats per minute)	65 ± 11	69 ± 9	0.3315
Cr (mg/dl)	0.81 ± 0.24	0.79 ± 0.22	0.7860
eGFR (ml/min/1.73m^2)	67.6 ± 14.5	67.8 ± 13.9	0.9511
UA (mg/dl)	4.8 ± 1.3	5.2 ± 1.3	0.2889
K (mEq/l)	4.4 ± 0.4	4.5 ± 0.4	0.1705
HbA_1c (%)	6.0 ± 1.4	5.8 ± 0.5	0.6970
LDL-Cho (mg/dl)	116 ± 27	113 ± 26	0.7068
HDL-Cho (mg/dl)	55 ± 11	62 ± 23	0.2961
TG (mg/dl)	162 ± 102	126 ± 60	0.3009
IHD (%)	4	0	0.9999
Stroke (%)	8	0	0.4929
Diabetes mellitus (%)	38	23	0.3506
Dyslipidemia (%)	50	41	0.5729
Hyperuricemia (%)	8	14	0.6492
CKD (%)	35	14	0.1797
Smoking (%)	20	0	0.0562
Habitual drinking (%)	24	15	0.7095

BMI, body mass index; systolic MHBP, morning home systolic blood pressure; diastolic MHBP, morning home diastolic blood pressure; MHPR, morning home pulse rate; systolic OBP, office systolic blood pressure; diastolic OBP, office diastolic blood pressure; OPR, office pulse rate; Cr, creatinine; eGFR, estimated glomerular filtration rate; K, potassium; UA, uric acid; HbA_1c, hemoglobin A_1c; LDL-Cho, low density lipoprotein cholesterol; HDL-Cho, high density lipoprotein cholesterol; TG, triglyceride; IHD, ischemic heart disease; CKD, chronic kidney disease.
P values were analyzed using Student's t-test, Mann-Whitney's U-test or Fisher's exact probability test, where appropriate.

3 patients were newly diagnosed with hyperuricemia after treatment. On the other hand, in the High-dose ARB group 3 patients had hyperuricemia at baseline, while none were newly diagnosed with hyperuricemia. There were no significant differences in the other parameters between the 2 groups.

Adverse events. Adverse events are shown in Table 4. The ratio of adverse events was 23.1% in the Losartan/HCTZ group and 9.1% in the High-dose ARB group. These ratios were fairly high, especially in the former group. However, there were no significant differences in any particular adverse event between groups (Table 4). All patients recovered from these events after cessation of the causative drugs. One patient in the Losartan/HCTZ group had a brain hemorrhage 1 month after treatment. Although she presented with dysarthria and paralysis in the right upper extremity at onset, both symptoms were diminished 6 months later.

Discussion

This study compared the blood pressure-lowering effect of losartan/HCTZ combination therapy to that of high-dose ARB therapy in patients who were treated with an ordinal dosage of ARB but had systolic MHBP of 135 mmHg or over in clinical practice. The results demonstrated that losartan/HCTZ combi-

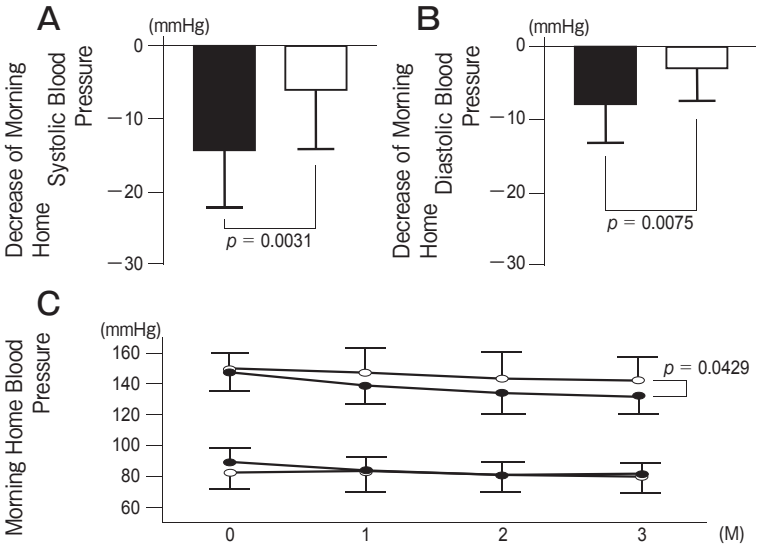

Fig. 3 Decreases of morning home blood pressure and morning home blood pressure levels. The closed boxes and circles show the Losartan/HCTZ group and the open boxes and circles show the High-dose ARB group. Panel **A** shows the decrease of morning home systolic blood pressure. The decrease of morning home systolic blood pressure in the Losartan/HCTZ group was significantly greater than that in the High-dose ARB group. Similarly, panel **B** shows that the decrease of morning home diastolic blood pressure in the Losartan/HCTZ group was significantly greater than that in the High-dose ARB group. Panel **C** shows the morning home blood pressure levels. The systolic morning home blood pressure level in the Losartan/HCTZ group was significantly lower than that in the High-dose ARB group after treatment. There was no significant difference in the morning home diastolic blood pressure levels between the two groups after treatment. *P* values were calculated by Mann-Whitney's U-test between both groups in panel **A** and **B**. *P* values were calculated by unpaired *t*-test between both groups in panel **C**.

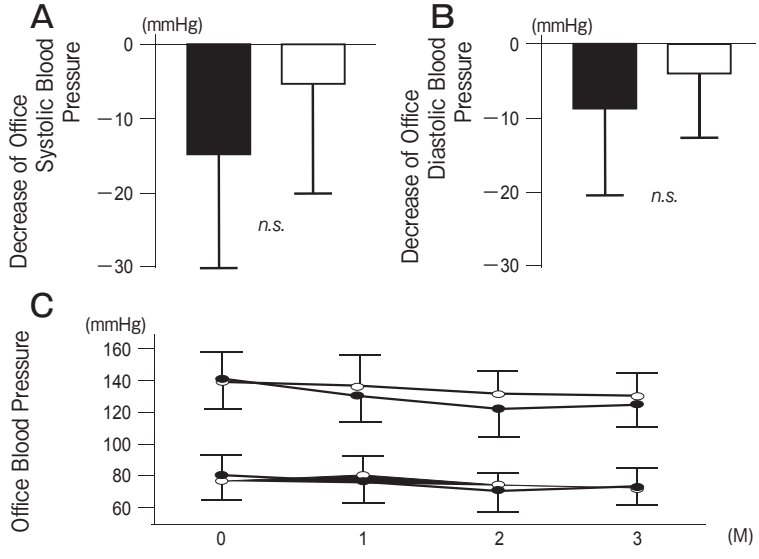

Fig. 4 Decreases of office blood pressure. The closed boxes and circules show the results for the Losartan/HCTZ group and the open boxes and circles show the results for the High-dose ARB group. Panel **A** shows the decrease of office systolic blood pressure, and panel **B** shows the decrease of office diastolic blood pressure. Decreases of both systolic and diastolic office blood pressure in the Losartan/HCTZ group were not significantly different from those in the High-dose ARB group. Panel **C** shows office blood pressure levels. There was no significant difference in the office blood pressure levels between the two groups at enrollment and after treatment. *P* values were calculated by Mann-Whitney's U-test between both groups in panel **A** and **B**. *P* values were calculated by unpaired *t*-test between both groups in panel **C**.

nation therapy achieved a significantly greater reduction in MHBP compared to high-dose ARB therapy. Furthermore, losartan/HCTZ combination therapy was superior to high-dose ARB therapy in terms of the ratio of patients with systolic MHBP under 135 mmHg. In this study, the decreases of both systolic and diastolic MHBP in patients receiving losartan/HCTZ combination therapy were significantly greater than those in patients receiving the high-dose ARB therapy.

ARBs are recommended as the first-line antihypertensive agents for treatment of hypertension by JSH 2009, JNC-7 and ESH/ESC 2007 [5, 9, 10]. However, most hypertensive patients require 2 or more antihypertensive agents to achieve their target blood pressure [9, 10]. The importance of second-line antihypertensive has raised the question of which combination therapies are most useful, and the present study was designed to examine this issue. One possible strategy to address an inadequate blood pressure decrease would be to increase of the dosage of

Table 3 Changes of laboratory data

	Losartan/HCTZ group ($n = 18$)	High-dose ARB group ($n = 17$)	*P* value
Δ Cr (mg/dl)	0.06 ± 0.07	0.00 ± 0.07	0.0393
Δ eGFR (ml/min/1.73m^2)	-3.8 ± 5.6	-0.0 ± 6.7	0.0849
Δ UA (mg/dl)	0.6 ± 0.7	0.0 ± 0.7	0.0369
Δ K (mEq/l)	-0.2 ± 0.3	-0.1 ± 0.4	0.4615
Δ HbA_1c (%)	-0.1 ± 0.4	0.1 ± 0.2	0.9723
Δ LDL-Cho (mg/dl)	-1 ± 16	-9 ± 22	0.2826
Δ HDL-Cho (mg/dl)	-1 ± 9	1 ± 9	0.5644
Δ TG (mg/dl)	16 ± 69	8 ± 81	0.7312

Δ indicates the value after treatment minus the value at baseline.
Cr, creatinine; eGFR, estimated glomerular filtration rate; K, potassium; UA, uric acid; HbA_1c, hemoglobin A_1c; LDL-Cho, low density lipoprotein cholesterol; HDL-Cho, high density lipoprotein cholesterol; TG, triglyceride.
P values were analyzed using Student's *t*-test or Mann-Whitney's U-test, where appropriate.

Table 4 Adverse events

	Losartan/HCTZ group ($n = 26$)	High-dose ARB group ($n = 22$)	*P* value
Brain hemorrhage	1 (4%)	0 (0%)	1.000
Hypotension	1 (4%)	1 (5%)	1.000
Headache	1 (4%)	0 (0%)	1.000
Chest discomfort	1 (4%)	0 (0%)	1.000
Syncope	0 (0%)	1 (5%)	0.4583
Eczema	2 (8%)	0 (0%)	0.4929

P values were analyzed using Fisher's exact probability test.

ARBs. Evidence from clinical studies also suggests that sustainable inhibition of the RAS at the tissue level, as provided by high-dose monotherapy with an ARB, might afford improved cardiovascular protection beyond that conferred by a reduction of blood pressure [12]. High-dose ARB therapy has been shown to have a renoprotective effect in hypertensive patients with diabetic nephropathy or non-diabetic proteinuric nephropathy, and this effect has been attributed to a decrease in the urine albumin creatinine ratio (UACR) [13, 20]. Although several studies have reported that blood pressure was significantly reduced by a high-dose ARB in uncontrolled hypertensive patients who had been receiving an ordinal dosage of ARB, the magnitude of blood pressure reduction by the high-dose ARB was less than twice that by the ordinal dosage of ARB [13]. In addition, clinical studies examining the efficacy of high-dose ARB for morning hypertension are sparse. This is why high-dose ARB therapy was an arm in this study. On the other hand, the efficacy of ARB/thiazide combination therapy in the treatment of hypertension has been described in several large and small studies [11, 21–25]. However, few studies have compared blood pressure-lowering effect between ARB/thiazide combination therapy and high-dose ARB therapy [25]. A study reported that there were no significant differences in the changes of OBP after 12 weeks of treatment between combination therapy with 16mg candesartan plus 12.5 mg HCTZ and monotherapy with 32 mg candesartan [27]. Although this result may support the present study in term of OBP reduction, there was no data of MHBP reduction.

There have been relatively few reports on interventions to treat morning hypertension. A recent study showed a greater MHBP reduction by combination therapy with an ARB plus a thiazide diuretic than by combination therapy with an angiotensin-converting enzyme inhibitor plus a thiazide diuretic or with a calcium channel blocker plus a thiazide diuretic [28].

Moreover, there was only one study compared combination therapy with an ARB plus a low-dose thiazide diuretic to high-dose ARB therapy in treatment of patients with morning hypertension other than the present study [29]. The previous study found that combination therapy with valsartan plus trichlormethiazide reduced not only a reduction of MHBP but also brachial-ankle pulse velocity significantly more than high-dose valsartan therapy. However, the current study showed significant differences in reduction of both systolic and diastolic MHBP between losartan/HCTZ combination therapy and high-dose ARB therapy after 3 months of treatment. Several explanations were considered for the different results. First, the patients in the current study were recruited using the criteria of morning hypertension defined only as a systolic MHBP level of 135 mmHg or over. The previous study recruited patients using the criteria of morning hypertension defined as a systolic MHBP of 140 mmHg or over and bed-time systolic blood pressure under 135 mmHg. Second, the former study enrolled only male patients, whereas the patients were enrolled irrespective of gender in the current study. Third, patients in the former study had been treated with only valsartan 80 mg once a day, whereas patients in the current study had been treated with any kind of ARB with the ordinal dosage. Fourth, the former study administered 80 mg valsartan plus 1 mg trichlormethiazide or 160 mg valsartan, whereas 50 mg losartan plus 12.5 mg HCTZ or the maximum dose of the previously described ARB was administered in the current study. Finally, while the blood pressure reduction after treatment was evaluated after 6 months in the previous study, it was done after 3 months in the current study. Although the blood pressure level after 3 months in the previous study was not shown, we presumed that the efficacy of ARBs on MHBP reduction might be developed after 6 months of treatment rather than after 3 months, especially when increasing the dosage of the ARB to the maximum dosage. Further studies are needed in order to clarify this hypothesis.

MHBP was decreased gradually during the treatment period in both the Losartan/HCTZ group and the High-dose ARB group in the current study. Although there was a significant difference in the systolic MHBP level but not in the diastolic MHBP level between the 2 groups, the decreases of both systolic and diastolic MHBP in the Losartan/HCTZ group were significantly greater than those in the High-dose ARB group. This discrepancy in diastolic MHBP might have been due to the inclusion criteria in this study. Patients were recruited regardless of their diastolic MHBP levels, thus it was likely that the change of the diastolic MHBP level tended to be greater. On the other hand, the OBP decreased similarly in both groups, and therefore there was no significant difference in either the achieved OBP levels or the reduction of OBP between the 2 groups. The change of OBP by each treatment was smaller than estimated because the OBP of around 140/80 mmHg at baseline was not high. In general, the magnitude of blood pressure reduction was associated with the baseline blood pressure level [27], which might explain the results.

The achievement of the target blood pressure level is a clinically important issue in the treatment of hypertension. The target blood pressure level was achieved in only 40% to 50% of hypertensive patients who took a single antihypertensive agent [30]. The achievement ratio of systolic MHBP under 135 mmHg in the Losartan/HCTZ group was 72% in the current study, whereas that in the High-dose ARB group was 35%. This result suggested that ARB/thiazide combination therapy might achieve a pronounced response exceeding that to high-dose ARB therapy in the treatment of uncontrolled morning hypertension.

The importance of morning hypertension has been reported in several studies. Morning hypertension is related to left ventricular hypertrophy [31–33], carotid intima-media thickness [34], brachial-ankle pulse wave velocity [35], UACR [36], silent brain infarction [37] and cardiovascular events [14–17]. Furthermore, several studies have reported that a reduction of morning blood pressure led to a reduction of UACR in hypertensive patients [36, 38]. It has not been elucidated yet whether the attenuation of morning hypertension could contribute to beneficial effects on morbidity and mortality. A study demonstrated a significant reduction in cardiovascular events and mortality with bed time administration of antihypertensive agents in comparison to morning treatment in patients with type 2 diabetes mellitus [16]. However, the morning blood pressure at baseline in that study was relatively low, and thus this case could not be considered to be an intervention for morning

hypertension. An interim analysis of the HOMED-BP (Hypertension Objective treatment based on Measurement by Electrical Devices of Blood Pressure) study, a randomized controlled trial to determine the optimal target of MHBP, is expected to show whether the reduction of morning hypertension contributes to the improvement of mortality and morbidity in hypertensive patients [39].

Losartan/HCTZ is thought to be superior in the suppression of hyperuricemia in comparison to combination therapy containing other ARBs, because losartan is able to inhibit urate/anion transport in brush-border cells of the renal proximal tubules [40, 41]. A recent report showed that the effect of 50 mg losartan on renal excretion of urate was significantly greater than that of 8 mg candesartan in hypertensive patients [42]. Moreover, the lack of a uricosuric response to losartan in patients harboring the mutant URAT1 gene demonstrated the contribution of URAT1 to the uricosuric action of losartan in humans. The current study found that the change of UA in the Losartan/HCTZ group was significantly higher than that in the High-dose ARB group. Furthermore, 3 patients were newly diagnosed with hyperuricemia in the Losartan/HCTZ group whereas none of patients were diagnosed with hyperuricemia in the High-dose ARB group. However, the occurrence of hyperuricemia in the Losartan/HCTZ group was as mild as estimated. Although the side effects of thiazide diuretics have been considered frequent and problematic, they are infrequent and trivial following the administration of a low dosage. Furthermore, thiazide diuretics have an advantage because they are less expensive than other antihypertensive agents.

As to the mechanism underlying the difference in MHBP reduction between therapies, it may have involved a difference in salt sensitivity between patients undergoing the two treatments. It is well recognized that RAS inhibitors enhance sodium sensitivity. It is also well known that the BP-lowering effect of RAS inhibitors is blunted by a high sodium diet. Therefore, diuretics enhance the efficacy of RAS inhibitors on BP reduction because of their natriuretic action. Since elevations in MHBP are associated with nocturnal hypertension, morning hypertension may be common in patients with high sodium sensitivity who have a high sodium intake. It has been reported that HCTZ reduced the nocturnal BP of hypertensive patients with a change of non-dipper to dipper status [43]. In our study, since all participants received an ordinal dosage of ARB, their salt sensitivity might have been enhanced.

Several limitations need to be recognized in interpreting the results of this study. First, this study enrolled a small number of participants, and therefore it failed to show a significant difference on diastolic MHBP levels between the 2 groups. Second, the dosage of previously prescribed ARBs was increased to the maximum dosage in the High-dose ARB group. There may be differences among the individual ARBs regarding the blood pressure-lowering effect in hypertensive patients, and such differences might have affected the results. Indeed, 3 patients (losartan), 4 patients (candesartan), 1 patient (valsartan), 5 patients (telmisartan), and 4 patients (olmesartan) were assigned to the High-dose ARB group. However, there were no significant differences among ARBs regarding the decrease of systolic and diastolic MHBP (data not shown). Third, the duration of our study was short, so that morbidity and mortality could not be evaluated. Finally, there was no ambulatory blood pressure monitoring and evening home blood pressure data in this cohort.

In conclusion, the present study demonstrated the efficacy of the combination therapy with losartan/HCTZ compared to high-dose ARB therapy for the treatment of MHBP. A combination therapy of ARB/thiazide may be recommended rather than increasing the dosage of ARB, when treatment of morning hypertension by ARB monotherapy is insufficient to achieve the target blood pressure level.

Appendix

Participants and participating centers

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