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ORIGINAL ARTICLE

# Effects of valsartan and amlodipine on cardiorenal protection in Japanese hypertensive patients: the Valsartan Amlodipine Randomized Trial

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**The Valsartan Amlodipine Randomized Trial, a multicenter, prospective, randomized, open-labeled, blinded-end point trial, was designed to compare the beneficial effects of the angiotensin II receptor blocker valsartan and the calcium channel blocker amlodipine on cardiovascular events in Japanese essential hypertensive patients. The primary end point was a composite of all-cause death, sudden death, cerebrovascular death, cardiac events, vascular events and renal events. The secondary endpoints were effects on left ventricular hypertrophy, cardiac sympathetic nerve activity and renal function. A total of 1021 patients were enrolled in the present trial. The mean follow-up period was 3.4 years. There were no significant differences in blood pressure (BP) levels between the valsartan group and the amlodipine group throughout the trial. There was no significant difference in the primary endpoint between the two groups (hazard ratio: 1.0, $P$=0.843). No difference in any event category of the primary endpoint was noted for either group. However, we observed a significant reduction of left ventricular mass index, as determined by echocardiography, in the valsartan group compared with the amlodipine group. We also observed a significant decrease in cardiac sympathetic nerve activity in the valsartan group but not in the amlodipine group. Moreover, there was a significant reduction in the urinary albumin to creatinine ratio in the valsartan group but not in the amlodipine group. Therefore, although BP levels were well controlled and remained equal in the two groups, valsartan had more protective effects on the heart and kidney than amlodipine in Japanese hypertensive patients.**
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**Keywords:** angiotensin II receptor blocker; calcium channel blocker; clinical trial; left ventricular hypertrophy

## INTRODUCTION

Hypertension is the most common disease in Japan. Antihypertensive agents, which inhibit the renin–angiotensin system, have been known to have beneficial effects on cardiovascular and renal functions that extend beyond their reduction of blood pressure (BP). Many clinical randomized trials have shown the beneficial effects of angiotensin II receptor blockers (ARBs) on cardiovascular mortality and morbidity in patients with hypertension, heart failure, stroke or end-stage renal disease.[1–6] ARBs and calcium channel blockers (CCBs) have effective BP-lowering effects and are widely used in Japan. Although the beneficial effects of ARBs on high-risk hypertensive patients in Japan were recently demonstrated, few trials have been performed to compare the efficacy of ARBs compared with CCBs in preventing cardiovascular events. It is important to investigate the differences in effects of these antihypertensive agents to determine the optimal approach to treatment.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was designed to investigate whether valsartan could reduce cardiac morbidity and mortality more effectively than amlodipine in hypertensive patients at high cardiovascular risk who were treated with the same approach to BP control in Europe and the United States.[7] BP was reduced by both treatments, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period. Furthermore, there was no significant difference between the two groups in the primary composite endpoint. It is possible that an unequal reduction of BP in both groups obscured the favorable effects of valsartan. Owing to the differential response to therapeutic agents and the variation in event rates of cardiovascular disease between Asian and Western populations, the data from trials performed in other countries are not necessarily applicable to Japanese patients. In this study, we aimed to compare the beneficial effects related to cardiovascular events exerted by valsartan compared with amlodipine in Japanese low-risk patients with mild to moderate hypertension.

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## METHODS

### Study population

Inclusion criteria in the Valsartan Amlodipine Randomized Trial (VART) included age ⩾30 years and recent diagnosis of hypertension (systolic ⩾140 mm Hg or diastolic BP ⩾90 mm Hg, with the patient in a sitting position at a clinic) or previous treatment with antihypertensive agents. The exclusion criteria were secondary hypertension, serious valvular disease or congenital heart disease requiring operative treatment, hypertrophic or dilated cardiomyopathy, percutaneous transluminal coronary angioplasty or coronary artery bypass graft within 6 months, stroke within the preceding 3 months and serious renal dysfunction (serum creatinine >3 mg per 100 ml). The detailed inclusion criteria and exclusion criteria have been described previously.[8] We enrolled 1021 patients with mild to moderate hypertension between July 2002 and February 2006. The VART was closed on March 2009.

### Study design

The VART was a multicenter, prospective, randomized, open-labeled, blinded-end point (PROBE) design. The trial sought to compare two antihypertensive treatment strategies involving 92 medical facilities in Japan. The ethics committee at Chiba University Graduate School of Medicine approved the VART protocol, which adhered to the principles of the Declaration of Helsinki. The rationale and design of the VART have been published elsewhere.[8] The random assignment of patients, data entry and data collection were performed at the homepage originally produced for the VART, and the participants were assigned randomly to either the valsartan group or the amlodipine group with the minimization[8] method after informed consent was obtained. The BP of each patient was measured with the individual in a sitting position with the use of a validated mercury sphygmomanometer at a clinic. The mean of three measurements was calculated and recorded. We aimed to control BP to <140/90 mm Hg in both treatment groups. The first dose of valsartan or amlodipine was 80 or 5 mg per day, respectively. When the patient's BP did not reach the BP target, the doses were increased to 160 or 10 mg per day, respectively. α-Blockers, β-blockers or diuretics were then added when necessary, as described previously.[8] If the patients were already receiving antihypertensive treatment before enrollment, their medication was changed to either 80 mg per day valsartan or 5 mg per day amlodipine without a run-in period. This trial has been registered at http://www.umin.ac.jp/ctr/index.htm (identifier C000000074).

### Outcome measurements

The primary endpoint was a composite of all-cause death, sudden death, cerebrovascular events (new occurrence or recurrence of a stroke or transient ischemic attack), cardiac events (new occurrence or recurrence of acute myocardial infarction or angina pectoris, or new occurrence or exacerbation of heart failure), vascular events (dissecting aneurysm of the aorta or hospitalization due to arteriosclerotic occlusion of a peripheral artery) and renal events (doubling of serum creatinine or end-stage renal disease), as described previously.[8] The secondary endpoints were effects on left ventricular hypertrophy (LVH), cardiac sympathetic nerve activity, blood norepinephrine level, renal function and incidence of recent-onset diabetes, as described previously.[8] After patient enrollment, routine laboratory tests were performed every 6 months. Plasma norepinephrine concentration and urinary albumin to creatinine ratio (UACR) were also measured every 12 months. Echocardiography was performed to examine the change in left ventricular mass index (LVMI) every 12 months. Left ventricular mass was measured using M-mode guided echocardiography, according to the formula introduced by Devereux *et al.*[9]: $0.80\times\{1.04\times[(\text{septal thickness}+\text{LV internal diameter})^3-(\text{LV internal diameter})^3]\}+0.6$ g; LVMI was calculated with body surface area correction. $^{123}$I-metaiodobenzylguanidine (MIBG) cardiac imaging was performed at the participating medical institutes. Recent-onset diabetes was diagnosed if treatment with hypoglycemic agents had been initiated and/or the plasma glycosylated hemoglobin concentration exceeded 6.5% during the trial.

### Statistical analysis

On the basis of previous studies, the incidence of cardiovascular events with amlodipine was estimated to be 5%.[10,11] We estimated that the incidence of cardiovascular events would be 40% lower in patients treated with valsartan than in those treated with amlodipine. Therefore, 1280 patients would be needed in each group (2560 in total), with a two-sided α-level of 0.05 and 90% power. Assuming a dropout rate of 15%, 3000 patients (1500 in each group) were considered to be required for the study. All primary analyses were performed utilizing an intention-to-treat approach.

We estimated hazard ratios and 95% confidence intervals (CI) to compare the treatment groups. Hazard ratios were calculated and adjusted for age, gender, smoking, diabetes and hypercholesterolemia with Cox's proportional hazard model. Statistical analysis of event rates over time was presented as Kaplan–Meier plots for specific treatment arms. The differences in the frequency of adverse events were analyzed with $\chi^2$-tests. To analyze changes in LVMI, we used repeated-measurement two-way analysis of variance; *P*-values were computed by the Newman–Keuls test for intergroup comparisons at the end of the trial. Statistical analysis of the results to evaluate changes in plasma norepinephrine concentration, the heart to mediastinum (H/M) ratio on delayed imaging of $^{123}$I-MIBG and UACR were estimated with regression model analysis. All the statistical tests were two sided, with an α-level of 0.05%.

### Study management

Data related to the primary and secondary endpoints and adverse events were collected at various time points, and interim analyses were performed every year after the initiation of the study. An independent endpoint committee, which was blinded to any information related to group allocations, evaluated each event and classified the results. An independent data and safety monitoring board reviewed all reports from the endpoint committee and advised the designers of the trial with regard to safety. A steering committee was responsible for the study design and scientific execution of the study. Data analyses were performed in the Department of Clinical Epidemiology, Osaka City University Graduate School, which was independent of the group that implemented the study.

## RESULTS

### Baseline characteristics

A total of 1021 patients were enrolled in the VART. Of those patients, 510 patients were assigned to the valsartan group, and 511 patients were assigned to the amlodipine group. As shown in Figure 1, 1021 randomly assigned patients were included in the analysis, and 16 patients (1.6%) were lost to follow-up. Table 1 shows the baseline characteristics of the patients. There were no significant differences between the two groups in baseline characteristics such as age, gender, body mass index, coronary artery disease, diabetes mellitus, hyperlipidemia, LVH and antihypertensive treatment before enrollment. Table 2 presents medications at baseline. There were no significant differences between the two groups in medications at baseline.

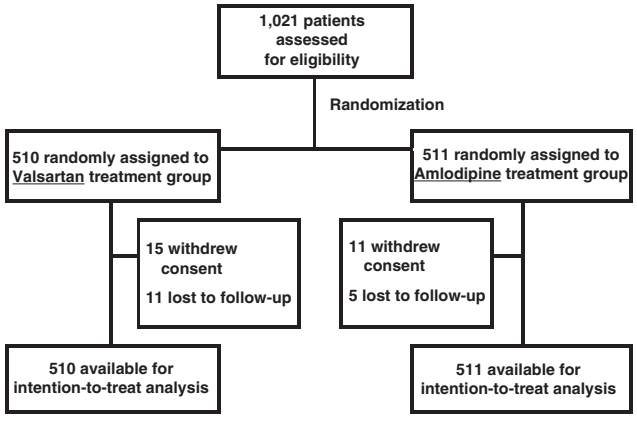


**Figure 1** Trial profile.

**Table 1 Baseline characteristics of patients**

| | *Valsartan (n=510)* | *Amlodipine (n=511)* |
|---|---|---|
| Age (years) | 60 ± 12 | 60 ± 11 |
| Men | 290 (56.9%) | 294 (57.5%) |
| Body mass index | 25 ± 4 | 24 ± 3 |
| Current smoker | 108 (21.2%) | 107 (20.9%) |
| Coronary artery disease | 18 (3.5%) | 17 (3.3%) |
| Heart failure | 1 (0.2%) | 7 (1.4%) |
| Diabetes mellitus | 37 (7.3%) | 46 (9.0%) |
| Hyperlipidemia | 136 (26.7%) | 145 (28.4%) |
| Left ventricular hypertrophy | 117 (22.9%) | 119 (23.3%) |
| Antihypertensive treatment before enrollment | 235 (46.1%) | 233 (45.6%) |
| Systolic blood pressure (mm Hg) | 158 ± 19 | 158 ± 18 |
| Diastolic blood pressure (mm Hg) | 93 ± 13 | 94 ± 13 |
| Ejection fraction | 63 ± 9 | 63 ± 9 |
| HDL-cholesterol (mg per 100 ml) | 58 ± 27 | 58 ± 16 |
| LDL-cholesterol (mg per 100 ml) | 127 ± 34 | 124 ± 33 |
| Triglyceride (mg per 100 ml) | 139 ± 103 | 147 ± 90 |
| Fasting plasma glucose | 106 ± 24 | 107 ± 25 |
| HbA1c (%) | 5.4 ± 0.9 | 5.4 ± 1.2 |
| Serum creatinine (mg per 100 ml) | 0.76 ± 0.18 | 0.76 ± 0.21 |

Abbreviations: HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Values are number (%) or mean ± s.d.

**Table 2 Medication at baseline**

| | *Valsartan (n=510) (%)* | *Amlodipine (n=511) (%)* |
|---|---|---|
| ACE inhibitors | 29 (6) | 22 (4) |
| Calcium channel blockers | 138 (27) | 135 (26) |
| α-Blockers | 4 (1) | 7 (1) |
| β-Blockers | 16 (3) | 22 (4) |
| Diuretics | 12 (2) | 13 (3) |
| ARBs | 47 (9) | 51 (10) |
| Statins | 56 (11) | 50 (10) |
| Fibrates | 8 (2) | 4 (1) |
| Oral hypoglycemic agents | 16 (3) | 16 (3) |
| Anticoagulation agents | 9 (2) | 16 (3) |

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers.

**Table 3 Ratios of the patients with monotherapy**

| | *6 months (%)* | *12 months (%)* | *24 months (%)* | *36 months (%)* |
|---|---|---|---|---|
| *Valsartan* | | | | |
| 80 mg | 64.8 | 60.4 | 58.2 | 55.9 |
| 160 mg | 12.9 | 13.1 | 9.7 | 13.3 |
| *Amlodipine* | | | | |
| 5 mg | 76.7 | 72.4 | 68.3 | 70.4 |
| 10 mg | 11.8 | 9.7 | 11.3 | 11.3 |

**Table 4 Adverse effects**

| | *Valsartan (n=510) number (%)* | *Amlodipine (n=511) number (%)* | P-*value* |
|---|---|---|---|
| Dizziness | 4 (0.8) | 2 (0.4) | 0.41 |
| Headache | 4 (0.8) | 0 (0.0) | 0.05 |
| Drowsiness | 1 (0.2) | 0 (0.0) | 0.32 |
| Hot flash | 1 (0.2) | 2 (0.4) | 0.56 |
| Palpitations | 1 (0.2) | 0 (0.0) | 0.16 |
| Hypotemperature | 1 (0.2) | 0 (0.0) | 0.32 |
| Sweat | 1 (0.2) | 0 (0.0) | 0.32 |
| Edema | 1 (0.2) | 3 (0.6) | 0.32 |
| Hypotension | 0 (0.0) | 0 (0.0) | |
| Abdominal fullness | 1 (0.2) | 0 (0.0) | 0.32 |
| Gastrointestinal bleeding | 1 (0.2) | 0 (0.0) | 0.32 |
| Heart burn | 1 (0.2) | 0 (0.0) | 0.32 |
| Malaise | 1 (0.2) | 0 (0.0) | 0.32 |
| Rash | 4 (0.8) | 0 (0.0) | 0.05 |
| Alopecia | 1 (0.2) | 0 (0.0) | 0.32 |
| Total | 25 (4.9) | 7 (1.4) | $P<0.001$ |

### Follow-up and adherence to treatment

The mean follow-up period was 3.4 years. The study accumulated 3390 person-years of follow-up (1742 person-years and 1648 person-years for the valsartan- and the amlodipine-based regimens, respectively). During follow-up, it was determined that more than 99% of patients received the appropriate drugs. At the end of the trial, the percentages of the patients who received only valsartan or amlodipine were 69.2% in the valsartan-based regimen and 81.7% in the amlodipine-based regimen, respectively (Table 3). Additional treatments in both groups were mainly diuretics, β-blockers and α-blockers. The average number of antihypertensive drugs taken during the study was slightly higher in the valsartan group than in the amlodipine group. The reported adverse events are summarized in Table 4. Few adverse events were recognized in either the valsartan group (4.9%) or the amlodipine group (1.4%).

### Blood pressure

Figure 2 shows that BP was reduced substantially in both treatment groups. The mean BP in the valsartan group was 158 ± 19/93 ± 13 mm Hg at baseline and 135 ± 13/80 ± 10 mm Hg after 3 years. The mean BP in the amlodipine group was 158 ± 18/94 ± 13 mm Hg at baseline and 135 ± 14/80 ± 10 mm Hg after 3 years. Both systolic and diastolic BPs were well controlled in both groups, and there were no significant differences between the groups in BP levels throughout the trial. The target BP (both systolic <140 mm Hg and diastolic BPs <90 mm Hg) was achieved in 261 (51%) patients in the valsartan group and 280 (55%) patients in the amlodipine group.

### Primary endpoint

The number of patients who reached a primary endpoint, which was a composite of all-cause death, sudden death, cerebrovascular events, cardiac events, vascular events and renal events, during the follow-up period was quite small. Primary events occurred in 21 (4.1%) patients in the valsartan group and 21 (4.1%) patients in the amlodipine group. There was no significant difference between the two groups in the primary composite endpoint (hazard ratio: 1.0; 95% confidence interval (CI): 0.57–1.97; $P=0.843$) (Figure 3). Table 5 compares the

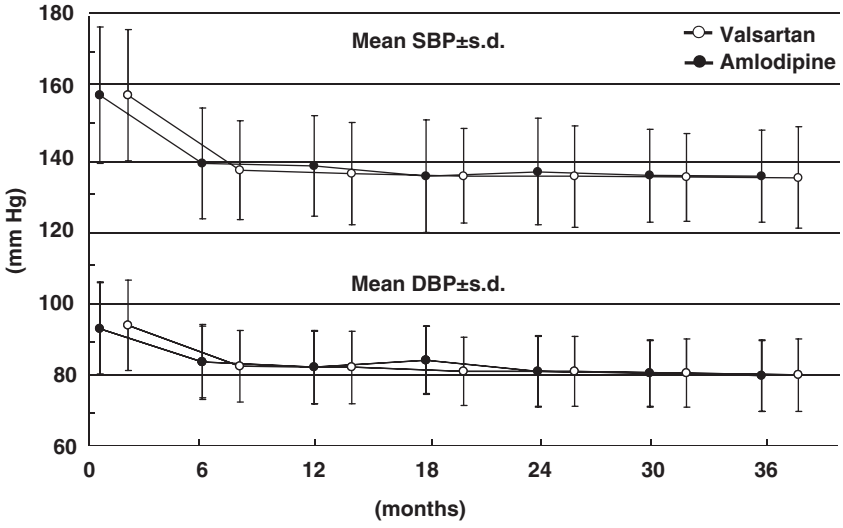


**Figure 2** Changes in systolic (SBP) and diastolic BPs (DBP). SBP and DBP during the follow-up period of the trial. Data are expressed as the mean ± s.d. *P*=NS.

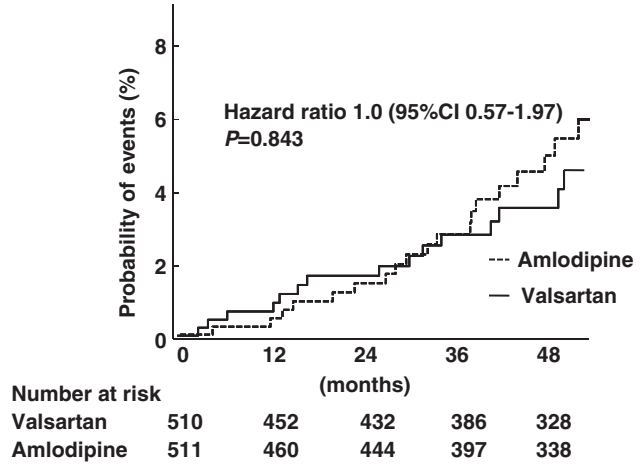


**Figure 3** Kaplan–Meier curves for the primary composite endpoint.

primary endpoint for both groups. The first event for each category was counted. There was no significant difference between the two groups in the rate of each primary endpoint category. Stroke, which was the most frequent event, occurred in 10 patients (2.0%) in the valsartan group and 10 patients (2.0%) in the amlodipine group. Heart failure occurred in three patients (0.6%) and in one patient (0.2%), respectively.

### Secondary endpoints

The secondary endpoints were effects on LVH, cardiac sympathetic nerve activity, blood norepinephrine level, renal function and incidence of recent-onset diabetes. We measured changes in LVMI from baseline by echocardiography to evaluate LVH. At 12 months, we observed similar decreases in LVMI in both the valsartan group and the amlodipine group. However, we observed a significant reduction in LVMI in the valsartan group compared with the amlodipine group at 36 months (valsartan group, 171.6 g m$^{-2}$ at baseline and 157.8 g m$^{-2}$ at 36 months; amlodipine group, 174.0 g m$^{-2}$ at baseline and 171.0 g m$^{-2}$ at 36 months; $P<0.05$) (Figure 4). Figure 5 shows the percent change in plasma norepinephrine concentration from baseline. At 36 months, we observed a significant decrease in the percent change in norepinephrine levels in the valsartan group but not in the amlodipine group ($P<0.01$). We measured H/M ratios by delayed imaging of $^{123}$I-MIBG to evaluate cardiac sympathetic nerve activity. Figure 6 shows the percent change in H/M ratio relative to baseline. At 24 months, we observed a significant increase in H/M ratio only in the valsartan group ($P<0.0001$). Figure 7 demonstrates the percent change in UACR relative to baseline, which indicates early-stage renal dysfunction. At 36 months, we observed a significant decrease in UACR in the valsartan group but not in the amlodipine group (−61.3% and 34.9%, respectively, $P<0.0001$). Table 6 shows the incidence of recent-onset diabetes. During the follow-up period, the incidence of new-onset diabetes was 1.7% in the valsartan group and 3.4% in the amlodipine group. There was a trend toward less frequent recent-onset diabetes in the valsartan group, but this did not reach statistical significance.

## DISCUSSION

The VART was designed to compare the ARB valsartan and the CCB amlodipine in terms of efficacy in preventing cardiovascular events in Japanese hypertensive patients. BP levels were well controlled and remained similar in the valsartan group and the amlodipine group throughout the trial. There was no significant difference between the two groups in the primary endpoints. However, in the valsartan group, significant improvements in secondary endpoints such as LVH, cardiac sympathetic nerve activity and UACR were observed.

Recent large-scale clinical trials have tested which types of antihypertensive agents have beneficial effects in reducing the risk for cardiovascular events. In the JIKEI Heart Study and the KYOTO HEART Study, the authors aimed to assess the effect of the ARB valsartan in addition to conventional treatment for high-risk hypertension in Japan.[12,13] There were no significant differences in BP levels between the valsartan add-on group and the conventional treatment group in either study. However, compared with the conventional treatment group without ARBs, the valsartan add-on group included fewer patients who reached the primary endpoint, which included stroke, angina pectoris and heart failure in the JIKEI Heart Study and stroke and angina pectoris in the KYOTO HEART Study.[12,13] The results of these studies demonstrate that ARBs might exert superior

**Table 5 Comparisons of the primary composite endpoint**

| *Endpoint* | *Valsartan* (n=*510) (%)* | *Amlodipine* (n=*511) (%)* | *Hazard ratio (95% CI)* | P-*value* |
|---|---|---|---|---|
| Primary endpoint | 21 (4.1) | 21 (4.1) | 1.0 (0.6–2.0) | 0.8432 |
| Sudden death | 0 (0.0) | 0 (0.0) | | |
| Stroke | 10 (2.0) | 10 (2.0) | 1.0 (0.4–2.4) | 0.8445 |
| AMI | 2 (0.4) | 1 (0.2) | 2.0 (0.2–22.0) | 0.6673 |
| Angina pectoris | 2 (0.4) | 2 (0.4) | 1.0 (0.1–0.7) | 0.9313 |
| Heart failure | 3 (0.6) | 1 (0.2) | 3.0 (0.3–28.8) | 0.7331 |
| Transition to dialysis or doubling of serum creatinine levels | 2 (0.4) | 4 (0.8) | 0.5 (0.1–2.72) | 0.5448 |
| Transition to dialysis | 0 (0.4) | 1 (0.2) | | |
| Doubling of serum creatinine levels | 2 (0.4) | 3 (0.6) | 0.7 (0.1–3.9) | 0.8976 |
| All-cause mortality | 2 (0.4) | 3 (0.6) | 0.7 (0.1–4.0) | 0.8865 |

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval.

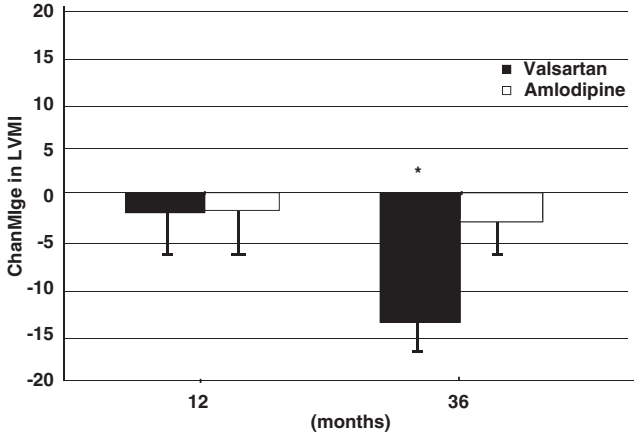


**Figure 4** Changes in left ventricular mass index (LVMI) (secondary endpoint). Changes in LVMI from baseline were significantly greater in the valsartan group at 36 months. *$P<0.05$ compared with amlodipine group at 36 months.

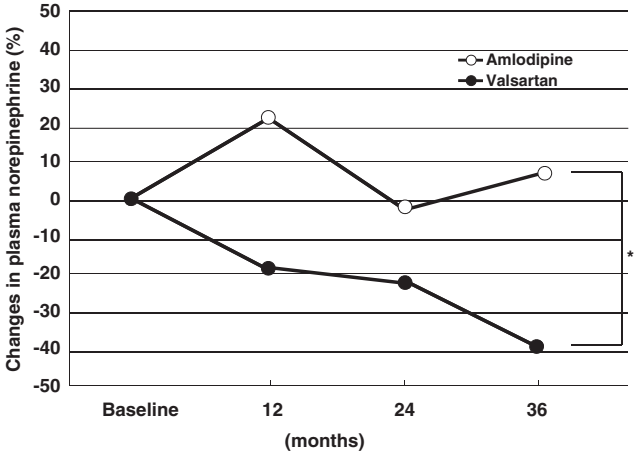


**Figure 5** Changes in plasma norepinephrine (secondary endpoint). Changes in plasma norepinephrine relative to baseline were significantly decreased in the valsartan group. *$P<0.01$ between groups.

cardiovascular protection as compared with other classes of antihypertensive drugs. Trials comparing the effects of ARBs and CCBs have also been performed. In the VALUE trial, the primary composite endpoint of cardiac morbidity and mortality did not differ between the valsartan group and the amlodipine group in hypertensive patients with high cardiovascular risk.[7] The CASE-J trial was designed to compare the long-term effects of the ARB candesartan and the CCB amlodipine on the prevention of cardiovascular events in high-risk Japanese hypertensive patients. The trial demonstrated no statistically significant differences between the two groups in the primary cardiovascular endpoint.[14] However, in these trials, the achieved BP was not equal between the two treatment groups. Furthermore, amlodipine-based therapy was significantly more effective in reducing BP, especially during the early phase of treatment. Therefore, it remains unclear whether there are differences between ARBs and CCBs in the beneficial effects on cardiovascular diseases. There are some differences between the VART and other trials in terms of the baseline characteristics of patients. In the VART, the proportions of patients with coronary artery disease, heart failure, diabetes mellitus and hyperlipidemia were 3.4, 0.8, 8.1 and 27.5%, respectively. The mean age of the patients in the VART was 60 years. These data suggest that the patients enrolled in the VART had fewer cardiovascular risk factors and were younger than those in other studies. The VART seems to be unique in its enrollment of patients at low risk for hypertension. LVH is an independent cardiovascular risk factor in the general population, especially among hypertensive patients. The Framingham Heart Study reported the relationship between an increase in left ventricular mass, as determined by echocardiography, and cardiovascular events.[15,16] A greater reduction in left ventricular mass has been associated with a lower incidence of cardiovascular events in hypertensive patients.[17,18] Activation of the renin–angiotensin system and an increase in the level of angiotensin II induce cardiomyocyte hypertrophy.[19] Increased plasma angiotensin II has been linked to left ventricular mass independently of BP.[20] Therefore, ARBs seem to be promising agents that could inhibit the progression of LVH. In experimental studies, valsartan showed better effects on LVH than amlodipine; these effects were mediated by the reduction of reactive oxygen species.[21]

Cardiac sympathetic nerve activity can be assessed through the use of $^{123}$I-MIBG, an analog of norepinephrine. In particular, the H/M ratio on delayed imaging of $^{123}$I-MIBG is used to evaluate cardiac sympathetic nerve activity in various diseases such as heart failure, diabetes mellitus and hypertension. It has been reported that heart failure patients with decreased H/M ratios upon delayed imaging of $^{123}$I-MIBG have worse prognoses than those with normal H/M

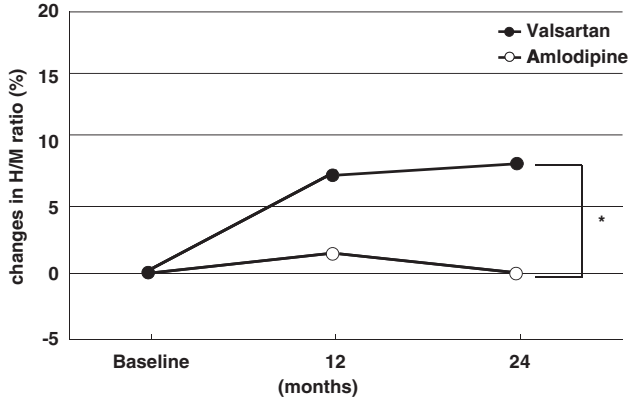


**Figure 6** Changes in the heart to mediastinum (H/M) ratios ($^{123}$I-metaiodobenzylguanidine ($^{123}$I-MIBG)) (secondary endpoint). H/M ratios by delayed imaging were significantly improved in the valsartan group. $*P<0.0001$ between groups.

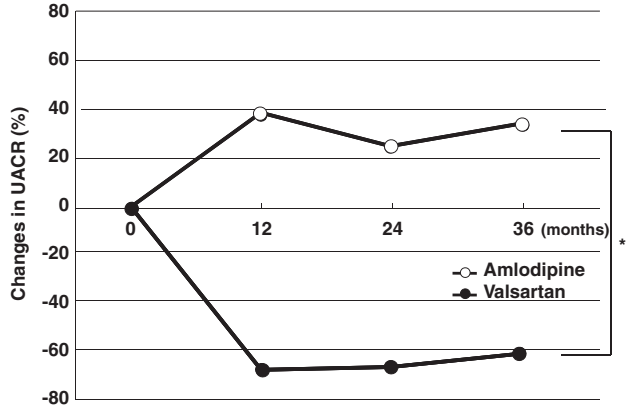


**Figure 7** Changes in urinary albumin to creatinine ratio (UACR) (secondary endpoint). Changes in UACR relative to baseline were significantly decreased in the valsartan group. $*P<0.0001$ between groups.

**Table 6 New diagnosis of diabetes (secondary endpoint)**

| | *Diabetes at baseline* | | *New-onset* | *Odds ratio* |
|---|---|---|---|---|
| | *+* | *–* | *diabetes mellitus* | *(95% CI)* |
| Valsartan | 37 | 473 | 8/473 (1.7%) | |
| | | | | 0.47 (0.20–1.11) |
| Amlodipine | 46 | 465 | 16/465(3.4%) | |

Abbreviation: CI, confidence interval.

ratios.[22] The H/M ratio was significantly lower in the hypertensive patients than in the normotensive and borderline hypertensive patients.[23] In addition to mechanical stress, increased sympathetic nerve activity has been proposed as one of the important factors in the development and progression of LVH. Thus, MIBG cardiac imaging might be useful in identifying hypertensive patients at risk of developing LVH in the early stages of the development of hypertension. In our study, the H/M ratio was significantly improved at 24 months in the valsartan-treated group but not in the amlodipine-treated group. Plasma norepinephrine levels were significantly reduced only in the valsartan group. Another study also reported that amlodipine did not affect plasma norepinephrine levels or renin activity.[24] ARBs are known to reduce central sympathetic nerve activity and enhance the sympathoinhibitory response to baroreceptor stimulation. Our results suggest that valsartan reduces cardiac sympathetic nerve activity and plasma norepinephrine levels by blocking the renin–angiotensin system.

Reduction of urinary albumin induces a decrease in cardiovascular events in patients with hypertension and type 2 diabetes.[25,26] Epidemiological data show that high levels of UACR are associated with increased cardiovascular mortality.[27–29] In the subanalysis of the Losartan Intervention For End-point reduction (LIFE) study and the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, UACR was reported to be a predictor of all causes of mortality in the general population.[25,30] Increased UACR predicts high risk for cardiovascular morbidity and mortality among hypertensive patients with LVH.[31] Furthermore, inhibition of the renin–angiotensin system has been shown to normalize estimated glomerular hydraulic pressure and glomerular permeability properties, as well as restore the charge selectivity of the glomerular membrane.[32–35] In the MicroAlbuminuria Reduction With VALsartan (MARVAL) study, for the same degree of BP reduction, valsartan lowered UACR more effectively than amlodipine in patients with type 2 diabetes and microalbuminuria.[36] The Shiga Microalbuminuria Reduction Trial (SMART) also showed that after 24 weeks of treatment, microalbuminuria decreased 36% in the valsartan group and increased 30% in the amlodipine group.[37]

In this study, we enrolled low-risk patients with mild to moderate hypertension. To date, many trials have been designed to evaluate the effects of antihypertensive agents on high-risk hypertensive patients. Although it is important to find the optimal treatment for high-risk hypertensive patients, it is also necessary to examine the appropriate treatment for low-risk patients with mild to moderate hypertension. However, there are few studies that have investigated the effects of the treatment on those patients. In the VART, the proportion of the patients treated with valsartan or amlodipine monotherapy was large, which allowed a valid comparison of valsartan and amlodipine. Our trial has limitations. As the number of the enrolled patients was smaller than first planned, it is possible that the follow-up period was too short to demonstrate statistical significance. In conclusion, valsartan treatment did not differ significantly from the amlodipine treatment among patients with similar BPs, as measured by the number of patients who reached a primary endpoint. Nonetheless, valsartan showed beneficial effects on heart and kidney function in Japanese hypertensive patients.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## APPENDIX

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## RETRACTION

# Retraction: Effects of valsartan and amlodipine on cardiorenal protection in Japanese hypertensive patients: the Valsartan Amlodipine Randomized Trial

**Hiroya Narumi, Hiroyuki Takano, Satoshi Shindo, Miwa Fujita, Hiroshi Mizuma, Yoichi Kuwabara and Issei Komuro on behalf of the VART Investigators**

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The authors have indicated to the journal that this paper should be retracted as it contains honest errors, which cannot be corrected accurately by the existing data. After careful consideration, *Hypertension Research* editorial committee formally retracts this paper with agreement of the authors.

This article has published corrigenda in Volume 34, Issue 1, page 152, doi:10.1038/hr.2010.219 and Volume 36, Issue 7, page 655, doi:10.1038/hr.2013.54. These corrigenda are retracted together with the Original Article.