Original Article

Comparison of Nifedipine Retard with Angiotensin Converting Enzyme Inhibitors in Japanese Hypertensive Patients with Coronary Artery Disease: The Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) Randomized Trial

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The Japan Multicenter Investigation for Cardiovascular Diseases-B was performed to investigate whether nifedipine retard treatment was associated with a significantly higher incidence of cardiac events than angiotensin converting enzyme inhibitor treatment in Japanese patients. The study used a prospective, randomized, open, blinded endpoint (PROBE) design. Patients were enrolled at 354 Japanese hospitals specializing in cardiovascular disease. The subjects were 1,650 outpatients aged under 75 years who had diagnoses of both hypertension and coronary artery disease. There were 828 patients subjected to intention-to-treat analysis in the nifedipine retard group and 822 patients in the angiotensin converting enzyme inhibitor group. The patients were randomized to 3 years of treatment with either nifedipine retard or angiotensin converting enzyme inhibitor. The primary endpoint was the overall incidence of cardiac events (cardiac death or sudden death, myocardial infarction, hospitalization for angina pectoris or heart failure, serious arrhythmia, and coronary interventions). The primary endpoint occurred in 116 patients (14.0%) from the nifedipine retard group and 106 patients (12.9%) from the angiotensin converting enzyme inhibitor group (relative risk, 1.05; 95% confidence interval, 0.81−1.37; $p=0.75$). In the Kaplan-Meier estimates, there were no significant differences between the two groups (log-rank test: $p=0.86$). The incidence of cardiac events and mortality did not differ between the nifedipine retard and angiotensin converting enzyme inhibitor therapies. Nifedipine retard seems to be as effective as angiotensin converting enzyme inhibitors in reducing the incidence of cardiac events and mortality. (*Hypertens Res* 2004; 27: 181−191)

***Key Words*: antihypertensive agents, nifedipine retard, angiotensin converting enzyme inhibitor, coronary artery disease**

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Introduction

Japanese patients show a higher incidence of coronary artery spasm than Caucasians. In fact, the findings from Pristipino and colleagues indicate that acetylcholine loading induced a three-fold higher incidence of coronary spasm among Japanese patients than among Caucasian patients after myocardial infarction (*1*). Therefore, calcium-channel blockers have been widely used in Japan for coronary artery disease and hypertension. The Japanese Society of Hypertension Guidelines Subcommittee for the Management of Hypertension (2000) (*2*) has recommended calcium-channel blockers for blood pressure control in hypertensive patients with angina pectoris and angiotensin converting enzyme (ACE) inhibitors in hypertensive patients with a history of myocardial infarction, but few clinical trials have compared the efficacy of these drugs (*3*, *4*). Under these circumstances, the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) was conducted to investigate which of nifedipine retard and ACE inhibitors could better prevent cardiac events in hypertensive patients with coronary artery disease.

After launching our study, arguments have arisen as to whether or not calcium-channel blockers and ACE inhibitors are equally effective in hypertensive treatment. In this study, we found that nifedipine retard was as effective as ACE inhibitors in preventing primary cardiac events, and this finding was consistent with the recent findings of ALLHAT (*5*).

Methods

Subjects

The subjects were outpatients aged under 75 years who had diagnoses of both hypertension and coronary artery disease. Patients were enrolled at 354 Japanese hospitals specializing in the management of cardiovascular disease between January 1994 and July 1997. Coronary artery disease was defined according to the criteria of the American Heart Association as $\geq$75% stenosis on coronary angiography (CAG) performed within 1 year before the study. Patients who did not undergo CAG were diagnosed as having coronary artery disease when both of the following criteria were met: 1) a history of more than 2 anginal attacks per week with a stable frequency, and 2) ST-segment depression of 1 mm or more during the treadmill exercise test using the multistage gradual increase method according to the Bruce protocol, or detection of myocardial ischemia with ^{201}Tl myocardial scintigraphy (*6–8*). Patients with acute myocardial infarction or unstable angina were excluded.

Patients were diagnosed as having hypertension when 1) systolic blood pressure (SBP) was $\geq$160 mmHg or diastolic blood pressure (DBP) was $\geq$95 mmHg, and SBP was $\geq$150 mmHg and DBP was $\geq$90 mmHg at the time of the enrollment or 2) they had been previously treated with any antihypertensive agents, their blood pressure (BP) before starting the treatment met the above criteria, and the antihypertensive agents were switched to the study drug without any washout period. Patients with DBP $\geq$120 mmHg or secondary hypertension were excluded. Other exclusion criteria were symptomatic cerebrovascular disease, overt heart failure, atrial fibrillation, serious arrhythmias (ventricular tachycardia, ventricular fibrillation), renal dysfunction (a serum creatinine concentration of more than 176.8 μmol/l), severe hepatic dysfunction, uncontrollable diabetes mellitus, and familial hypercholesterolemia. The institutional ethical committee at each participating hospital approved the study, and all patients gave written informed consent to participate in the study.

Study Design, Study Drugs, and Concomitant Medications

The study employed a prospective, randomized, open blinded endpoint (PROBE) design (*9–11*). The patients were randomized to 3 years of treatment with either nifedipine retard (nifedipine) or any ACE inhibitor. A computer-generated random number sequence obtained from an external biostatistician was used for randomization. The sealed envelope method was used for randomization of the study drug. After determining the eligibility of patients, the investigators at each institute opened the envelopes allocated to each institute to determine the study drugs to be administered. The investigators were required to prescribe the study drug indicated and not to change to another drug during the treatment period. Assessment of endpoints was done by the endpoint committee in a blinded manner. All events were assessed without any knowledge of the treatment group to which the patients had been assigned.

The patients in the nifedipine group received nifedipine (a long-acting nifedipine formulation that is given at a dose of 10–20 mg twice daily in Japan) for 3 years, while patients in the ACE inhibitor group received an ACE inhibitor (enalapril at 5–10 mg, imidapril at 5–10 mg, or lisinopril at 10–20 mg, once daily as recommended in Japan (*12–14*)) for 3 years. The treatment target was an office SBP lower than 150 mmHg and a DBP lower than 90 mmHg. If BP reduction was unsatisfactory, an α-blocker (doxazosin, bunazosin or prazosin) was administered concomitantly. If the antianginal effect of the treatment was inadequate, long-acting or short-acting nitrates and/or β-blockers were used concomitantly.

Assessment of Outcomes

BP measurement; Baseline data were assessed during the 1 month observation period prior to study drug administration. Nifedipine was taken after breakfast and dinner. ACE inhibitor was taken after breakfast. BP was measured three times and the average of the last two readings was calculated.

Heart rate was measured only once at the first BP measurement. Measurement was done at a regular time in the morning at each medical institution, with the patient in the sitting or supine position (whichever had been decided upon initially), during the observation period and every 6 months after initiation of the study. The achieved BP was calculated as the mean SBP and mean DBP for the follow-up period from 6 months to the end of the study.

Occurrence of Cardiac Events; The primary endpoint of the study was the overall incidence of cardiac events, which were defined as 1) cardiac death or sudden death; 2) myocardial infarction (initial and recurrent; detected by clinical symptoms combined with Q waves, ST-segment elevation, or both on the electrocardiogram and elevated levels of cardiac enzymes); 3) angina pectoris requiring hospitalization; 4) heart failure requiring hospitalization (dyspnea or fatigue at rest or on minimal exertion [New York Heart Association class III or IV] and a left ventricular ejection fraction of less than 30%); 5) serious arrhythmia (ventricular tachycardia, ventricular fibrillation); or 6) performance of coronary interventions (percutaneous transluminal coronary angioplasty [PTCA], coronary artery bypass grafting, or stenting).

Other Events and Adverse Events; The secondary endpoints were cerebrovascular accidents, renal dysfunction, non-cardiovascular events such as cancer, and total mortality. Cerebrovascular accidents were defined as events causing a severe neurological deficit, and all institutes were encouraged to refer their patients for computed tomography. Transient ischemic attack (TIA) was included in cerebrovascular accidents. A serum creatinine level above 353.6 μmol/l was used as a sign for worsening of renal dysfunction.

New symptoms that had not been observed during the observation period, abnormal laboratory data, and worsening of symptoms or signs that were initially seen during the observation period were classified as adverse events.

Withdrawal and Loss to Follow-Up

Patients who could not be followed up due to the development of adverse reactions, worsening of symptoms, refusal to continue the study, or protocol deviations were handled as withdrawals. Patients who stopped visiting the hospital and whose condition could not be confirmed despite follow-up by letter or telephone were handled as being lost to follow-up. If the target BP (150/90 mmHg) was not achieved despite the co-administration of an α-blocker, the attending physician judged that the treatment was not effective.

Statistical Analysis

Determination of the sample size; According to the "Vital Statistics of Japan" published in 1992 (*15*), the mortality due to coronary artery disease in the Japanese population was approximately 60/100,000 patient-years. According to Hosoda *et al*., the risk of death in patients with coronary artery disease receiving secondary prevention therapy is 20 times as high as that in healthy individuals (*16*). The aim of the present study was to investigate the secondary prevention in hypertensive patients who had an increased risk of death from coronary artery disease. Based on Hosoda's report, and taking into account the fact that there were likely to be some patients with only mild disease, we set the increased level of risk as 15 times, and so the predicted mortality rate became 0.9/100 patient-years. The number of non-fatal events was assumed to be four times greater than that of deaths due to coronary artery disease (*17*), and the number of events in the ACE inhibitor group was assumed to be $0.9 \times 4/100$ patient-years (*i.e.*, approximately 4/100 patient-years). This study was designed to investigate whether nifedipine would increase the risk of cardiac events in comparison with ACE inhibitors based on the assumption that the odds ratio was 2.0 for nifedipine *vs.* ACE inhibitor treatment. In order to achieve a power of 99% with a two-sided test of significance at an α level of 0.05, 865 patients per arm were required for the study.

The primary endpoint of this study was the incidence of cardiac events. Statistical analysis included all of the randomized patients (intention-to-treat analysis). The Kaplan-Meier method was used to estimate the cumulative rates of cardiac events and other vascular events. The log-rank test was applied to assess the effect of treatment on the incidence of cardiac events. In addition, the Cox proportional hazard

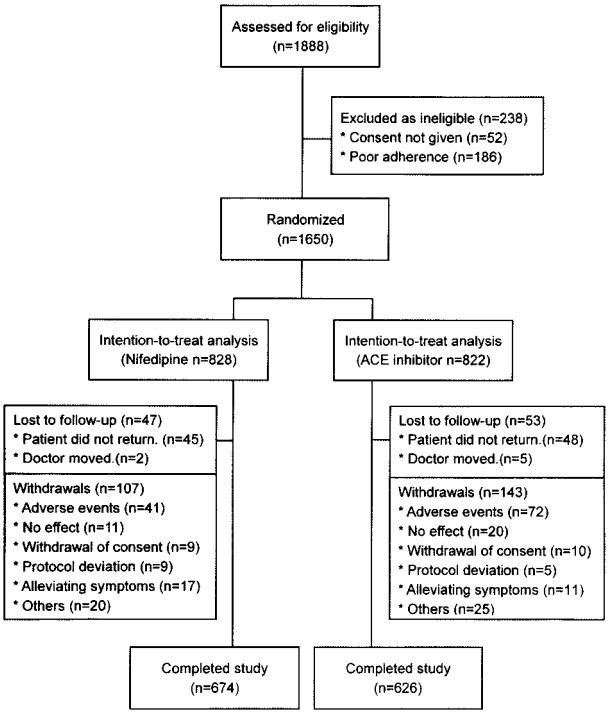

Fig. 1. *Flow of subjects through the trial.*

Table 1. Baseline Clinical Characteristics

			Number of patients (%)	
			Nifedipine (828 patients)	ACE inhibitor (822 patients)
Sex	Male/female		560 (67.6)/268 (32.4)	575 (70.0)/247 (30.0)
Age (years)			65±8	64±9
Coronary artery disease	Myocardial infarction		315 (38.0)	381 (46.4)
	Angina pectoris		566 (68.4)	507 (61.7)
	Asymptomatic myocardial ischemia		95 (11.5)	104 (12.7)
Complications	Hyperlipidemia		212 (25.6)	173 (21.1)
	Diabetes mellitus		199 (24.0)	173 (21.1)
	Others		147 (17.8)	167 (20.3)
History of smoking			277 (33.5)	286 (34.8)
CAG (within past 1 year)			514 (62.1)	512 (62.3)
PTCA (within past 1 year)			238 (28.7)	234 (28.5)
Number of diseased vessels (AHA ≥ 75%)		1-vessel	275 (33.2)	267 (32.5)
		2-vessel	152 (18.4)	136 (16.6)
		3-vessel	43 (5.2)	53 (6.5)
		Left main trunk	2 (0.2)	7 (0.9)
BP (mmHg)	Total patients	Systolic BP	147±19	145±20
		Diastolic BP	82±11	82±12
	Previously treated hypertensive patients	Systolic BP	146±17	144±19
		Diastolic BP	81±11	81±12
	Untreated hypertensive patients	Systolic BP	160±25	163±21
		Diastolic BP	91±14	93±13
Heart rate (total) (/min)			72±10	72±10
Body-mass index (kg/m^2)			24.1±3.0	24.0±2.9
Serum creatinine (μmol/l)			82.2±32.7	81.3±32.7
Serum cholesterol (mmol/l)			5.25±0.96	5.12±0.85
Medications used before observation period	Nitrates		557 (67.3)	537 (65.3)
	Diuretics		45 (5.4)	39 (4.7)
	β-Blockers		176 (21.3)	152 (18.5)
	α-Blockers		36 (4.4)	35 (4.3)
	Calcium-channel blockers		435 (52.5)	405 (49.3)
	ACE inhibitors		117 (14.1)	102 (12.4)
	Antihyperlipidemic drugs		242 (29.2)	216 (26.3)
	Antiplatelets		439 (53.0)	466 (56.7)

ACE, angiotensin converting enzyme; CAG, coronary angiography; PTCA, percutaneous transluminal coronary angioplasty; AHA, American Heart Association; BP, blood pressure.

model was used to estimate relative risks (RR) and 95% confidence intervals (CI) after adjusting for demographic variables such as sex, age, and other important covariates. Event rates per 1,000 patient-years were also calculated. The Student's *t*-test was used for comparison of the BP and heart rate data. All *p* values were two-sided, and significance was defined as $p<0.05$. Values are reported as mean or mean± SD. All statistical analyses were performed by using SAS software, version 6.14 (SAS Institute Inc., Cary, USA).

Results

Outline of the Flow of Subjects

A flow chart of the trial is shown in Fig. 1. A total of 1,888 patients who were enrolled at 354 Japanese hospitals specializing in cardiovascular disease from January 1994 to July 1997 were assessed for eligibility. Among them, 238 patients were excluded as ineligible because consent was not given ($n=52$), or for deviations from the randomization process (poor adherence: $n=186$). In this study, poor adherence meant deviation from the sealed envelope method, such as

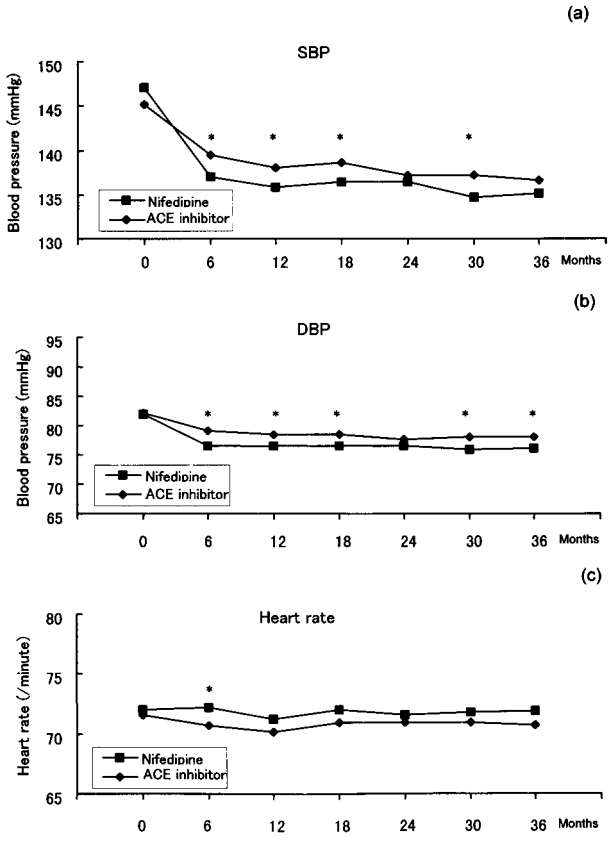

Fig. 2. *Changes of blood pressure and heart rate. Mean (a) SBP, (b) DBP, and (c) heart rate. Unpaired Student's* t*-test (comparison with angiotensin converting enzyme inhibitor).* * p$<$*0.05.*

inconsistency between group numbers and dates on patient registers or the presence of missing group numbers on the patient registers. External biostatisticians strictly checked all patient registers, and cases of poor adherence were completely excluded from the study. Therefore, 1,650 eligible patients underwent randomization. Follow-up of all the patients was completed in July 2000. There were 828 and 822 patients subjected to intention-to-treat analysis in the nifedipine group and the ACE inhibitor group, respectively. Among these patients, 674 patients (81.0%) from the nifedipine group and 626 patients (76.0%) from the ACE inhibitor group completed the study, while 107 patients and 143 patients withdrew from the study, respectively, and 47 patients and 53 patients were lost to follow-up. The follow-up rate was 94.0%. There was a significantly higher withdrawal rate in the ACE inhibitor group (12.9% in the nifedipine group and 17.3% in the ACE inhibitor group, $p=0.004$). The main reasons for withdrawal were adverse events (nifedipine, 5.0% [vasodilatory effect]; ACE inhibitors, 8.8% [predominately cough], $p=0.002$), no efficacy (1.3% *vs.* 2.4%), withdrawal of consent (1.1% *vs.* 1.2%), and protocol deviations (1.1% *vs.* 0.6%). The median follow-up period was 35.7 months and 1,931 patient-years were accumulated in the nifedipine group, as compared with 35.7 months and 1,784 patient-years in the ACE inhibitor group.

Baseline Characteristics

The baseline characteristics of the 1,650 patients who were included in the intention-to-treat analysis are shown in Table 1. There were 1,135 men and 515 women, and their average age was 65±6 years. Sixty-five percent of the subjects had a medical history of angina pectoris and 42% had a history of myocardial infarction at baseline. At the time of enrollment in this study, 92% of patients (1,515/1,650) had been previously treated for hypertension. The rest, 8% (135/1,650), were untreated hypertensive patients. In the previously treated patients, the mean BP (SBP/DBP) before starting the treatment was 167±20/93±13 mmHg and 165±20/93±13 mmHg in the nifedipine group and ACE inhibitor group, respectively. And their baseline blood pressures before switching to the study drug were 146±17/81±11 mmHg and 144±19/81±12 mmHg in the nifedipine group and ACE inhibitor group, respectively, with no significant difference between the two groups. On the other hand, the baseline BP in the untreated patients were 160±25/91±14 mmHg and 163±21/93±13 mmHg in the nifedipine group and ACE inhibitor group, respectively, also with no significant difference. The patients who did not meet the BP criteria for enrollment were also included in the analysis in accordance with the principles of intention-to-teat analysis (*18*). Therefore, the BP levels before antihypertensive treatment of all the enrolled patients were SBP $\geq$150 mmHg and/or DBP $\geq$90 mmHg.

Changes of BP and Heart Rate

After 3 years of treatment, the mean dose of nifedipine was 31.9±10.7 mg/day, while those of ACE inhibitors were 5.6±2.5 mg/day for enalapril, 10.2±3.9 mg/day for lisinopril, and 6.8±2.4 mg/day for imidapril. The number of patients who were given ACE inhibitors at the last visit was 427 (52%) for enalapril, 197 (24%) for imidapril, 164 (20%) for lisinopril, and 34 (4%) for the others. Figure 2 shows the changes of BP and heart rate over the 3 year follow-up period. SBP (Fig. 2a) and DBP (Fig. 2b) showed a significant decrease after 6 months in both groups. SBP and DBP at 6, 12, 18, and 30 months, as well as DBP at 36 months, were significantly lower in the nifedipine group when compared with the ACE inhibitor group ($p<0.05$). The achieved BP was 136/77 mmHg in the nifedipine group and 138/79 mmHg in the ACE inhibitor group; these values were significantly lower in the nifedipine group when compared with the ACE inhibitor group ($p<0.01$). The mean reduction of BP (SBP/DBP) was −11/−5 mmHg in the nifedipine group and −7/−4 mmHg in the ACE inhibitor group, and the BP reduction was significantly greater in the nifedipine group

Table 2. Relative Risk and Occurrence of Endpoints (Nifedipine *vs*. ACE Inhibitor)

	Number of patients with events		Event rate per 1,000 patient-years		Relative risk (nifedipine *vs*. ACE inhibitor)*	
	Nifedipine (n=828)	ACE inhibitor (n=822)	Nifedipine	ACE inhibitor	Point estimate (95% Cl)	p value
Cardiac events	116 (14.0%)	106 (12.9%)	64.69	63.42	1.05 (0.81−1.37)	0.75
Sudden death/cardiac death	6 (0.7%)	6 (0.7%)	3.11	3.36	0.96 (0.31−3.04)	0.95
Myocardial infarction	16 (1.9%)	13 (1.6%)	8.36	7.31	1.31 (0.63−2.74)	0.47
Angina pectoris requiring hospitalization	50	56	26.72	32.49	0.80 (0.55−1.18)	0.26
Heart failure requiring hospitalization	12	9	6.23	5.06	1.25 (0.52−2.98)	0.62
Serious arrhythmia	4	4	2.07	2.24	0.98 (0.24−3.98)	0.98
Coronary intervention†	81	75	44.47	44.37	1.04 (0.76−1.43)	0.81
Cerebrovascular accidents	16	16	8.34	9.03	1.00 (0.50−2.02)	0.99
Worsening of renal dysfunction	6	2	3.11	1.12	2.70 (0.54−13.49)	0.23
Non-cardiac death	6	9	3.11	5.04	0.64 (0.23−1.81)	0.40
Total mortality	12 (1.4%)	15 (1.8%)	6.21	8.40	0.76 (0.35−1.63)	0.48

*The estimates and p values for the relative risks were determined by using the Cox proportional hazard model with adjustment for sex, age, and history of myocardial infarction and angina pectoris. †Coronary intervention: percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting, stenting. ACE, angiotensin converting enzyme; CI, confidence interval.

($p<0.01$). Heart rate (Fig. 2c) showed no significant changes in each group, among either previously treated or untreated patients.

Use of Concomitant Medications

The number of patients who concomitantly received a nitrate preparation to treat angina pectoris was 587 (70.9%) in the nifedipine group and 567 (69.0%) in the ACE inhibitor group, with no significant difference between the two groups. The number of patients who were co-administered a β-blocker was 205 (24.8%) in the nifedipine group and 192 (23.4%) in the ACE inhibitor group, with no significant difference observed between the two groups. The number of patients who were concomitantly treated with an α-blocker was 52 (6.3%) in the nifedipine group and 88 (10.7%) in the ACE inhibitor group, and the difference was statistically significant ($p=0.0012$). However, this difference in the rate of the α-blocker use had no significant influence on the incidence of cardiac events (the results of the subgroup analysis which excluded the patients concomitantly treated with α-blocker were almost the same as the results of the total analysis).

Occurrence of Cardiac Events and Other Events

Cardiac events and other events occurring in patients for the intention-to-treat analysis are shown in Table 2. There were 116 (14.0%) patients who suffered from cardiac events in the nifedipine group *vs.* 106 patients (12.9%) in the ACE inhibitor group. The incidence rates were 64.69/1,000 patient-years and 63.42/1,000 patient-years for nifedipine and ACE inhibitor, respectively. The Kaplan-Meier estimates showed that the cumulative incidence rates of the primary endpoint during the 3 year follow-up period in each group were superimposed and that there were no significant differences between the two groups (log-rank test: $p=0.86$) (Fig. 3a). The RR of cardiac events during the nifedipine treatment compared to ACE inhibitor treatment was estimated to be 1.05, and the 95% CI was 0.81 to 1.37. There was no significant difference between the two groups ($p=0.75$). Myocardial infarction occurred in 16 patients (1.9%) from the nifedipine group and 13 patients (1.6%) from the ACE inhibitor group (RR 1.31; 95% CI 0.63−2.74), with no significant difference between the two groups. There were 6 patients (0.7%) who suffered from sudden death or cardiac death in the nifedipine group, as well as 6 patients (0.7%) in the ACE inhibitor group (RR 0.96; 95% CI 0.31−3.04). The total mortality was 12 (1.4%) in the nifedipine group and 15 (1.8%) in the ACE inhibitor group (RR 0.76; 95% CI 0.35−1.63), again with no significant difference between the two groups. Cerebrovascular accidents occurred in 16 patients from each group (RR 1.00; 95% CI 0.50−2.02).

Subgroup analyses were performed to assess the occurrence of cardiac events in relation to various risk factors (Fig. 4a). These showed that there were no significant differences in the occurrence of cardiac events between the two groups when stratification was done according to each baseline characteristic. At the start of the study, 24.0% of patients in the nifedipine group and 21.1% of those in the ACE inhibitor group had diabetes mellitus, but there was no significant difference in the risk of cardiac events between the two

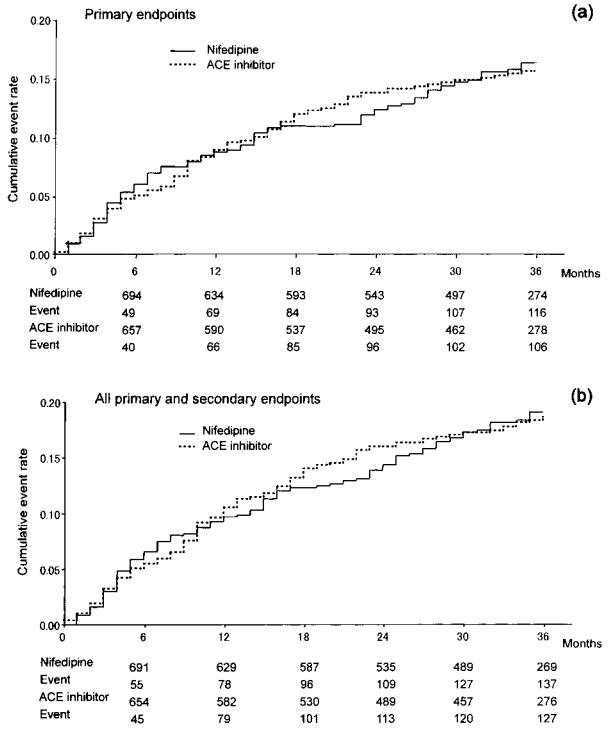

Fig. 3. *Kaplan-Meier curves and life tables for (a) the primary endpoints, and (b) all primary and secondary endpoints. Life tables show the number of patients and number of events every 6 months. (a) log-rank test,* p=*0.8609; (b) log-rank test,* p=*0.9381.*

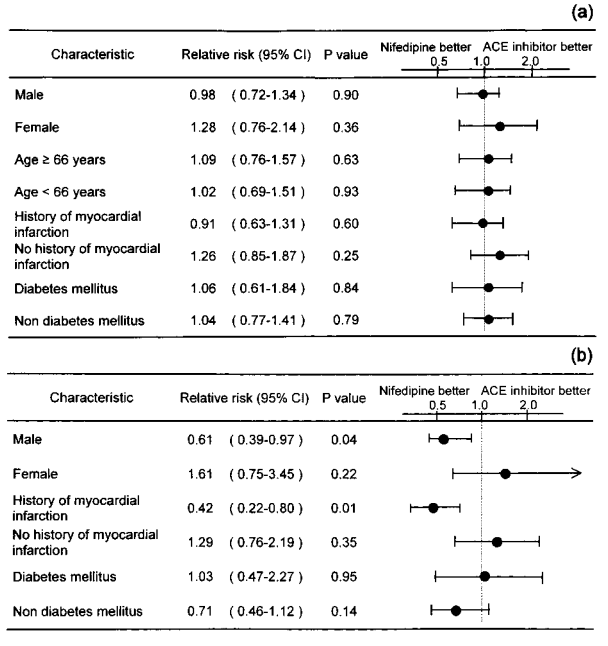

Fig. 4. *Relative risk of cardiac events stratified by clinical characteristics (nifedipine* vs. *angiotensin converting enzyme inhibitor) adjusted for sex, age, history of myocardial infarction and angina pectoris using the Cox proportional hazard model. (a) Overall incidence of cardiac events, (b) hospitalization for angina pectoris.*

Table 3. Withdrawals Due to Adverse Events

Symptoms	No. of patients (%)	
	Nifedipine (n=828)	ACE inhibitor (n=822)
Hypotension	8 (1.0)**	2 (0.2)
Palpitations, tachycardia	7 (0.8)**	0
Edema	7 (0.8)**	0
Facial erythema, hot flushes	6 (0.7)*	0
Dry cough	0	60 (7.3)**
Headache, dull headache	3 (0.4)	3 (0.4)
Gingival hypertrophy	3 (0.4)	1 (0.1)
Digestive intestinal disorder	2 (0.2)	3 (0.4)
Malaise, fatigue	3 (0.4)	0
Others	2 (0.2)	3 (0.4)
Total	41 (5.0)	72 (8.8)**

* $p<0.05$, ** $p<0.01$ for the comparison between the two treatment groups, by the χ^2 test. ACE, angiotensin converting enzyme.

groups, either for diabetic or nondiabetic patients. In the nifedipine group, patients with a history of myocardial infarction showed a reduction in the risk of hospitalization for angina pectoris of 58% when compared with the ACE inhibitor group (Fig. 4b).

Adverse Events

The number of adverse events was 76 in the nifedipine group and 121 in the ACE inhibitor group. The major adverse events occurring in the nifedipine group were those related to vasodilatory effect, including hypotension, facial erythema, and hot flushes. On the other hand, dry cough accounted for most of the adverse events occurring in the ACE inhibitor group. The rate of withdrawal due to these adverse events was 5.0% and 8.8% in the nifedipine and ACE inhibitor groups, respectively, and the difference between groups was significant (p=0.002). They are shown in Table 3.

Discussion

After the starting of this study, Psaty *et al*. (*19*) and Furberg *et al*. (*20*) reported a case-control study and a meta-analysis of studies that had investigated the efficacy of short-acting calcium-channel blockers in patients with hypertension who suffered from myocardial infarction or coronary artery disease and concluded that these drugs worsened the prognosis of such patients. Although these were retrospective investigations, the conclusions cast some doubts on the safety of calcium-channel blockers. The prospective ABCD trial in hypertensive patients with diabetes mellitus (*21, 22*) and the FACET (*23*) study both revealed a higher incidence of cardiac events in patients treated with calcium-channel blockers than in those treated with ACE inhibitors. In STOP-Hyper-

tension 2 (*24*), old and new antihypertensive drugs were similar in their prevention of cardiovascular mortality or major events. However, there were significantly fewer fatal and non-fatal cases of myocardial infarction during treatment with ACE inhibitors than during calcium-channel blocker treatment. The WHO/ISH meta-analysis (*25*) showed that both ACE inhibitors and calcium-channel blockers were beneficial for the treatment of hypertension, although the number of studies reported in that analysis had insufficient statistical power for a definitive comparison. In ALLHAT, a calcium-channel blocker (amlodipine), a diuretic (chlorthalidone), and an ACE inhibitor (lisinopril) (*5*) were equally effective for the prevention of fatal coronary heart disease or nonfatal myocardial infarction in high-risk hypertensive patients. Thus, our results were considered to be consistent with those of ALLHAT.

Our study was performed to investigate the hypothesis that the risk of cardiac events in Japanese patients receiving nifedipine treatment would be up to twice as high as that in patients receiving ACE inhibitor treatment. However, this hypothesis was not supported in this study. Furthermore, the 95% CI of the risk ratio for cardiac events suggested that the possible RR for patients on nifedipine treatment would be a maximum of 1.37 times. In several randomized clinical trials published after the present study was initiated, the point estimates of the RR for fatal or nonfatal myocardial infarction were higher in patients taking calcium-channel blockers than in patients taking ACE inhibitors (ABCD trial; risk ratios of 7.0 and 4.2, respectively (*21*, *22*)) and the estimates of the risk of any major vascular event were also higher for calcium-channel blockers than ACE inhibitors (FACET study; risk ratio of 2.0 (*23*)). The results of the ABCD trial are likely to be biased, as the trial was terminated early due to an excess of myocardial infarction in the hypertensive group.

The nifedipine group achieved BP levels of 136/77 mmHg and a reduction in BP of −11/−5 mmHg. These levels were significantly lower than those seen in the ACE inhibitor group (138/79 mmHg, decrease of −7/−4 mmHg). When achieved BP levels during the study period were included in the covariates for analysis, the RR in the nifedipine group was 1.09 *vs*. the ACE inhibitor group (95% CI 0.83−1.43). This suggests that the relative risk of cardiac events would be approximately equal between the two treatments, even if ACE inhibitor treatment achieved a hypotensive effect that was equivalent to that of nifedipine. The heart rate did not increase significantly in either group, suggesting that neither drug induced reflex sympathetic hyperactivity. The lack of any between-group difference in the incidence of cardiac events might be attributed to good BP control in both groups. The baseline and achieved BP of patients in the JMIC-B study were comparable to those of patients in ALLHAT. BP was well controlled in both trials, and this might be the reason for the consistent results between the present primary endpoint and ALLHAT.

Recently, Staessen *et al*. performed a meta-analysis of the relationship between odds ratios for cardiovascular events and achieved BP differences, and concluded that SBP lowering was important to reduce the incidence of cardiovascular events (*26*). Taking into account the results of this meta-analysis, we speculate that, when the achieved SBP became 2 mmHg lower in the nifedipine group than in the ACE inhibitor group, the RR of myocardial infarction would have been 0.85−1.00. In the JMIC-B study, the estimated RR of myocardial infarction was 1.31, which appears to contradict Staessen's analysis. However, the 95% CI in the JMIC-B study was 0.63−2.74, which showed the true risk in the nifedipine group. These values include the range of 0.85−1.00 indicated by Staessen, hence, the results of the JMIC-B study do not necessarily conflict with Staessen's theory. If the JMIC-B study had employed as many samples as Staessen's meta-analysis, such that its statistical power were increased, the results of the JMIC-B study would be consistent with Staessen's theory.

Subgroup analysis revealed that patients with a history of myocardial infarction had a 58% lower risk of hospitalization for angina pectoris in the nifedipine group. The antispastic effect of this drug on the coronary arteries may be one of the factors contributing to the reduced incidence of hospitalization for angina pectoris in post-myocardial infarction patients. A comparison of changes in BP in patients with a history of myocardial infarction between the two treatment groups showed that SBP tended to be lower ($p < 0.10$) and DBP was significantly lower ($p < 0.05$) in the nifedipine group than in the ACE inhibitor group. There was no difference in heart rate between the groups. Thus, in addition to the involvement of coronary artery spasm, the difference in the level of BP reduction between the two groups is considered to be a possible reason for the influence on the results of the present subgroup analysis.

In this study we used once-daily treatment with the ACE inhibitors enalapril, imidapril, and lisinopril as the control drugs. The standard doses of these ACE inhibitors were determined in multicenter clinical studies based on the Japanese guidelines for evaluating antihypertensive drugs (*12*−*14*, *27*). Although the dosage regimens were no more than half the dose used in Europeans and Americans, these dose levels are considered optimum for both efficacy and safety in Japanese patients. The J-MIND study, implemented by Baba and colleagues, provides further evidence on optimal dose based on a comparative study of the effects of ACE inhibitors and a long-acting calcium-channel blocker on long-term treatment (*28*). That study also compared the effects of nifedipine retard and enalapril on renal function in hypertensive patients with type 2 diabetes over a 2-year period. The results showed that urinary albumin excretion was similar in the 2 groups (renoprotective effect), while there was no significant difference in the incidence of cardiovascular events (*29*). In the J-MIND study, the mean doses of enalapril and nifedipine were 6.4±2.5 mg/day and 28.2±11.5 mg/day, re-

spectively.

In our study, patients with diabetes accounted for 22.5% of the subjects. We also conducted a subgroup analysis of the risk of cardiac events in our patients with diabetes and found no significant difference between the groups with and without diabetes.

We adopted the PROBE study design (*9*−*11*), which was one of the standard at the time the study was designed. This involves blinded assessment of endpoints. Even with a blinded endpoint committee, this does not exclude the possibility that investigators may be biased in picking-up and reporting endpoints depending on their expectations.

At the start of the present study, the sealed envelope method was the standard for randomization in open-label studies in Japan. However, the envelopes were not opened in accordance with the protocol in 186 patients. These cases were regarded as significant violation of the randomization rule, and thus were excluded from intention-to-treat analysis by an external biostatistician.

In addition, although some of the enrolled hypertensive patients did not meet the criteria (they were below the reference values), at the Steering Committee held in 1999 after completion of patient enrollment, they were included in analysis in accordance with the principles of intention-to-treat analysis (*18*). Therefore, the BP levels before antihypertensive treatment of all the enrolled patients were SBP $\geq$150 mmHg and/or DBP $\geq$90 mmHg.

The withdrawal rate was significantly lower in the nifedipine group than in the ACE inhibitor group ($p=0.004$). In the ACE inhibitor group, a significantly larger number of patients withdrew due to adverse events (predominately dry cough) ($p=0.002$). This suggests that a long-acting nifedipine formulation may be more desirable for use in hypertensive patients who need long-term treatment.

In conclusion, we found that in Japanese hypertensive patients with coronary artery disease, the nifedipine retard was as effective as ACE inhibitors.

Appendix

JMIC-B Committee

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