Original Article

Controlled Release Nifedipine and Valsartan Combination Therapy in Patients with Essential Hypertension: The Adalat CR and Valsartan Cost-Effectiveness Combination (ADVANCE-Combi) Study

Ikuo SAITO[1)] and Takao SARUTA[2)], ADVANCE-Combi Study Group*

This study was designed to compare the clinical efficacy of two calcium channel blocker–based combination therapies with an angiotensin receptor blocker in Japanese patients with essential hypertension. A 16-week, double-blind, parallel-arm, randomized clinical trial was performed to compare the efficacy and safety of the combination therapy of controlled release nifedipine (nifedipine CR) plus valsartan *vs.* that of amlodipine plus valsartan. The primary endpoint was the target blood pressure achievement rate. Eligible patients were randomly allocated to nifedipine CR–based or amlodipine-based treatment groups. Patients were examined every 4 weeks to determine whether the blood pressure had reached the target level. When the target level was not achieved, the drug regimen was changed; when the target blood pressure was achieved, the same study medication was continued. A total of 505 patients were enrolled in the study (nifedipine CR group: 245 cases; amlodipine group: 260 cases). After 16 weeks of treatment, blood pressure was significantly reduced in both groups, but to a larger extent in the nifedipine CR group than in the amlodipine group ($p<0.01$). The target blood pressure achievement rate was also significantly higher in the nifedipine CR group ($p<0.001$). There was no significant difference in the incidence of drug-related adverse events between the groups. These results indicate that the nifedipine CR–based combination therapy was superior to the amlodipine-based therapy for decreasing blood pressure and achieving the target blood pressure in patients with essential hypertension. (*Hypertens Res* 2006; 29: 789–796)

***Key Words*: nifedipine, valsartan, amlodipine, combination therapy, hypertension**

Introduction

Many epidemiological studies (*1–3*) have shown that hypertension is one of the main risk factors for cardiovascular diseases (CVD). Various large-scale clinical studies have shown that treatment of hypertension with medication can prevent onset of CVD and reduce mortality and morbidity (*4*, *5*) and that treating hypertension has been associated with an approximately 40% reduction in the risk of stroke and an approximately 15% reduction in the risk of myocardial infarction (*6*). Furthermore, it has recently been demonstrated that the clinical outcome is dependent on the degree of blood pressure reduction rather than on the types of antihypertensive agents used (*7*). Therefore, the guidelines for the treatment of hypertension (*8–11*) state that strict control of blood pressure is

From the [1)]Health Center, Keio University, Yokohama, Japan; and [2)]Internal Medicine, School of Medicine, Keio University, Tokyo, Japan.
*Refer to the Appendix.

Support was received in the form of a grant from Bayer Yakuhin, Ltd.

Address for Reprints: Ikuo Saito, M.D., Health Center, Keio University, 4–1–1, Hiyoshi, Kohoku-ku, Yokohama 223–8521, Japan. E-mail: saito@hc.cc.keio.ac.jp

Received February 20, 2006; Accepted in revised form July 7, 2006.

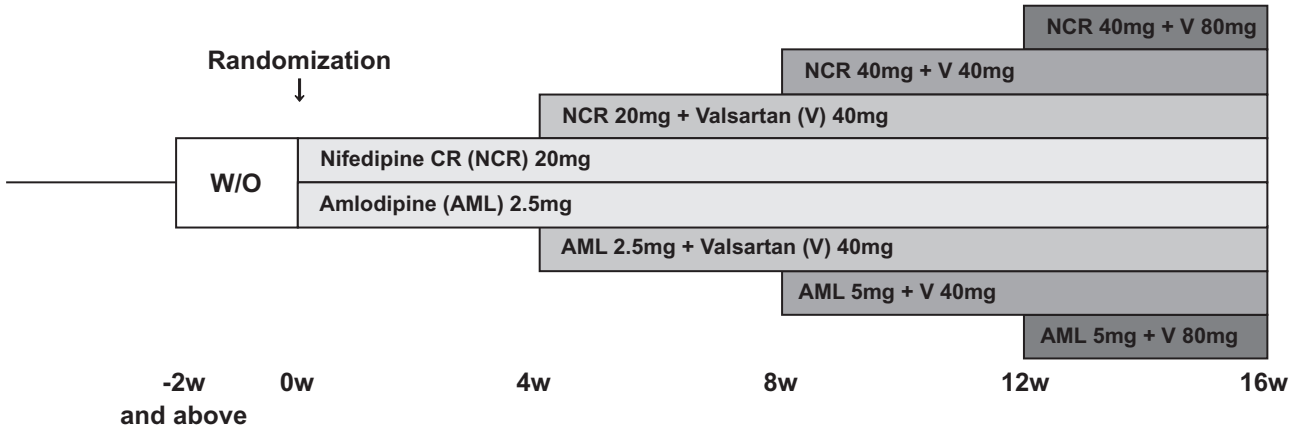

Fig. 1. *Study design for the ADVANCE-Combi study. w, week(s).*

essential in order to prevent organ damage and to reduce mortality and morbidity.

Combination therapy with multiple agents is also emphasized in the guidelines as a practical way of reducing patients' blood pressure to the desired target levels (*8–11*). In fact, combination therapy has already been applied to many cases, because monotherapy is often not sufficiently effective to achieve the target blood pressure.

The guidelines issued by the Japanese Society of Hypertension in 2000 (JSH 2000) (*12*) refer to combination therapy using a calcium channel blocker (CCB) plus an angiotensin converting enzyme (ACE) inhibitor, and combination therapy using a CCB plus an angiotensin II receptor blocker (ARB). In Japan, CCBs have long been the most widely used antihypertensives, mainly because of their reliable blood pressure–lowering effects (*13*). ARBs are a relatively new class of drugs that suppress the renin-angiotensin system in a manner similar to ACE inhibitors. However, due to their excellent safety profile and demonstrated mechanism for organ protection, the clinical use of ARBs has become increasingly popular in Japan.

Recently, the efficacy of combination therapy with a CCB, controlled release nifedipine (nifedipine CR), and an ARB, low-dose candesartan, was investigated in a clinical study conducted in Japan, and this combination therapy was found to have a greater antihypertensive effect than an up-titrated monotherapy of candesartan (*14*). In addition, this combination was shown to achieve normal blood pressure at a much lower cost (*15*), and there was no difference in tolerability between the two treatment groups.

However, there has been no double-blind study confirming the optimal CCB-based combination therapy strategy. Nifedipine CR and amlodipine are the most widely available drugs for clinical use in Japan. Therefore, in order to investigate the efficacy of combination therapy of CCBs concomitantly used with ARBs, we have performed a clinical study in patients with essential hypertension with combination therapy of valsartan, as the ARB, and each of two selected CCBs, *i.e.* nifedipine CR and amlodipine.

Methods

The JSH 2000 (*12*) has established the target blood pressure for hypertension treatment according to the age of patients as follows: for patients aged 20–59 years, systolic/diastolic blood pressure (SBP/DBP) $<130/85$ mmHg; for those 60–69 years, SBP/DBP $<140/90$ mmHg; and for those 70–79 years, SBP/DBP $<150/90$ mmHg. In the present study, untreated essential hypertensive patients or patients who had previously been treated with antihypertensive agents and whose blood pressure in the sitting position at the time of enrollment was 1) SBP ≥ 160 mmHg or DBP ≥ 100 mmHg for untreated patients, or 2) SBP ≥ 150 mmHg or DBP ≥ 95 mmHg for patients with previous treatment by antihypertensive agents, were enrolled on an outpatient basis. Those who met the following criteria were excluded from the study: SBP/DBP $\geq 200/120$ mmHg, secondary hypertension, or a hypertensive emergency such as malignant hypertension. Patients with the following complications were also excluded from the study: a history of CVD or cerebrovascular disease within 6 months prior to enrollment, uncontrolled diabetes (HbA1c $\geq 8\%$), severe hematopoietic dysfunction or malignant tumor, cardiogenic shock, congestive heart failure, current receipt of hemodialysis, bilateral renal artery constriction, hyperkalemia, severe liver dysfunction or renal dysfunction (serum creatinine ≥ 3.0 mg/dl). All patients provided written informed consent prior to the start of the study. The study was conducted after approval by the Institutional Review Boards of all the participating institutes.

After an at least 2-week washout period with no antihypertensive medication, eligible subjects were randomly allocated to either the nifedipine CR treatment group or the amlodipine treatment group, with a double-blind setting. The randomization list was generated by the Biometry Administration Group

Table 1. Baseline Patient Characteristics for Both Treatment Groups

	Nifedipine CR (*N*=245)	Amlodipine (*N*=260)	*p* value
Gender (*N* (%))			
Male	152 (62.0)	169 (65.0)	0.490
Fimale	93 (38.0)	91 (35.0)	
Age (*N* (%))			
<60 years	141 (57.6)	151 (58.1)	
≥60 years	104 (42.4)	109 (41.9)	
All	57.5±10.7	56.3±11.0	0.233
Blood pressure (mmHg)	161.9±12.7/100.4±9.1	161.6±13.1/102.3±8.0	0.733/0.010
Pulse rate (beats/min)	72.2±9.2	72.4±8.6	0.812
Height (cm)	162.5±9.7	162.8±7.9	0.703
Weight (kg)	66.4±12.4	67.2±10.9	0.441
Prior antihypertensive medication			
Yes	125 (51.0)	130 (50.0)	0.819
No	120 (49.0)	130 (50.0)	
Diabetes mellitus (*N* (%))	6 (2.4)	13 (5.0)	0.132
Hyperlipidemia (*N* (%))	45 (18.4)	43 (16.5)	0.588
Smoking (*N* (%))	54 (22.0)	60 (23.1)	0.781

Mean±SD.

of Bayer AG using a randomization program. Clinical samples were prepared with the assignment of random numbers according to the randomization list.

Following the washout period, the 16-week double-blind treatment period was started with a visit to the clinic every 4 weeks. The study involved the use of four medication steps, regimens I, II, III, and IV, and was started with regimen I (Fig. 1). At 4 weeks, if the blood pressure had reached the target level with regimen I, the study medication remained unchanged, but if the target blood pressure was not achieved, the treatment was shifted to regimen II. Likewise at weeks 8 and 12, if the blood pressure had reached the target level, the medication was continued, but if not, the treatment was shifted to the next drug regimen. The dosing schedule used in this study was once a day and was within the "dosage and administration" approved in Japan, with the low dose chosen as the starting dose (regimen I).

1) Regimen I (Low-dose CCB): Nifedipine CR group: nifedipine CR 20 mg; Amlodipine group: amlodipine 2.5 mg.

2) Regimen II (Low-dose CCB + Low-dose ARB): Nifedipine CR group: nifedipine CR 20 mg + valsartan 40 mg; Amlodipine group: amlodipine 2.5 mg + valsartan 40 mg.

3) Regimen III (High-dose CCB + Low-dose ARB): Nifedipine CR group: nifedipine CR 40 mg + valsartan 40 mg; Amlodipine group: amlodipine 5 mg + valsartan 40 mg.

4) Regimen IV (High-dose CCB + High-dose ARB): Nifedipine CR group: nifedipine CR 40 mg + valsartan 80 mg; Amlodipine group: amlodipine 5 mg + valsartan 80 mg.

The study drugs were encapsulated by Kanae Co., Ltd. (Osaka, Japan). Individual capsules were filled with the appropriate combinations of test drugs and were indistinguishable in appearance.

Patients visited the clinic 5 times, once each at 0, 4, 8, 12, and 16 weeks. They were instructed to visit the clinic in the morning after taking their medication. At each clinic visit, blood pressure and pulse rate were measured with the subject in a sitting position after an at least 15 min rest, and two stable readings measured (<5-mmHg difference) at 1 or 2 min intervals were averaged. A resting electrocardiograph was recorded at the beginning of the washout, and clinical laboratory tests were performed at the beginning and the end of the washout, and at the end of the 16-week treatment period.

This study was assessed with two primary endpoints: the target blood pressure achievement rate at the end of the treatment period and the mean treatment cost during the 16-week treatment period. Although the protocol was generated according to JSH 2000 (*12*), the recommendations from JSH 2004 (*16*) (SBP/DBP <130/85 mmHg for patients aged under 60 years; SBP/DBP <140/90 mmHg for those aged 60 years and over) were applied for estimation of the achievement rate, since the JSH 2004 was introduced during the study period. This report focuses on the achievement rate for the target blood pressure, and the cost-effectiveness aspects of the study will be reported separately.

The target blood pressure achievement rates were compared between the treatment groups using the Cochran-Mantel-Haenszel test with stratification according to age group (younger than 60 years old, 60 years old, and older than 60 years old). Blood pressure and pulse rate were also compared between the groups using ANCOVA with the baseline value as the covariate and the treatment group as the main effect.

The sample size was calculated based on the assumption that the nifedipine CR group would demonstrate superiority to the amlodipine group with respect to the treatment cost

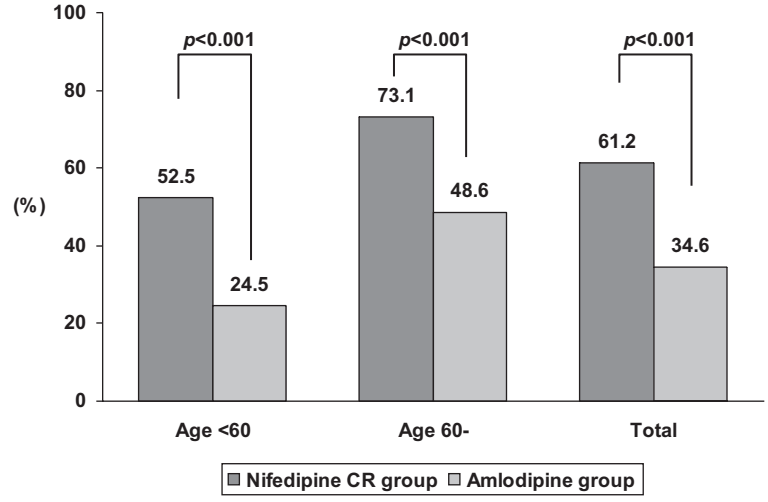

Fig. 2. *Achievement rate of target blood pressure during double-blind treatment in the nifedipine CR group and the amlodipine group.*

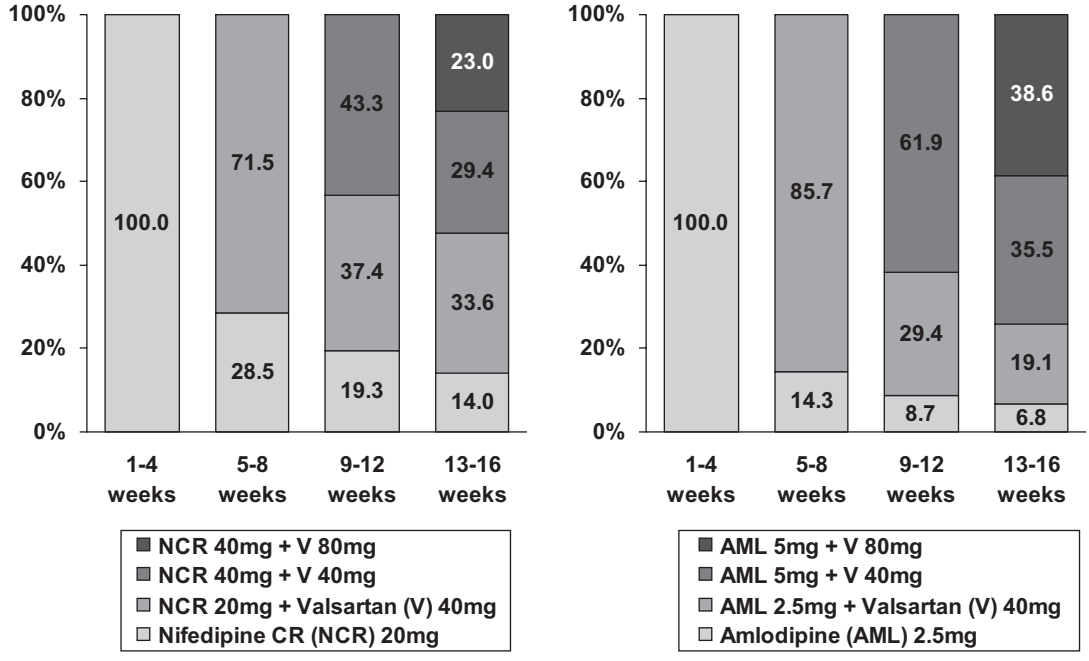

Fig. 3. *Disposition of study drug. More patients in the amlodipine-based combination therapy group required addition and/or uptitration of the treatment regimen, than in nifedipine CR group.*

endpoint and non-inferiority with respect to the target blood pressure achievement rate, with a statistical power of 90% (based on unpublished data). The actual sample size specified in the protocol was 270 subjects per group, 540 in total, which had a 94% statistical power for both pre-defined endpoints, using a two-sided test at an α level of 0.05 and assuming 10% drop-out from the full analysis set.

All statistical tests were two-sided with a significance at the α level of 0.05. The statistical analyses were conducted using SAS software (SAS Institute, Cary, USA). Data were expressed as the mean±SD.

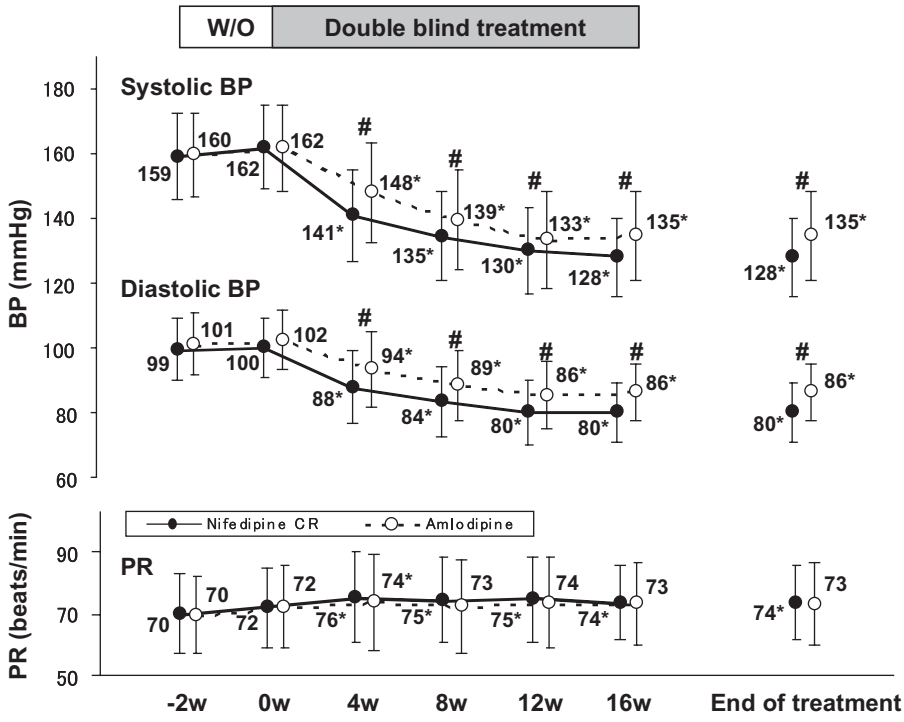

Fig. 4. *Blood pressure (BP) and pulse rate (PR) during double-blind treatment in the nifedipine CR group (●) and the amlodipine group (¡). Data are expressed as mean±SD.* *p*< 0.05: compared with baseline value (0 w) in each treatment group,* #p*< 0.05: comparison between two treatment groups. w, week(s).*

Results

Baseline Patient Demographics

Of the 570 patients who submitted written informed consent, 56 patients deviated from the randomization criteria or met the exclusion criteria. Consequently, the remaining 514 patients were entered for the 16-week double-blind treatment period. The baseline patient characteristics for both groups are shown in Table 1. There were no significant differences between the groups, except for baseline DBP, which was higher by 1.9 mmHg in the amlodipine group than in the nifedipine CR group.

Effects on Blood Pressure and Pulse Rate

The target blood pressure achievement rates after 16 weeks of treatment were significantly higher in the nifedipine CR group than in the amlodipine group (nifedipine CR group: 69.8% for SBP, 75.1% for DBP and 61.2% for both SBP and DBP; amlodipine group: 48.5% for SBP, 50.0% for DBP, and 34.6% for both SBP and DBP; $p<0.001$). The difference of achievement rates between the groups was observed irrespective of the age subgroups (Fig. 2).

The distribution of patients on drug regimens I to IV during the four 4-week treatment periods is shown in Fig. 3. During the fourth 4-week treatment period (weeks 13–16), 14.0% and 6.8% of patients were still being administered drug regimen I in the nifedipine CR group and amlodipine group, respectively, while 23.0% and 38.6% of patients had moved up to regimen IV in the two groups, respectively. Thus patients in the amlodipine treatment group were more likely to be coadministered an ARB and to be up-titrated than those in the nifedipine CR group ($p<0.05$).

A significant reduction in blood pressure from the baseline levels was observed in both groups after the first 4 weeks of treatment. Comparing the two groups in the first 4-week period when CCB low-dose monotherapies were applied, a significantly higher decrease in blood pressure was observed in the group receiving nifedipine CR 20 mg than in the group receiving amlodipine 2.5 mg, and this difference in blood pressure between the two groups remained until the end of the 16-week treatment period. There was no significant difference in the pulse rate between the two groups, although an increase of 2 beats per min from the baseline was recorded in the nifedipine CR group and an increase of 1 beat per min was observed in the amlodipine group (Fig. 4). The reduction in blood pressure from the baseline after 16 weeks of treatment was again significantly higher in the nifedipine CR group (SBP/DBP: −34.0±15.0/−20.1±9.5 mmHg; range, 162/100 to 128/80 mmHg) than in the amlodipine group (−27.0±14.5/

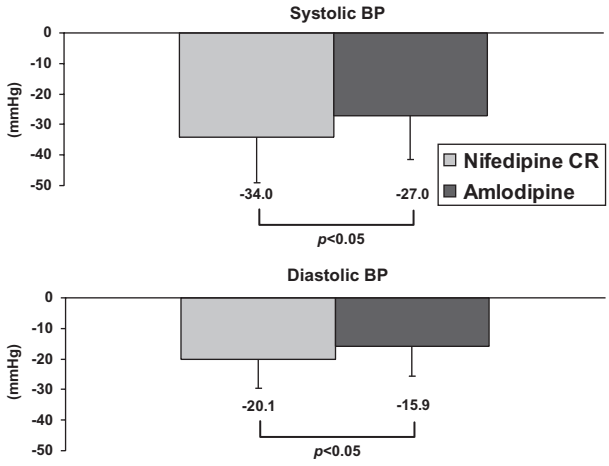

Fig. 5. *Changes in blood pressure (BP) during double-blind treatment in the nifedipine CR group, and the amlodipine group. Data are expressed as mean±SD.*

−15.9±9.7 mmHg; range, 162/102 to 135/86 mmHg) ($p<0.05$) (Fig. 5).

Safety

Adverse events related to the study drugs occurred in 31 patients (12.4%) in the nifedipine CR group and 20 patients (7.6%) in the amlodipine group, with no significant difference between the groups (Table 2) ($p=0.07$). Most of the events were mild to moderate in severity. Serious drug-related adverse events were reported in 1 subject (hypotension) in the nifedipine CR group and 1 subject (cerebral infarction) in the amlodipine group. Drug-related adverse events leading to discontinuation of the study medication occurred in 7 subjects (2.8%) in the nifedipine CR group and 6 subjects (2.3%) in the amlodipine group.

Table 2. Drug-Related Adverse Events Observed during the 16-Week Treatment Period

	Nifedipine CR ($n=250$)	Amlodipine ($n=263$)
Drug-related adverse events	31 (12.4%)	20 (7.6%)
Headache, dizziness	8 (3.2%)	5 (1.9%)
Flushing, hot flush	6 (2.4%)	2 (0.8%)
Palpitation, tachycardia	5 (2.0%)	
Peripheral edema	5 (2.0%)	1 (0.4%)
Cough	1 (0.4%)	1 (0.4%)
Gastrointestinal disorder	1 (0.4%)	3 (1.1%)
Hypotension	1 (0.4%)	
Thirst	1 (0.4%)	
Cerebral infarction		1 (0.4%)
Liver disorder		1 (0.4%)
Asthenia		1 (0.4%)
Chest pain		1 (0.4%)
Malaise		1 (0.4%)
Laboratory test abnormalities	12 (4.8%)	4 (1.5%)
Others	9 (3.6%)	4 (1.5%)

Discussion

CVD is responsible for one-third of global deaths and is a leading and increasing contributor to the world's disease burden (*17*). It is estimated that in Japan in 2003, about 5 trillion Japanese yen (45 billion US dollars; $1=JPY 110) of the National Health Insurance budget was spent on CVD, according to government statistics (http://www.mhlw.go.jp/toukei/saikin/hw/k-iryohi/03/index.html). Hypertension is a major risk factor for CVD, which plays a major etiologic role in the development of cerebrovascular disease, ischemic heart disease, and cardiac and renal failure.

CVD is eminently preventable by medical treatment of patients with hypertension. Recent studies, particularly those published in 1999 or later, support the use of a further decrease in the threshold of SBP (*18–21*). Studies published since 1999 suggest that even low-risk patients with blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic are likely to benefit from decreased blood pressure (*18, 19*). The Blood Pressure Lowering Treatment Trialists' Collaboration also indicates that the decrease in cardiovascular risk is dependent on the degree of blood pressure reduction (*8*).

Among medications used for hypertension treatment, CCBs, such as nifedipine CR, are the most frequently used antihypertensive agents in Japan, since they have a long, proven track record and are considered to be the most effective drugs for controlling blood pressure. However, ARBs, a newer class of drugs which suppress the renin-angiotensin system in a manner similar to ACE inhibitors, have been rapidly and widely accepted.

Long-term data from the Systolic Hypertension in Europe trial (Syst-Eur) show that antihypertensive drug treatment starting with a CCB reduces the rate of cardiovascular complications compared with a placebo in elderly patients with isolated systolic hypertension (*22*). A report of the INSIGHT trial indicates that fatal events (a composite of all-cause mortality, death from a vascular cause, and death from a non-vascular cause) of patients treated with nifedipine GITS were reduced by 50% in historical comparison with epidemiological data due mainly to strict blood pressure control throughout the study period (*23*).

Recently, the ACTION study also demonstrated the long-term benefits of a long-acting CCB in conjunction with treatment for angina in that the incidences of new overt heart failure and debilitating stroke were reduced by 38% and 33%, respectively, which was substantially attributed to aggressive blood pressure control (*24*).

However, the efficacy of CCBs coadministered with ARBs

has not yet been sufficiently assessed, although a CCB-based regimen used together with an ACE inhibitor prevented more major cardiovascular events and induced less diabetes than a β-blocker–based regimen used together with diuretics (*25*).

The results of this study indicate that the nifedipine CR–based combination is more effective than the amlodipine-based combination in a range of approved dosages in lowering BP levels and achieving the BP targets (Figs. 4 and 5), thereby resulting in a reduction in cardiovascular risk in patients with essential hypertension.

There was no significant difference in the incidence of drug-related adverse events between the two groups, although the incidence of hot flushes, pollakisuria and headache were numerically higher in the nifedipine CR group than in the amlodipine group (2.0% *vs*. 0.4%, 2.0% *vs*. 0% and 2.4% *vs*. 0.8%, respectively). Although two serious adverse events were reported—an incident of hypotension in the nifedipine CR group and one of cerebral infarction in the amlodipine group—in general, no unexpected adverse events were observed for the two CCBs during the course of the study.

There was no significant difference in the pulse rate between the two groups, although an increase of 2 beats per min from the baseline and an increase of 1 beat per min were recorded in the nifedipine CR group and the amlodipine group, respectively. It has been demonstrated that nifedipine CR does not affect the pulse rate in patients with essential hypertension or with ischemic heart disease (*26*, *27*), although short-acting CCBs are believed to activate the sympathetic nervous system *via* the arterial baroreflex mechanism as an acute effect (*28*). Therefore, the increase observed in this study is considered to be within the physiologically normal range and does not indicate sympathetic nervous system activation.

To our knowledge, this is the first report to compare the efficacy/safety of nifedipine CR and amlodipine in a double-blind setting, although there have been some reports comparing the efficacy/safety of nifedipine GITS and amlodipine. These reports also demonstrated comparable (*29*, *30*) or beneficial (*31*) efficacy/safety profile of nifedipine GITS against amlodipine.

The primary goal of treating patients with hypertension is to reduce their blood pressure to the target level, which eventually leads to a reduction in the long-term total risk of cardiovascular morbidity and mortality. In this regard, although some considerations are necessary before generalizing the results, the present study clearly demonstrated that combination therapy with a CCB and an ARB is an effective method to achieve the target blood pressure without major safety issues. The combination of these two agents had a synergistic effect on total cardiovascular risk management. This study has thus revealed a possible regimen for optimizing the daily treatment of hypertension. However, the study also highlights the need for large, long-term cardiovascular studies in Japanese patients.

Acknowledgements

The support of Bayer Yakuhin, Ltd. to this work is gratefully acknowledged.

Appendix

ADVANCE-Combi Study Group

Investigators: Fumishi Tomita (Tomita Medical Clinic Internal/Cardiovascular Medicine), Hajime Kimura (Shinjuku Oak Tower Clinic), Toshikazu Nagakura (Yoga Allergy Clinic), Tetsuro Hiraoka (Hiraoka Medical Clinic).

References

1. Kannel WB, Casteili WP, McNamara PM, McKee PA, Feinleib M: Role of blood pressure in the development of congestive heart failure. The Framingham Study. *N Engl J Med* 1972; **287**: 781–787.
2. MacMahon S, Peto R, Cutler J, *et al*: Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; **335**: 765–774.
3. Flack J, Neaton J, Grimm R, *et al*, for the Multiple Risk Factor Intervention Trial Research Group: Blood pressure and mortality among men with prior myocardial infarction. *Circulation* 1995; **92**: 2437–2445.
4. Medical Research Council Working Party: MRC trial of treatment of mild hypertension: principal results. *BMJ* 1985; **291**: 97–104.
5. Hansson L, Zanchetti A, Carruthers SG, *et al*, for the HOT Study Group: Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1998; **351**: 1755–1762.
6. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA: Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990; **335**: 827–838.
7. Blood Pressure Lowering Treatment Trialists' Collaboration: Effects of different blood-pressure–lowering regimens on major cardiovascular events: results of prospective-designed overviews of randomised trials. *Lancet* 2003; **362**: 1527–1535.
8. Chobanian AV, Bakris GL, Black HR, *et al*: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 2003; **289**: 2560–2572.
9. Whitworth JA, World Health Organization, International Society of Hypertension Writing Group: 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003; **21**: 1983–1992.
10. Guidelines Committee: 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**:

1011–1053.
11. Staessen JA, Li Y, Thijs L, Wang J: Blood pressure reduction and cardiovascular prevention: an update including the 2003–2004 secondary prevention trials. *Hypertens Res* 2005; **28**: 385–407.
12. Japanese Society of Hypertension Guidelines Subcommittee for the Management of Hypertension: Guidelines for the Management of Hypertension for General Practitioners. *Hypertens Res* 2001; **24**: 613–634.
13. Mori H, Ukai H, Yamamoto H, *et al*: Current status of antihypertensive prescription and associated blood pressure control in Japan. *Hypertens Res* 2006; **29**: 143–151.
14. Hasebe N, Kikuchi K: Controlled release nifedipine and candesartan low-dose combination therapy in patients with essential hypertension: NICE Combi (Nifedipine and Candesartan Combination) Study. *J Hypertens* 2005; **23**: 445–453.
15. Fujikawa K, Hasebe N, Kikuchi K: Cost-effectiveness analysis of hypertension treatment: controlled release nifedipine and candesartan low-dose combination therapy in patients with essential hypertension—NICE Combi (Nifedipine and Candesartan Combination) Study—. *Hypertens Res* 2005; **28**: 585–591.
16. Saruta T: The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004). *Nippon Rinsho* 2005; **63**: 952–958.
17. World Health Organization: The World Health Report 2002: Risks to Health 2002. Geneva, World Health Organization.
18. Van den Hoogen PCW, Feskens EJM, Nagelkerke NJD, Menotti A, Nissinen A, Kromhout D, for the Seven Countries Study Research Group: The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. *N Engl J Med* 2000; **342**: 1–8.
19. Vasan RS, Larson MG, Leip EP, *et al*: Impact of high-normal pressure on the risk of cardiovascular disease. *N Engl J Med* 2001; **345**: 1291–1297.
20. The Heart Outcomes Prevention Evaluation Study Investigators: Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342**: 145–153.
21. Progress Collaborative Group: Randomised trial of a perindopril based regimen on blood pressure lowering among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; **358**: 1033–1041.
22. Staessen JA, Fagard R, Thijs L, *et al*, The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators: Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; **350**: 757–764.
23. Mancia G, Brown M, Castaigne A, *et al*: INSIGHT. Outcomes with nifedipine GITS or co-amilozide in hypertensive diabetics and nondiabetics in intervention as a goal in hypertension (INSIGHT). *Hypertension* 2003; **41**: 431–436.
24. Lubsen J, Wagener G, Kirwan BA, de Brouwer S, Poole-Wilson PA: Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with symptomatic stable angina and hypertension: the ACTION trial. *J Hypertens* 2005; **23**: 641–648.
25. Dahlöf B, Sever PS, Poulter NR, *et al*: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required *versus* atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366**: 895–906.
26. Minami J, Numabe A, Andoh N, *et al*: Comparison of once-daily nifedipine controlled-release with twice-daily nifedipine retard in the treatment of essential hypertension. *Br J Clin Pharmacol* 2004; **57**: 632–639.
27. Sato H, Yamamoto M, Fu L: Effects of nifedipine-controlled release tablet on heart rate and the autonomic nervous system in patients with ischemic heart disease. *Jpn J Clin Pharmacol Ther* 2004; **35**: 15–18.
28. Iimura O, Kikuchi K, Shimamoto K, *et al*: Effects of nisoldipine on sympathetic activity, the renin-angiotensin-aldosterone system, and water-sodium-calcium metabolism in patients with essential hypertension. *Arzneim-Forsch/Drug Res* 1989; **39**: 710–714.
29. Byyny RL, Shannon T, Schwartz LA, Rotolo C, Jungerwirth S: Efficacy and safety of nifedipine coat-core *versus* amlodipine in patients with mild to moderate essential hypertension: comparison of 24-hour mean ambulatory diastolic blood pressure. *J Cardiovasc Pharmacol Ther* 1997; **2**: 77–84.
30. Zidek W, Spiecker C, Knaup G, Steindl L, Breuer HWM: Compariosn of the efficacy and safety of nifedipine coat-core *versus* amlodipine in the treatment of patients with mild-to-moderate essential hypertension. *Clin Ther* 1995; **17**: 686–700.
31. Testa MA, Turner RR, Simonson DC, Krafcik MB, Calvo C, Luque-Otero M: Quality of life and calcium channel blockade with nifedipine GITS *versus* amlodipine in hypertensive patients in Spain. *J Hypertens* 1998; **16**: 1839–1847.