Original Article

Effectiveness of Add-On Low-Dose Diuretics in Combination Therapy for Hypertension: Losartan/Hydrochlorothiazide *vs*. Candesartan/Amlodipine

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In guidelines, a combination therapy of two or more antihypertensives is recommended for treatment of hypertension where monotherapy is ineffective. Although diuretics or calcium channel blockers are commonly used as add-ons to angiotensin receptor blocker (ARB), the most effective and safe combination has not been established. In this randomized 4-month study, the efficacy and safety were compared between an ARB/diuretics (losartan/hydrochlorothiazide [HCTZ]) combination and the most prescribed combination, ARB/calcium channel blocker (candesartan/amlodipine) in hypertensive patients for whom 8 mg/day of candesartan proved ineffective. After 36 patients were recruited and allocated into two groups, changes in blood pressure (BP) and laboratory values were analyzed in 31 patients: 16 patients received losartan (50 mg/day)/HCTZ (12.5 mg/day) (L/H group), and 15 patients received candesartan (8 mg/day)/amlodipine (5 mg/day) (C/A group) after 5 patients were withdrawn. After 4 months, L/H significantly ($p<0.001$) reduced mean systolic BP (SBP)/diastolic BP (DBP) from baseline 160/89±13/11 mmHg to 140/80±9/8 mmHg, and C/A reduced BP from 161/90±10/11 mmHg to 141/79±10/7 mmHg. The efficacy in reducing BP was similar between the two combination therapies. L/H significantly reduced serum potassium, but within the normal range, and did not increase serum uric acid or serum triglyceride. With L/H, the percentage of patients who attained the BP goal in SBP was higher in elderly patients than in younger patients. As L/H is more cost-effective than candesartan/amlodipine and has fewer adverse effects on uric acid and other metabolic parameters than diuretic monotherapy, it is concluded to be useful for the management of hypertension. (*Hypertens Res* 2007; 30: 831–837)

***Key Words*: guidelines, potassium, uric acid**

Introduction

Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) is recommended as a front-line therapy for lowering target blood pressure for patients with diabetes, ischemic heart disease, or chronic kidney disease (*1–3*). However, monotherapy with either of these drugs is effective only in some cases, and in most cases two or three drugs with different mechanisms are required. In the guidelines of the European Society of Hypertension/European Society of Cardiology, combination therapy of ARB/diuretics or ARB/calcium channel blocker (CCB) is recommended for the management of difficult-to-control hypertension. According to pharmacological and physiological mechanisms, either diuretics or CCB is a reasonable choice for combination with renin-angiotensin blockers (ACEI and ARB), because both diuretics and CCB reduce circulating blood volume, which is otherwise hard to control by renin-angiotensin blockers (*4*). Recently the combination therapy of ARB and CCB were

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reported to protect organs in a rodent model (*5*, *6*). Although CCB and ARB are considered front-line drugs in Japan, the rate of attainment to a blood pressure goal (<140/90 mmHg) was about 12 to 40% with monotherapy using either drug (*7*, *8*). According to a Japanese cross-sectional survey, CCB and the CCB/ARB combination are the most prescribed antihypertensive agents in Japan, and the percentage of patients who achieve the blood pressure goal with CCB was 31%, lower than that with CCB/diuretic (40.7%) (*8*). No prospective study on the safety and efficacy of ARB-based combination therapy has been conducted in Japan. In this study, we compared the efficacy and safety of therapy combining losartan/hydrochlorothiazide (HCTZ) and candesartan/amlodipine in Japanese hypertensive patients. We chose those combinations for three reasons: losartan has been widely used for its safety and efficacy worldwide in recent years, HCTZ is established as a potent hypertensive drug in the United States and Europe for a long time, and the candesartan/amlodipine combination is the most frequently prescribed combination of drugs for hypertension in Japan at this time.

Methods

Subjects

The subjects of the study were hypertensive patients who had visited the outpatient clinic of the Department of Internal Medicine, San-ikukai Hospital, Tokyo, Japan and had not attained the blood pressure goal of 130/85 mmHg for patients aged less than 65 years or 140/90 mmHg for those aged 65 years or more in response to administration of 8 mg/day candesartan for at least 2 months. Patients were excluded if they did not meet these criteria, secondary hypertension, defined by cardiovascular, cerebrovascular, renal, or hepatic disease, recent myocardial infarction, or severe hypertension (systolic blood pressure [SBP]≥180 mmHg or diastolic blood pressure [DBP]≥110 mmHg).

Study Design

This was an open-label, parallel-prospective, randomized study conducted to compare two treatment combinations for 4 months between February and December 2005. A total of 36 patients were randomly allocated into two groups: the L/H group, receiving 50 mg/day of losartan plus 12.5 mg/day of HCTZ, and the C/A group, receiving 8 mg/day of candesartan plus 5 mg/day of amlodipine. Sitting blood pressure, serum potassium, uric acid, cholesterol, creatinine, and hemoglobin A1c (HbA1c) were measured before and after the treatment period. The SBP/DBP treatment goals were ≤130/85 mmHg for patients aged less than 65 years and ≤140/90 mmHg for patients aged over 65 years. The percentages of patients who attained treatment goals at the end of the study period were calculated and compared between the two groups. Other drugs were not changed during the study period.

Table 1. Patient Baseline Characteristics

	L/H group (n=16)	C/A group (n=15)	p values of comparisons
Sex (female/male)	11/5	8/7	
Age (years old)	62.9±10.1	64.3±12.7	0.741
BMI (kg/m^2)	24.9	24.3	0.652
SBP (mmHg)	160±13	160±11	0.883
DBP (mmHg)	89±14	90±11	0.796
Potassium (mEq/L)	4.4±0.4	4.3±0.3	0.286
Serum uric acid (mg/dL)	6.3±1.8	5.6±1.2	0.380
Serum creatinine (mg/dL)	0.77±0.33	0.78±0.36	0.967
Total cholesterol (mg/dL)	222±39	203±17	0.758
Triglycerides (mg/dL)	162±77	146±86	0.720
HbA1c (%)	5.50±0.38	5.76±0.71	0.297

L/H, losartan/hydrochlorothiazide; C/A, candesartan/amlodipine; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

The study was conducted in accordance with the principles of the Helsinki Declaration. All the patients provided written informed consent before any procedures were performed. Documents explaining the protocol, to patients and the patient consent form was approved by the Ethics Committee of San-ikukai Hospital.

Additionally, after being treated with L/H or C/A for 4 months, the patients were switched to the other treatment for an additional 4 months. The effect of combination therapy on blood pressure was compared after each treatment period to assess the response to diuretics or CCB.

Statistical Analysis

Providing that the reduction in SBP was 9 mmHg with 12.5 mg of HCTZ and 17 mmHg with 5 mg of amlodipine, and assuming that the SD was at least 10 mmHg based on previous studies (*9*, *10*), a minimum sample size of 16 patients was required in each group to detect significant differences in SBP with a power of 80% and an α type error of 5% in the statistical analysis.

Values are expressed as means±SD. Patient baseline characteristics in the two groups were compared by unpaired t-test or χ^2 test. The differences in blood pressure reduction from the baseline were compared between the two groups by unpaired t-test. Differences in measured parameters were analyzed between pre- and post-treatment by paired t-test. The percentage of patients who achieved the blood pressure management goal was compared between the groups by the χ^2 test. Values of $p<0.05$ were considered statistically significant.

Results

Originally, 36 patients were randomized into the L/H group

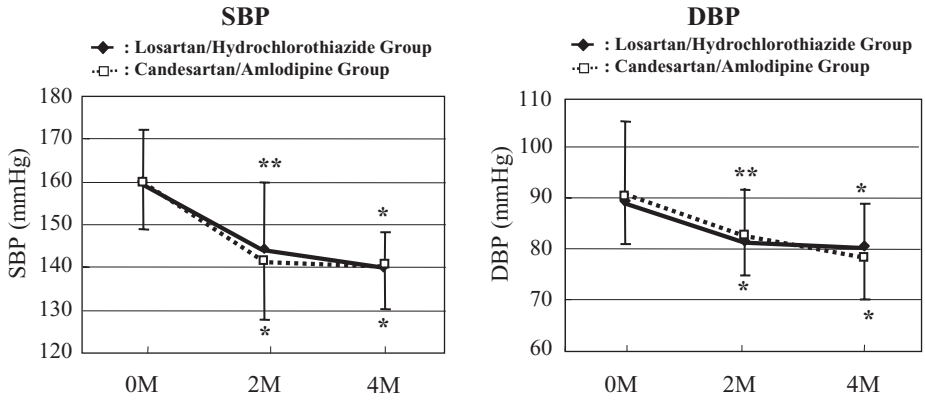

Fig. 1. *Blood pressure in both treatment groups. ◆, L/H group (losartan 50 mg/HCTZ 12.5 mg); □, C/A group (candesartan 8 mg/amlodipine 5 mg). SBP, systolic blood pressure; DBP, diastolic blood pressure; M, months. Means±SD. Significant changes of SBP/DBP from the baseline (0 M) were observed in both groups. *p<0.001, **p<0.01.*

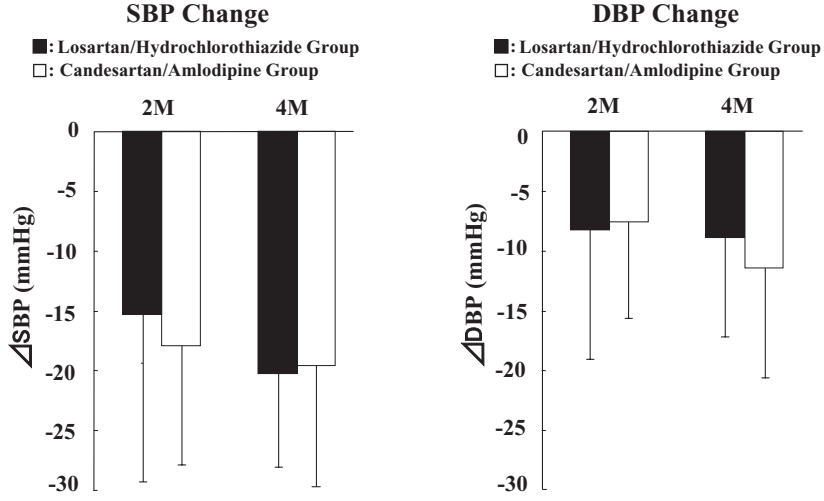

Fig. 2. *Changes in blood pressure at months 2 and 4. Black bar: L/H group (losartan 50 mg/HCTZ 12.5 mg); white bar: C/A group (candesartan 8 mg/amlodipine 5 mg). SBP, systolic blood pressure; DBP, diastolic blood pressure; M, months. Means±SD. There was no significant difference between the groups in the changes in SBP and DBP.*

and the C/A group. Five patients did not undergo follow-up and were therefore discontinued from the study. As a result, data on 31 patients (16 in the L/H group and 15 in the C/A group) were analyzed in this study. The baseline characteristics of the two groups did not differ significantly in patient sex, age, body mass index (BMI), mean SBP, mean DBP, serum potassium, serum uric acid, serum creatinine, serum total cholesterol, triglycerides, and HbA1c (Table 1). The candesartan treatment periods before the study were 4.3 months (4–6 months) in the L/H group and 5.5 months (3–8 months) in the C/A group. Three patients in the C/A group had diabetes. In the 4-month treatment, the L/H combination significantly reduced SBP/DBP from baseline 160/89±13/11 mmHg to 145/81±15/8 mmHg after 2 months (both $p<0.001$ in SBP/DBP) and 140/80±9/8 mmHg after 4 months ($p<0.001$ for both SBP/DBP), as shown in Fig. 1. Likewise, the C/A combination significantly reduced SBP/DBP from 161/90±10/11 mmHg to 143/83±13/8 after 2 months ($p<0.001$ for both SBP/DBP) and 141/79±10/7 mmHg after 4 months ($p<0.001$ for both SBP/DBP). There were no significant differences in reducing SBP or DBP between the L/H and C/A groups (Fig. 2). The changes in SBP/DBP were similar in both treatments: −15.3/−8.3±13.8/10.8 mmHg in the L/H group and −17.9/−7.5 ±9.7/8.4 mmHg in the C/A group at 2 months, and −20.3/−8.9±7.6/8.4 mmHg and −19.6/−11.4±10.0/9.2 mmHg at 4 months, respectively.

Among all study patients, the percentages who attained the blood pressure goal were similar between the combination

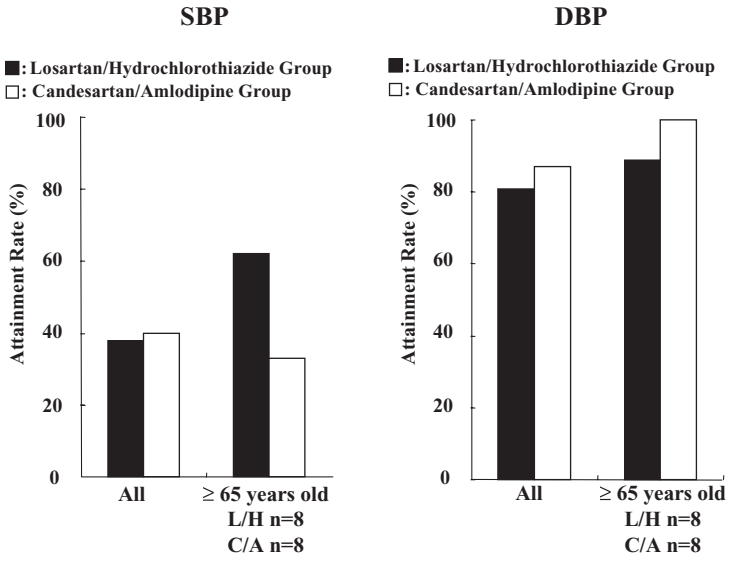

Fig. 3. *Percent of patients who attained the treatment goal in each group. Black bar: L/H group (losartan 50 mg/HCTZ 12.5 mg); white bar: C/A group (candesartan 8 mg/amlodipine 5 mg). SBP, systolic blood pressure; DBP, diastolic blood pressure. Means±SD.*

Table 2. Changes in Laboratory Values

	L/H group	C/A group
Potassium (mEq/L)		
Baseline	4.4±0.4	4.3±0.3
4 months	4.2±0.4*	4.3±0.3
Serum uric acid (mg/dL)		
Baseline	6.3±1.8	5.6±1.2
4 months	5.6±1.5	5.5±1.5
Serum creatinine (mg/dL)		
Baseline	0.77±0.33	0.82±0.40
4 months	0.76±0.31	0.81±0.42
Total cholesterol (mg/dL)		
Baseline	222±39	203±17
4 months	217±35	203±22
Triglycerides (mg/dL)		
Baseline	162±77	146±86
4 months	138±41	145±74
HbA1c (%)		
Baseline	5.50±0.38	5.76±0.71
4 months	5.54±0.33	5.84±0.71

L/H, losartan/hydrochlorothiazide; C/A, candesartan/amlodipine; SBP, systolic blood pressure; DBP, diastolic blood pressure. *$p=0.005$ *vs.* baseline as determined by paired *t*-test.

therapies: 38% with L/H and 40% with C/A in SBP. This was also true in DBP, 81% in the L/H group and 87% in the C/A group but the rate was higher when compared with the rate in SBP (Fig. 3).

When data on patients over the age of 65 were analyzed separately, the SBP attainment rate for those patients was higher, 63% with L/H and 33% with C/A, and the DBP attainment rates were similar, 89% with L/H and 100% with C/A. These results demonstrated that L/H was more effective than C/A in reducing SBP. The reduction of blood pressure was comparable between the two therapies. L/H reduced the mean SBP/DBP by 20.1/7.1±7.1/8.3 mmHg and C/A by 24.0/12.1±9.5/8.7 mmHg.

The changes in laboratory values are shown in Table 2 and Fig. 4. The L/H combination significantly reduced serum potassium after 4 months ($p=0.005$), though the ending level was within normal ranges. The change in other parameters, such as HbA1c or cholesterol, was significant between the two therapies within this study period. Also, no statistically significant differences in the occurrence of adverse experiences were observed between the L/H group and the C/A group. Hypotension and related adverse events were not observed in either group.

In the switched-over results, each patient responded differently to each treatment. At 4 months after the 27 patients were switched to the other treatment, changes in blood pressure were observed (Fig. 5). Among those patients, the mean SBP and the mean DBP at the end of the L/H combination therapy were similar to those at the end of the C/A combination treatment, 139.6/80.9±8.7/7.1 mmHg and 140.3/79.8±10.5/7.6 mmHg, respectively. When a patient who had lower blood pressure at the end of L/H treatment than at the end of C/A treatment was defined as a responder to L/H, and when a patient who had lower blood pressure at the end of C/A than at the end of L/H treatment was defined as a responder to C/A, the number of responders to L/H treatment was 15 and that

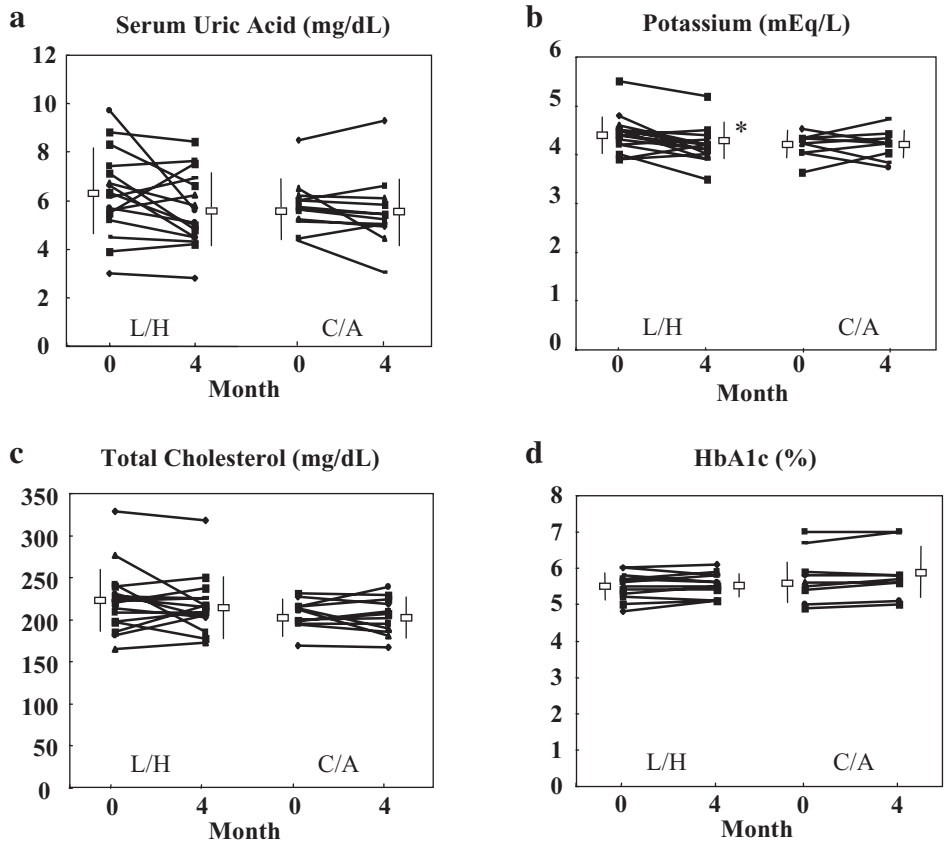

Fig. 4. *Changes in serum uric acid (a), potassium (b), total cholesterol (c), and HbA1c (d) during the 4-month treatment. L/H, losartan/HCTZ; C/A, candesartan/amlodipine.*

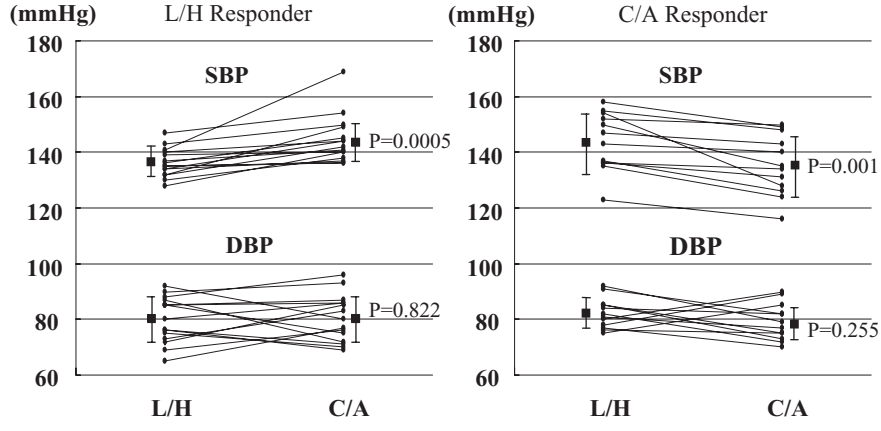

Fig. 5. *Change in SBP/DBP levels at the end of the L/H treatment and at the end of the C/A treatment in each patient.*

to C/A treatment was 12. The baseline characteristics of the two responder groups were not significantly different (Table 3). Both combination therapies significantly reduced blood pressure among their responders, and the reduction was similar between the two treatments in SBP and DBP; the reduction was from baseline 159/89±9/11 mmHg to 136/80±5/8 mmHg in H/L responders (both $p<0.001$ in SBP/DBP) and from 164/94±9/8 mmHg to 135/79±11/7 mmHg in C/A responders ($p<0.001$ for both SBP/DBP) after the 4-month treatment.

Table 3. Patient Baseline Characteristics

	L/H responder ($n=15$)	C/A responder ($n=12$)	p values of comparisons
Sex (female/male)	10/5	7/5	
Age (years old)	65.2±13.5	59.8±8.1	0.281
SBP (mmHg)	159±9	164±9	0.179
DBP (mmHg)	89±11	94±8	0.225
Potassium (mEq/L)	4.3±0.4	4.4±0.2	0.411
Serum uric acid (mg/dL)	5.7±1.7	6.1±1.3	0.503
Serum creatinine (mg/dL)	0.78±0.39	0.70±0.12	0.488
Total cholesterol (mg/dL)	218±42	211±22	0.636
Triglycerides (mg/dL)	143±67	177±92	0.300
HbA1c (%)	5.4±0.4	5.7±0.4	0.107

L/H, losartan/hydrochlorothiazide; C/A, candesartan/amlodipine; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Discussion

The ultimate goal for the treatment of hypertension is to prevent or delay cardio- and cerebrovascular disease. Recent advances in hypertensive drugs provided better blood pressure control than was possible several decades ago and better cardiovascular protection as shown in large-scale studies. However, according to studies on multi-drug therapy, 30 to 50% of cohorts required multi-drug therapy to reduce blood pressure and to protect organs with the addition of a diuretic, β-blocker, or CCB to ARB (*11*). Because diuretic and CCB are shown to be effective in reducing cardiovascular events and inducing natriuresis, their additive or synergistic effects on blood pressure are predicted with ARB. Our study is the first to compare the efficacy and safety losartan/HCTZ and candesartan/amlodipine.

In the present study, both losartan/hydrochlorothiazide and candesartan/amlodipine combinations significantly reduced both SBP and DBP to the same extent. And, the attainment rate of JSH 2004–defined target blood pressure was around 40% in both combination therapies, demonstrating that the efficacy of the two therapies was comparable. The attainment rate in elderly patients aged 65 years or more was slightly, not significantly, higher with the losartan/HCTZ combination. Diuretics and calcium possess different mechanisms to reduce blood pressure, and the combination therapy with these drugs may produce different attainment rates in specific patient populations. The rate of attaining the SBP goal in this study was similar to that in a Japanese cross-sectional survey, 31%, with the CCB/ARB combination (*8*).

Although the effectiveness of diuretics is well established, its adverse metabolic effects are of great concern for physicians. Low doses of thiazide diuretics were reported to reduce blood pressure with minimal metabolic changes, in contrast to the larger doses previously used (*12*, *13*). In the present study, we used a low dose of the diuretic to reduce its adverse metabolic effects, and abnormal metabolic changes, such as increased serum triglyceride, were not observed with therapy of 50 mg/day of losartan potassium and 12.5 mg of HCTZ. Losartan/HCTZ significantly reduced serum potassium level but to within normal ranges, which was also reported in the previous study. A low dose of HCTZ (12.5 mg/day) produced less hypokalemia than a dose of 25 mg/day or more (*14*). Diuretic-induced hypokalemia, potassium level <3.5 mmol/L, is known to cause an indirect reduction in insulin secretion leading to elevated serum glucose concentration (*15*). But none of the patients in this study had abnormal glucose tolerance, although mean potassium decreased slightly. Another adverse effect occuring with diuretics is elevated serum uric acid. The losartan/low-dose HCTZ combination slightly reduced serum uric acid, suggesting that losartan cancels uric acid elevation by producing a transient uricosuric response (*16*). There also is a concern about diuretic-induced hypotension in elderly patients, but hypotension and adverse events related to it were not observed with either combination therapy. These results demonstrated that the combination of losartan/HCTZ and the candesartan/amlodipine has an excellent safety profile.

There are limitations to this study. The cohort was rather small, and the observation period was relatively short. The overall safety and efficacy should be confirmed with a larger-scale clinical study in the future. From an economic aspect, low-dose diuretics are more cost-effective than CCBs. Thus the combination of ARB with low-dose diuretics is a superior therapy to the ARB/CCB combination.

In conclusion, the losartan/HCTZ combination and the candesartan/amlodipine combination are equally effective in reducing both systolic and diastolic blood pressure in patients for whom candesartan monotherapy is ineffective for controlling blood pressure. Considering that HCTZ-induced adverse effects were absent with the losartan/HCTZ combination and that HCTZ is more cost effective, we concluded that losartan/HCTZ is more useful than candesartan/amlodipine for the management of hypertension.

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