Additive Antihypertensive and Antihypertrophic Effects of Long-Acting Ca Blockers in Uncontrolled Hypertensive Patients With Angiotensin-Receptor Blocker Based Treatment

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SUMMARY

The aim of the present study was to examine the antihypertensive and antihypertrophic effects of combined treatment with a long-acting calcium antagonist on top of an angiotensin II receptor blocker (ARB) in uncontrolled hypertensive patients. Patients with essential hypertension and a blood pressure > 140/90 mmHg on ARB monotherapy (losartan 50 mg/day or candesartan 8 mg/day) were randomly assigned to a nifedipine controlled release (CR) group ($n = 15$) or amlodipine group ($n = 11$). A significant additional antihypertensive effect was noted from 1 month with nifedipine and 2 months with amlodipine. The average daily dose was 25 mg for nifedipine and 5 mg for amlodipine. The cardiothoracic ratio was significantly reduced in both groups after 3 months. Left ventricular wall thickness and left ventricular mass index also decreased. Metabolic parameters, hepatic function, and renal function did not change significantly. Additional treatment with a long-acting calcium antagonist achieved further blood pressure reduction as well as an antihypertrophic effect in the uncontrolled patients with prior ARB monotherapy. (Int Heart J 2009; 50: 555-570)

Key words: Angiotension receptor blocker, Calcium antagonist, Combined therapy, Hypertension

EPIDEMIOLOGIC studies have shown that cardiac hypertrophy is one of the independent risk factors that determines the prognosis of patients with hypertension, and it is related to a high incidence of cardiovascular events.¹⁾ A lower incidence of cardiac events has been reported in patients who show regression of cardiac hypertrophy after treatment of hypertension compared with those who

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do not demonstrate such regression.²⁾

Although meta-analysis has shown that renin-angiotensin system (RAS) inhibitors such as angiotension-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) are highly effective for reducing cardiac mass,³⁾ the most important factor in achieving regression of cardiac hypertrophy is actually the extent of blood pressure reduction. Therefore, long-acting calcium (Ca) antagonists, which are commonly used as first-line antihypertensive drugs in Japan, can also have a beneficial effect on cardiac hypertrophy.⁴⁾ In this study, a long-acting Ca antagonist was administered to hypertensive patients who were not adequately controlled by ARB monotherapy to examine the effect on blood pressure and the progression of cardiac hypertrophy.

METHODS

Subjects: Patients with essential hypertension who did not show sufficient blood pressure reduction with ARB monotherapy were eligible. The subjects were 29 outpatients of the Department of Cardiovascular Diseases at Fukuoka University Chikushi Hospital who consented to participation in this study. The local Ethics Committee of Fukuoka University Chikushi Hospital approved the study protocol. Informed consent was obtained from all patients recruited into the study.

The patients had essential hypertension and a blood pressure greater than

Figure 1. Disposition of the subjects.

140 mmHg (systolic) and/or 90 mmHg (diastolic) measured twice at the outpatient clinic during the observation period despite treatment with an ARB (losartan at 50 mg/day in 26 patients and candesartan at 12 mg/day in 3 patients) alone for more than 4 weeks. These patients were also assessed as showing good tolerance to the long-acting Ca antagonists (nifedipine controlled release (CR), which consists of a fast dissolving core surrounded by a slowly dissolving coat, or amlodipine) (Table II). As shown in Figure 1, 24 of the 29 subjects were included in the analysis after exclusion of 5 patients. Four of the five patients ex-

Table I. Clinical Profile of the Subjects ($n = 24$)

Age (years)	68 ± 10
Gender (% male)	58
Systolic blood pressure (mmHg)	161 ± 15
Diastolic blood pressure (mmHg)	92 ± 12
Pulse rate (/min)	74 ± 11
BMI (kg/m ²)	24.3 ± 3.1
CTR (%)	50 ± 5
Sv ₁ +Rv ₃ (mV)	3.0 ± 1.1
LP1 (msec)	129 ± 24
LP2 (μV)	36 ± 19
LP3 (msec)	34 ± 19
LV mass (g)	197 ± 70
LVMI (g/m ²)	120.0 ± 40.3
LVDd (cm)	4.66 ± 0.58
LVDs (cm)	2.87 ± 0.58
EF (%)	70 ± 8
Serum creatinine (mg/dL)	0.9 ± 0.2
BUN (mg/dL)	15.8 ± 4.0
Total cholesterol (mg/dL)	191 ± 30
HDL cholesterol (mg/dL)	55 ± 21
Triglycerides (mg/dL)	100 ± 39
BNP (pg/mL)	44 ± 49
ARB (dose)	
Losartan	50 mg/day (n)
Losartan	100 mg/day (n)
Candesartan	12 mg/day (n)
Candesartan	16 mg/day (n)
CCB (dose)	
Amlodipine	5 mg/day (n)
Nifedipine CR	20 mg/day (n)
Nifedipine CR	40 mg/day (n)

Data are shown as the mean ± SD, or number of patients (n).

BMI indicates body mass index; CTR, cardio-thoracic ratio; LP, late potential; LP1, filtered QRS duration; LP2, root-mean square voltage of the last 40 ms of the QRS complex; LP3, duration of low amplitude signal of the terminal portion of the QRS; LV mass, left ventricular mass; LVMI, left ventricular mass index; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; EF, ejection fraction; BUN, blood urea nitrogen; HDL, high density lipoprotein; BNP, brain natriuretic peptide; ARB, angiotensin receptor blocker; and CCB, calcium channel blocker.

Table II. Comparison of Background Factors Between the Two Groups

Parameter	NIF group (<i>n</i> = 11)	AML group (<i>n</i> = 13)	<i>P</i>
Age (years)	71 ± 13	65 ± 7	0.16
Gender (% male)	45	69	0.41
Systolic blood pressure (mmHg)	160 ± 11	162 ± 18	0.75
Diastolic blood pressure (mmHg)	90 ± 9	94 ± 14	0.42
Pulse rate (/min)	77 ± 9	72 ± 12	0.27
BMI (kg/m ²)	24.8 ± 3.5	23.9 ± 2.7	0.48
CTR (%)	51 ± 5	49 ± 5	0.34
Sv _i +Rv _s (mV)	2.6 ± 0.7	3.4 ± 1.2	0.07
LP1 (msec)	124 ± 23	128 ± 22	0.67
LP2 (μV)	31 ± 9	36 ± 22	0.49
LP3 (msec)	35 ± 18	36 ± 20	0.90
LV mass (g)	180 ± 43	218 ± 87	0.20
LVMI (g/m ²)	114.6 ± 25.6	127.6 ± 47.2	0.51
LVDd (cm)	4.58 ± 0.43	4.74 ± 0.71	0.55
LVDs (cm)	2.77 ± 0.42	2.97 ± 0.70	0.44
EF (%)	70 ± 7	71 ± 8	0.75
Serum creatinine (mg/dL)	0.8 ± 0.1	0.9 ± 0.2	0.87
BUN (mg/dL)	14.3 ± 2.9	17.6 ± 4.5	0.05
Total cholesterol (mg/dL)	193 ± 34	190 ± 30	0.82
HDL cholesterol (mg/dL)	55 ± 10	51 ± 22	0.58
Triglycerides (mg/dL)	109 ± 47	92 ± 32	0.31
BNP (pg/mL)	60 ± 61	30 ± 31	0.13

Data are shown as the mean ± SD.

BMI indicates body mass index; CTR, cardio-thoracic ratio; LP, late potential; LP1, filtered QRS duration; LP2, root-mean square voltage of the last 40 ms of the QRS complex; LP3, duration of low amplitude signal of the terminal portion of the QRS; LV mass, left ventricular mass; LVMI, left ventricular mass index; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; EF, ejection fraction; BUN, blood urea nitrogen; and BNP, brain natriuretic peptide.

cluded from analysis did not meet the blood pressure criteria during the observation period, and 1 stopped attending the follow-up appointments within 4 weeks of the start of the study for personal reasons. The background factors of the 24 cases subjected to analysis are shown in Table I. Their mean age was 68 ± 10 years and there were 14 men and 10 women. Comparison of background factors between the two Ca antagonist groups did not show any statistical differences other than the blood urea nitrogen level (Tables I-IV).

Treatment: After patients had been observed for at least 4 weeks while taking an ARB alone, a long-acting Ca antagonist (either a 20 mg nifedipine CR tablet or a 5 mg amlodipine tablet) was administered once a day in the morning for 52 weeks (1 year). If the attending physician decided that the blood pressure reduction was insufficient, either the dose of the Ca antagonist was increased or an antihypertensive agent of another class was added. In the nifedipine group, the dose was increased to 40 mg/day in 2 out of 11 patients and an α -blocker was added in 3

Table III. Changes in Left Ventricular Hypertrophy and Left Ventricular Function ($n = 24$)

Variable	Observation period	Treatment period	
		Week 12	Week 52
IVST (cm)	1.01 $\pm$ 0.15	0.93 $\pm$ 0.38*	0.85 $\pm$ 0.18**
LVDd (cm)	4.68 $\pm$ 0.57	4.74 $\pm$ 0.51	4.63 $\pm$ 0.32
LVDs (cm)	2.87 $\pm$ 0.58	2.85 $\pm$ 0.49	2.79 $\pm$ 0.41
PWT (cm)	1.00 $\pm$ 0.14	0.94 $\pm$ 0.20	0.88 $\pm$ 0.15**
LV mass (g)	197.0 $\pm$ 70.0	180.6 $\pm$ 72.9	152.9 $\pm$ 45.8*
LVMI (g/m ²)	120.0 $\pm$ 40.3	109.4 $\pm$ 39.6	95.6 $\pm$ 28.3*
E/A	0.87 $\pm$ 0.29	0.85 $\pm$ 0.22	0.86 $\pm$ 0.22
CTR (%)	50 $\pm$ 5	48 $\pm$ 4**	49 $\pm$ 5*
Sv ₁ + Rv _s (mV)	3.0 $\pm$ 1.1	2.9 $\pm$ 1.0*	2.7 $\pm$ 0.9*
LP1 (msec)	129 $\pm$ 24	127 $\pm$ 19	128 $\pm$ 20*
LP2 (μ V)	36 $\pm$ 19	37 $\pm$ 13	38 $\pm$ 13**
LP3 (msec)	34 $\pm$ 19	26 $\pm$ 11	24 $\pm$ 9**

Data are shown as the mean $\pm$ SD.

*; $P < 0.05$ (versus baseline), **; $P < 0.01$ (versus baseline).

IVST indicates intraventricular septal thickness; LVDd, left ventricular end-diastolic diameter; PWT, posterior wall thickness; LV mass, left ventricular mass; LVMI, left ventricular mass index; LVDs, left ventricular end-systolic diameter; E/A, early wave/atrial wave ratio; CTR, cardio-thoracic ratio; LP, late potential; LP1, filtered QRS duration; LP2, root-mean square voltage of the last 40 ms of the QRS complex; and LP3, duration of low amplitude signal of the terminal portion of the QRS.

patients. In the amlodipine group, a diuretic was added in 3 out of 13 patients.

Blood pressure and pulse rate: During the observation period, the blood pressure and pulse rate were measured at 2 weeks before starting administration of the Ca antagonist and immediately prior to the start of treatment. During treatment with the Ca antagonist, the blood pressure and pulse rate were checked every 4 weeks while the patient rested in a sitting position.

Echocardiography: The left ventricular end-diastolic diameter (LVDd), intra-ventricular septal thickness (IVST), and left ventricular posterior wall thickness (PWT) were measured by two-dimensional M-mode echocardiography before the start of Ca antagonist therapy (observation period), at 12 weeks after the start of treatment, and after 52 weeks of treatment. Left ventricular mass (LV Mass) was calculated by the formula of Devereux, and the left ventricular mass index (LV Mass index) was calculated with correction for body surface area. As an index of left ventricular diastolic performance, the ratio of the maximum blood flow velocity during rapid LV inflow (E) to the maximum blood flow velocity during atrial contraction (A) was obtained by pulsed Doppler echocardiography. All echocardiographic examinations were performed by the same technical assistant who was blinded to the patient's clinical information.

Electrocardiography and chest radiography: The sum of Sv₁ and Rv_s on the electrocardiogram, the signal-averaged electrocardiogram (LP1, LP2, and LP3), and

Table IV. Changes in Left Ventricular Hypertrophy and Left Ventricular Function in Each Treatment Group and Comparison Between the Groups

Variable	NIF group			AML group			P
	Observation period	Week 12	Week 52	Observation period	Week 12	Week 52	
IVST (cm)	0.98 ± 0.16	0.92 ± 0.24	0.85 ± 0.16	1.04 ± 0.12	0.95 ± 0.29	0.86 ± 0.19	0.82
LVDd (cm)	4.58 ± 0.43	4.60 ± 0.38	4.56 ± 0.38	4.74 ± 0.71	4.79 ± 0.62	4.66 ± 0.25	0.21
LVDs (cm)	2.77 ± 0.42	2.83 ± 0.54	2.79 ± 0.52	2.97 ± 0.70	2.86 ± 0.46	2.79 ± 0.30	0.94
PWT (cm)	0.99 ± 0.16	0.90 ± 0.12	0.88 ± 0.15	1.02 ± 0.12	0.94 ± 0.15	0.89 ± 0.16	0.89
LV mass (g)	180.1 ± 43.0	161.0 ± 36.7	148.9 ± 50.6	218.1 ± 86.5	181.1 ± 69.4	156.5 ± 43.2	0.85
LVMI (g/m ²)	114.6 ± 25.6	103.0 ± 25.6	95.8 ± 31.7	127.6 ± 47.2	109.7 ± 37.6	96.4 ± 23.1	0.52
E/A	0.90 ± 0.27	0.80 ± 0.22	0.76 ± 0.14	0.84 ± 0.26	0.84 ± 0.27	0.95 ± 0.24	0.31
CTR (%)	51 ± 5	49 ± 4	51 ± 6	49 ± 5	48 ± 5	47 ± 4	0.96
Sv ₁ + Rv ₅ (mV)	2.6 ± 0.7	2.5 ± 0.6	2.6 ± 0.8	3.4 ± 1.2	3.2 ± 1.1	2.8 ± 1.0	0.63
LP1 (msec)	124 ± 23	127 ± 22	132 ± 23	128 ± 22	126 ± 16	126 ± 17	0.38
LP2 (μV)	31 ± 9	35 ± 7	35 ± 7	36 ± 22	38 ± 16	42 ± 16	0.81
LP3 (msec)	35 ± 18	27 ± 9	23 ± 7	36 ± 20	25 ± 13	24 ± 10	0.90

Data are shown as the mean ± SD.

IVST indicates intraventricular septal thickness; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; PWT, posterior wall thickness; LV mass, left ventricular mass; LVMI, left ventricular mass index; E/A, early wave/atrial wave ratio; CTR, cardio-thoracic ratio; LP, late potential; LP1, filtered QRS duration; LP2, root-mean square voltage of the last 40 ms of the QRS complex; and LP3, duration of low amplitude signal of the terminal portion of the QRS.

the cardiothoracic ratio (CTR) on the chest radiograph were measured before starting treatment with a Ca antagonist (observation period), 12 weeks after the start of treatment, and after 52 weeks of treatment. LP1, LP2, and LP3 of the signal-averaged electrocardiogram indicate the filtered QRS duration, the root-mean-square voltage of the last 40 ms of the QRS complex, and the duration of low amplitude signal of the terminal portion of the QRS, respectively.

Laboratory tests: Biochemistry tests (BNP, creatinine, total cholesterol, HDL-cholesterol, triglycerides, and BUN) were performed before treatment with a Ca antagonist (observation period), 12 weeks after the start of treatment, and after 52 weeks of treatment.

Statistical analysis: A decrease in the LVMI due to treatment with a long-acting Ca antagonist was defined as an endpoint. According to a report by Shimoyama, *et al*,⁵⁾ LVMI was reduced by 40% when nifedipine CR was administered to 15 hypertensive patients with left ventricular hypertrophy for 1 year. The target number of subjects was thus determined by setting a sample size of at least 20 patients to allow for dropouts. Results are expressed as the mean ± standard deviation. The paired *t*-test or Wilcoxon signed ranked test was used for comparisons between before and after Ca antagonist therapy. For comparisons between the two Ca antagonists, a linear mixed-effects model that included the change over time from week 0 to week 52 and the intersubject variation was used. Data

were analyzed using SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Blood pressure and pulse rate: Changes in blood pressure are shown in Figure 2A. During the observation period prior to Ca antagonist treatment, blood pressure (SBP/DBP) was $161 \pm 15/92 \pm 12$ mmHg. After 4 weeks of treatment, both the systolic and diastolic blood pressures were significantly reduced to $149 \pm 18/83 \pm 14$ mmHg ($P < 0.05$ for SBP and $P < 0.01$ for DBP, respectively). The blood pressure continued to decrease slowly until week 52, at which time a

Figure 2. A: Changes in blood pressure. B: Changes in blood pressure with each Ca antagonist.

A **B** **C**

Figure 3. A: Changes in ventricular septal thickness. ($n = 24$) B: Changes in LV posterior wall thickness. ($n = 24$) C: Changes in LV mass index. ($n = 24$) D: Changes in LV end-systolic diameter. ($n = 24$) E: Changes in ECG findings. ($Sv_1 + Rv_5$) ($n = 24$)

further significant decrease was observed for both systolic and diastolic blood pressure ($136 \pm 17/78 \pm 14$ mmHg, $P < 0.01$ for SBP and $P < 0.01$ for DBP, respectively). In the nifedipine CR group, the baseline blood pressure was $160 \pm 11/90 \pm 9$ mmHg and this was significantly reduced to $140 \pm 21/81 \pm 13$ mmHg in week 8, with the decrease in blood pressure being maintained until week 52 ($130 \pm 15/73 \pm 16$ mmHg, $P < 0.01$ for both systolic and diastolic) (Figure 2B).

In the amlodipine group, the baseline blood pressure was $162 \pm 18/94 \pm 14$ mmHg and it decreased to $145 \pm 15/89 \pm 12$ mmHg after 8 weeks later, showing a significant decrease in the diastolic blood pressure ($P < 0.05$), but not a signif-

icant reduction of systolic pressure. The blood pressure remained higher in week 52 ($141 \pm 17/82 \pm 9$ mmHg) compared with that of the nifedipine group. As shown in Figure 2B, there was no significant difference in the changes of blood pressure between the two groups during the treatment period. Comparison of the trends in blood pressure throughout the 52-week treatment period by the mixed-effects model also showed no significant differences between the two groups.

There was no significant change in the pulse rate after the start of Ca antagonist therapy ($74 \pm 11/\text{min}$ before treatment and $74 \pm 9/\text{min}$ after 52 weeks), and there were no differences between the two drugs throughout the treatment period (nifedipine group: $77 \pm 9/\text{min}$ before treatment and $73 \pm 10/\text{min}$ after 52 weeks; amlodipine group: $71 \pm 12/\text{min}$ before treatment and $75 \pm 9/\text{min}$ after 52 weeks).

Echocardiographic parameters: The changes in left ventricular hypertrophy and left ventricular diastolic performance with Ca antagonist therapy are shown in Table III and Figure 3A-D. The LVMI was significantly reduced by 20.3% after 52 weeks ($P < 0.05$), and significant reductions were also seen in other markers of cardiac hypertrophy such as intraventricular septal thickness and posterior wall thickness (15.8% and 12.0%, respectively). However, there was no significant change in the E/A ratio, which is an index of left ventricular diastolic performance. When the changes in these parameters after treatment were compared between the two drugs (Table IV, Figure 4), there were no significant differences in IVST (A), PWT (B), or LVMI (C). Furthermore, there was no significant difference in the changes in the E/A ratio between the two groups.

Electrocardiography and chest radiography findings: The sum of Sv_1 and Rv_5 and the signal-averaged electrocardiograms (LP1, LP2, and LP3) before and after Ca antagonist treatment are shown in Table III. The sum of Sv_1 and Rv_5 displayed a significant decrease from 12 weeks of treatment ($P < 0.01$), and continued to show a significant decrease after 52 weeks ($P < 0.05$) (Figure 3E). A significant reduction in the CTR was also seen in week 12 and week 52 ($P < 0.01$ and $P < 0.05$, respectively).

Assessment of the changes after treatment with the two Ca antagonists did not reveal any significant differences in Sv_1 and Rv_5 or CTR between the groups (Table IV). Signal-averaged electrocardiograms (Table III) displayed significant decreases in LP1 and LP3, and a significant increase in LP2. When the changes after treatment were compared between the two drugs, no differences were found (Table IV).

Adverse events and dropouts: Neither Ca antagonist caused any serious adverse reactions. Changes in laboratory values after treatment with nifedipine CR or amlodipine were all within the normal range (Table V). One patient from the nifedipine CR group dropped out within 4 weeks of starting the study because

Figure 4. **A:** Comparison of the changes in ventricular septal thickness. **B:** Comparison of the changes in posterior wall thickness. **C:** Comparison of the changes in LV mass index.

Table V. Changes in Other Laboratory Values in Each Group and Comparison Between the Groups

Variable	NIF group			AML group			<i>P</i>
	Observation period	Week 12	Week 52	Observation period	Week 12	Week 52	
BNP (pg/mL)	60 ± 61	40 ± 24	37 ± 47	30 ± 31	41 ± 45	30 ± 35	0.53
Total cholesterol (mg/dL)	193 ± 34	199 ± 43	192 ± 41	190 ± 30	198 ± 29	190 ± 30	0.77
HDL cholesterol (mg/dL)	55 ± 10	58 ± 14	58 ± 19	51 ± 22	57 ± 25	49 ± 19	0.42
Triglycerides (mg/dL)	109 ± 47	97 ± 40	112 ± 54	92 ± 32	96 ± 29	96 ± 41	0.48
Serum creatinine (mg/dL)	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.22
BUN (mg/dL)	14.3 ± 2.9	15.6 ± 5.4	15.6 ± 3.9	17.6 ± 4.5	18.6 ± 6.1	18.9 ± 4.9	0.08

Data are shown as the mean ± SD. BNP indicates brain natriuretic peptide; HDL, high density lipoprotein; and BUN, blood urea nitrogen.

of a unilateral decision to switch to ginseng. Nifedipine CR was restarted at 40 mg/day when the blood pressure increased again, and the patient's blood pressure was stabilized as a result.

DISCUSSION

This study showed that combined therapy with an ARB and a long-acting Ca antagonist could achieve further reduction in blood pressure and left ventricular mass compared to those during prior ARB monotherapy. Improvement of cardiac hypertrophy by Ca antagonists has already been evaluated in some studies, such as the ELVERA trial⁶⁾ of amlodipine and the PRESERVE trial⁷⁾ of nifedipine. LVMI improved by 12.7% in the former study and by 16.9% in the latter.

In our study, LVMI was reduced by 20.3%. In a study performed by Shimoyama, *et al*⁵⁾ in Japan using nifedipine CR, the reduction in LVMI was 41.1%. When blood pressure changes in these studies were compared, the blood pressure reduction in our study was -25/-14 mmHg compared with -27/-8 mmHg in ELVERA and -21/-13 mmHg in PRESERVE, suggesting a relation between improvement of LVMI and the extent of blood pressure reduction.

In the study performed by Shimoyama, *et al*, the subjects had severe hypertension with a mean blood pressure of 197/111 mmHg. It was controlled to below 140/80 mmHg in only two months after the start of treatment, and the actual blood pressure reduction was -56/-30 mmHg. They used a high dose of nifedipine CR (40 mg/day), so afterload was reduced by its powerful hypotensive action. In our study, the mean systolic blood pressure did not fall below 140 mmHg until 48 weeks, since we employed relatively low doses of nifedipine CR and amlodipine (an average dose of 25.5 mg/day and 5 mg/day, respectively). In addition, Ca antagonist therapy in the present study was added to a conventional

dose of ARB, therefore, the further reduction in blood pressure and left ventricular mass were far smaller compared to those of Shimoyama, *et al.*⁵⁾ Since the present study did not intend to make a direct comparison of the beneficial effects between a Ca antagonist versus ARB, the only conclusion we could draw was that the reductions in blood pressure and LVMI were due to the combination, but not each separately, of ARB and Ca antagonist treatment. This could be a limitation of this type of clinical study.

Regarding other parameters relating to the regression of left ventricular hypertrophy, the sum of $Sv_1 + Rv_5$ decreased significantly after the combination therapy with a Ca antagonist together with an ARB, however, other ECG changes such as the changes in ST segment or QRS duration in the left side leads were not analyzed in the present study. Changes in those parameters by ARB and/or Ca antagonist treatment would be an interesting target in future study because our data suggested that the combination of both drugs apparently reduced LVMI, but, as stated above, the effect of each drug was not clear.

Comparison between the two Ca antagonists showed no significant differences, including no significant difference in the improvement of left ventricular hypertrophy. The JSH2004 guidelines recommend a target blood pressure of less than 140/90 mmHg, and a lower target blood pressure of less than 130/80 mmHg for high risk patients with organ damage. The ESH-ESC2007 stresses the importance of strict blood pressure control (lower than 130/80 mmHg) for patients with myocardial infarction, stroke, renal complications, or diabetes.

Both of the long-acting Ca antagonists were well tolerated by the patients in the present study, so it is possible that left ventricular hypertrophy may have been further improved by a greater reduction of blood pressure if higher doses had been used.

The ACTION study⁸⁾ assessed the effect of once-daily nifedipine on the long-term prognosis in patients with stable angina pectoris, and showed that the onset of new episodes of heart failure could be prevented in patients with hypertension.⁹⁾ In that study, prevention of heart failure due to diastolic dysfunction was thought to be related to afterload reduction by nifedipine that prevented the progression of cardiac hypertrophy.

Regarding actions other than an antihypertensive effect that may contribute to the prevention of cardiac hypertrophy, a Ca antagonist has been reported to suppress myocardial hypertrophy and interstitial fibrosis.⁹⁾ Hayashi, *et al.*¹⁰⁾ also reported that a combination of ARB and nifedipine enhances this effect, and increases the myocardial capillary density. On the other hand, Komuro, *et al.*¹¹⁾ suggested that long-acting Ca antagonists may prevent cardiac hypertrophy by altering calcineurin activation due to Ca^{2+} inflow into the myocardium during the onset and progression of cardiac hypertrophy.

The results of the present study suggested that both an antihypertensive effect and a synergistic effect of multiple actions occurred with the combined use of an ARB and a long-acting Ca antagonist. There have been several reports on the influence of an increased heart rate on cardiovascular events. In the Framingham study,¹²⁾ an increased heart rate was an independent contributing factor to cardiovascular events in women.

The results of the FINE study¹³⁾ suggested that heart rate is an important predictor of all-cause mortality in elderly men. In the present study, an increase in heart rate was not observed during combined therapy with an ARB and a long-acting Ca antagonist. This would be an additional benefit of this combination because Ca antagonist monotherapy usually increases the heart rate.¹⁴⁾ In the NICE Combi study Group Hasebe and Kikuchi, it was suggested that ARBs may decrease the release of noradrenaline from sympathetic nerve terminals and thus suppress reflex activation of the sympathetic nervous system by Ca antagonists.¹⁵⁾ It is conceivable that suppression of an increase in the heart rate by combination therapy prevents cardiac hypertrophy and cardiac events.

In addition, the late potential data obtained by signal-averaged electrocardiography were interesting because the filtered QRS duration and the duration of low amplitude signal of the terminal portion of the QRS were significantly decreased and the root-mean-square voltage of the last 40 ms of the QRS complex was significantly increased by the additional treatment of long-acting Ca antagonist treatment on top of the prior ARB treatment. To the best of our knowledge, this is the first time that Ca antagonist treatment has exhibited beneficial effects on the changes in the late potential of QRS complex. These changes observed in the present study correspond to previous reports with renin-angiotensin system inhibitors such as ACE inhibitors¹⁶⁾ or ARB.¹⁷⁾ Collectively, these results suggest that combination therapy with a Ca antagonist on top of prior ARB therapy is likely to provide an antiarrhythmogenic effect in hypertensive patients because it has been reported that the worsening of the late potential data in cardiovascular disease patients is linked with a fatal cardiac arrhythmia.¹⁸⁻²⁰⁾

The results of the present study also suggest that combining drugs with different mechanisms of action to achieve stricter blood pressure control may contribute to preventing the onset and progression of cardiac hypertrophy and cardiac events.

The two long-acting Ca blockers used in this study, nifedipine CR (mean dose: 25.5 mg) and amlodipine (mean dose: 5 mg), were comparable with respect to their antihypertensive effect, suppression of cardiac hypertrophy, and tolerability. Since the cost of amlodipine (5 mg/day) is approximately twice that of nifedipine CR (20 mg/day) and similar to Adalat CR[®] 40 mg/day, a standard dose of ARB combined with nifedipine CR (20-40 mg) seems to be a preferable

strategy for achieving strict blood pressure control in an economical fashion.

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