

# Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART Study

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## Aims

The objective was to assess the add-on effect of valsartan on top of the conventional treatment for high-risk hypertension in terms of the morbidity and mortality.

## Methods and results

The KYOTO HEART Study was of a multicentre, Prospective Randomised Open Blinded Endpoint (PROBE) design, and the primary endpoint was a composite of fatal and non-fatal cardiovascular events (clinicaltrials.gov NCT00149227). A total of 3031 Japanese patients (43% female, mean 66 years) with uncontrolled hypertension were randomized to either valsartan add-on or non-ARB treatment. Median follow-up period was 3.27 years. In both groups, blood pressure at baseline was 157/88 and 133/76 mmHg at the end of study. Compared with non-ARB arm, valsartan add-on arm had fewer primary endpoints (83 vs. 155; HR 0.55, 95% CI 0.42–0.72,  $P = 0.00001$ ).

## Conclusion

Valsartan add-on treatment to improve blood pressure control prevented more cardiovascular events than conventional non-ARB treatment in high-risk hypertensive patients in Japan. These benefits cannot be entirely explained by a difference in blood pressure control.

## Keywords

High-risk hypertension • Angiotensin receptor blockers • Cardiovascular mortality–morbidity • Valsartan

## Introduction

Cardiovascular disease is the leading cause of mortality worldwide.<sup>1</sup> Hypertension is the most common cause of coronary heart disease and heart failure in Japan; however, cerebrovascular disease is still more prevalent in Japan than in Western societies.<sup>2</sup> The percentage of cerebral bleeding is two or three times greater than in white people, and cerebral infarction is mostly caused by lacunar-type ischaemic stroke due to hypertensive small vessel disease.<sup>3</sup>

The renin–angiotensin system (RAS) plays a major role in the homeostasis of blood pressure, electrolytes, and fluid balance.<sup>4</sup> However, chronic activation of RAS contributes to the development of hypertension and cardiovascular organ damage.<sup>5</sup> Numerous trials have investigated the benefits of ACEI, e.g. The Heart Outcomes Prevention Evaluation (HOPE) Study reported that

ACE inhibitors significantly reduced mortality, myocardial infarction, and stroke in high-risk patients.<sup>6</sup> Another important study, in this case with ARB, was the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study, where losartan-based therapy prevented more cardiovascular morbidity and death, in particular stroke, than atenolol-based regimen despite similar blood pressure control.<sup>7</sup> There are now numerous studies showing beneficial effects of RAS blockers on cardiovascular outcomes, in particular with ARBs, in various stages of the CV continuum.<sup>8</sup> However, these studies have included as maximum a few percent of Asian patients in general and very few Japanese in particular.

Cardiovascular disease incidence in Japan differs from those in Western countries. CAD mortality is one-third of that in the USA, and cerebrovascular disease mortality is ~1.5 times higher than in the USA.<sup>9</sup> The dietary habits in Japan differ from

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Western populations as reflected by lower body mass index (BMI).<sup>10,11</sup> There are three major trials in Japanese hypertensive patients with high-risk published: (i) candesartan vs. amlodipine in high-risk hypertensive patients (CASE-J trial,<sup>12</sup>  $n = 4768$ ), (ii) candesartan vs. non-ARB therapy in hypertensive patients with CAD (HIJ-CREATE,<sup>13</sup>  $n = 5005$ ), and (iii) add-on effect of valsartan in hypertensive patients with CAD and/or heart failure (JIKEL-Heart Study,  $n = 3081$ ).<sup>14</sup> Neither CASE-J nor HIJ-CREATE showed that candesartan is superior to either amlodipine-based or non-ARB therapy, respectively, whereas valsartan in JIKEL-Heart Study significantly reduced cardiovascular morbidity and mortality. It remains to be determined whether this discrepancy is due to a difference between the ARB molecules used or differences in study designs. The KYOTO HEART Study was designed to examine whether valsartan added to the conventional anti-hypertensive treatment influences the cardiovascular events in the high-risk Japanese patients with uncontrolled hypertension.

## Methods

### Study design

The design, organization, clinical measurements, and endpoint definitions of the KYOTO HEART Study have been previously published.<sup>15</sup> Briefly, we recruited patients between January 2004 and June 2007. Participating centres included 31 associated hospitals led by physicians (cardiology specialists) from Kyoto Prefectural University School of Medicine. We used the Prospective, Randomized, Open-labeled, Blinded Endpoints (PROBE),<sup>16</sup> two-arm parallel treatment group comparison study design with a response-dependent dose titration scheme.

### Patient population

The eligible population consisted of Japanese hypertensive patients (men and women,  $\geq 20$  years old) whose blood pressures had been uncontrolled for at least 4 weeks. Blood pressure was measured at least greater than two times in consecutive every 2 weeks for the first 4 weeks and then if still uncontrolled, patients are considered to be candidates. (see the design paper<sup>15</sup>) Uncontrolled hypertension was defined as a mean sitting systolic blood pressure  $\geq 140$  mmHg, and/or a mean sitting diastolic blood pressure  $\geq 90$  mmHg at two consecutive measurements in the out-patient clinic. When patients were already treated for hypertension, anti-hypertensive drugs other than ARBs were used for the first 4 weeks and then if still uncontrolled (BP  $\geq 140/90$  mmHg), they were considered for recruitment. Uncontrolled hypertensive patients treated with ACE inhibitors could participate in the study, while ACE inhibitors were not allowed as an add-on therapy in both valsartan add-on and non-ARB groups. The protocol was approved by the Ethics committee at each participating centre, and a written consent was obtained from each patient (refer the design paper<sup>15</sup>).

If the patients with uncontrolled hypertensive also had at least one of coronary artery diseases (angina pectoris or a history of myocardial infarction  $>6$  months before the screening), cerebrovascular diseases [a history of stroke or transient ischaemic attack (TIA)  $>6$  months before the screening] or peripheral arterial occlusive disease (previous limb bypass surgery or angioplasty, limb ulcer/gangrene or intermittent claudication with ankle/brachial blood pressure index  $<0.8$ ), and/or one or more of the below-mentioned cardiovascular risk factors and

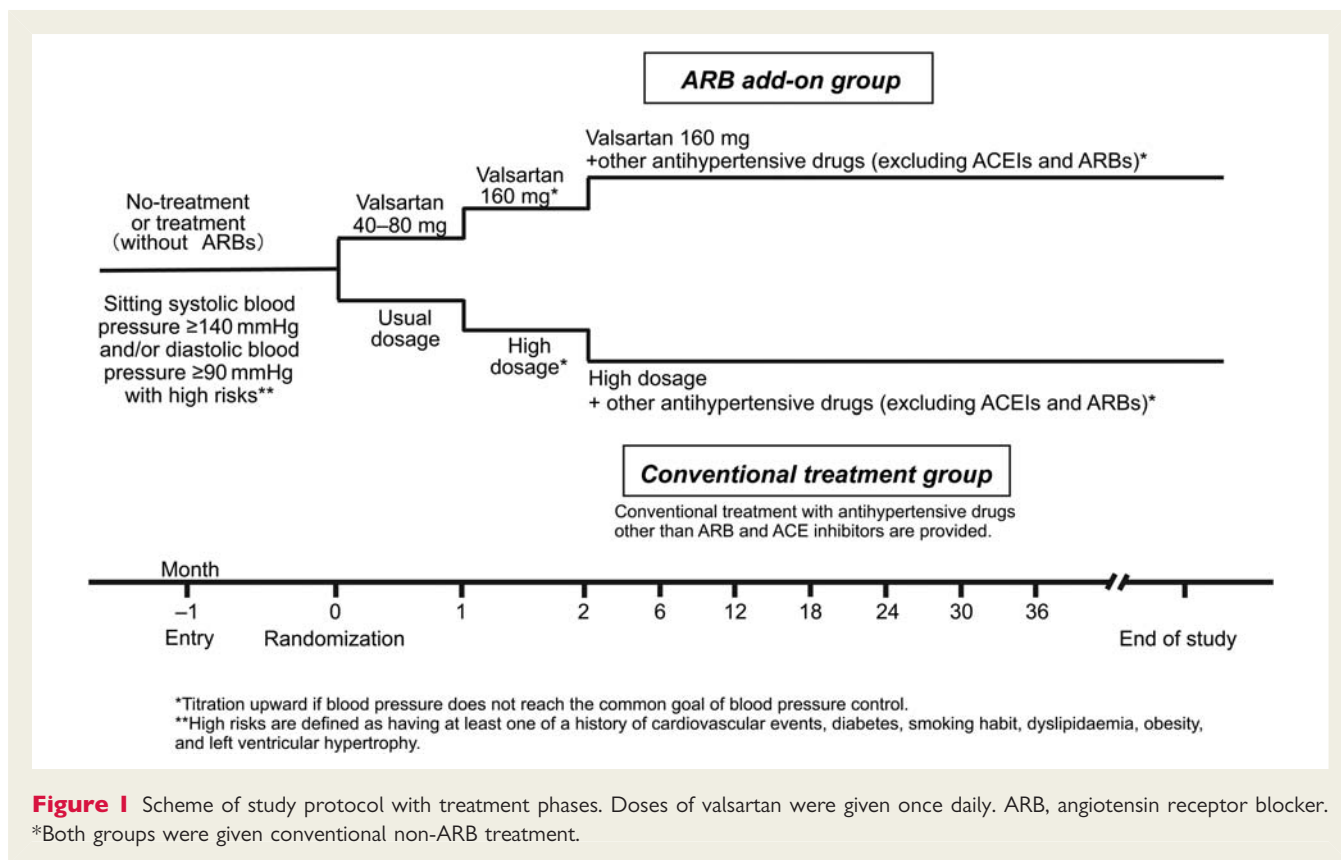
not any exclusion criteria, they were randomized into the trial. The cardiovascular risk factors included type 2 diabetes mellitus (defined as fasting plasma glucose  $\geq 126$  mg/dL, casual blood glucose  $\geq 200$  mg/dL, HbA1C  $\geq 6.5\%$ , and/or plasma glucose 2 h after 75 g glucose load  $>200$  mg/dL, or current treatment with anti-diabetic agents), current smoking, lipid metabolism abnormality (defined as low-density lipoprotein  $\geq 140$  mg/dL, and/or high-density lipoprotein  $\leq 40$  mg/dL, and/or TG  $\geq 150$  mg/dL, or current treatment with anti-dyslipidaemia agents), obesity (defined as BMI  $\geq 25$  kg/m<sup>2</sup>), and/or left ventricular hypertrophy defined by electrocardiogram.<sup>17</sup> Patients who were treated with ARB before randomization, or had history of worsening heart failure, unstable angina, myocardial infarction, PCI, or CABG within the preceding 6 months were excluded. For more details on exclusion criteria see the design paper.<sup>15</sup>

### Study procedures

The study design and the titration schedule of the study are shown in Figure 1. After confirming, eligibility patients were randomized in accordance with the minimization method with eight factors (age, gender, dyslipidaemia, diabetes mellitus, smoking, obesity, history of CAD and/or cerebrovascular disease, and history of congestive heart failure), either to the valsartan add-on group or to the conventional treatment group. All eligible patients were applied to the minimization method for randomization to require that the treatment allocation was identified for each patient. For the valsartan add-on group, valsartan 80 mg once daily in the morning was administered to the patient as an initial dose, the dose was doubled after 4 weeks if the initial dose could not achieve the target blood pressure of less than 140/90 mmHg (in patients with diabetes or renal disease, target blood pressure was set to less than 130/80 mmHg). After 8 weeks, an additional administration of other antihypertensive drugs with flexible dosing regimen other than ARBs and ACE inhibitors was allowed if necessary. Meanwhile, for the conventional treatment group, the anti-hypertensive drugs other than ARB and ACE inhibitors were provided for the patients to reach the target blood pressure. The periodical follow-up was implemented every 6 months after setting the sustainable dose. Investigative measurements and data management were described in the design paper.<sup>15</sup>

### Evaluation of outcomes

New onset and/or worsening of cardio- and cerebro-vascular events were assessed as the primary endpoints. They are the following events: stroke (hospitalization and diagnosed by CT and/or MRI), new or recurrent TIA (hospitalization and diagnosed by CT and/or MRI and sudden onset of neurological deficit persisting for less than 24 h without the history of atrial arrhythmia that causes embolism), new or recurrent acute myocardial infarction (hospitalization, ECG-change, and biomarkers for myocardial infarction), new occurrence or exacerbation of angina pectoris (hospitalization and diagnosed by both ECG changes corresponding with chest symptoms and coronary angiography showing  $>75\%$  stenosis according to AHA/ACC guidelines), new occurrence or exacerbation of heart failure (hospitalization and clinical symptoms together with left ventricular dysfunction by echocardiography according to the guidelines of the AHA/ACC), dissecting aneurysm of the aorta (hospitalization and diagnosed by imaging technique), lower limb arterial obstruction, emergency thrombosis, transition to dialysis, and doubling of plasma Cr levels. The first of any of these events to occur in a specific patient was classified as an event to be counted in the primary endpoint by the Endpoint Committee.



The following were secondary endpoints: all cause mortality, worsening of cardiac function, new occurrence or exacerbation of arrhythmias, new occurrence or exacerbation of diabetes mellitus or impaired glucose tolerance, and uncontrolled blood pressure. Only first event was calculated as a component of composite events, and multiple events in the same patients were not counted after the first event. The review was made under the condition that the result of drug allocation was blinded. The study was registered at register.clinical.gov with the identification number NCT00149227.

## Statistical analysis

On the basis of the large trials in Western countries and the trials in Japan, we had hypothesized that Japanese hypertensive patients with high-risk might have approximately 12% of composite cardiovascular events in 3 years follow-up. We estimated the number of enrolled patients as 3000 (1500 in each group) to validate the hypothesis under the assumption that the valsartan add-on group achieves a 20% risk reduction compared with the conventional treatment group and gives 80% statistical power for detecting a clinical significance with a two-tailed 5% statistical significant level.

Analyses will be made by the independent Statistical Analysis Organization based on the intention-to-treat principle and time to first event in accordance with the principle of ICH E9, harmonized tripartite guideline 'Statistical Principles for Clinical Trials'. The blood pressure during the trial was analysed by analysis of variance with Levene's test. The event curves were shown by Kaplan–Meier estimates. Event rates were adjusted for sex, age, diabetes, smoking, dyslipidaemia, and concomitant antihypertensive treatment, and Cox's proportional hazard regression analysis was used to compare the event rate between two treatment groups. For primary analysis of

intergroup differences in endpoints, we used inference testing (95% CI) with significance defined at a level of less than 5%. To assess significance, we compared categorical data with  $\chi^2$  test or Fisher's exact test and compared quantitative data with the *t*-test or analysis of variance.

## Results

Table 1 shows the baseline characteristics for all the 3031 patients who were assigned to treatment. All patients were Japanese and both treatment groups were well matched for baseline characteristics, and had no statistically significant differences. Patients were censored at death or at last known visit, with a median follow-up of 3.27 years [1.96–4.08 (25–75%)]. In total, the study gathered information for 8864 patient years (valsartan add-on group, 4448; non-ARB group, 4416). Figure 2 shows that 17 patients (0.56%) withdrew consent after eligibility and 17 patients (0.56%) were lost to follow-up.

Figure 3 shows that blood pressure at baseline in both groups was a mean of 157/88 mmHg and the level similarly fell to 133/76 mmHg at the end of study. The decline in blood pressure from the baseline to the end was 24/12 mmHg and there was no significant difference in blood pressure levels throughout the study by the Levene's test.

Table 2 shows the medications at baseline: 54–55% of patients were receiving calcium channel blockers, 19–20% ACE-inhibitors, 17–18%  $\beta$ -blockers, 8–9% diuretics, and 32–33% statins. The number of patients with dyslipidaemia was 70.7% of total patients,

**Table 1** Baseline characteristics

	Valsartan, n = 1517	Non-ARB, n = 1514
Age	66 (11)	66 (11)
Men/women	861/656 (57/43%)	867/647 (57/43%)
Current smoker	341 (22%)	332 (22%)
Obesity BMI $\geq 25$	593 (39%)	584 (39%)
Coronary artery disease	355 (23%)	352 (23%)
Cerebrovascular disease	58 (4%)	65 (4%)
Heart failure	84 (6%)	109 (7%)
Diabetes	401 (26%)	406 (27%)
Dyslipidaemia	1065 (70%)	1079 (71%)
LVH by electrocardiogram	122 (8%)	129 (9%)
Systolic blood pressure (mmHg)	157 (14)	157 (14)
Diastolic blood pressure (mmHg)	88 (11)	88 (11)
Heart rate (b.p.m.)	70 (18)	70 (16)
EF (%)	63 (10)	63 (9)
HDL cholesterol (mg/dL)	55 (15)	55 (15)
LDL cholesterol (mg/dL)	121 (31)	123 (31)
Triglyceride (mg/dL)	147 (83)	150 (84)
Fasting plasma glucose (mg/dL)	121 (43)	121 (43)
HbA1c (%)	6.1 (2.3)	6.0 (1.3)
Serum creatinine (mg/dL)	0.87 (0.35)	0.84 (0.38)
Sodium (mEq/L)	142 (2.7)	142 (2.5)
Potassium (mEq/L)	4.5 (2.2)	4.3 (2.2)

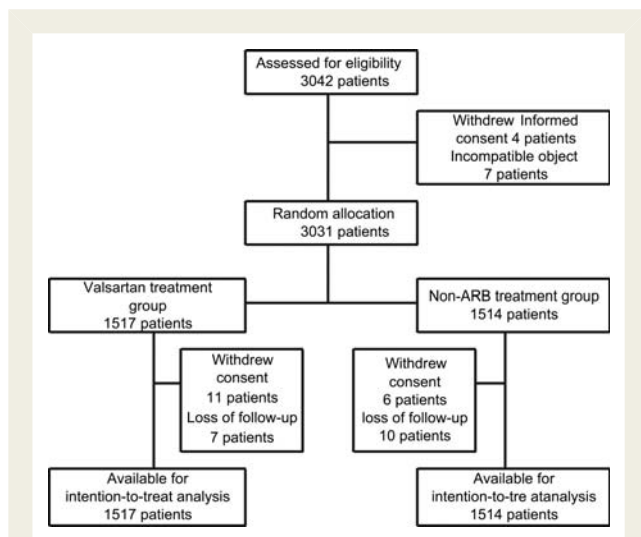
Data are mean (SD) or number (%).

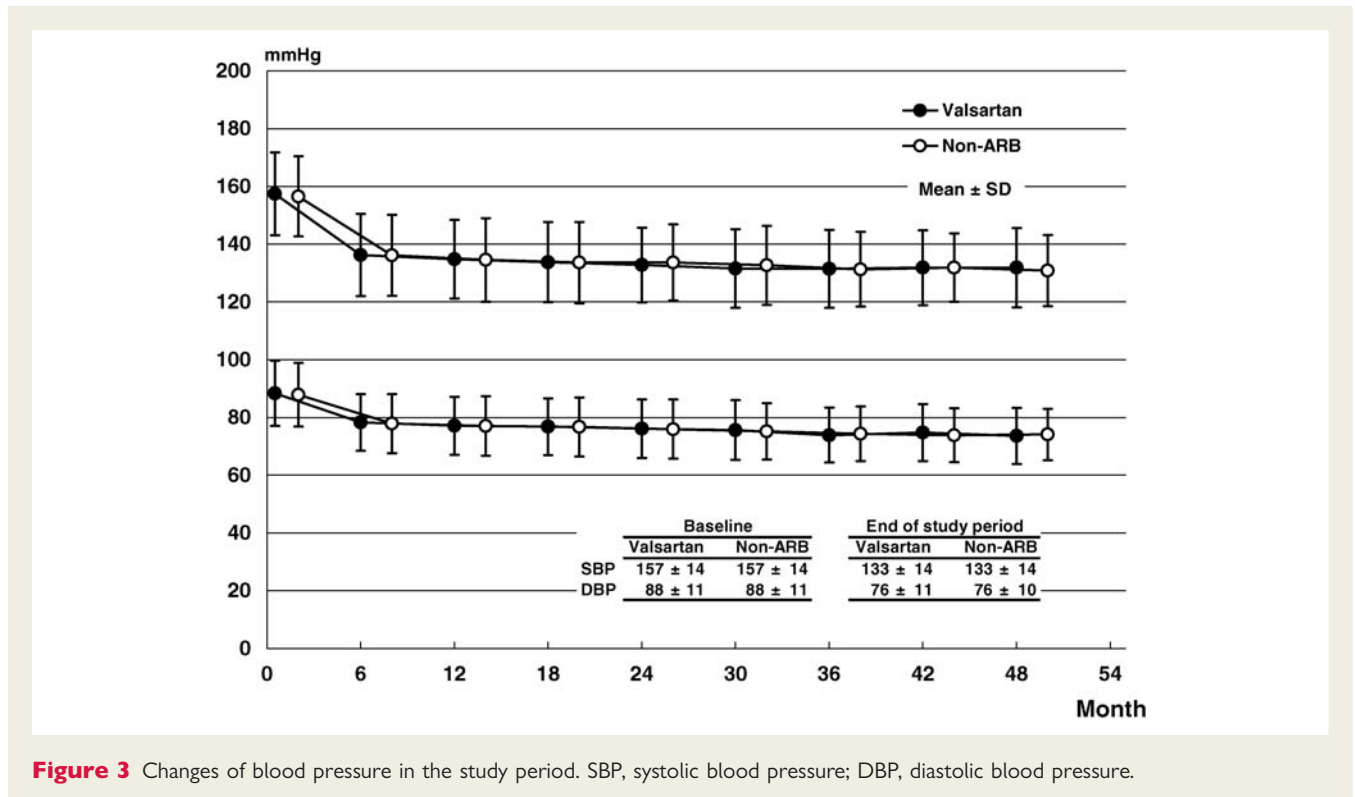
ARB, angiotensin receptor blocker; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Hb, haemoglobin; EF, ejection fraction; LVH, Left ventricular hypertrophy.

of which 46.4% was treated with statins and 49.5% was untreated (dietary restriction therapy), resulting in low use (32.7%) of statins in total drugs. The proportion of patients with high TG was 48% in total dyslipidaemic patients, which could explain the fact that more patients were treated with dietary restriction therapy rather than statins.

Blood pressure was well controlled within first 12 months in both groups (Figure 3). To achieve the appropriate blood pressure at month 12, the proportion of patients using calcium channel blockers was increased by 8% (55% at baseline, see Table 2, increased to 63% at month 12) and that of  $\beta$ -blockers was 3% (18–21%), which were the main additional antihypertensive drugs in non-ARB group, while the patients using other antihypertensive agents, such as  $\alpha$ -blockers (3–3%), anti-aldosterone agents (2–2%), thiazide (3–2%), or other diuretics (6–6%), did not show the significant changes. In the valsartan add-on group, there was no significant increase in the number of other additional antihypertensive agents, suggesting that the addition of valsartan was sufficient to control the blood pressure for the first 12 months. The number of patients who were not treated with antihypertensive drugs at baseline (diet or salt reduction therapy more than 4 weeks) was 968 and they were randomized to valsartan ( $n=476$ ) or non-ARB groups ( $n=492$ ). Therefore, the baseline number of antihypertensive drugs was 1.02 in both valsartan and non-ARB groups. The most often used combination therapies at baseline were calcium channel blockers (54–55% of total patients, see the baseline data in Table 2) +ACE inhibitors (19–20%), or calcium channel blockers (54–55%) + $\beta$ -blockers (17–18%), and this combination pattern was similar between both groups (Table 2). At the end of study period, no biochemical markers showed significant differences between two groups.

Figures 4 and 5 show Kaplan–Meier curves for the primary endpoint and the hazard ratio and 95% confidence intervals, respectively. The primary endpoint was recorded in fewer patients given valsartan add-on (83, 5.5%) than in those given additional non-ARB treatment (155, 10.2%); the hazard ratio was 0.55 (95% CI 0.42–0.72,  $P=0.00001$ ). The difference in the number of primary endpoints was mainly attributable to reduced frequency of stroke and TIA, and angina pectoris; 25 patients given valsartan had stroke (19 patients) or TIA (6 patients), compared with 46 in the control group (stroke, 42 patients; TIA, 4 patients) (HR 0.55, 95% CI 0.34–0.89,  $P=0.01488$ ); 22 patients given valsartan had angina pectoris compared with 44 controls (HR 0.51, 95% CI 0.31–0.86,  $P=0.01058$ ). When the early occurring primary endpoints in the 0–6 months were excluded (valsartan, 24; non-ARB, 39), the remaining primary event numbers were 59 (valsartan) and 116 (non-ARB), and this sub-analysis did not significantly affect total final result of this study. Gender difference was not a significant factor affecting endpoints ( $P=0.687$ ). When the data were separately analysed between male and female groups, the hazard ratio was 0.57 (95% CI 0.41–0.80,  $P=0.0001$ ) in male and 0.51 (95% CI 0.34–0.79,  $P=0.002$ ) in female. The number of new-onset diabetes was significantly fewer in valsartan add-on group (58 vs. 86,  $P=0.0282$ ). Table 3 shows the adverse events during the study, which were not significant between two groups.

**Figure 2** Trial profile.



**Figure 3** Changes of blood pressure in the study period. SBP, systolic blood pressure; DBP, diastolic blood pressure.

**Table 2 Medications at baseline**

	Valsartan, n = 1517	Non-ARB, n = 1514
Angiotensin converting enzyme inhibitor	289 (19%)	305 (20%)
Calcium channel	825 (54%)	832 (55%)
α-Blocker	45 (3%)	51 (3%)
β-Blocker	264 (17%)	277 (18%)
Anti-aldosterone agents	31 (2%)	26 (2%)
Thiazide	52 (3%)	45 (3%)
Other diuretics	76 (5%)	86 (6%)
Statin	491 (32%)	503 (33%)
Fibrate	35 (2%)	30 (2%)
Oral hypoglycaemic agents	219 (14%)	202 (13%)
Anti-coagulation agents	89 (6%)	106 (7%)
Anti-platelet agents	402 (26%)	427 (28%)

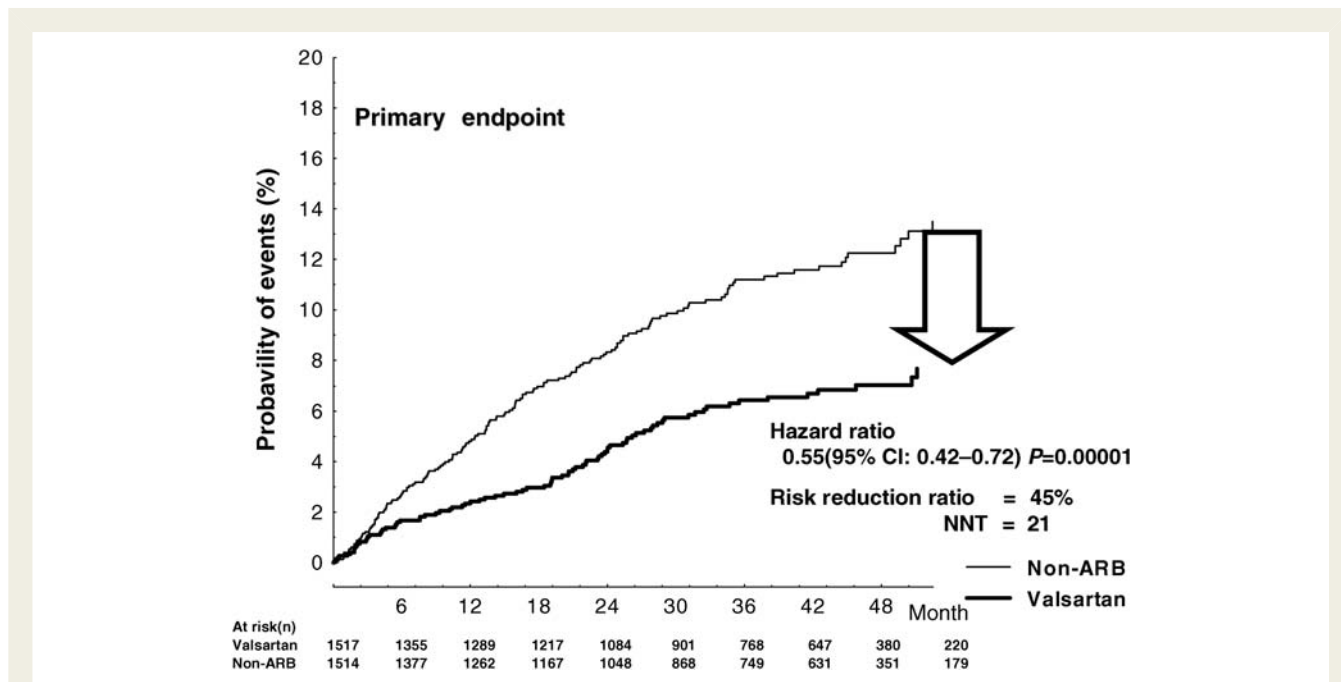
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## Discussion

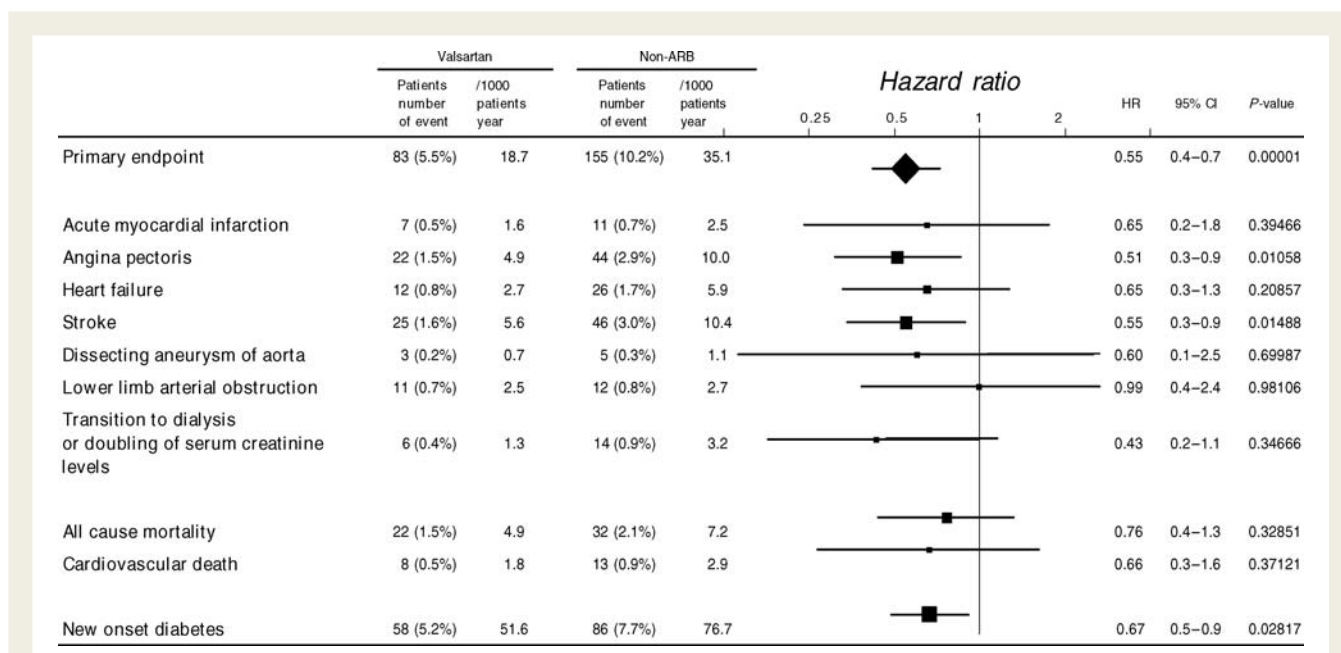
The KYOTO HEART Study demonstrates that addition of valsartan to standard treatment for Japanese hypertensive patients with high-risk reduced the incidence of the composite of cardiovascular complications. The main effect of addition of valsartan was to reduce stroke and angina pectoris. These substantial benefits were noted despite a short median follow-up of 3.27 years and with blood pressure lowering rates being similar

between valsartan add-on treatment and non-ARB groups. The incidence of cardiovascular events was 10.2 and 5.5% in non-ARB and valsartan add-on groups, respectively, which was relatively lower compared with the predicted value (12% in 3 years follow-up). However, the statistical power was 92%, which exceeded the 80% of that we had predicted.

Cerebrovascular disease is more prevalent in Japan than in Western societies.<sup>9</sup> The percentage of cerebral bleeding is two or three times greater than in a white people in Western countries, and cerebral infarction is mostly caused by lacunar-type ischaemic stroke due to hypertensive small vessel disease.<sup>3</sup> Unfortunately, Asian patients have been underrepresented in cardiovascular trials, including trials of ARB. Only less than 3.5% of Asians were included in the populations in the Val-HeFT,<sup>18</sup> the VALUE,<sup>19</sup> and the LIFE trials,<sup>7</sup> and no Japanese were included in these trials. Currently, there are three large open trials in Japanese hypertensive patients; (i) candesartan vs. amlodipine in hypertensive patients with high risk (CASE-J trial, n = 4768), (ii) candesartan vs. non-ARB therapy in hypertensive patients with CAD (HIJ-CREATE, n = 5005), and (iii) add-on effect of valsartan in hypertensive patients with CAD and/or heart failure (JIKEI-Heart Study, n = 3081). Neither CASE-J<sup>12</sup> nor HIJ-CREATE<sup>13</sup> trials showed that candesartan is superior to either amlodipine-based therapy or the non-ARB therapy in reducing the cardiovascular complications, whereas valsartan treatment in JIKEI-Heart Study significantly inhibited the incidence of cardiovascular mortality and morbidity.<sup>14</sup> The JIKEI result is well consistent with our present trial testing the add-on effect of valsartan in patients with high risk, while the impressive reduction in angina pectoris with valsartan treatment in both JIKEI- and KYOTO HEART



**Figure 4** Kaplan–Meier estimate and effect of treatment on all endpoints.



**Figure 5** Hazard ratio and 95% confidence intervals adjusted for sex, age, diabetes, smoking, dyslipidaemia, and concomitant antihypertensive treatment. Diamonds and squares indicate the hazard ratio estimate for each type of event; horizontal lines show 95% CIs.

Studies does not match up with the effect on myocardial infarction in both studies. Angina pectoris was all diagnosed by both ECG changes corresponding with chest symptoms and coronary angiography showing >75% stenosis. Figure 5 shows that Forrest Plots in angina pectoris and myocardial infarction are both favourable to valsartan group. All patients were diagnosed by cardiology specialists and treated in their hospitals. Such excellent and intensive care

might enable to diagnose angina pectoris in an earlier stage of onset, resulting in lower incidence in myocardial infarction.

We could speculate that RAS has a larger role in the development of angina than in myocardial infarction, in which other factors more related to rupture of atheromas and thrombosis are major determinants. Since valsartan has the highest selectivity for angiotensin type 1 (AT1) receptor vs. the AT2 receptor

**Table 3** Adverse events throughout the study

Adverse events ( $n \geq 2$ )	Valsartan	Non-ARB
Cancer or metastasis	12 (0.8%)	14 (0.9%)
Stomach discomfort	9 (0.6%)	11 (0.7%)
Dizziness	8 (0.5%)	9 (0.6%)
Haemoptysis	5 (0.3%)	7 (0.5%)
Rashes	4 (0.3%)	6 (0.4%)
Headache	2 (0.1%)	6 (0.4%)
Gastrointestinal bleeding	3 (0.2%)	4 (0.3%)
Liver dysfunction	3 (0.2%)	4 (0.3%)
Dry cough	2 (0.1%)	4 (0.3%)
Elevated serum potassium	4 (0.3%)	2 (0.1%)
Cellulitis	1 (0.1%)	3 (0.2%)
Palpitations	2 (0.1%)	2 (0.1%)
Fracture	1 (0.1%)	3 (0.2%)
Other adverse event	41 (2.7%)	39 (2.6%)
	97 (3.2%)	114 (3.8%)

compared with other ARBs,<sup>20</sup> it is possible that AT2 receptor-mediated vascular protection via activation of bradykinin/NO system<sup>21</sup> is more enhanced with valsartan treatment. In fact, AT2 receptor is expressed in atherosclerotic lesions,<sup>22</sup> and valsartan treatment effectively blocks coronary artery thickening and perivascular fibrosis.<sup>23</sup> Thus, combined with the result in the previous JIKEI Heart Study, the KYOTO HEART Study may suggest that the more potent anti-angina action of valsartan is a unique pharmacological property that contrasts with other ARBs, and especially noted in hypertensive patients with atherosclerotic lesions in coronary arteries.

The significant reduction in the stroke events in KYOTO HEART Study was consistent with that reported in JIKEI Heart Study.<sup>14</sup> Although the stroke endpoint combines both stroke and TIA, stroke was all diagnosed by hospitalization and CT and/or MRI, and TIA was defined as hospitalization, and diagnosis by CT and/or MRI and sudden onset of neurological deficit persisting for less than 24 h. Transient ischaemic attack incidence was very low in our study, which were six patients in valsartan group (stroke, 19) and four in non-ARB group (stroke, 42), similar as in JIKEI Heart Study. Thus, stroke and TIA were differentially diagnosed and it is unlikely that the diagnosis for stroke reveals a thin line towards TIA.

The mean dose of valsartan in this study (88 mg) might seem low, but studies in Japanese people have shown that 80 mg of valsartan produced similar anti-hypertensive effects to those of nifedipine (20 mg)<sup>24</sup> and amlodipine (5 mg).<sup>25</sup> Doses of all anti-hypertensive drugs, including valsartan, were based on the guideline of the Japanese Hypertension Society.<sup>26</sup>

Candesartan-based therapies have reported that candesartan prevented new-onset diabetes more effectively than amlodipine (CASE-J) in patients with high-risk<sup>12</sup> or non-ARB treatment (HIJ-CREATE) in patients with CHD.<sup>13</sup> However, in neither studies, there was any benefit of candesartan on overall cardiovascular outcomes. The VALUE study also showed that the treatment

with valsartan significantly inhibited the new onset of diabetes in patients with high risk ( $n = 15313$ ).<sup>19</sup> Consistent with these studies, KYOTO HEART Study presented a significant effect of valsartan in inhibiting the onset of diabetes. These findings suggest that the anti-diabetic action of ARBs should be considered in treating the hypertensive patients with high risk.

Our study could include nearly all patients who were judged to be eligible (withdrawn consent, 0.56%; lost of follow-up, 0.56%). Participating patients were not enrolled by public advertisement but consisted of patients who were visiting our hospitals associated with the University. Patients have a good knowledge about hypertension and complications, as well as the importance of the study. Such background might yield the higher follow-up rate of this study.

In summary, the KYOTO HEART Study confirms that ARB valsartan exerts an overall cardiovascular protective effect in high-risk Japanese hypertensive patients and in particular exerts anti-stroke and anti-angina actions, and thus provide an useful information about Asian populations that have similar genetic predisposition and lifestyles as the Japanese population.

## Limitations

PROBE design is a cost-effective alternative to the classical double-blind trial, and has advantages of being more similar to clinical practice and improved patient compliance without losing valuable blinded endpoint information.<sup>16</sup> However, PROBE does not exclude possible bias in event reporting, especially for softer endpoints such as angina pectoris/TIA.<sup>27</sup> In our study, all coronary lesions were ascertained by angiography, and cerebrovascular attacks were diagnosed using CT and/or MRI. The investigators were kept uninformed about the diagnostic criteria for softer endpoints which had been determined by the endpoint committee. In fact, among 558 provisional reports, only 238 (42.7%) were confirmed as the primary endpoint by the endpoint committee. We believe that the possible bias would be highly unlikely to account for differences. Rather, PROBE design may put the study close to daily clinical practice.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

## Acknowledgements

We thank the participating investigators (see Supplementary material online), medical staff, and contributors to the Kyoto Heart Study.

## Funding

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**Conflict of interest:** the sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The executive committee had full access to all the data at the end of the study, and has final responsibility for the decision to submit for publication.

## Appendix

### Study organization

H.M. supervises the KYOTO HEART Study as the chief investigator, and several staffs have been appointed to support the management of the study.

### Executive committee

H.M., Department of Cardiovascular Medicine, Kyoto Prefectural University of Medicine is the study chairman. B.D., Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden, is the honorary supervisor of the logistics, and conducts the reporting of the study.

### Steering committee

Kyoto Prefectural University of Medicine—T.S. (Main Steering Committee Member), H.Y., and Tomosaburo Takahashi.

### Endpoint committee

Jitsuo Higaki, Department of Integrated Medicine and Informatics, Ehime University Graduate School of Medicine; Shohei Kim-Mitsuyama, Department of Pharmacology and Molecular Therapeutics, Kumamoto University School of Medicine; Toshihiro Ichiki, Department of Cardiovascular Medicine, Kyushu University School of Medicine, Japan.

### Safety committee

Masafumi Kitakaze, National Cardiovascular Center; Tetsuro Sugiura, Department of Clinical Laboratory Medicine, Kochi University School of Medicine; Hiromi Rakugi, Department of Geriatric Medicine, Osaka University School of Medicine, Japan.

### Data and safety monitoring board

Katsumi Yagi, Louis Pasteur Center for Medical Research; Keiichi Kanda, Chouhei Sakakura, Kyoto Prefectural University of Medicine, Japan.

### Statistical analysis organization

Katsumi Yagi, Louis Pasteur Center for Medical Research, Japan.

### Data monitoring board

Marika Miki, Sachiko Toyoda, Kyoto Prefectural University School of Medicine, Japan.

### References

- Bonow RO, Smaha LA, Smith SC Jr, Mensah GA, Lenfant C. World Heart Day 2002: the international burden of cardiovascular disease: responding to the emerging global epidemic. *Circulation* 2002;**106**:1602–1605.
- Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, Nakamura H, Okubo K, Iida M. Trends in the incidence, mortality, and survival rate of cardiovascular diseases in a Japanese community: the Hisayama study. *Stroke* 2003;**34**:2349–2354.
- Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, Arima H, Tanaka K, Ibayashi S, Fujishima M. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. *Stroke* 2000;**31**:2616–2622.
- Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. *Circulation* 1998;**97**:1411–1420.
- Hollenberg NK. European Society of Cardiology: angiotensin II antagonists in hypertension and beyond. Angiotensin II antagonists: why is there so much excitement? *Am J Manag Care* 1998;**4**(Suppl. 7):S384–S387.
- Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–153.
- Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Opas S, Wedel H, for the LIFE study group. 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.
- Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, Popma JJ, Stevenson W. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: part II: Clinical trial evidence (acute coronary syndromes through renal disease) and future directions. *Circulation* 2006;**114**:2871–2891.
- World Health Organization. Death and DAILY estimates for 2002 by cause for WHO member states: burden of disease statistics. <http://www.who.int/entity/healthinfo/statistics/bodgbddeathdalyestimates.xls> (December 2004).
- Miyazaki T, Hirata M, Moriyama K, Sasaki Y, Aono H, Saito N, Nakao K. Metabolic syndrome in Japan diagnosed with visceral fat measurement by computed tomography. *Proc Jpn Acad Ser* 2005;**81**:471–479.
- Calle E, Thun M, Petrelli J, Rodriguez C, Health C. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Eng J Med* 1999;**341**:1097–1105.
- Ogihara T, Nakao K, Fukui T, Fukiyama K, Ueshima K, Oba K, Sato T, Saruta T, for the Candesartan Antihypertensive Survival Evaluation in Japan Trial Group. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. *Hypertension* 2008;**51**:393–398.
- Kasanuki H, Hagiwara N, Hosoda S, Sumiyoshi T, Honda T, Haze K, Nagashima M, Yamaguchi J, Origasa H, Urashima M, Ogawa H, and for the HIJ-CREATE Investigators. Angiotensin II receptor blocker-based vs. non-angiotensin II receptor blocker-based therapy in patients with angiographically documented coronary artery disease and hypertension: the Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE). *Eur Heart J* 2009;**30**:1203–1212.
- Mochizuki S, Dahlöf B, Shimizu M, Ikewaki K, Yoshikawa M, Taniguchi I, Ohta M, Yamada T, Ogawa K, Kanai K, Kawai M, Seki S, Okazaki F, Taniguchi M, Yoshida S, Tajima N, for the Jikei Heart Study group. Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study). *Lancet* 2007;**369**:1431–1439.
- Sawada T, Takahashi T, Yamada H, Dahlöf B, Matsubara H, KYOTO HEART Study Group. Rationale and design of the KYOTO HEART study: effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high risk of cardiovascular events. *J Hum Hypertens* 2009;**23**:188–195.
- Hansson L, Hedner T, Dahlöf B. Prospective randomized open blind endpoint (PROBE) study. A novel design for intervention trials. *Blood Press* 1992;**1**:113–119.
- Kannel WB, Gordon T, Castelli WP, Margolis JR. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease: the Framingham Study. *Ann Intern Med* 1970;**72**:813–822.
- 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.
- Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A, VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;**363**:2022–2031.
- Siragy HM. Angiotensin receptor blockers: how important is selectivity? *Am J Hypertens* 2002;**15**:1006–1014.
- Tsutsumi Y, Matsubara H, Masaki H, Kurihara H, Murasawa S, Takai S, Miyazaki M, Nozawa Y, Ozono R, Nakagawa K, Miwa T, Kawada N, Mori Y, Shibasaki Y, Tanaka Y, Fujiyama S, Koyama Y, Fujiyama A, Takahashi H, Iwasaka T. Angiotensin II type 2 receptor overexpression activates the vascular kinin system and causes vasodilation. *J Clin Invest* 1999;**104**:1013–1014.
- Daugherty A, Rateri DL, Lu H, Inagami T, Casis LA. Hypercholesterolemia Stimulates Angiotensin Peptide Synthesis and Contributes to Atherosclerosis Through the AT1A Receptor. *Circulation* 2004;**110**:3849–3857.
- Wu L, Iwai M, Nakagami H, Chen R, Suzuki J, Akishita M, de Gasparo M, Horiuchi M. Effect of angiotensin II type 1 receptor blockade on cardiac remodeling in angiotensin II type 2 receptor null mice. *Arterioscler Thromb Vasc Biol* 2002;**22**:49–54.



24. Munakata M, Nagasaki A, Nunokawa T, Sakuma T, Kato H, Yoshinaga K, Toyota T. Effects of valsartan and nifedipine coat-core on systemic arterial stiffness in hypertensive patients. *Am J Hypertens* 2004;**17**:1050–1055.
25. Yasunari K, Maeda K, Watanabe T, Nakamura M, Yoshikawa J, Asada A. Comparative effects of valsartan versus amlodipine on left ventricular mass and reactive oxygen Species formation by monocytes in hypertensive patients with left ventricular hypertrophy. *J Am Coll Cardiol* 2004;**43**: 2116–2123.
26. Saruta T. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004). *Nippon Rinsho* 2005;**63**:952–958.
27. Staessen JA, Richart T. Sum and substance in the Jikei Heart Study. *Lancet* 2007; **369**:1407–1408.

## CARDIOVASCULAR FLASHLIGHT

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# Coronary and vertebral subclavian steal demonstrated by subclavian angiography

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A 60-year-old woman who had previous coronary bypass surgery presented to the emergency room with progressive angina pectoris, left arm claudication, coldness, and intermittent dizziness. On physical examination, left arm pulses were weak and a systolic blood pressure difference of 100 mmHg between the left (50/0 mmHg) and right (150/90 mmHg) arms was noted. Coronary angiography showed totally occluded left anterior descending (LAD) and circumflex artery with normal right coronary artery. Saphenous vein graft to obtuse marginal artery was patent. Left subclavian angiography revealed a severe proximal stenosis (Panel A, asterisk). Coronary subclavian and vertebral subclavian steal were clearly seen during left subclavian angiography. Selective dilution of contrast dye at the LIMA-left subclavian junction indicated retrograde blood flow from LIMA (Panel A, long arrow). A similar finding was observed in the left vertebral artery, which indicates retrograde blood from vertebral to subclavian artery (Panel A, short arrows). Considering total occlusion of LAD artery in this case, we searched for a second bypass graft to LAD artery, which is responsible for coronary subclavian steal. We noted a sequential saphenous vein graft to diagonal and LAD artery, and there was a severe stenosis at its distal end (Panel B, long arrow). In addition, a brisk retrograde flow was noted in the LIMA anastomosed to the LAD artery (Panels B and C, short arrows). A clear left subclavian angiography was obtained through contrast injection into the saphenous vein graft (Panel C, long arrow). Vertebral subclavian steal was also confirmed with ultrasonography (Panels D and E). Note reversed blood flow in the left vertebral artery (Panels D and E, short arrows). Flow in the ipsilateral common carotid artery remains cephalad in direction (Panels D and E, long arrows).

Left subclavian artery stenosis was dilated and stented. Patient remained asymptomatic after procedure and at 1 year follow-up. Considering presence of dual graft to LAD (saphenous vein and LIMA) in our patient, it is likely that she had subclavian stenosis before coronary bypass surgery. The surgeons probably determined that another bypass graft to LAD artery was indicated when they noticed failure of blood flow in the LIMA during surgery. This case underlines the importance of a complete clinical evaluation in all patients undergoing coronary bypass surgery. Patients who have symptoms suggestive of vertebral or coronary subclavian steal syndrome and a significant blood pressure difference between left and right arms should have a subclavian angiography at the time of coronary angiography to exclude significant subclavian stenosis.

