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ORIGINAL ARTICLE

Antihypertensive effect of a fixed-dose combination of losartan / hydrochlorothiazide in patients with uncontrolled hypertension: a multicenter study

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Abstract
Background Achieving adequate blood pressure (BP) control often requires more than one antihypertensive agent. The purpose of this study was to determine whether a fixed-dose formulation of losartan (LOS) plus hydrochlorothiazide (HCTZ) (LOS/HCTZ) is effective in achieving a greater BP lowering in patients with uncontrolled hypertension.
Methods The study was a prospective, multicenter, observational trial exploring the antihypertensive effect of a single tablet of LOS 50 mg/HCTZ 12.5 mg. A total of 228 patients whose BP had previously been treated with more than one antihypertensive agents without having achieved BP goal below 130/80 mmHg enrolled in the study.
Results A significant decrease in systolic and diastolic BP was observed in both clinic and home measurement after switching from the previous treatment to LOS/HCTZ. There was a significant decrease in both B-type natriuretic peptide (BNP) and urinary albumin creatinine (Cr) excretion ratio (ACR), especially in patients with elevated values. In contrast, there was a significant increase in serum Cr concentration in conjunction with a decrease in estimated glomerular filtration rate (eGFR). Overall serum uric acid (UA) concentration increased, whereas in patients with hyperuricemia there was a significant reduction in this value.
Conclusion Switching to LOS/HCTZ provides a greater reduction in clinic and home BP in patients with uncontrolled hypertension. This combination therapy may lead to cardio-, reno protection and improve UA metabolism.

Keywords Losartan · Hydrochlorothiazide · Hypertension · BNP · Albuminuria

The list of authors on behalf of the JOINT Study Group is listed in "Appendix".

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Introduction

A plethora of evidence has indicated that strict BP reduction is indispensable to improve patients' prognosis, inadequate control of BP is thus leaving patients at risk of cardiovascular disease, particularly in patients with chronic kidney disease (CKD) and uncontrollable hypertension [1]. Despite the increasing awareness of antihypertensive treatment, only a small proportion of patients achieve the recommended target goals around the world [2–5]. For instance, the BP goals set by hypertension management guidelines in Japan are currently

being achieved in only about 40% of treated patients [2, 5]. Similar low rates of hypertension control have been reported worldwide [3, 4]. The reason for the inadequacy of controlling hypertension could at least in part be accounted for by physician's insufficient knowledge on how to prescribe appropriate antihypertensive agents.

Through reviewing the literature, Bakris et al. [6] have suggested that in order to achieve lower BP of less than 130/80 mmHg, more than two drugs are needed in most patients. Indeed, many guidelines for the management of hypertension have recommended that combination of multiple antihypertensive agents with different pharmacological mode of action is more efficacious than a single agent alone [3]. In this context, the combination of an angiotensin II receptor blocker (ARB) and hydrochlorothiazide (HCTZ) has been widely recognized as a preferable prescription, because combining ARB with HCTZ exerts a complementary pharmacological effect by suppressing renin angiotensin system (RAS) with the former and body fluid system with the latter, which provides a greater reduction in BP than either agent alone. LOS combined with the small dose HCTZ as a fixed dose single-tablet formulation, is one such option that has demonstrated substantial antihypertensive effect [7]. LOS is unique in that it is the only ARB that has a uricosuric effect that leads to a decreased serum uric acid (UA) levels. This effect could be mediated by the inhibition of the urate transporter URAT-1 in the renal tubules [8]. Owing to this specific benefit on UA metabolism, LOS has been known to ameliorate diuretic-induced hyperuricemia [8, 9].

Despite substantial antihypertensive effect, thiazide diuretics including HCTZ often induce adverse effects such as hypokalemia, impaired glucose tolerance and an increase in serum UA concentration. These side effects of HCTZ could be minimized if prescribed in a lower dosage. A fixed-dose combination formula of LOS (50 mg; the optimal dose) plus a low dose HCTZ (12.5 mg; a half of the optimal dose) (LOS/HCTZ) is thus worth evaluating in terms of BP lowering potency and avoiding side effects.

In the present study, we made an attempt to evaluate the clinical benefit of a single-tablet formulation of LOS/HCTZ, by conducting a multicenter observational trial, the Jikei Optimal Antihypertensive Treatment (JOINT) study in uncontrolled hypertensive patients.

Methods

Study subjects

Eligible patients were men and women between 20 and 75 years of age with essential hypertension and those with CKD with hypertension. Ethnic extraction of all participants was Japanese with all four biological grandparents born in Japan and of Japanese descent. The inclusion criteria were outpatients whose BP was more than 130/80 mmHg despite the antihypertensive agents prescribed for more than 3 months prior to study entry. The exclusion criteria were patients whose serum creatinine (Cr) concentration exceeded 220 μmol/L (compatible with CKD stage 5), those with liver dysfunction (defined as an elevation of aspartate aminotransferase/alanine aminotransferase 3 times higher than the upper normal limit), pregnant, expecting, or lactating women, CKD patients with massive proteinuria of nephrotic range (defined as a daily protein excretion of 3 g/day or more), and patients whose doctor in charge judged it inappropriate to enroll.

Study protocol

All institutions received prior ethics committee and or institutional review board approval, and the trial was conducted in accordance with the principles of Good Clinical Practice and the ethical principles of the concurrent Declaration of Helsinki which also protected the privacy of the patients. All patients gave written informed consent before study enrollment. The JOINT was a multicenter observational self-controlled study to evaluate the antihypertensive effect of a fixed-dose combination formulation of LOS/HCTZ (Clinical trial Number by UMIN 000001950). The study was conducted at 28 centers and clinics for the JOINT study group ("Appendix") in the vicinity of Tokyo, Japan.

Patients were previously treated with either one or more antihypertensive agents on an outpatient basis. The protocol for the administration of LOS/HCTZ was the following. If the patient was being treated with either ARB or calcium channel blocker (CCB) alone or together, LOS/HCTZ was substituted for either drug or the combination. If the patient was being treated with three drugs including RAS inhibitors, the RAS inhibitor was switched to LOS/HCTZ. In all of the protocol patterns, LOS/HCTZ was administered once a day in the morning.

Advices on life-style modification plan were carried out throughout the study. Namely, from the run-in and the observation period, the patients were required to maintain a daily salt intake of 6 g or less. A protein restriction of 0.6–0.8 g/kg/day was also required when the patient's CCr was below 30 mL/min/1.73 m^2. The other lifestyle modifications included smoking cessation, weight reduction, moderation in alcohol consumption, mild to moderate regular exercise, and reduction in saturated and total fat intake.

Endpoints

The primary endpoint was the change in clinic systolic and diastolic BP after 6 months of treatment. Secondary endpoints included change in home BP, urinary albumin

creatinine excretion ratio (ACR), B-type natriuretic peptide (BNP) and serum UA concentration.

BP measurements and laboratory tests

The clinic BP was measured in a sitting position during a morning visit (9–11 am) every 4 weeks. We followed all American Heart Association Recommendations published in 1988 [8, 10] including using a 47 × 13 cm cuff and 24 × 13 cm bladder to avoid cuff hypertension. The cuff was strictly positioned 2 cm above the antecubital crease to obtain a similarly leveled complete compression of the brachial artery. All BP values were expressed as the average of two measurements obtained at the same time-point.

Patients were required to measure home BP in the morning in a sitting position within 30 min after awakening before taking medications in a fasting state. Night time home BP measurement was also required to measure at any given time between supper and bedtime with having patient's habitual drinking unrestricted. BP measuring devices equipped with upper arm cuff were encouraged to use. The averages of several measured values were used for analysis.

Laboratory tests carried out after 6 months of treatment were BNP, serum Cr concentration, ACR, estimated-GFR (eGFR), serum UA concentration, and others including lipid profiles. The urinary albumin level was determined from a spot urine sample using a turbidimetric immunoassay (SRL, Tokyo, Japan). Plasma BNP was measured using high-sensitivity, noncompetitive radioimmunoassays (Shiono-RIA BNP, Shionogi Inc, Osaka, Japan)

Statistical analyses

The paired student's *t* test, Wilcoxon's signed rank test, and one-way analysis of variance (ANOVA) and Bonferroni's post hoc test were carried out with JMP 9.0 software. The computer used for the analysis was a Dynabook Satellite 2590X (Toshiba, Tokyo, Japan).

Data are presented as the mean ± standard deviation (SD) for continuous variables with normal distribution. Continuous variables without normal distribution are presented as median and interquartile range (IQR) with 25 and 75 percentiles. Because of their skewed distribution, logarithmic transformation of BNP and ACR values were performed as the geometric means with 95% confidence intervals. A P value of less than 0.05 was considered statistically significant.

Results

Prescription of antihypertensive agents

A total of 277 patients were registered in the JOINT study, of whom 49 were excluded (33 were lost during follow-up, 7 had protocol violations, and 9 had inadequate data for analyses). Consequently a total of 228 patients with clinical index data were included in the analysis. The majority of the patients ($n = 142$, 62%) had an eGFR more than 60 mL/min/1.73 m^2 (Table 1).

The baseline medications were monotherapy in 55%, dual therapy in 32% and therapy with 3 or more drugs in 13%. The majority of patients were taking ARBs (72%) or CCBs (54%), with only low numbers taking beta-blockers (6%), alpha-blockers (6%), or angiotensin converting enzyme inhibitors (ACE-I) (5%). At the beginning of the study, almost half of the patients (48%) switched from ARB to LOS/HCTZ, while 18% switched from CCB to LOS/HCTZ, 15% switched from ARB + CCB to LOS/HCTZ, and 20% switched to the prescriptions in which one of the pre-prescribed drugs was substituted by LOS/HCTZ.

Changes in clinic and home BP

Figure 1 shows the antihypertensive effect of LOS/HCTZ on clinic BP. After 6 months of switching from the baseline medications to LOS/HCTZ, significant decreases in clinic BP were observed in both systolic (145 ± 13 to 135 ± 15 mmHg) and diastolic BP (87 ± 9 to 81 ± 9 mmHg, both comparisons $P < 0.001$). The overall achieving rate of BP goal of either systolic BP less than 130 mmHg or diastolic BP less than 80 mmHg was 53% (120/228 cases).

Decreases in the clinic systolic and diastolic BP were observed in all of the following 3 patterns (Fig. 2); patients switched from ARB to LOS/HCTZ (145 ± 12/88 ± 8 to 134 ± 12/80 ± 10 mmHg, both systolic and diastolic, $P < 0.001$); from CCB to LOS/HCTZ (147 ± 11/87 ± 10 to 134 ± /80 ± 10 mmHg, both systolic and diastolic, $P < 0.001$); and from ARB + CCB to LOS/HCTZ + CCB (140 ± 11/87 ± 11 to 131 ± 9/82 ± 9 mmHg, both systolic and diastolic, $P < 0.001$).

Table 1 Patient baseline characteristics ($n = 228$)

Age (years)	60.3 ± 11.5
Gender (male/female)	158 (69%)/70 (31%)
BMI (kg/m^2)	25.3 ± 4.4
Diabetes (*n*)	35 (15%)
Dyslipidemia (*n*)	76 (33%)
Heart disease (*n*)	8 (4%)
CKD stage (*n*)	
1 (eGFR ≥90)	23 (10%)
2 (60 ≤ eGFR < 90)	119 (52%)
3 (30 ≤ eGFR < 60)	70 (31%)
4 (15 ≤ eGFR < 30)	11 (5%)

BMI body mass index, *eGFR* estimated glomerular filtration rate

With respect to the difference of patients background classified by BP response, the responders defined as a reduction in systolic BP of ≥10 mmHg, had a greater systolic (responders, 150 ± 13 mmHg vs. non-responders, 140 ± 10 mmHg, $P = 0.044$) and diastolic BP (responders, 88 ± 9 mmHg vs. non-responders, 86 ± 10 mmHg, $P = 0.041$) at the entry of the trial.

Figure 3 shows the results of home BP measurements. Morning BP was significantly decreased from 142 ± 12/87 ± 11 mmHg at baseline to 130 ± 17/80 ± 11 mmHg (both systolic and diastolic, $P < 0.001$). Night time BP was also decreased from 137 ± 12/86 ± 9 mmHg to 124 ± 10/78 ± 9 mmHg (both systolic and diastolic, $P < 0.001$). The significant BP reduction was apparent from month 1 and continued throughout the study period of 6 months.

Changes in laboratory tests

Table 2 shows changes in various parameters at the beginning and end of the observation period. There was an increase in serum Cr concentration (84.9 ± 34.5 to 89.3 ± 38.9 μmol/L, $P < 0.001$) in conjunction with a decrease in eGFR (from 65.6 ± 21.2 to 63.4 ± 20.7 mL/min/1.73 m^2, $P < 0.001$). Additionally, there was a significant decrease in serum sodium (Na) concentration (from 141.5 ± 2.1 to 140.8 ± 2.7 mEq/L, $P < 0.001$). No changes were found in blood lipids and serum potassium (K) concentration.

Figure 4 depicts changes in BNP after switching from the original prescription to LOS/HCTZ ridden regimen. The overall median BNP level significantly decreased from 18.8 to 15.4 pg/dL ($P < 0.05$). In patients whose BNP at baseline was more than 18.4 pg/dL (above the normal range, $n = 96$), the median level of BNP also decreased from 34.4 to 25.4 pg/dL ($P < 0.01$).

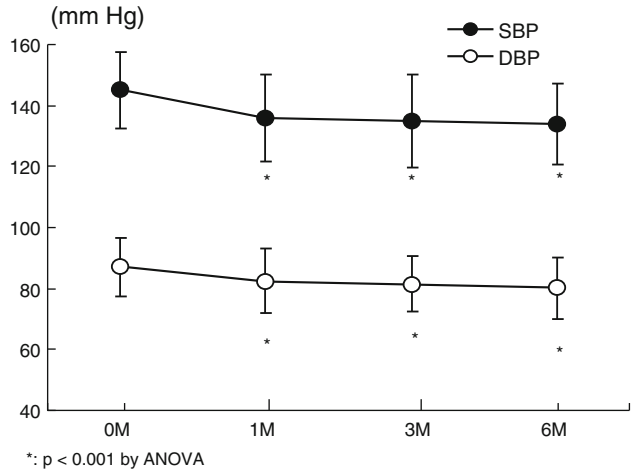

Fig. 1 Effect of LOS/HCTZ on clinic BP (all patients). *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LOS/HCTZ* losartan/hydrochlorothiazide, *ANOVA* one-way analysis of variance

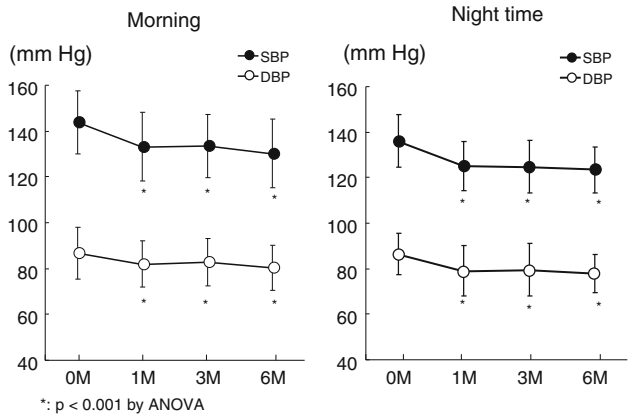

Fig. 3 Effect of LOS/HCTZ on home BP (all patients). *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LOS/HCTZ* losartan/hydrochlorothiazide, *ANOVA* one-way analysis of variance

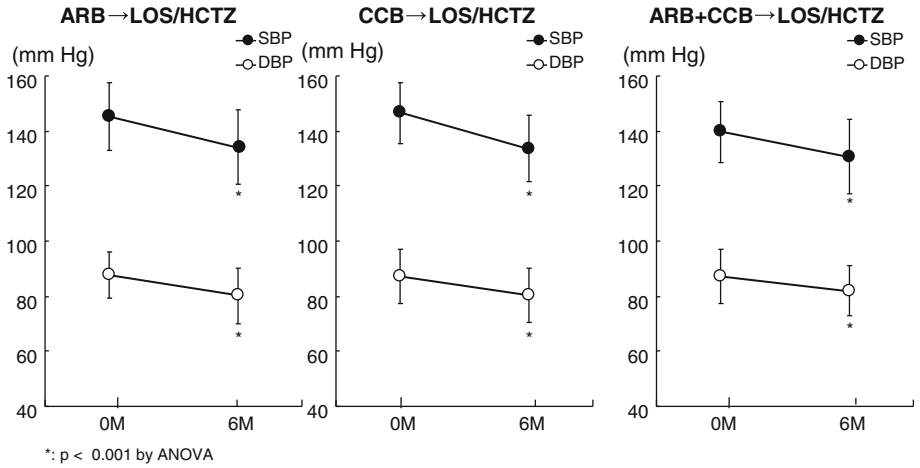

Fig. 2 Effect of LOS/HCTZ on clinic BP (various switching patterns). *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LOS/HCTZ* losartan/hydrochlorothiazide, *CCB* Ca channel blockers, *ANOVA* one-way analysis of variance

Figure 5 shows the BNP response as a function of BP response. In 135 responders defined as a reduction in systolic BP of ≥10 mmHg, the median BNP fell from 21.7 to 14.4 pg/dL ($P < 0.05$), whereas there was no change in BNP in 93 non-responders whose systolic BP reduction was less than 10 mmHg.

Figure 6 shows changes in ACR. The overall median value decreased from 21.7 to 13.9 mg/gCr ($P < 0.05$). In patients whose baseline ACR more than 30 mg/gCr (above the abnormal range, $n = 67$), the median value decreased from 108.0 to 52.0 mg/gCr ($P < 0.01$).

Changes in ACR between BP responders defined as a reduction in systolic BP of ≥10 mmHg after 6 months and non-responders (systolic BP reduction <10 mmHg) to treatment with LOS/HCTZ were comparable, with a significant reduction in both groups (data not shown).

Figure 7 shows changes in serum UA concentration. Although the fluctuation remained within the normal range, overall serum UA concentration increased (355 ± 93 to 367 ± 92 μmol/L, $P < 0.05$). When patients were classified into a high-UA group (UA ≥416 μmol//L) and a low-UA group (UA <416 μmol/L), a significant increase was observed in the low-UA group (315 ± 65 to 333 ± 77 μmol/L, $P < 0.01$). In contrast, in the high-UA group there was a significant decrease in UA value (473 ± 47 to 454 ± 63 μmol/L, $P < 0.05$).

Changes in BNP, ACR and serum UA levels were analyzed in the presence and absence of CKD (defined as e-GRF ≤60 mL/min/1.73 m^2). The reduction in ACR in the non-CKD group was greater than that in the CKD group (CKD: −0.12 ± 0.31 mg/gCr vs. non-CKD: −0.24 ± 0.36 mg/gCr, $P = 0.044$). No difference in the other parameters was found between the two groups.

Changes in BNP and ACR were also analyzed in conjunction with changes in clinic BP. A significant association was found between the reduction in systolic BP and the decrease in BNP ($r = 0.208$, $P = 0.004$), and ACR ($r = 0.290$, $P < 0.001$). The reduction in diastolic BP was correlated only with the decrease in ACR ($r = 0.291$, $P < 0.001$).

Table 2 Laboratory tests before and after the treatment with LOS/HCTZ

	Baseline	6 months	*P* value
s-Cr (μmol/L)	84.9 ± 34.5	89.3 ± 38.9	<0.001
Na (mmol/L)	141.5 ± 2.1	140.8 ± 2.0	<0.001
K (mmol/L)	4.3 ± 0.6	4.3 ± 0.6	0.940
LDL-C (mmol/L)	3.0 ± 0.7	3.0 ± 0.7	0.356
HDL-C (mmol/L)	1.5 ± 0.4	1.5 ± 0.4	0.118
TG (mmol/L)	1.9 ± 1.5	1.9 ± 1.3	0.938
Hb (g/L)	139 ± 18	139 ± 17	0.903
Ht (%)	42.1 ± 4.5	41.8 ± 4.6	0.141
RBC ($\times 10^{12}$/L)	4.49 ± 0.5	4.47 ± 0.51	0.428
WBC ($\times 10^9$/L)	6.2 ± 1.7	6.3 ± 1.8	0.508
Platelets ($\times 10^9$/L)	232 ± 55	233 ± 55	0.670
eGFR(mL/min/1.73 m^2)	65.6 ± 21.2	63.4 ± 20.7	<0.001

Laboratory tests before (baseline) and after (6 months) the treatment with LOS/HCTZ

s-Cr serum creatinine concentration, *Na* serum sodium concentration, *K* serum potassium concentration, *LDL-C* LDL cholesterol, *HDL-C* HDL cholesterol, *TG* triglyceride, *Hb* hemoglobin, *Ht* hematocrit, *eGFR* estimated glomerular filtration rate

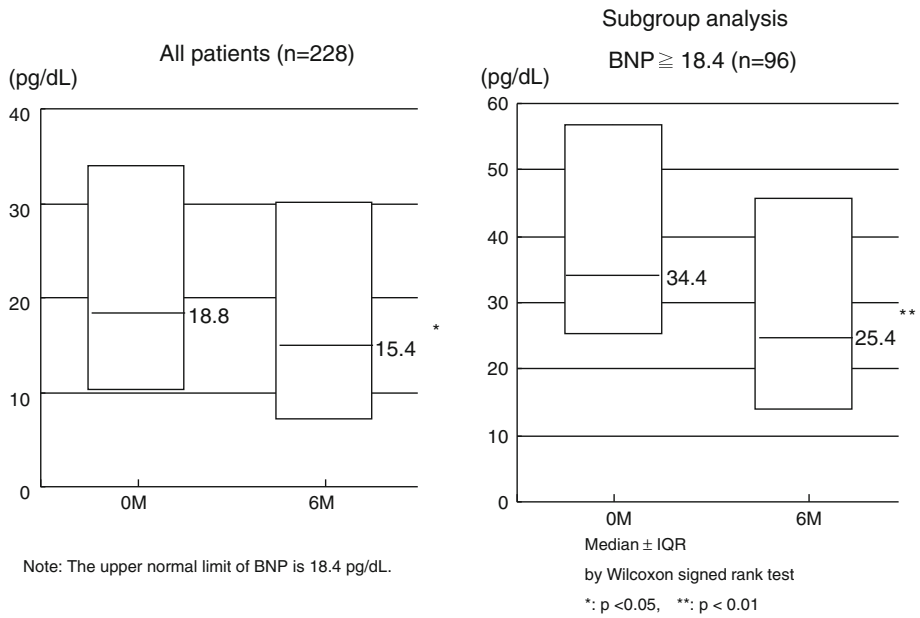

Fig. 4 Changes in BNP in response to LOS/HCTZ. *BNP* B-type natriuretic peptide, *LOS/HCTZ* losartan/hydrochlorothiazide

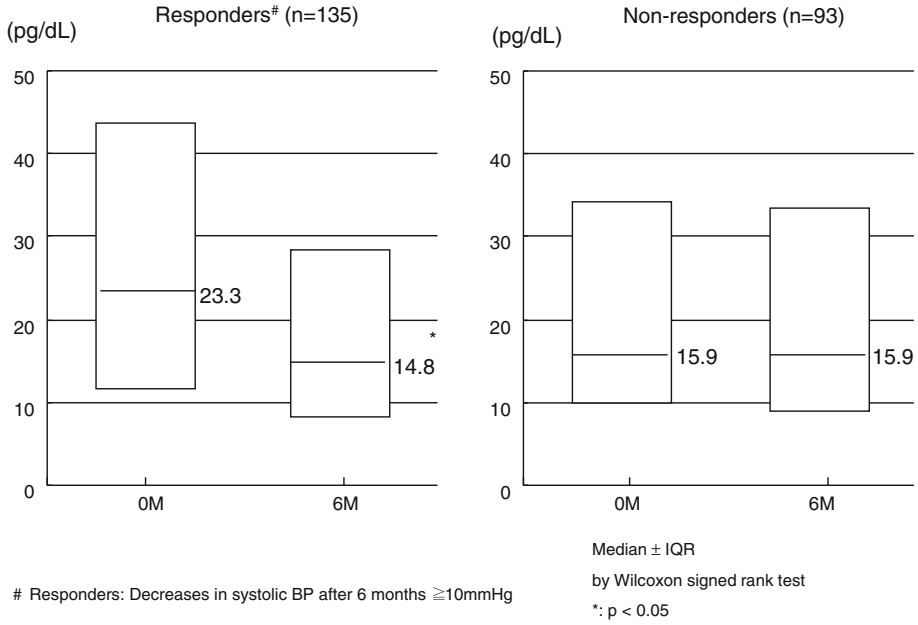

Fig. 5 Changes in BNP classified by BP response. Responders were defined as patients whose systolic BP reduction was more than 10 mmHg. *LOS/HCTZ* losartan/hydrochlorothiazide

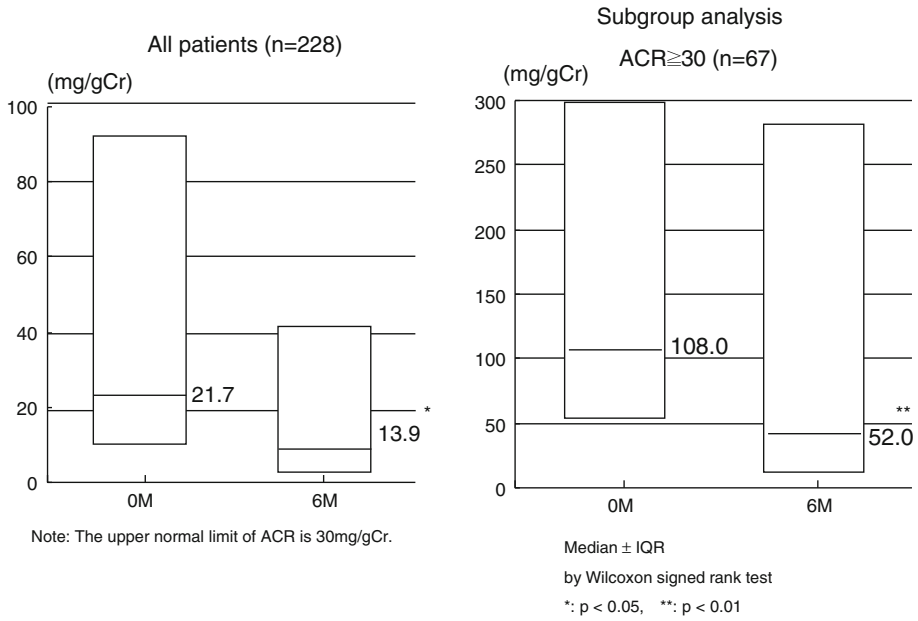

Fig. 6 Changes in ACR in response to LOS/HCTZ. *LOS/HCTZ* losartan/hydrochlorothiazide, *ACR* albumin creatinine excretion ratio

Discussion

BP lowering effect of LOS/HCTZ

Similar to the recommendations from hypertension guideline worldwide [1, 4, 11, 12], the guideline of Japanese Society of Hypertension (JSH) recommends the use of diuretics as first-line antihypertensive treatment [5]. A fixed dose combination of LOS/HCTZ which contains normal dose of LOS (50 mg) and a low dose HCTZ (12.5 mg) has lately come into clinical practice. The present study clearly demonstrated that switching to LOS/HCTZ consistently led to a potent antihypertensive effect regardless of the mode of BP (clinic or home, morning or night: Figs. 1, 2), or the types of the pre-prescribed drugs (switching patterns: Fig. 3). Similar results were reported by Kita et al. [7] in a 1-year study of Japanese patients in which switching from ARBs or ACE-Is to LOS/HCTZ was carried out (The PALM-1 study). Their observation showed that after the treatment with LOS/HCTZ, 50% of patients fulfilled the targeted goals of the JSH guideline for systolic BP and 79% for diastolic BP. The achieving rate of 130/80 mmHg in the present study (53%) coincides with these results. A randomized controlled study reported by

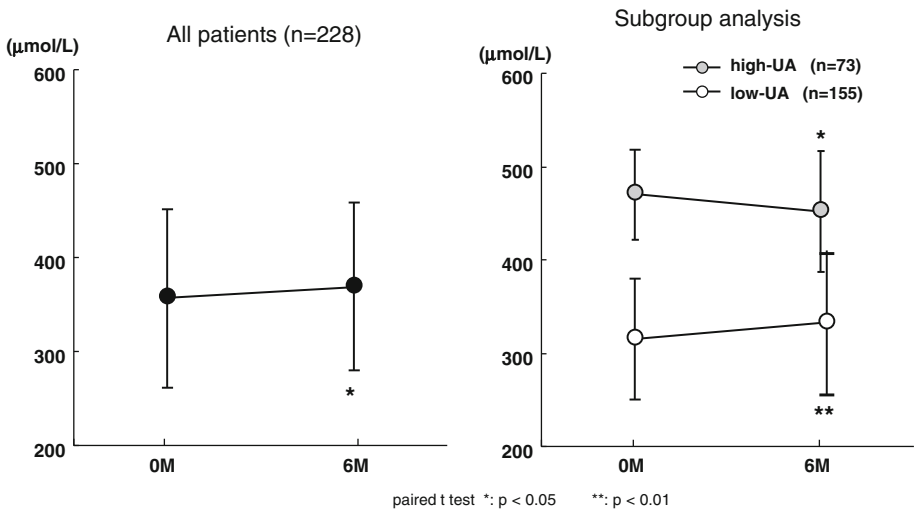

Fig. 7 Changes in UA in response to LOS/HCTZ UA: serum uric acid concentration. High UA: patients whose serum UA concentration ≥416 μmol// L. Low-UA group patients whose serum UA concentration <416 μmol/L

Ando et al. evaluated the effect of telmisartan, an ARB, plus low dose HCTZ compared with an increased dose of amlodipine, a CCB, when switched from amlodipine. The Effect of lowering BP was more profound in the telmisartan plus HCTZ group than in the increased dose of amlodipine group (The ONEAST study) [13].

The potent antihypertensive effect of LOS/HCTZ may partially be derived from the characteristics of the Japanese, whose intake of salt is traditionally high with the main sources including soy sauce, miso, salted fish, and salt added at the table [14, 15]. Salt-sensitive hypertension is associated with an impaired renal capacity to properly excrete sodium and water, resulting in a therapy-resistant hypertension. Of importance is that high salt suppresses the RAS, thereby diminishing the action of RAS inhibitors. Indeed, in 40–50% of the essential hypertensive population, adrenal and renal vascular responses to AII do not exhibit the expected changes predicted by changes in sodium intake [15]. In contrast, diuretics potentiate the RAS by contracting circulation volume, leading to an effective BP reduction, especially if salt intake of patients is high. The combination of an ARB and a diuretic is, therefore, considered advantageous in terms of strict BP control in salt sensitive patients with hypertension. Of note is that the present study showed that the responders had higher BP at entry, suggesting "the higher the BP, the better the response" characteristic with the combination of LOS/HCTZ in patients with uncontrolled hypertension.

Effect of LOS/HCTZ on renal function and electrolytes

Although the fluctuations were kept within the normal range, decrease in eGFR in conjunction with increased serum Cr concentration is a matter for debate. It is apparent that both are attributable to the use of diuretic. Substantial evidences have demonstrated that diuretic reduces GFR. For instance, studies exploring the effect of ARB/HCTZ repeatedly showed a reduction in eGFR in association with an increase in serum Cr concentration [7, 16, 17]. Decreased eGFR owing to the use of diuretics could be explained by the contraction of circulating plasma volume. Whether the decreased eGFR is a precipitating factor for the preservation of residual renal function is unknown. However, to date, a large body of reports has confirmed that diuretics are unequivocally efficacious in preventing major cardiovascular events, which include SHEP [18], ALLHAT [19], ACCOMPLISH [20], EWPHE [21], HYVET [22] and ADVANCE [23]. Moreover, a large scale PROBE trial exploring the effect of combination therapy performed in Japan suggested that the diuretic-ridden regimen was effective to prevent composite cardiovascular events [24]. One can, therefore, speculate that both the increased serum Cr concentration and the decreased eGFR could have been the result of a transient volume contraction due to the use of diuretic.

Although the change was subtle and entirely asymptomatic, the significance of decrease in the serum Na concentration may also be disputable. Adverse effect of hyponatremia is a well-recognized complication of treatment with thiazide that occurs predominantly in patients older than 70 years [25]. Two elements are associates with symptomatic hyponatremia. Such factors are diuretic at higher dosage (HCTZ dose between 35 and 50 mg) and low salt intake with a preexisting reduction in free water clearance or a high fluid intake [12]. Unless these two conditions meet, serious hyponatremia is unlikely occur particularly if patients are mobile. Uzu et al. [26] showed that treatment with HCTZ 12.5 mg and LOS 50 mg did not induce significant reduction in serum Na concentration. The present study, however, cast a caution that careful monitoring of serum Na concentration is indispensable in the treatment with HCTZ, even in a low prescribed dose of 12.5 mg.

With respect to serum K concentration, our study showed that there was no change in this parameter. Combining LOS with HCTZ exerts a beneficial offsetting effect in K metabolism, because the former increases serum K concentration and the latter decreases, diminishing the risk of either hyper-, or hypokalemia.

Effect of LOS/HCTZ on BNP and ACR

There was a substantial decrease in BNP, a marker for cardiac hypertrophy (Fig. 4). Furthermore, the reduction in BNP was obvious in patients with elevated BNP values and in those who responded well to the therapy, suggesting that the BNP lowering effect depends on BP reduction (Fig. 5). Strict BP control, therefore, appears to be indispensable for cardio-protection.

There was a substantial decrease in ACR, and the effect was profound especially in patients with elevated ACR (Fig. 6). The reno-protective effects of LOS have been demonstrated in the RENAAL study in patients with type 2 diabetic nephropathy [27]. The risk of a doubling of the serum Cr concentration, end-stage renal disease, or death from any cause, was reduced by about 16–28% with LOS. In addition, the LIFE study, demonstrating the superiority of LOS over atenolol for reduction of CV morbidity and mortality, was accompanied by the reduction in albuminuria [28–30]. The present study clearly confirmed that treatment with LOS/HCTZ is effective to improve microalbuminuria.

Decreases in BNP and ACR may portend good clinical outcomes for cardio- and reno-protection. However, longer term follow up would be needed to prove such.

Effect of LOS/HCTZ on UA metabolism

Despite the potent antihypertensive effect, diuretics have been less frequently used in clinical practice for fear of their adverse effects, including increase in serum UA concentration. In the present study, a subtle but significant increase in serum UA concentration was observed in overall patients, although such changes still remained within the normal range (Fig. 7). Of note is that when patients were stratified into a high-UA group and a low-UA group, significant decrease was observed only in the former. The same results were noted in the study by Kita et al. [7] who reported that while UA levels were kept within normal ranges a significant decrease in UA levels was observed in patients with hyperuricemia (The PALM-1 study). A recent post hoc analysis also confirmed that LOS lowers serum UA levels compared with placebo in patients with diabetic nephropathy [31]. The mechanisms by which LOS/HCTZ reduces UA levels in patients with hyperuricemia is largely attributable to uricosuric action of LOS, which has been known to be mediated by the inhibition of the UA transporter URAT-1 in the renal tubules [8, 9]. In the high-UA group, the uricosuric action of LOS might offset the hyperuricemic action of HCTZ, resulting in a decreased UA level in the high-UA group.

Limitation of the present study

The present study has limitation. It is not a randomized controlled study and no control group was used. Further study in a randomized, controlled fashion will help to strengthen the findings of this study.

In conclusion, a fixed dose combination formula of LOS plus HCTZ is efficacious in achieving BP goal in patients with uncontrolled hypertension. In addition, cardio-, reno-protective effects may also be anticipated.

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Conflict of interest None.

Appendix

The JOINT stands for The Jikei Optimal Antihypertensive Treatment Study, which included the following investigators in addition to the members listed on the title: Endo S, Fukui A, Gomi H, Hamaguchi A, Hanaoka K, Hara Y, Hara Y, Hasegawa T, Hayakawa H, Hikida M, Hirano K, Horiguchi M, Hosoya M, Ichida K, Imai T, Ishii T, Ishikawa H, Kameda C, Kasai T, Kobayashi A, Kobayashi H, Kurashige M, Kusama Y, Maezawa H, Maezawa Y, Maruyama Y, Matsuda H, Matsuo N, Matsuo T, Miura Y, Miyajima M, Miyakawa M, Miyazaki Y, Mizuguchi M, Nakao M, Nokano H, Ohkido I, Ohtsuka Y, Okada K, Okamoto H, Okonogi H, Saikawa H, Saito H, Sekiguchi C, Suetsugu Y, Sugano N, Suzuki T, Suzuki T, Takahashi H, Takahashi Y, Takamizawa S, Takane K, Morita T, Takazoe K, Tanaka H, Tanaka S, Terawaki H, Toyoshima R, Tsuboi N, Udagawa T, Ueda H, Ueda Y, Uetake M, Unemura S, Utsunomiya M, Utsunomiya Y, Yamada T, Yamada Y, Yamaguchi Y, Yamamoto H,Yokoo T, Yokoyama K, Yonezawa H, Yoshida H, Yoshida M and Yoshizawa T.

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