Original Article

Valsartan Amlodipine Randomized Trial (VART): Design, Methods, and Preliminary Results

Keiko NAKAYAMA[1)], Yoichi KUWABARA[1)], Masao DAIMON[1)], Satoshi SHINDO[1)], Miwa FUJITA[1)], Hiroya NARUMI[1)], Hiroshi MIZUMA[1)], and Issei KOMURO[1)]

Antihypertensive therapy has been well established to reduce hypertension-related morbidity and mortality, but the optimal therapy for Japanese patients remains unknown. The Valsartan Amlodipine Randomized Trial (VART), a prospective randomized open-label trial, was designed to determine whether treatment with an angiotensin II type 1 receptor blocker (valsartan) or a calcium channel blocker (amlodipine) lowers cardiovascular disease events in essential hypertensives in Japan. Registration, randomization and data entry were performed over the Internet. The minimization method (to control for age, gender, blood pressure level and history) was used at random assignment to ensure that the background factors were equivalent between the groups at baseline. After the registration, patients were followed-up for cardiovascular events (primary endpoints), echocardiography, ^{123}I-metaiodobenzylguanidine (MIBG) imaging, laboratory tests and blood pressure for 3 years. Currently, 797 patients have been enrolled and assigned to two groups: a valsartan (*n*=399) and an amlodipine (*n*=398) group. At baseline, controlled factors (age, gender, blood pressure level, and left ventricular hypertrophy) and the proportions of patients with diabetes and hyperlipidemia were equally allocated. At 12 months, both drugs evenly and significantly lowered blood pressure to the target level (valsartan: 133/79 mmHg; amlodipine: 132/79 mmHg). In conclusion, by combining the data on cardiovascular events with the results of echocardiographic, radionuclide imaging, and blood/urine studies, the VART study will provide mechanistic insights into the clinical outcomes and treatment effects of the trial. (*Hypertens Res* 2008; 31: 21–28)

***Key Words*: hypertension, randomized trial, valsartan, amlodipine**

Introduction

Hypertension is the most common disease in the Japanese population, and many large randomized clinical trials using antihypertensive drugs have established that reduction of blood pressure reduces hypertension-related morbidity and mortality (*1*). Several basic and clinical studies suggest that antihypertensive drugs which inhibit the renin-angiotensin system (RAS) have cardiovascular and renal benefits beyond their reduction of blood pressure (*2–8*), and thus these drugs are now being widely used as a first-choice therapy. However, since most of the clinical trials have been performed in Western countries, it remains to be determined whether RAS inhibitors also have beneficial effects in the Japanese population.

Since angiotensin II receptor blockers (ARBs) directly block angiotensin II type 1 (AT1) receptors, which are involved in hypertension, myocyte hypertrophy and fibrosis, they are expected to have beneficial effects in protecting major organs, such as the heart, kidney and arteries (*9–14*). Valsartan is a highly selective AT1 subtype blocker with potent blood pressure reduction ability. Several clinical trials have revealed the cardio-protective effects of valsartan in patients with heart failure and acute myocardial infarction (*13–16*).

From the [1)]Department of Cardiovascular Science and Medicine, Chiba University Graduate School of Medicine, Chiba, Japan.

Address for Reprints: Issei Komuro, M.D. Ph.D., Department of Cardiovascular Science and Medicine, Chiba University Graduate School of Medicine, 1–8–1 Inohana, Chuo-ku, Chiba 260–8670, Japan. E-mail: komuro-tky@umin.ac.jp

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In the Valsartan Heart Failure Trial (Val-HeFT) (*13*, *14*), patients who had already received heart failure treatment were assigned to receive valsartan or placebo. The results of this trial showed a significant decrease in symptoms, combined mortality, and morbidity from heart failure, and a significant improvement of cardiac function in those who received valsartan. The Valsartan in Acute Myocardial Infarction Trial (VALIANT) (*16*) enrolled patients with heart failure or left ventricular dysfunction during the immediate postinfarction period, and compared the incidence of hard cardiac events among the patients treated with captopril alone (angiotensin converting enzyme [ACE] inhibitor), valsartan alone (ARB) or their combination. Valsartan was found to be as effective as captopril.

On the other hand, calcium channel blockers (CCBs) have long been established as a first-line treatment for hypertension due to their clear blood pressure–lowering effects and the evidence of their efficacy provided by several large clinical trials (*17–20*). Among CCBs, amlodipine, which is a long-acting, third-generation calcium channel blocker, has been widely used in Japan (*21*, *22*). Recently, the results of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) (*16*) trial were released. This study directly compared amlodipine and valsartan in terms of incidence of cardiac events in high-risk patients with hypertension. In this study, no significant difference was shown for the primary endpoint, although the incidence of myocardial infarction and stroke was lower in those with amlodipine, and the incidence of heart failure was lower in those with valsartan. Because comparable blood pressure reduction was not obtained between the groups in this study, further comparison of the effects of these drugs is warranted. Furthermore, because most of the patients were recruited in Europe and the United Sates, it is unknown whether the results of these studies are extensible to a Japanese population.

Both valsartan and amlodipine are good representatives of their drug classes (ARBs and CCBs, respectively), with effective blood pressure–lowering effects and wide use among Japanese hypertensive patients. Thus, to determine which of these drugs is optimal for Japanese hypertensives, we designed and are conducting a prospective randomized open-label clinical trial, the Valsartan Amlodipine Randomized Trial (VART).

Study Design

Overview

The VART, a prospective, multicenter, randomized, open-label trial, was designed to measure the effects of treatment with the ARB valsartan and the CCB amlodipine on cardiovascular disease events in essential hypertensives. Eligible patients have been enrolled since July 2002. Follow-up data will be collected every 6 months for at least 3 years in each subject.

Table 1. Patient Eligibility Criteria

Inclusion criteria
1. 30 years old or older
2. Patients newly diagnosed hypertension (SBP≥140 mmHg or DBP≥90 mmHg in a sitting position at clinic) or treated with hypertensive drugs

Exclusion criteria
1. Secondary hypertension
2. Severe valvular disease or congenital heart disease requiring operative treatment
3. Hypertrophic or dilated cardiomyopathy
4. PTCA or CABG performed within 6 months
5. Stroke occurred within 3 months
6. Renal dysfunction (serum creatinine ≥3 mg/dL)
7. Hepatic dysfunction (AST and/or ALT ≥100 IU/L)
8. Electrolyte abnormality resistant to treatment
9. Severe ventricular arrythmia
10. Severe cerebrovascular disease
11. Pregnancy, possible pregnancy
12. Active cancer
13. Contraindication for valsartan or amlodipine
14. Not suitable for the clinical trial as judged by a physician

SBP, systolic blood pressure; DBP, diastolic blood pressure; PTCA, percutaneous coronary angioplasty; CABG, coronary artery bypass graft; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Randomization and data entry are performed at the homepage originally produced for the VART study, and the minimization method was used at the random assignment to ensure that the background factors were equivalent between the groups at baseline. The primary endpoints are non-fatal cardiovascular events or death from any cause. The secondary endpoints are the effects on left ventricular hypertrophy, left ventricular systolic and diastolic function, blood neurohormonal levels, cardiac sympathetic activity, renal function and daily change in blood pressure levels.

Sample Size and Data Analysis

Based on previous studies, the incidence of cardiovascular events with amlodipine was estimated as 5% (Veterans Affairs Study [VA study] (*23*), STOP Hypertension (*17*)). We further estimated that rate of incidence of cardiovascular events would be 40% lower in patients receiving valsartan than in those treated with amlodipine. As a result, we calculated that 1,280 patients would be needed in each group (2,560 in total), with a two-sided α level of 0.05 and 90% power. Assuming a dropout rate of 15%, 3,000 subjects (1,500 in each group) were considered to be required for the study. In the VART study, the intention-to-treat approach will be used for primary endpoint analysis. All statistical tests will be performed by two-sided test and values less than 0.05 will

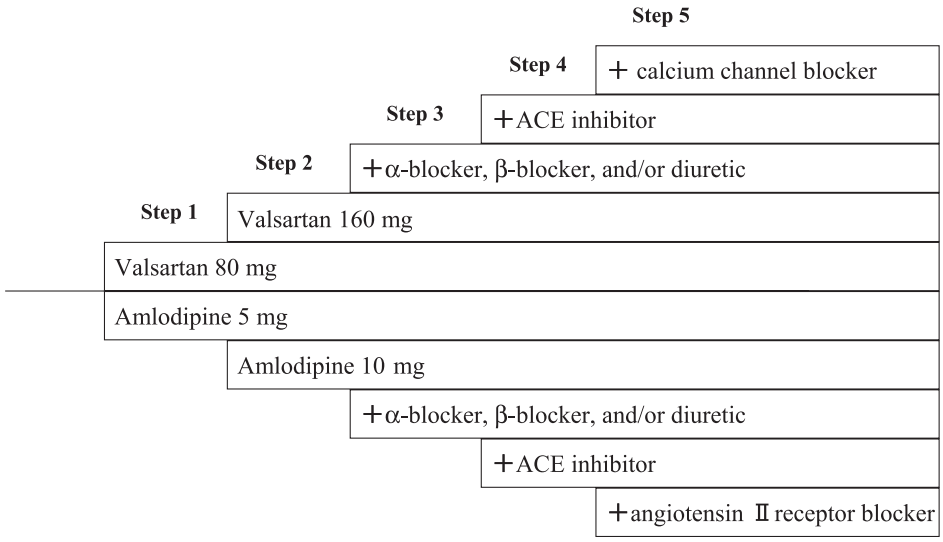

Fig. 1. *Treatment protocol. The initial dose is 80 mg/day valsartan or 5 mg/day amlodipine (step 1). These doses will be increased to 160 mg and 10 mg, respectively (step 2), and α-blockers, β-blockers or diuretics will be added (step 3) in patients whose blood pressure is > 135/85 mmHg.*

Table 2. Schedule for Data Collection

Data to be collected at baseline
Patient information: age, gender, height, weight, hypertensive period, present treatment, family history of hypertension, smoking, complications (hyperlipidemia, diabetes, obesity, hyperuricaemia, valvular disease, ischemic heart disease, stroke, respiratory disease)
Tests: blood pressure at clinic, blood chemistry, complete blood count, urinalysis, chest X-ray, electrocardiography, echocardiography. Specific laboratory tests (insulin, renin, norepinephrine [NE], brain natriuretic peptide [BNP], urinary albumin/creatinine ratio), and ^{123}I-MIBG cardiac imaging are performed at some institutes
Data to be collected every 6 months
Treatment information: daily dosage, treatment period, concomitantly used antihypertensive drugs
Tests: blood pressure (both at clinic and home), pulse rate, blood chemistry, complete blood count, urinalysis
Data to be collected every 12 month
Same tests at baseline and treatment information
Information on cardiovascular events: specified as primary events
Information on adverse events: adverse symptoms, adverse signs, abnormal data of laboratory tests
Information at the time of discontinuation/dropout

MIBG, metaiodobenzylguanidine.

be considered to indicate statistical significance. Any difference in the incidence of cardiovascular events between the treatment groups will be assessed by the life table method. Statistical significance will be assessed by log-rank test for univariate analysis, and the Cox proportional hazard model will be used for multivariate analysis.

Patient Eligibility Criteria

All participants are 30 years old or older with treated or untreated essential hypertension at baseline. All untreated patients meet the hypertension criteria defined by World Health Organization/International Society of Hypertension (WHO/ISH) (*24*). Inclusion criteria and exclusion criteria for the VART study are shown in Table 1.

Randomization

After their baseline data were obtained, eligible participants were randomly assigned to the valsartan group or amlodipine group by using the minimization method to allocate the possible confounding factors: age, gender, blood pressure level, the presence of left ventricular hypertrophy, history of ischemic heart disease, prevalence of heart failure, prevalence

Table 3. The VART Primary and Secondary Endpoints

Primary endpoints
1. All death
2. Sudden death: death of endogenous origin within 24 h after acute onset
3. Cerebrovascular events: new occurrence or recurrence of a stroke or transient ischemia attack
4. Cardiac events: new occurrence or recurrence of acute myocardial infarction or pectoris, new occurrence of aggravation of heart failure
5. Vascular events: new occurrence or recurrence of dissecting aneurysm of aorta, hospitalization due to arteriosclerotic occlusion of peripheral artery
6. Renal dysfunction: doubling of serum creatinine, end stage renal disease
Secondary endpoints
1. Effect on left ventricular hypertrophy (assessment by echocardiography or electrocadiogram) and left systoloic and diastolic function by echocardiography
2. Effect on renal function (assessment by albuminuria or urinary albumin/creatinine ratio, serum creatinine)
3. Effect on cardiac sympathetic activity (assessment by MIBG cardiac imaging)
4. Effect on blood neurohormonal level
5. Effect on blood pressure at home
6. new onset of diabetes

VART, Valsartan Amlodipine Randomized Trial; MIBG, metaiodobenzylguanidine.

of stroke, and previous treatment with antihypertensive drugs. Participating physicians can register patients eligible for this study *via* the Internet, or by telephoning or faxing the VART staff. Since this system randomizes the patients and returns the allocation results to the physician in just a few moments, the patients can receive antihypertensive treatment on the day of the registration.

Treatment Protocol

Figure 1 shows the treatment protocol used in this study. The initial dose is 80 mg/day valsartan or 5 mg/day amlodipine (step 1). These doses are then increased to 160 mg and 10 mg, respectively (step 2), and α-blockers, β-blockers or diuretics are added (step 3) if blood pressure is >135/85 mmHg. If patients are already receiving antihypertensive treatment, they must discontinue the treatment and change to either valsartan 80 mg or amlodipine 5 mg without a run-in period.

Patient Follow-Up

After the registration and baseline data collection, follow-up data will be accumulated every 6 months. The data collection protocol is shown in Table 2. Patient information such as blood pressure, treatment details, and blood and urinary test results will be periodically collected in all subjects. Patients will be encouraged to measure their blood pressure 4 times a day (early morning, noon, evening, and late night) while at rest in a sitting position. Annual echocardiographic exams and ^{123}I-metaiodobenzylguanidine (MIBG) cardiac imaging are routinely performed for patients in the selected institutes. Specific laboratory tests (insulin, renin, norepinephrine, brain natriuretic peptide, urinary albumin/creatinine ratio) were also performed to evaluate neurohormonal levels, albuminuria and insulin-resistance in specific patients. These imaging and laboratory tests were performed at the participating institutes, and all subjects receiving them provided their informed consent. Detailed data on cardiovascular events, adverse events, and dropout will be sent to the Research Center immediately, and the Event Evaluation Committee will examine the validity of the information. The registration was started in July 2002 and follow-up data will be collected for at least 3 years in each patient.

Endpoint

The primary and secondary endpoints are shown in Table 3. The follow-up will be terminated if one of these primary endpoints occurs. The participating physicians will record all cardiovascular events or death on the event case card and send this information to the Data Center or enter it directly at the homepage of the VART study. The Event Evaluation Committee will adjudicate all cases of primary events without knowledge of assigned treatment.

Informed Consent

Written informed consent will be provided by all patients after the physicians have explained the objectives and protocol of the study, the possible adverse effects of the two study drugs, the privacy protection measures, and the freedom to withdraw from the study at anytime.

Table 4. Baseline Characteristics of the Patients

Characteristics	Valsartan group (n=399)	Amlodipine group (n=398)	
Age (years)	60.3±11.2	60.4±11.5	n.s.
Male (% of patients)	59.1	57.1	n.s.
Blood pressure (mmHg)			
Systolic	157±19	157±18	n.s.
Diastolic	92±13	93±13	n.s.
Body mass index (kg/m^2)	24.3±4.2	24.5±3.6	n.s.
Previous treatment for hypertension (%)	49.8	50.6	n.s.
ACE inhibitor (%)	8.6	5.7	n.s.
Angiotensin receptor blocker (%)	10.2	13.2	n.s.
Calcium channel antagonist (%)	31.7	30.1	n.s.
α-Blocker (%)	1.3	2.0	n.s.
β-Blocker (%)	4.3	5.4	n.s.
Diuretic (%)	3.3	3.0	n.s.
History of cardiovascular disease			
Angina pectoris (%)	1.3	2.0	n.s.
Old myocardial infarction (%)	0.7	0.3	n.s.
Chronic heart failure (%)	0.3	1.0	n.s.
Stroke (%)	2.6	2.7	n.s.
Left ventricular hypertrophy (%)	34.4	34.9	n.s.
Left ventricular mass (g)	171±52	173±43	n.s.
Risk factors			
Diabetes mellitus (%)	7.6	9.8	n.s.
Hyperlipidemia (%)	31.4	28.4	n.s.
Family history (%)	46.5	43.6	
Smoking (%)	26.5	23.1	n.s.

ACE, angiotensin converting enzyme.

Results

Baseline Characteristics of the Patients

On September 2004, 797 patients were enrolled and assigned to a valsartan (n=399) or amlodipine (n=398) treatment group. The baseline characteristics of the patients are shown in Table 4. The proportion of risk factors, such as diabetes and hyperlipidemia, as well as of the factors controlled by minimization (age, gender, blood pressure level, left ventricular hypertrophy, and history of cardiovascular disease) were equally distributed. There were no significant differences in the proportion of those who had taken antihypertensive agents or the kinds of the agents.

Change in Blood Pressure

At 6 months and 12 months after the start of treatment, both drugs significantly reduced blood pressure to the defined target level (135/85 mmHg) (Fig. 2). In the valsartan group, systolic blood pressure (SBP) changed from 157 to 139 mmHg at 6 months, and further decreased to 133 mmHg at 12 months (p<0.001, respectively). Diastolic blood pressure (DBP) changed from 92 to 83 mmHg at 6 months, and to 80 mmHg at 12 months (p<0.001, respectively). In the amlodipine group, SBP changed from 157 to 136 mmHg at 6 months, and further decreased to 134 mmHg at 12 months (p<0.001, respectively). DBP changed from 93 to 81 mmHg at 6 months (p<0.001), and to 80 mmHg at 12 months (p<0.001). Although the SBP level of the amlodipine group was significantly lower than that of the valsartan group (p=0.046) at 6 months, this difference in blood pressure level disappeared at 12 months. For DBP no significant difference was seen at 6 or 12 months after treatment.

Discussion

The VART study was designed to directly compare the treatment effects between of the ARB valsartan and the calcium channel blocker amlodipine. A large clinical trial with a similar protocol, the VALUE trial, was recently performed in Western countries (*15*). In this study, endpoints were compared under the condition that patients in both groups achieved the same blood pressure control. The results of the VALUE trial showed no significant difference for the primary

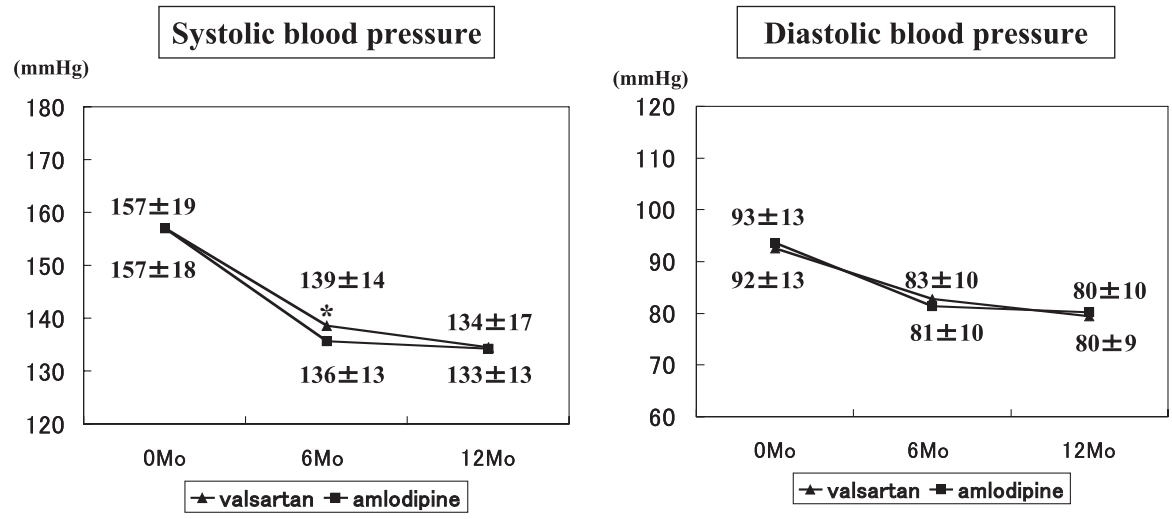

Fig. 2. *Change in blood pressure. In both treatment groups, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) significantly decreased at 6 months and 12 months after the start of treatment. Although the SBP level of the amlodipine group was significantly lower than that of the valsartan group (*p = 0.046) at 6 months, this difference disappeared at 12 months. Mo, month(s).*

endpoint, although the incidence of myocardial infarction and stroke was lower in the patients receiving amlodipine, and the incidence of heart failure was lower in those administered valsartan. Unfortunately, in the VALUE trial there was a significant difference in blood pressure favoring amlodipine throughout the trial, and especially in the early months. Previous studies and some meta-analyses have indicated that such differences in blood pressure can have major effects on the endpoints (*25*), and thus their presence may preclude valid comparison of the specific cardioprotective effect of valsartan. In the preliminary results of the VART study, the two drugs achieved an equivalent degree of control of both SBP and DBP at 12 months, although amlodipine realized a slightly greater reduction in SBP at 6 months. Therefore, the VART study will allow a more precise comparison between this ARB and CCB, and may confirm that ARBs have beneficial effects beyond their blood pressure–lowering effects.

In the VALUE trial (*16*), since most of the patients were recruited in Europe and the United Sates, Caucasians and African Americans were the major groups represented, and Asians were in the minority. In another valsartan trial, Val-HeFT (*13*, *14*), Asians made up only 2.8% of the total population. Therefore, the results of these trials are not necessarily extensible to the Japanese population. Racial differences have been identified in renin activity, the prevalence of salt sensitivity, and environmental factors (*26–29*). Several studies have administered valsartan in Japanese populations, such as the VALISH (*30*) trial and Jikei Heart Study (*31*). The VALISH study, which is still underway, is investigating the effects of different blood pressure target levels in elderly patients with hypertension, and the Jikei Heart study has demonstrated that addition of valsartan to a conventional treatment protocol reduced the incidence of cardiac events in high risk patients with hypertension. However, these studies did not directly compare the effects of varsartan and other antihypertensive agents. Discrepant treatment effects have often been reported among clinical trials evaluating drugs of the same class. Such discrepancies have often been explained by racial differences, such as the percentages of African Americans or Hispanics in the cohort. Generally, African Americans have high salt sensitivity and low renin activity, so diuretics are more effective than ACE inhibitors or ARBs in African American patients, while it is less effective for Caucasians. Thirty to forty percent of the Japanese population is estimated to be salt sensitive, and the proportion of those with high renin activity is thought to be low in Japanese compared with Caucasians. Moreover, the prevalence and incidence rate of cerebrovascular diseases and cardiovascular diseases in Japan is different from those in Western countries (*32*). So, it is uncertain whether the results of many of the large trials performed in Europe and the United States are actually applicable to the Japanese population.

In addition to evaluating the protection of cardiovascular events (primary endpoints) of ARB, the VART study will address several hypotheses promoted in the previous clinical and basic studies in the Japanese population. First, valsartan's effect on left ventricular hypertrophy will be evaluated annually by left ventricular mass or wall thickness using 2-dimensional echocardiography. Diastolic function will be also addressed by the *E*/*A* ratio and the deceleration time in the Doppler echocardiography. Since blocking AT1 receptor reportedly inhibits myocyte hypertrophy, we hypothesized that the volume reduction by ARBs would be greater than that by calcium channel blockers. Secondly, cardiac sympathetic

nerve activity will be evaluated annually by ^{123}I-MIBG single photon emission CT (SPECT) imaging. Abnormal findings in MIBG images, such as accumulation defect in the inferior wall or attenuated global uptake (low heart mediastinum uptake ratio, *H*/*M*) have been observed in patients with hypertension, especially in cases complicated with hypertrophy (*33*, *34*). We expect that control of blood pressure will recover the abnormality of MIBG images, and the improvement will be a sign of amelioration of left ventricular hypertrophy. In addition, patients with congestive heart failure or arrhythmia show abnormal MIBG uptake, and that is associated with poor prognosis or presence of ventricular tachycardia. If either of the therapeutic agents showed a significant recovery and lower cardiovascular event rate, the cardioprotection effect may be partly attributed to the recovery of sympathetic nerve activity of the heart. Thirdly, circadian rhythms of blood pressure will be surveyed in the participants. All patients are given a portable manometer so that the change in circadian rhythm of blood pressure can be evaluated. Since variance of blood pressure is associated with poor prognosis in patients with ischemic heart disease, the agents with less fluctuation of blood pressure may be desirable.

By combining the data on cardiovascular events with the results of the echocardiographic, radionuclide imaging and blood/urine studies, the VART study will provide mechanistic insights into the clinical outcomes and treatment effect in the trial. If optimal blood pressure control is obtained in both the valsartan and amlodipine groups, we will be able to propose antihypertensive medicine beyond the reduction of blood pressure for the Japanese population.

References

1. 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: the JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
2. Wing LM, Reid CM, Ryan P, *et al*: A comparison of outcomes with angiotensin-converting–enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003; **348**: 583–592.
3. Dahlof B, Devereux RB, Kjeldsen SE, *et al*: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 995–1003.
4. Lindholm LH, Ibsen H, Dahlof B, *et al*: Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 1004–1010.
5. Viberti G, Wheeldon NM: Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure–independent effect. *Circulation* 2002; **106**: 672–678.
6. Wright JT Jr, Bakris G, Greene T, *et al*: Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002; **288**: 2421–2431.
7. Derosa G, Cicero AF, Murdolo G, Ciccarelli L, Fogari R: Comparison of metabolic effects of orlistat and sibutramine treatment in type 2 diabetic obese patients. *Diabetes Nutr Metab* 2004; **17**: 222–229.
8. Ishimitsu T, Kameda T, Akashiba A, *et al*: Effects of valsartan on the progression of chronic renal insufficiency in patients with nondiabetic renal diseases. *Hypertens Res* 2005; **28**: 865–870.
9. Pitt B, Segal R, Martinez FA, *et al*: Randomised trial of losartan *versus* captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997; **349**: 747–752.
10. Pitt B, Poole-Wilson P, Segal R, *et al*: Effects of losartan *versus* captopril on mortality in patients with symptomatic heart failure: rationale, design, and baseline characteristics of patients in the Losartan Heart Failure Survival Study—ELITE II. *J Card Fail* 1999; **5**: 146–154.
11. Pitt B, Poole-Wilson PA, Segal R, *et al*: Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; **355**: 1582–1587.
12. Dickstein K, Kjekshus J: Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet* 2002; **360**: 752–760.
13. Cohn JN, Tognoni G, Glazer RD, Spormann D, Hester A: Rationale and design of the Valsartan Heart Failure Trial: a large multinational trial to assess the effects of valsartan, an angiotensin-receptor blocker, on morbidity and mortality in chronic congestive heart failure. *J Card Fail* 1999; **5**: 155–160.
14. Cohn JN, Tognoni G: A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345**: 1667–1675.
15. Weber MA, Julius S, Kjeldsen SE, *et al*: Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. *Lancet* 2004; **363**: 2049–2051.
16. Pfeffer MA, McMurray JJ, Velazquez EJ, *et al*: Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349**: 1893–1906.
17. Hansson L, Lindholm LH, Ekbom T, *et al*: Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999; **354**: 1751–1756.
18. Tuomilehto J, Rastenyte D, Birkenhager WH, *et al*, Systolic Hypertension in Europe Trial Investigators: Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. *N Engl J Med* 1999; **340**: 677–684.
19. Liu L, Wang JG, Gong L, Liu G, Staessen JA, Systolic Hypertension in China (Syst-China) Collaborative Group: Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. *J Hypertens* 1998; **16**: 1823–1829.
20. Kuwajima I, Kuramoto K, Ogihara T, *et al*: Tolerability and

safety of a calcium channel blocker in comparison with a diuretic in the treatment of elderly patients with hypertension: secondary analysis of the NICS-EH. *Hypertens Res* 2001; **24**: 475–480.
21. Kloner RA, Sowers JR, DiBona GF, Gaffney M, Wein M, The Amlodipine Cardiovascular Community Trial Study Group: Sex- and age-related antihypertensive effects of amlodipine. *Am J Cardiol* 1996; **77**: 713–722.
22. Spratt KA: Sex- and age-related antihypertensive effects of amlodipine. *Am J Cardiol* 1997; **79**: 843–844.
23. Lakshman MR, Reda DJ, Materson BJ, Cushman WC, Freis ED, Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents: Diuretics and beta-blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. *Arch Intern Med* 1999; **159**: 551–558.
24. Guidelines Subcommittee: 1999 World Health Organization–International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens* 1999; **17**: 151–183.
25. Staessen JA, Wang JG, Thijs L: Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001; **358**: 1305–1315.
26. Douglas JG, Thibonnier M, Wright JT Jr: Essential hypertension: racial/ethnic differences in pathophysiology. *J Assoc Acad Minor Phys* 1996; **7**: 16–21.
27. Flack JM, Ensrud KE, Mascioli S, *et al*: Racial and ethnic modifiers of the salt-blood pressure response. *Hypertension* 1991; **17**: I115–I121.
28. Mtabaji JP, Moriguchi Y, Nara Y, Mizushima S, Mano M, Yamori Y: Ethnic differences in salt sensitivity: genetic or environmental factors? *Clin Exp Pharmacol Physiol Suppl* 1992; **20**: 65–67.
29. Rutledge DR: Race and hypertension. What is clinically relevant? *Drugs* 1994; **47**: 914–932.
30. Ogihara T, Saruta T, Matsuoka H, *et al*: Valsartan in elderly isolated systolic hypertension (VALISH) study: rationale and design. *Hypertens Res* 2004; **27**: 657–661.
31. Mochizuki S, Dahlof B, Shimizu M, *et al*: Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. *Lancet* 2007; **369**: 1431–1439.
32. Khor GL: Cardiovascular epidemiology in the Asia-Pacific region. *Asia Pac J Clin Nutr* 2001; **10**: 76–80.
33. Kuwahara T, Hamada M, Hiwada K: Direct evidence of impaired cardiac sympathetic innervation in essential hypertensive patients with left ventricular hypertrophy. *J Nucl Med* 1998; **39**: 1486–1491.
34. Sakata K, Shirotani M, Yoshida H, Kurata C: Cardiac sympathetic nervous system in early essential hypertension assessed by ^{123}I-MIBG. *J Nucl Med* 1999; **40**: 6–11.