Original Article

Effects of Strict Blood Pressure Control by a Long-Acting Calcium Channel Blocker on Brain Natriuretic Peptide and Urinary Albumin Excretion Rate in Japanese Hypertensive Patients

Hideyuki UNO[1)], Joji ISHIKAWA[2)], Satoshi HOSHIDE[2)], Tomoyuki KABUTOYA[2)], Shizukiyo ISHIKAWA[1)], Kazuyuki SHIMADA[2)], and Kazuomi KARIO[2)]

Strong adherence to antihypertensive therapy has been shown to reduce the frequency of cardiovascular events by strictly controlling blood pressure. Although calcium channel blockers (CCBs) are among the most popular antihypertensive drugs in Japan, few trials have been conducted using high CCB doses in Japanese patients. In this study, we administered amlodipine 5 mg or 10 mg to patients with hypertension in order to compare the efficacy and tolerability of low and high doses, and measured two surrogate markers of hypertensive target organ damage, *i.e.*, brain natriuretic peptide (BNP) as a risk marker of cardiac overload and microalbuminuria as a measure of renal damage. Seventy-two patients were randomly assigned to either amlodipine 5 mg (n=35) or 10 mg (n=37) dose groups. The latter group achieved greater reductions in clinic as well as both morning and evening home BP levels without an increase in pulse rate (the differences between the two groups in clinic/morning/evening systolic BP were 4.7/4.7/5.4 mmHg, and for diastolic BP they were 4.2/3.6/3.8 mmHg). Reductions in BNP and urinary albumin/creatinine ratio (UAR) levels were significantly correlated with the reductions in systolic BP levels (BNP, clinic/morning BP: r=0.256, p=0.030/r=0.330, p=0.005; UAR, clinic BP: r=0.316, p=0.007). In conclusion, the higher dose (10 mg) of amlodipine induced greater reductions in all BP levels than did the lower dose, without increasing the pulse rate. These additional reductions were significantly correlated with reductions in hypertensive cardiac overload, as evaluated by BNP levels, and a reduction in renal damage, as evaluated by microalbuminuria levels. Moreover, a reduction in the microalbuminuria may have occurred concomitant with a reduction in clinic systolic BP level. (*Hypertens Res* 2008; 31: 887–896)

***Key Words*: amlodipine, strict blood pressure control, hypertensive targeted organ damage, microalbuminuria, brain natriuretic peptide**

Introduction

Recent large clinical trials have demonstrated that strict antihypertensive therapy reduced the rates of cardiovascular (*1*–*3*) and stroke events (*3*). However, recent Japanese surveys have demonstrated that only about half of patients with hypertension (*4*, *5*) and less than half of those with diabetic hypertension (*6*) on home BP therapy including antihypertensive medications achieve their BP goal even when using antihypertensive medications. Ishikawa *et al*. (*7*) demonstrated that about 60% of patients with hypertension who had well-

From the [1)]Division of Community and Family Medicine, Center for Community Medicine and [2)]Division of Cardiovascular Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan.

Address for Reprints: Kazuomi Kario, M.D., COE (Center of Excellence) Program, Division of Cardiovascular Medicine, Jichi Medical University School of Medicine, 3311–1, Yakushiji, Shimotsuke 329–0498, Japan. E-mail: kkario@jichi.ac.jp

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controlled clinic BP achieve their BP goal at home. These facts led us to consider the difficulty of achieving sufficient BP control by antihypertensive therapy.

Calcium channel blockers (CCBs) are among the most popular antihypertensive medications in Japan, because they are known to reliably decrease BP levels and may reduce the risk of stroke events (*8*, *9*). Amlodipine is the most popular CCB, because it provides a sufficient antihypertensive effect by a single daily dose, and because its half-life of 39 h is the longest among CCBs (*10–13*). Recent large clinical trials (ALLHAT, VALUE) have demonstrated that amlodipine therapy up to 10 mg significantly reduced the incidence of major cardiovascular events among patients with hypertension, including cardiovascular mortality, myocardial infarction, and stroke events (*14*, *15*). However, it remains uncertain whether the results of these studies can be applied directly to the Japanese population, because Japanese patients may require different doses than Western patients. In addition, even though a Japanese study (*16*) reported that amlodipine at 2.5 mg to 10 mg dose-dependently reduced ambulatory BP level, no randomized study has evaluated dose-dependent BP reduction by amlodipine in Japan.

In this study, we compared the antihypertensive efficacy and tolerability between 5 and 10 mg doses of amlodipine, as well as the effects of strict BP control on two measures of hypertensive target organ damage: brain natriuretic peptide (BNP) (as a marker of left ventricular overload) (*17*, *18*) and microalbuminuria (as a marker of early renal damage and an independent predictor of cardiovascular disease) (*19*, *20*).

Methods

Study Design

The present study is a multicenter, open-label, randomized, and parallel-groups comparison study. The study was conducted from April to December 2006 by six doctors at six institutions (five hospital-based outpatient clinics and one specialized university hospital) in Japan. The study was conducted in accordance with the Helsinki Declaration. The institutional review board of Jichi Medical University School of Medicine, Tochigi, Japan approved the study, and written informed consent was obtained from all patients.

Inclusion Criteria

We selected outpatients with essential hypertension, defined as systolic blood pressure (SBP) $\geq$150 mmHg and diastolic blood pressure (DBP) $\geq$90 mmHg, who were more than 20 years old. The enrolled outpatients also fulfilled one or both of the following criteria: 1) they were newly diagnosed, or had a history of essential hypertension but had not received any antihypertensive medications for at least 4 weeks; or 2) they were receiving antihypertensive monotherapy, but not with any CCB, including amlodipine.

Habitual drinkers were defined as patients who reported drinking alcohol more than 5 d per week. Smoking was defined as having a current smoking habit. Hyperlipidemia was defined as a total cholesterol (TC) level greater than 5.7 mmol/L (220 mg/dL) or triglycerides (TG) level above 1.7 mmol/L (150 mg/dL). Diabetes mellitus was defined as a fasting plasma glucose (FPG) level of more than 7.0 mmol/L (126 mg/dL) or casual glucose level of more than 11.1 mmol/L (200 mg/dL), irrespective of whether or not patients were being treated for diabetes mellitus. Clinical histories of the patients were obtained from interviews conducted by the physicians managing the patients in the patients' hospitals.

Exclusion Criteria

Patients who met one or more of the following criteria were excluded: 1) secondary hypertension; 2) SBP $>$200 mmHg and/or DBP $>$120 mmHg; 3) unstable coronary artery disease (acute coronary syndrome); 4) presence of renal impairment defined by a clinically abnormal serum creatinine (S-Cr) $>$2.0 mg/dL; 5) presence of hepatic impairment defined by a clinically abnormal liver function test result (aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $>$3 times the upper limit of normal for the respective institution); 6) presence of congestive heart failure of NYHA class II or worse; 7) serious arrhythmia; 8) poorly controlled diabetes mellitus (hemoglobin A1c [HbA1c] $>$12.0%); 9) stroke, myocardial infarction or either percutaneous coronary intervention or coronary bypass operation within 6 months prior to this study; 10) history of malignant tumors within 5 years; 11) known previous hypersensitivity to amlodipine; 12) previous treatment with amlodipine; and 13) a physician's opinion that the patient would be inappropriate as a study subject.

Study Protocol

Prior to enrollment, patients were screened as candidates for participation. Patients who met the inclusion criteria without any of the exclusion criteria were included in the study after they provided their agreement with informed consent. At the end of enrollment, an informational interview and physical examination were performed.

The study protocol is shown in Fig. 1. We divided enrolled outpatients into low-dose (amlodipine 5 mg/d) and high-dose (10 mg/d) treatment groups. An independent study center randomly allocated the study patients into one group or the other by a telephone interview at the time of enrollment. Patients in the low-dose group started or added amlodipine 5 mg for 6 weeks. Patients in the high-dose group started or added amlodipine 5 mg for 2 weeks, followed by up-titration to 10 mg for 4 weeks (total 6 weeks). Patients in both groups were checked for tolerance to adverse effects of the drug at 2 weeks after the study administration period began. If patients in the high-dose group had sufficient BP reduction for 2 weeks, they were then down-titrated to amlodipine 5 mg for 4 weeks at the discre-

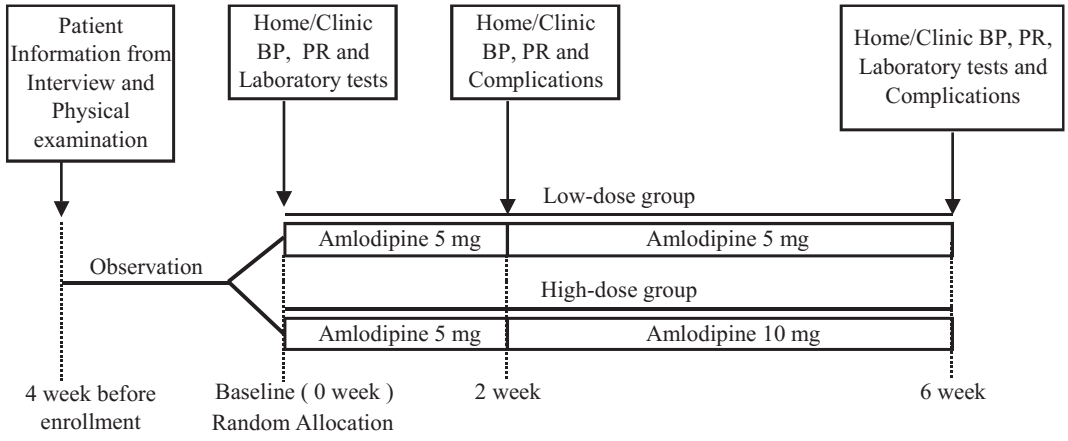

Fig. 1. *Clinical trial timeline of the study protocol.*

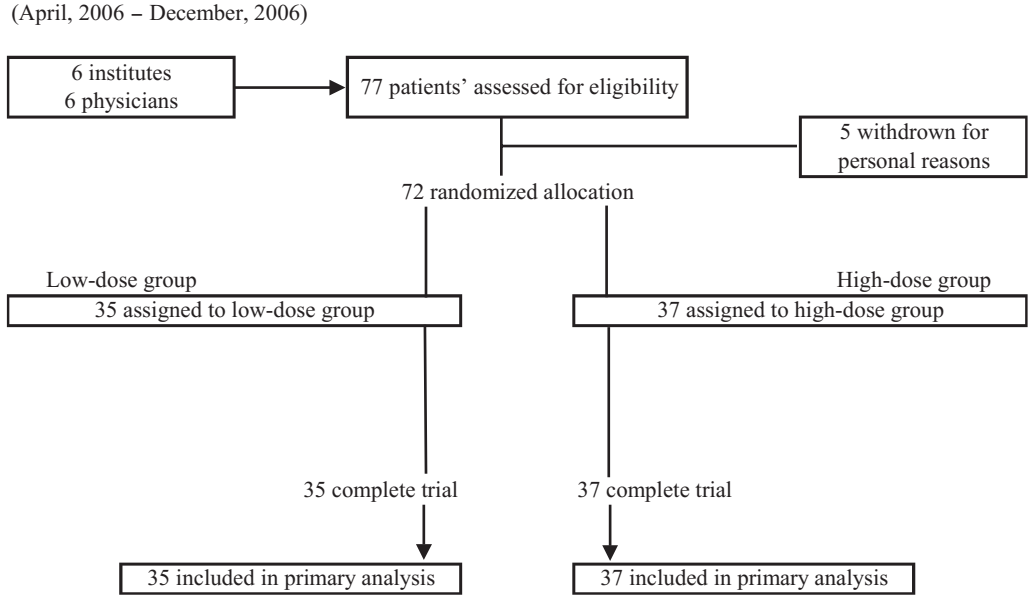

Fig. 2. *Outpatients recruited for the study.*

tion of their physicians in order to avoid surplus BP reduction. If they did not achieve BP goal despite of BP reduction >30 mmHg and if they had had insufficient BP reduction for 2 weeks but no remarkable adverse events, they were then up-titrated to 10 mg for 4 weeks. Patients in both groups took amlodipine once a day in the morning.

Self-Measurement of BP at Home and in the Clinic

BP measurements at the clinic and at home were performed according to the 2003 JSH guidelines (*21*). Patients in the present study self-measured their BPs using a validated cuff oscillometric device (HEM-705IT; Omron Healthcare, Kyoto, Japan) (*22*, *23*). Home BPs were measured daily for 3 d with the subject in a sitting position; measurement was made twice per occasion within a 15-s interval (6 readings in total) (*24*). Home BPs were also taken just before patients consulted their own physicians at the time of random assignment, and after 2 and 6 weeks (Fig. 1). The patients were instructed to place the cuff on the same arm for all measurements, and to measure BP after remaining at rest for at least 2 min in a seated position. The patients were instructed to write down all of the measured values of BP and pulse rate (PR) and report these values to their physicians. Morning BP and PR were measured within 1 h after waking, after urination, before breakfast, and before taking antihypertensive medication. Evening BP and PR were measured before going to bed.

The patients were instructed to avoid measuring BP and PR just after taking a bath, drinking alcohol or smoking.

BPs and PRs were measured in the clinic or the hospital at the baseline and at 2 and 6 weeks after the beginning of treatment. All BPs were calculated as the mean of three consecutive measurements by each patient's physician (Fig. 1).

Blood and Urinary Examinations

Blood samples were drawn from a vein in the morning in a fasting state. Spot samples of urine were collected in the morning. Blood examinations (blood cell count, TC, TG, high-density lipoprotein cholesterol [HDL-C], FPG, HbA1c, immunoreactive insulin [IRI], S-Cr, BNP, high sensitive C-reactive protein [hsCRP]) and urinary examinations were performed at the baseline and 6 weeks later (Fig. 2). The blood samples were centrifuged at 3,000× *g* for 15 min at room temperature. Plasma/serum samples after separation and urine samples were kept at 4°C and sent for analysis within 24 h. All assays were performed within 24 h at a single laboratory (SRL, Tokyo, Japan).

Urinary microalbumin was measured using the immunoturbidimetric method (Mitsubishi Chemical Iatron, Tokyo, Japan) and expressed as the urinary albumin/creatinine ratio (UAR) (mg/g Cr). Both serum and urinary creatinine were measured by the enzymatic method and then quantified by a photometric method. The correlation of variation was less than 5%. The estimated glomerular filtration ratio (eGFR) was calculated afterward using the Cockcroft-Gault formula (*25*, *26*).

Statistical Analysis

As shown in Fig. 2, we explained the purpose and meaning of the study to 77 qualifying patients, 72 of whom provided informed consent and were included in the statistical analyses. All primary analyses of SBPs/DBPs/PRs and hsCRP were performed on an intention-to-treat basis, because there were two deficits in SBP/DBP/PR and two deficits in hsCRP. The hsCRP data on 2 patients were excluded, as those patients clearly had common colds.

Data were expressed as the means±SD or as the median and percentage. The unpaired *t*-test was used to compare the means in baseline data for the two groups. The Mann-Whitney *U*-test and the Wilcoxon rank sum test were used to compare the median changes in BNP, UAR, and hsCRP between the groups. The relationships among the changes in SBP, BNP, UAR, and hsCRP before and after amlodipine treatment were assessed by Spearman's correlation coefficient, because the SBP, BNP, UAR, and hsCRP values had skewed distributions. Associations/differences with a p value <0.05 (two-tailed) were considered statistically significant. All statistical analyses were performed with SPSS version 11.0 (SPSS, Chicago, USA).

Results

Patients

As shown in Fig. 2, 72 patients were randomly assigned to either a low-dose group ($n=35$) or a high-dose group ($n=37$). Of the 72 patients, 5 declined to continue the study. As shown in Table 1, there were no significant differences in the baseline characteristics between the treatment groups. There were no remarkable adverse events in either group, including tachycardia (*27*), flushing (*27–30*), dizziness (*28*, *31*), headache (*27–33*), and peripheral edema (*30*, *31*, *34*, *35*) throughout the study period.

Home and Clinic BP and PR

Clinic SBPs/DBPs, as well as both morning and evening home SBPs/DBPs, decreased similarly in both groups, and there were no statistically significant differences in the BPs between the baseline and at 2 weeks (Fig. 3A and C) in either group. Between 2 and 6 weeks, SBPs and DBPs decreased in the high-dose group to a greater extent than in the low-dose group (the differences between the two groups in clinic/morning/evening SBP were 4.7/4.7/5.4 mmHg, $p=0.121/0.025/0.017$; and in clinic/morning/evening DBP they were 4.2/3.6/3.8 mmHg, $p=0.033/0.005/0.010$) (Fig. 3B and D). Clinic/morning/evening PRs in both groups increased similarly between the baseline and 2 weeks, then decreased similarly between 2 and 6 weeks. However, there were no statistically significant differences (Fig. 3E and F).

Changes in BNP, UAR, and hsCRP Levels

As shown in Table 2, BNP levels significantly decreased between baseline and 6 weeks in both groups (in the low-dose group, the values at 0 weeks/6 weeks were 27.6/16.0 pg/mL, $p=0.024$; and in the high-dose group they were 18.1/9.7 pg/mL, $p<0.001$). Furthermore, at 6 weeks, the BNP levels differed significantly between the groups (low-dose/high-dose: 16.0/9.7 pg/mL, $p=0.013$), although there was no significant difference in BNP levels at the baseline. UAR levels were significantly different between baseline and 6 weeks in the low-dose group (the values at 0 weeks/6 weeks were 12.3/8.3 mg/g Cr, $p=0.019$) but not in the high-dose group (the values at 0 weeks/6 weeks were 13.3/13.1 mg/g Cr, $p=0.177$). There were no significant differences in UAR levels between the groups at baseline or at 6 weeks. hsCRP levels did not decrease significantly between baseline and 6 weeks in either group. No statistically significant differences in hsCRP levels with time were observed between the groups.

Table 1. Patients' Baseline Characteristics

	Amlodipine 5 mg (n=35)	Amlodipine 10 mg (n=37)	p value
Characteristics			
Age (years): range	60.5±10.0: 39–82	59.0±10.4: 36–79	0.531
Male (%)	60.0	70.3	0.367
Body mass index (kg/m^2)	24.4±4.1	24.4±3.7	0.984
Height (cm)	161.2±8.2	162.8±8.8	0.414
Duration of hypertension (years)	6.1±6.6	8.5±10.6	0.254
Duration of antihypertensive therapy (years)	4.0±6.0	5.0±7.4	0.528
Waist (cm)	84.1±10.9	85.6±8.3	0.501
Hip (cm)	94.2±7.2	95.7±7.2	0.399
Current smokers (%)	14.3	16.2	0.823
Habitual drinkers (%)	45.7	44.4	0.916
Hyperlipidemia (%)	25.7	29.7	0.709
Diabetes mellitus (%)	2.9	5.4	0.595
Angina pectoris (%)	0.0	5.4	0.160
Stroke (%)	0.0	5.4	0.160
Medication			
Antihypertensive drug (%)	48.6	37.8	0.365
ARB (%)	22.9	27.0	0.688
ACE-I (%)	2.9	2.7	0.969
Diuretic (%)	11.4	13.5	0.793
α-Blocker (%)	2.9	2.7	0.969
β-Blocker (%)	8.6	5.4	0.603
Antihyperlipidemic drug (%)	11.4	5.4	0.362
Antihypoglycemic drug (%)	2.9	0.0	0.324
Blood pressure and pulse rate			
Clinic SBP (mmHg)	163.0±17.7	158.0±16.2	0.213
Clinic DBP (mmHg)	95.5±12.4	93.4±11.9	0.462
Clinic PR (bpm)	72.4±11.4	71.3±9.8	0.660
Morning SBP (mmHg)	153.3±16.1	156.5±17.7	0.439
Morning DBP (mmHg)	92.4±9.9	92.1±11.0	0.898
Morning PR (bpm)	66.6±8.9	67.1±11.0	0.831
Evening SBP (mmHg)	142.5±14.8	147.4±17.3	0.206
Evening DBP (mmHg)	82.3±12.4	83.6±12.4	0.655
Evening PR (bpm)	72.3±8.2	70.8±10.8	0.506
Laboratory data			
TC (mg/dL)	196.7±32.7	212.5±41.3	0.077
TG (mg/dL)	117.4±69.9	138.2±57.7	0.172
HDL-C (mg/dL)	61.4±13.9	56.9±16.0	0.207
FPG (mg/dL)	106.8±19.4	101.2±14.0	0.162
HbA1c (%)	5.1±0.4	5.1±0.4	0.634
IRI (μIU/mL)	13.1±10.9	12.7±18.9	0.909
S-Cr (mg/dL)	0.8±0.2	0.8±0.2	0.405
eGFR (mL/min)	89.2±25.5	92.1±29.6	0.667

Values are mean±SD or percentages. ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; bpm, beats per minute; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; IRI, immunoreactive insulin; S-Cr, serum creatinine; eGFR, estimated glomerular filtration rate. p values were calculated by unpaired t-test or χ^2 test.

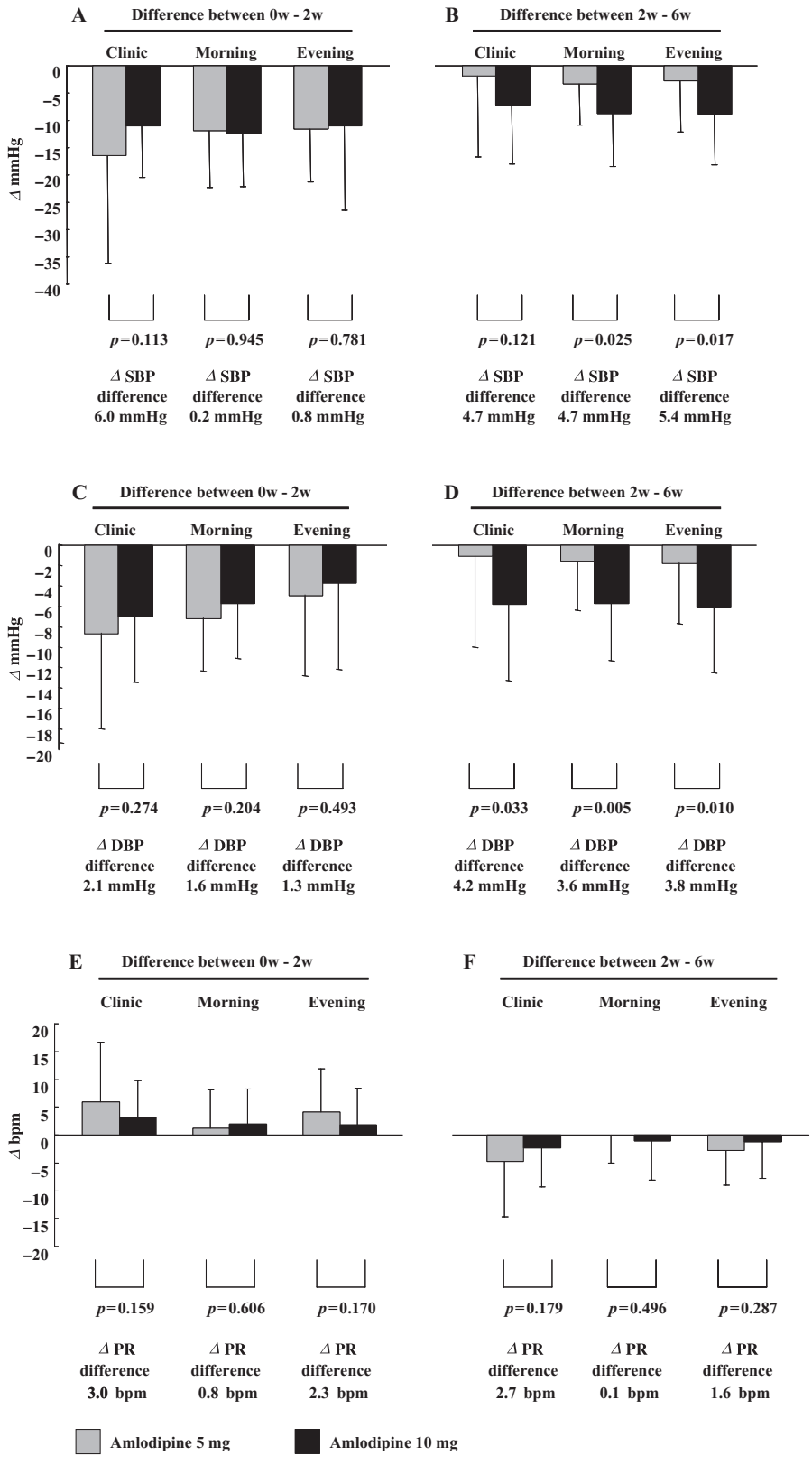

Fig. 3. *A and B: Changes in systolic blood pressure (SBP) in the low- and high-dose groups. C and D: Changes in diastolic blood pressure (DBP) in the low- and high-dose groups. p values were calculated by unpaired t-test. E and F: Changes in pulse rate in the low- and high-dose groups. p values were calculated by unpaired t-test.*

Table 2. BNP, UAR and hsCRP before and after Amlodipine Treatment

	0 week	*p value	6 week	*p value	**p value
Amlodipine 5 mg					
BNP (pg/mL)	27.6 (13.0–45.2)		16.0 (7.7–37.1)		0.024
UAR (mg/g Cr)	12.3 (7.7–21.7)		8.3 (5.1–17.4)		0.019
hsCRP (ng/mL)	581.0 (315.0–918.0)		428.0 (258.0–1160.0)		0.915
Amlodipine 10 mg					
BNP (pg/mL)	18.1 (9.0–38.2)	0.253	9.7 (4.6–17.9)	0.013	<0.001
UAR (mg/g Cr)	13.3 (7.9–41.3)	0.645	13.1 (8.2–26.2)	0.198	0.177
hsCRP (ng/mL)	496.5 (266.0–753.0)	0.550	539.5 (363.3–722.5)	0.895	0.574

Changes in UAR (n=72), BNP (n=72) and hsCRP (n=70) before and after amlodipine treatment in essential hypertensive patients. BNP, brain natriuretic peptide; UAR, urinary albumin/creatinine excretion ratio; hsCRP, high sensitive C-reactive protein. BNP, UAR and hsCRP levels are shown as median (25 percentile–75 percentaile). **p* values were compared between each factors of amlodipine 5 mg and 10 mg at 0 week and 6 week, validated by the Mann-Whitney *U*-test. ***p* values were compared between each factors in both groups between 0 week and 6 week, validated by the Wilcoxon rank sum test.

Table 3. Correlations of Changes in Systolic Pressures with Changes in BNP, UAR and hsCRP before and after Amlodipine Treatment

	ΔClinic SBP (mmHg)		ΔMorning SBP (mmHg)		ΔEvening SBP (mmHg)	
	r	p value	r	p value	r	p value
ΔBNP (pg/mL)	0.256	0.030	0.330	0.005	−0.064	0.591
ΔUAR (mg/g Cr)	0.316	0.007	0.058	0.626	0.229	0.053
ΔhsCRP (ng/mL)	−0.085	0.481	−0.064	0.596	−0.029	0.810

Correlations of changes in systolic blood pressures with changes in UAR (n=72), BNP (n=72) and hsCRP (n=70) between in 0 week and 6 week. BNP, brain natriuretic peptide; UAR, urinary albumin/creatinine excretion ratio; hsCRP, high sensitive C-reactive protein. p values were assessed by the Spearman's correlation coefficient.

Correlation of Changes in SBP with Changes in BNP, UAR, and hsCRP

As shown in Table 3, there were significant positive correlations between changes in clinic/morning SBP and changes in BNP level (for clinic SBP, r=0.256 and p=0.030; for morning SBP, r=0.330 and p=0.005), not taking amlodipine dose into account. The change in UAR level was correlated with that in clinic BP (r=0.316, p=0.007). The changes in hsCRP levels were not correlated with BPs.

Discussion

In the present study, a multicenter, open-label, randomized, parallel-groups analysis, we demonstrated that amlodipine had dose-dependent antihypertensive effects on the reduction in both SBP and DBP. In addition, SBP/DBP decreased more significantly in the high-dose group (10 mg/d) than in the low-dose group (5 mg/d) without increasing pulse rate. The present study also revealed significant positive correlations between changes in clinic SBP and changes in BNP, and changes in UAR levels, as well as significant positive correlations between changes in morning SBP and BNP level. There were no adverse events in either treatment group.

Clinic and both morning and evening SBPs/DBPs were reduced by approximately the same amount even though amlodipine was taken only in the morning. Also, all SBPs/DBPs, even in the low-dose group, decreased slightly between 2 weeks and 6 weeks. We attributed the reductions in all SBPs and DBPs to a cumulative antihypertensive effect of amlodipine, because the plasma half-life ($t_{1/2}$) of amlodipine averages 39 h (*12–15*). Amlodipine has been reported to affect the dose-dependent reduction in BP (*36*). The present study found that a higher dose of amlodipine (10 mg) achieved additional statistically significant reductions in clinic and home BP compared with the lower dose (5 mg). Amlodipine is known to have vasodilation-induced side effects, including tachycardia (*27*), flushing (*27–30*), and dizziness (*28*, *31*), as are other CCBs. Headache (*27–33*) and peripheral edema (*30*, *31*, *34*, *35*) have been reported as particularly prevalent dose-dependent adverse effects. However, neither of these adverse events were observed in this study.

PRs in both groups increased between baseline and 2 weeks, but decreased between 2 and 6 weeks. In our previous study (*37*) we observed 46 hypertensive patients (mean age: 68 years; baseline SBP/DBP: 168/92 mmHg). In that study,

the mean clinic SBP and DBP were reduced to 29 and 10 mmHg at 4 to 8 weeks of amlodipine treatment, and PR in the higher-dose group (8.6 mg mean) increased significantly. This reduction in clinic BP after amlodipine treatment was greater than that in the present study. The increased PR in the previous study may have been a physiologic reaction caused by the sharper reduction in SBP and DBP, or it may have been related to the older mean age of the subjects compared to the present study. On the other hand, Hamada *et al*. (*38*) reported that mean ambulatory SBP and DBP in patients with a mean age of 60 years (baseline SBP/DBP＝164/92 mmHg) were reduced to 36 and 15 mmHg after 4 weeks of 5 mg amlodipine treatment, but PR did not increase. These results support those of our present study. SBP/DBP reductions were greater in the two prior studies (*37*, *38*) that observed pretreatment hypertensive patients than in the present study. The present study contributed the new finding that amlodipine treatment temporarily increased PR between baseline and 2 weeks. However, the PR decreased between 2 and the 6 weeks in both groups.

In the present study, amlodipine at either dose significantly reduced BNP. At 6 weeks, the BNP level was significantly lower in the high-dose group than in the low-dose group. There were significant positive correlations between changes in clinic or morning SBPs and the change in BNP level. BNP is a marker of LV diastolic dysfunction, and reduced BNP is reportedly related with an improved prognosis of cardiovascular disease (*17*, *18*). Wang *et al*. (*39*) showed that a small increase in plasma BNP level was a risk factor for future stroke events and cardiovascular mortality in a population without a history of heart failure. Therefore, BNP reduction by amlodipine treatment may improve the prognosis of cardiovascular and stroke events in Japanese hypertensive patients.

On the other hand, the change in UAR level between baseline and 6 weeks was significant in low-dose group, but not in high-dose group. The finding that the UAR level did not change significantly between the two measurement time points in the high-dose group may have been related to the short observation period in the present study. The differences of the UAR levels between both groups at baseline and 6 weeks were not significant, as there was a certain degree of reduction in each UAR levels in high-dose group to short term. However, the change in clinic SBP was correlated with that in UAR level. Although UAR is a marker of early renal damage, a previous study reported that amlodipine treatment did not reduce UAR (*40*). This supports our present findings. A change in the UAR level may directly reflect a change in intra-glomerular pressure during the patients' visit to their own physicians, because urine was taken when patients were in the office. Therefore, a change in the UAR level might be correlated with clinic SBP.

In addition, hsCRP levels, which are markers of inflammation and the progress of atherosclerosis for 10 weeks in an experiment on mice (*41*), were not statistically different over time in either group or between the groups. In the present study, therefore, amlodipine treatment did not appear to reduce inflammation or prevent the progression of atherosclerosis. To confirm whether amlodipine treatment prevent the progress of atherosclerosis, a longer observation than 6 weeks in our present study period may be necessary in human beings.

In this study, we confirmed that higher-dose amlodipine treatment brought on additional reductions in SBP and DBP. These reductions could contribute to decreases in mortality from stroke and ischemic heart disease (*42*).

In conclusion, a higher dose of amlodipine achieved additional reductions in clinic and both morning and evening home BP levels compared with a lower dose without increasing pulse rate. These additional reductions were significantly correlated with reductions in hypertensive cardiac overload, as evaluated by BNP levels, and a reduction in renal damage, as evaluated by microalbuminuria levels. Moreover, a reduction in the microalbuminuria may have occurred concomitant with a reduction in clinic systolic BP level.

Appendix

Participants and Participating Centers

Hideyuki Uno, Saitama-Tsukuba Hospital, Jichi Medical University School of Medicine; Joji Ishikawa, Koga Red Cross Hospital, Jichi Medical University School of Medicine; Satoshi Hoshide, Yuki Hospital, Jichi Medical University School of Medicine; Tomoyuki Kabutoya, Chichibu Municipal Hospital, Jichi Medical University School of Medicine; Shizukiyo Ishikawa and Kazuomi Kario, Washiya Hospital, Jichi Medical University School of Medicine.

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