Efficacy and Safety of the Losartan-Hydrochlorothiazide Combination Tablet in Patients with Hypertension Uncontrolled by Angiotensin II Receptor Antagonist Therapy: The Aichi Research on Combination Therapy for Hypertension (ARCH) Study

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Abstract

Background The guidelines recommend combination therapy for patients who are unable to achieve target BP with monotherapy; some fixed dose therapies including an angiotensin II receptor blocker (ARB) and diuretics are available in Japan. However, to date there have been few reports on this long-term treatment and the patient profiles suited for this combination remain ambiguous.

Method The Aichi Research on Combination therapy for Hypertension Study was a multicenter, open-label, prospective observational study that investigated the efficacy and safety of 1-year treatment with the losartan-hydrochlorothiazide (HCTZ) combination tablet in patients with hypertension uncontrolled by either ARB monotherapy or combination therapy with a calcium channel blocker (CCB). An ARB was switched to a losartan-HCTZ tablet after a pre-observation period.

Results A total of 614 of 648 patients were evaluable (mean age, 66.3 years; 52.8% men; mean baseline blood pressure, BP, 157.7/87.9 mmHg). The BP had decreased significantly to 138.0/78.2 mmHg by month 3 ($p < 0.001$, t -test), and 36.2% of the patients had achieved their target BP. The hypotensive effect lasted for 1 year and was found equally in the losartan-HCTZ arm and the losartan-HCTZ plus CCB arm. A stratified analysis showed significant hypotensive effects in patients with higher baseline BP, women, and patients who did not drink alcohol ($p < 0.001$, unpaired t -test).

Conclusion The losartan-HCTZ combination tablet was found to have an early hypotensive effect, good tolerability, and stable long-term benefits in patients with hypertension uncontrolled by ARB monotherapy or combination therapy with a CCB.

Key words: angiotensin II receptor antagonist, antihypertensive agent, hydrochlorothiazide, hypertension, losartan

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Introduction

There has been tremendous progress in the development of antihypertensive agents, consequently it is now much easier to control blood pressure (BP) in patients with hyperten-

sion. Nevertheless, many patients fail to achieve BP control. The international guidelines, including those of the Japanese Society of Hypertension (JSH), recommend combination therapy for patients unable to achieve their target BP with monotherapy. One such combination therapy is an angiotensin II receptor antagonist (angiotensin receptor

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blocker, ARB) and a diuretic agent. The combination of the traditional high intake of sodium and the recent increase in the number of individuals with metabolic syndrome has emerged as an important problem of public health in Japan. Excessive sodium intake in particular is a major cause of hypertension in Japan. It is generally accepted that reducing sodium intake could reduce BP (1), but sufficient dietary sodium restriction is not achievable in most elderly in Japan.

Diuretic agents block the reabsorption of sodium by uniniferous tubules, and thereby reduce body fluid volume and cardiac output. These effects, in turn, shift the pressure-natriuresis-diuresis curve of patients with salt-sensitive hypertension toward that of patients with non-salt-sensitive hypertension. Therefore, diuretic agents seem to be particularly effective in reducing BP in salt-sensitive patients, in patients such as those who ingest excessive amounts of salt, patients with diabetes mellitus, women, and patients with chronic kidney disease. The combination of antihypertensive agents in a single tablet would be expected to improve dose compliance, which would thus facilitate hypertensive patients to achieve better control of their BP (2). Therefore, some fixed dose medications that include an ARB and a diuretic agent have been approved and are clinically used in Japan. This combination has a synergistic effect and is expected to reduce BP more effectively. However, to date there have been few reports on the long-term treatment, and the patient profiles that are better suited for this combination treatment remain to be elucidated.

Therefore, this study investigated the efficacy and safety of intensive treatment in which an ARB was replaced with a losartan-hydrochlorothiazide (HCTZ) combination tablet in hypertensive patients who were unable to achieve their target BP. Each tablet contains 50 mg of losartan potassium and 12.5 mg of HCTZ. The efficacy was assessed by changes in BP and the percentage of patients achieving their target BP. Moreover, a stratified analysis was performed at the end of the study to specify in which patient subgroups the losartan-HCTZ tablet was the most effective.

Materials and Methods

Patients

The study was a multicenter, open-label, prospective observational study that investigated the efficacy and safety of losartan-HCTZ in hypertensive outpatients. Patients who were 20-80 years old and unable to achieve their target BP (based on JSH 2004 guidelines) with ARB monotherapy at a standard dosage or combination therapy using a standard dosage of ARB with amlodipine 5 mg were recruited. Each ARB was replaced with the losartan-HCTZ tablet after a pre-observation period (1 month). Patients with secondary hypertension, severe heart failure (more than New York Heart Association class III), or renal function impairment (serum creatinine concentration ≥ 2.0 mg/dL) were excluded. Fig. 1 shows the study design.

Chronic renal disease and diabetes mellitus were diagnosed by each physician, based on the laboratory analysis measurements. The history of cerebrovascular disease was confirmed by case report forms. The study was performed at 95 centers from September 2007 to December 2009. Case report forms were collected from all patients who received losartan-HCTZ. The study protocol was approved by the ethics committee of each site, and the study complied with the ethical principles of the Declaration of Helsinki. All patients provided their informed consent for their data being used for research purposes before participation in the study.

Treatment

The patients first received hypotensive therapy with an ARB at a standard dosage for ≥ 1 month, either by monotherapy or combination therapy with amlodipine 5 mg. Patients unable to achieve their target BP then received either losartan-HCTZ monotherapy or losartan-HCTZ combination therapy with amlodipine 5 mg once daily for 3 months. No other hypotensive drugs were allowed during this period. Add-on treatment with other antihypertensive agents (amlodipine, diuretic agents, β -blockers, α -blockers, or sympathetic inhibitors) was allowed if the target BP of JSH 2004 ($<140/90$ mmHg for patients equal or older than age 65; $<130/85$ mmHg for patients younger than age 65; $<130/80$ mmHg for patients with diabetes mellitus or chronic renal disease; $<140/90$ mmHg for patients with a history of cerebrovascular disease) was not achieved after 3 months of intensive treatment. The intensive treatment period was 1 year.

Measurement of study variables

The blood pressure, pulse rate, and dose compliance were recorded at the start of intensive treatment (baseline) and at months 3, 6, 9, and 12. Hematologic tests were done at baseline and at months 3, 6, and 12. The blood measurements included hemoglobin, hematocrit, white blood cell, platelet, low density lipoprotein cholesterol, total cholesterol, triglyceride, high density lipoprotein cholesterol, aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transpeptidase, lactate dehydrogenase, albumin, total bilirubin, creatine phosphokinase, blood urea nitrogen, uric acid, serum creatinine, sodium, potassium, chlorine, blood glucose and hemoglobin A1c. Blood samples were taken either after fasting or otherwise, provided that it was consistent throughout the study. However, fasting blood samples were mandatory for patients with diabetes mellitus. Blood pressure was measured according to the JSH 2004 guidelines, which advise that outpatient BP should be measured in the seated position after 5 minutes of rest, with caffeine-containing beverages and smoking prohibited within 30 minutes of measurement. BP was measured several times during each session, at 1- to 2-min intervals, and the average of two consecutive stable measurements (i.e. difference ≤ 5 mmHg) was used. BP measurements were taken from both arms, and the measurement from the arm with the highest BP was used.

Figure 1. Study design. *Target blood pressure (BP); <140/90 mmHg for patients age 65 or older; <130/85 mmHg for patients younger than age 65; <130/80 mmHg for patients with diabetes mellitus or chronic renal disease; <140/90 mmHg for patients with a history of cerebrovascular disease. †Angiotensin II receptor antagonist (ARB) at standard dosage: losartan 50 mg, valsartan 80 mg, candesartan 8 mg, olmesartan 20 mg, or telmisartan 40 mg daily. CCB: calcium channel blocker, HCTZ: hydrochlorothiazide

Statistical analysis

The primary endpoint (systolic BP at month 3) was compared with the baseline values using one-sample *t*-test. In addition, a stratified analysis was done on these 3-month changes, stratifying patients by baseline values, gender, alcohol consumption, age, diabetes complications, and body mass index (BMI). Multiple regression analyses were done with the level of effect as the dependent variable to evaluate the effects of various independent variables on changes in systolic and diastolic BP. The independent variables were alcohol consumption, gender, low-density lipoprotein cholesterol concentration, smoking, blood glucose concentration, uric acid concentration, age, and BMI. Other endpoints (systolic BP at month 3, achievement of target BP, and serial changes in BP over 1 year) were analyzed using *t*-test, ANOVA, or the chi-squared test as appropriate. Safety was assessed based on adverse events and clinical laboratory values reported during the study. In addition, summary statistics were collected on safety variables using the means and SD for quantitative data and frequency and proportion for qualitative data.

Results

Patient characteristics

Case report forms were collected from all 648 patients who received losartan-HCTZ. Data from 614 patients were included in the analysis after 34 patients were excluded because of protocol violations. Summary statistics with means and SD were available for all measurements at each time point. A total of 76 patients (12.4%) withdrew from or dropped out of the study within 1 year of intensive treatment; the most common reason for withdrawal or dropout was loss to follow-up (30 patients), and 25 patients withdrew or dropped out because of adverse events.

The patient characteristics at baseline are shown in Table 1. Most of the 614 patients had had hypertension for <5 years, and lipid abnormality was the most common associated risk factor. The ARBs most commonly used during the pre-observation period were losartan, valsartan, and candesartan. More patients were in the monotherapy arm (378, 61.6%) than in the combination therapy arm.

Changes in BP after 3 months of intensive treatment

The mean change in the systolic BP, the primary end-

Table 1. Baseline Patient Characteristics

Baseline characteristic	Mean $\pm$ SD or n (%)
Age (years)	66.3 $\pm$ 11.2
Men	324 (52.8)
Body mass index (kg/m ²)	24.1 $\pm$ 3.6
Abdominal circumference (cm)	86.8 $\pm$ 11.0
Systolic blood pressure (mmHg)	157.7 $\pm$ 14.6
Diastolic blood pressure (mmHg)	87.9 $\pm$ 11.2
Pulse rate (beats/min)	74.2 $\pm$ 10.3
Hypertension history (years)	
< 1	64 (13.1)
< 5	184 (37.6)
< 10	127 (26.0)
$\geq$ 10	114 (23.3)
Smokers ¹	153 (27.0)
Alcohol drinkers ²	198 (35.4)
Monotherapy arm	378 (61.6)
Risk factors	
Lipid abnormality	185 (30.1)
Diabetes mellitus	108 (17.6)
Hyperuricemia	39 (6.4)
Chronic kidney disease	86 (14.0)
History and complications	
Cerebral stroke	30 (4.9) ³
Cardiac failure	13 (2.1)
Occlusive arterial disease	11 (1.8)
Angina pectoris	10 (1.6)
Atrial fibrillation	10 (1.6)
Arrhythmia	8 (1.3)
Cardiac infarction	6 (1.0)
ARB used in preobservation period	
Losartan	144 (23.5)
Valsartan	133 (21.7)
Candesartan	117 (19.0)
Olmesartan	113 (18.4)
Telmisartan	107 (17.4)

ARB, angiotensin II receptor antagonist.

¹ Mean duration of smoking, 32.3 years.² Mean daily alcohol consumption equivalent to 300 mL of sake.³ Hemorrhagic, 7; infarcted, 23.

point, in all 614 patients was -19.7 mmHg, a significant decrease from 157.7 mmHg at baseline to 138.0 mmHg at month 3 ($p < 0.05$, t -test; Fig. 2A). The mean pulse rate remained almost unchanged (74.2 beats/min at baseline, 73.6 beats/min at month 3).

The mean systolic BP in the 354 patients in the losartan-HCTZ monotherapy arm at month 3 was 137.4 mmHg, a significant decrease of 20.8 mmHg from 158.2 mmHg at baseline ($p < 0.05$, t -test; Fig. 2B). Likewise, the mean systolic BP in the 260 patients in the combination therapy arm was 139.4 mmHg at month 3, a significant decrease of 17.8 mmHg from 157.2 mmHg at baseline ($p < 0.05$, t -test; Fig. 2C).

The mean change in the diastolic BP in all 614 patients was -9.7 mmHg, a significant decrease from 87.9 mmHg at baseline to 78.2 mmHg at month 3 ($p < 0.05$, t -test; Fig. 2A).

The mean diastolic BP in the patients in the monotherapy arm was 78.5 mmHg at month 3, a significant decrease of 10.4 mmHg from 88.9 mmHg at baseline ($p < 0.05$, t -test; Fig. 2B). Likewise, the mean diastolic BP in the patients in the combination therapy arm was 77.9 mmHg at month 3, a significant decrease of 8.4 mmHg from 86.3 mmHg at baseline ($p < 0.05$, t -test; Fig. 2C).

The results showed that 36.2% of patients had achieved their target BP based on JSH 2004 at month 3 ($p < 0.05$ ver-

sus baseline, chi-squared test; data not shown); 39.6% (243/614) and 71.7% (440/614) of the patients had achieved their target systolic and diastolic BP, respectively. This represented a significant increase from 1.8% (11/614) and 36.5% (224/614), respectively, at baseline ($p < 0.05$, chi-squared test; data not shown).

Patient profiles suited for the losartan-HCTZ combination tablet

Patients with BP (when seated) which decreased by 20/10 mmHg at month 3 of the intensive treatment protocol from baseline were categorized as responders to treatment. Patients with systolic BP which decreased by 20 mmHg at month 3 of intensive treatment from baseline were categorized as systolic BP responders. Likewise, patients with diastolic BP which decreased by 10 mmHg at month 3 and/or from baseline were categorized as diastolic BP responders. At month 3, 70.8% of patients (435/614) were systolic BP responders, 88.9% (546/614) were diastolic BP responders, and 61.7% (379/614) were systolic and diastolic BP responders (data not shown).

Systolic BP responders and non-responders were compared for each relevant patient characteristic. Age, BMI, smoking, concurrent diseases, and ARB treatment during the pre-observation period showed no significant difference between the groups. However, significant differences were found for gender and alcohol consumption; the percentages of responders and non-responders were 50.1% (218/435) and 59.2% (106/179) for gender (men) and 32.8% (131/399) and 41.9% (67/160) for alcohol consumption (both $p < 0.05$, chi-squared test, data not shown).

Stratified analyses of changes in systolic BP from baseline to month 3 were done according to the following stratifications: baseline systolic BP (≥ 160 mmHg or < 160 mmHg), gender, alcohol consumption, smoking, age (≥ 65 years or < 65 years), diabetes, hyperlipidemia, hyperuricemia and BMI (≥ 25 kg/m² or < 25 kg/m²). Therefore, patients with high baseline systolic BP, women, patients who did not drink alcohol, and elderly patients (aged ≥ 65 years) showed a significantly greater hypotensive response ($p < 0.001$, unpaired t -test, Table 2A). A multiple regression analysis was done using the influences on changes in systolic BP as dependent variables. Only alcohol consumption significantly affected changes in the systolic BP ($p = 0.045$; Table 3A).

Furthermore, stratified analyses of changes in diastolic BP from baseline at month 3 were performed as in systolic BP. Table 2B showed that the hypotensive effect of the losartan/HCTZ tablet was significantly greater in patients with high baseline diastolic BP (≥ 100 mmHg), patients who did not drink alcohol, and younger patients (aged < 65 years). Women tended to have a lower BP after 3 months of treatment, although the difference was not significant. A multiple regression analysis revealed that alcohol consumption and gender significantly affected the changes in diastolic BP ($p = 0.001$, 0.043, respectively, Table 3B).

A, All patients (n=614)

B. Monotherapy (n=354)

C. Combination (n=260)

Figure 2. Changes in the blood pressure (means±SD) at month 3 of intensive treatment with losartan-hydrochlorothiazide: a, all patients (n=614); b, monotherapy arm alone (n=354); and c, combination therapy arm alone (n=260). *p<0.05 (t-test).

Efficacy and safety of losartan-HCZ based therapy during 1 year of treatment

Both systolic and diastolic BP decreased significantly by month 3, and the hypotensive effect persisted for 1 year ($p<0.001$, ANOVA; Fig. 3). An adequate hypotensive effect was found soon after intensive treatment was begun, and BP was well controlled over 1 year, although add-on drugs were often provided after month 3. The pulse rate remained unchanged from baseline through 1 year.

The laboratory measurements that changed significantly at month 3 were hematocrit, concentrations of total cholesterol, lactate dehydrogenase, blood urea nitrogen, serum creatinine, sodium, potassium, and chloride. Overall, these changes were within reference ranges and considered not clinically relevant. Measurements sensitive to diuretic

agents, such as blood glucose concentration, hemoglobin A1c value, and uric acid concentration, showed no significant changes. The fasting blood glucose concentration, hemoglobin A1c value, and lipid concentrations other than total cholesterol (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride concentration) also showed no significant changes (paired *t*-test).

Only 5.2% of the patients (32/614) experienced a total of 35 adverse events over the entire observation period. The adverse events experienced by at least two patients included; dizziness in eight patients (1.3%), and hypokalemia, hypotension, rash, diarrhea, impaired liver function, impaired renal function, and cerebral infarction, each of which occurred in two patients (0.3%). These events were mostly mild, none were severe, and they resolved during the study. Hypokalemia, which is commonly associated with diuretic

Table 2. Stratified Analysis of Changes in Blood Pressure after 3 Months of Intensive Treatment

A. systolic BP					
Stratified factor	n	Baseline	Month 3	Change	p value ¹
Baseline systolic BP					
≥ 160 mmHg	259	170.9	142.8	28.1	< 0.001
< 160 mmHg	355	148.1	134.5	13.5	
Gender					
Men	324	156.1	138.6	17.4	< 0.001
Women	290	159.6	137.4	22.2	
Alcohol consumption					
Yes	198	154.8	138.6	16.2	< 0.001
No	361	159.8	138.1	21.7	
Age (years)					
≥ 65	358	160.0	138.5	21.5	< 0.001
< 65	252	154.5	137.3	17.2	

B. diastolic BP					
Stratified factor	n	Baseline	Month 3	Change	p value ¹
Baseline diastolic BP					
≥ 100 mmHg	89	104.8	86.1	18.7	< 0.001
< 100 mmHg	525	85.1	76.8	8.3	
Gender					
Men	324	88.4	79.0	9.4	0.052
Women	290	87.4	77.3	10.1	
Alcohol consumption					
Yes	198	88.9	79.6	9.3	0.021
No	361	87.8	77.4	10.4	
Age (years)					
≥ 65	358	84.8	75.5	9.3	< 0.001
< 65	252	92.4	81.9	10.5	

BP, blood pressure; NS, not significant.

¹Unpaired *t*-test.**Table 3. Effect on Changes in Systolic Blood Pressure (Multiple Regression)**

A. systolic BP					
Influence rank	Independent variable	Partial regression coefficient	Standardized partial regression coefficient	t value	p value
1	Constant	31.784		1.464	0.148
2	Alcohol consumption	−9.304	−0.293	−1.995	0.045
3	Gender	6.440	0.211	1.487	0.142
4	LDL-C concentration	−0.058	−0.103	−0.829	0.410
5	Smoking	3.302	0.096	0.713	0.479
6	Blood glucose concentration	−0.032	−0.086	−0.724	0.471
7	Uric acid concentration	−0.271	−0.026	−0.203	0.840
8	Age	0.015	0.010	0.083	0.934
	Body mass index	−0.048	−0.010	−0.080	0.937

B. diastolic BP					
Influence rank	Independent variable	Partial regression coefficient	Standardized partial regression coefficient	t value	p value
1	Constant	35.875		2.380	0.020
2	Alcohol consumption	−5.509	−0.480	−3.360	0.001
3	Gender	3.153	0.286	2.070	0.043
4	Age	−0.211	−0.205	−1.690	0.096
5	LDL-C concentration	−0.055	−0.135	−1.120	0.269
6	Blood glucose concentration	−0.032	−0.116	−1.010	0.316
7	Uric acid concentration	−0.940	−0.126	−1.000	0.321
8	Body mass index	0.086	0.025	0.200	0.839
	Smoking	0.140	0.011	0.090	0.932

BP, blood pressure; LDL-C, low-density lipoprotein cholesterol.

Figure 3. Changes in the blood pressure (means $\pm$ SD) over 1 year of intensive treatment with losartan-hydrochlorothiazide. * $p<0.05$ (ANOVA).

agents, occurred in only three patients, and all cases were mild. All adverse events that occurred during the study have been previously reported.

Discussion

The present study confirmed the efficacy of the losartan-HCTZ combination tablet, and no excessive hypotension was noted with the combination of two active ingredients. The results in the present study proved the safety of the long-term use of losartan-HCTZ. Intensive treatment with losartan-HCTZ for patients with hypertension uncontrolled by ARB therapy is particularly effective in patients with high baseline BP and in women. On the other hand, losartan-HCTZ is less effective in patients who drink alcohol, thus suggesting the importance of lifestyle intervention as well as drug therapy to treat hypertension.

Hypertension is a crucial risk factor for potentially fatal complications such as cerebrovascular and cardiovascular diseases. The meta-analysis indicated that BP should be appropriately controlled in patients with hypertension to improve their prognosis (3). Unfortunately, only 50% of patients treated with a single antihypertensive agent achieve their target BP (4-8). Therefore, the guidelines for hypertension treatment recommend combination therapy with antihypertensive agents, which is more effective in reducing BP than an increased dosage of a single agent in patients whose BP is uncontrolled by monotherapy (9, 10). The combination of a RAS inhibitor and a diuretic agent is recommended by the Japanese, US, and European guidelines. Although substantial reductions in BP from baseline were achieved by losartan/HCTZ therapy, only 36.2% of patients achieved the target BP of $<140/90$ mmHg by month 3 of intensive treatment, thus indicating the difficulty in achieving a strict control of BP. Actually, more than half of the patients required combination therapy with three or more drugs, including ARBs, diuretic agents, and CCBs during the observation period.

The stratified analyses of changes in systolic BP from baseline to month 3 showed significantly greater hypoten-

sive effects in patients with high baseline systolic BP, women, patients who do not drink alcohol, and patients ≥ 65 years. It is plausible that general pharmacological effects of antihypertensive drugs contribute to the association between higher baseline BP and greater hypotensive effect. Elderly and female patients have clinical features of salt-sensitive hypertension which might contribute to greater hypotensive effect of losartan-HCTZ. Elderly patients usually have low renin and low aldosterone concentration and are generally considered to have volume retention associated with renal dysfunction (11). Therefore, many elderly patients tend to be salt-sensitive and show a good response to diuretic agents. In addition, the combination of multiple drugs into a single tablet could improve adherence to treatment particularly in elderly patients. The present study shows losartan-HCTZ tablets to be a combination agent with significant hypotensive effects in elderly patients without severe complications and therefore they are particularly useful for treating hypertension in this group of patients.

Responses to RAS inhibitors differ between genders; women tend to have lower renin activity, and men tend to respond better to RAS inhibitors (12). One characteristic of hypertension in women is that the prevalence of hypertension greatly increases after menopause (9, 10). An imbalance of estrogens and progesterone leads menopausal women to fluid retention, which might be associated with a salt-sensitive hypertension in women (13). The diuretic effect of losartan-HCTZ activates the RAS as a result of volume loss, leading to the synergistic hypotensive effect of ARB, losartan. The present study found a significantly strong hypotensive effect in women, thus suggesting that losartan-HCTZ is effective in women with hypertension and a low renin activity.

It is interesting to note that younger patients achieved a greater decrease in their diastolic BP, while older patients achieved a larger decrease in their systolic BP. One of the characteristics of hypertension in elderly patients is isolated systolic hypertension caused by arterial stiffening. Actually, the baseline diastolic BP was lower in elderly patients, while the baseline systolic BP was higher (Table 2). Al-

though speculative, it is plausible that more severe arterial stiffening in elderly patients attenuated the vasodilating effect of the losartan/HCTZ tablet.

A multiple regression analysis was performed on various factors influencing changes in BP. Only alcohol consumption has a significant negative effect on changes in both systolic and diastolic BP. A long period of alcohol intake increases BP (14). In addition, previous reports have indicated that the less alcohol a patient drinks, the lower his or her BP tends to be (15). As a result, reducing alcohol consumption by 80% has been demonstrated to rapidly reduce BP (16). Although the present study did not analyze the diet and lifestyle of the study population in detail, it is likely that people who drink more alcohol generally have a more disordered diet and lifestyle than those who do not drink alcohol. The attenuated hypotensive effect in drinkers might therefore be associated with these problems.

Two drug combinations, ARB-diuretic agent and ARB-CCB, are used in clinical practice in Japan. Hypertension specialists suggest that patients with hypertension that is uncontrolled by RAS inhibitors should therefore receive either combination therapy with diuretic agents if the disease is associated with excessive fluid retention, or combination therapy with CCB if it is associated with arteriosclerosis. The results of future comparison studies to elucidate the optimal usage of such losartan-HCTZ combination tablets and the ARB-CCB are therefore highly anticipated.

Author's disclosure of potential Conflicts of Interest (COI).

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