Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study

*Seibu Mochizuki, Björn Dahlöf, Mitsuyuki Shimizu, Katsunori Ikewaki, Makoto Yoshikawa, Ikuo Taniguchi, Makoto Ohta, Taku Yamada, Kazuhiko Ogawa, Kiyoshi Kanae, Makoto Kawai, Shingo Seki, Fumiko Okazaki, Masayuki Taniguchi, Satoru Yoshida, Naoko Tajima, for the Jikei Heart Study group**

Summary

Background **Drugs that inhibit the renin–angiotensin–aldosterone system benefit patients at risk for or with existing cardiovascular disease. However, evidence for this effect in Asian populations is scarce. We aimed to investigate whether addition of an angiotensin receptor blocker, valsartan, to conventional cardiovascular treatment was effective in Japanese patients with cardiovascular disease.**

Methods **We initiated a multicentre, prospective, randomised controlled trial of 3081 Japanese patients, aged 20–79 years, (mean 65 [SD 10] years) who were undergoing conventional treatment for hypertension, coronary heart disease, heart failure, or a combination of these disorders. In addition to conventional treatment, patients were assigned either to valsartan (40–160 mg per day) or to other treatment without angiotensin receptor blockers. Our primary endpoint was a composite of cardiovascular morbidity and mortality. Analysis was by intention to treat. The study was registered at clintrials.gov with the identifier NCT00133328.**

Findings **After a median follow-up of 3·1 years (range 1–3·9) the primary endpoint was recorded in fewer individuals given valsartan than in controls (92 *vs* 149; absolute risk 21·3 *vs* 34·5 per 1000 patient years; hazard ratio 0·61, 95% CI 0·47–0·79, p=0·0002). This difference was mainly attributable to fewer incidences of stroke and transient ischaemic attack (29 *vs* 48; 0·60, 0·38–0·95, p=0·028), angina pectoris (19 *vs* 53; 0·35, 0·20–0·58, p<0·0001), and heart failure (19 *vs* 36; 0·53, 0·31–0·94, p=0·029) in those given valsartan than in the control group. Mortality or tolerability did not differ between groups.**

Interpretation **The addition of valsartan to conventional treatment prevented more cardiovascular events than supplementary conventional treatment. These benefits cannot be entirely explained by a difference in blood pressure control.**

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*Members listed at end of article

Division of Cardiology (Prof S Mochizuki MD, Prof M Shimizu MD, K Ikewaki MD, M Yoshikawa MD, I Taniguchi MD, M Ohta MD, T Yamada MD, K Ogawa MD, K Kanae MD, M Kawai MD, S Seki MD, F Okazaki MD, M Taniguchi MD, S Yoshida MD), **and Division of Diabetes, Metabolism, and Endocrinology** (Prof N Tajima MD), **Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan**; **and Institute of Medicine, Department of Emergency and Cardiovascular Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden** (B Dahlöf MD)

Correspondence to:
Prof Seibu Mochizuki, Division of Cardiology, Department of Internal Medicine, The Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo, Japan
m_seibu@jikei.ac.jp

Introduction

Cardiovascular disorders are the leading cause of mortality worldwide,[1] and are expected to continue to increase with general ageing of the world's population and rapid socioeconomic changes in the developing world. Hence, optimum pharmacotherapy for cardiovascular disease is urgently needed, in addition to lifestyle changes, to provide symptomatic relief and long-term protection. Hypertension is the most common cause of coronary heart disease and heart failure in Japan, and cerebrovascular disease is more prevalent in the Japanese population than in western societies.[2] Angiotensin II has a well defined role in the pathogenesis of hypertensive left ventricular hypertrophy, stroke, coronary heart disease, and heart failure.[3–5] Over the past decade, several clinical trials have shown the benefits of treatments that specifically block the renin–angiotensin–aldosterone system. Angiotensin receptor blockers were originally targeted at hypertension, but also benefit patients with a range of diseases[6–15] and reduce the incidence of new onset type II diabetes.[7,11,16]

Direct implementation of available evidence into clinical practice in Japan might not be warranted by the available data, since responses to drug intervention and its clinical consequences might differ between ethnic groups. Clinical trials of angiotensin receptor blockers on end-organ damage in Japanese patients show cardiovascular benefits, but because of shortcomings such as small sample sizes and observational data, these results are not conclusive and cannot be directly translated into clinical outcomes.[17–21] Thus, further large-scale Japanese clinical trials are needed.

We aimed to implement a large-scale clinical trial to investigate the effect of control of blood pressure (to a target of less than 130/80 mm Hg) with an added angiotensin receptor blocker, valsartan, compared with conventional treatment in a large Japanese population that was representative of the cardiovascular continuum of disease.[22] Our hypothesis was that treatment with valsartan would yield additional protective benefits, compared with conventional treatment, beyond those attributable to control of blood pressure.

Methods

Participants

Our study design, organisation, clinical measurements, endpoint definitions, power calculations, and recruitment rates have been published previously.[23] Briefly, between January, 2002, and December, 2004, we recruited patients to an investigator-initiated, independent, investigator-led, multicentre, controlled trial.[23] Participating centres included the four hospitals of the Jikei University in Tokyo, which has some of the largest inpatient and outpatient facilities in Japan, and 17 associated hospitals led by physicians from Jikei University.[23] We used a prospective randomised open blinded endpoint (PROBE) design.[24]

We recruited patients with hypertension, coronary heart disease, heart failure, or a combination of these cardiovascular disorders. The study population was selected and stratified to be representative of the range of cardiovascular disease in a Japanese population. Participants could be 20–79 years of age, and of either sex. Patients with hypertension must have been diagnosed at least 3 months before enrolment, and have been under treatment with antihypertensive drugs. Patients with coronary heart disease were enrolled if they had either a history of the disease or had been newly diagnosed on the basis of typical symptoms, with coronary angiography showing at least one coronary stenosis of more than 75%. Patients with heart failure (New York Heart Association [NYHA] class II–IV), diagnosed on the basis of a historically low ejection fraction (echocardiography) or diastolic dysfunction, were enrolled if they had received standard treatment (diuretics, angiotensin-converting enzyme [ACE] inhibitors, β blockers, or a combination of these) for at least 4 weeks before enrolment.

Exclusion criteria included acute coronary syndrome or myocardial infarction within 6 months, any cerebrovascular event within 3 months, serum creatinine higher than 265 μmol/L, potassium higher than 5 mmol/L, treatment with an angiotensin receptor blocker 4 weeks or less before randomisation, or judgment by the physician that participation was unwise on the basis of patient characteristics and drug safety.

We used good clinical practice guidelines in accordance with the Declaration of Helsinki. Institutional review boards at every participating hospital approved the protocol and subsequent amendments. At the first hospital visit, 4 weeks before randomisation, we carefully explained the trial objectives and study design, and the risks and benefits of participation to all patients and obtained written informed consent. Patient privacy was strictly protected. The study was registered at register.clintrials.gov with the identification number NCT00133328.

Study design

Eligible patients with more than one cardiovascular disorder were stratified into groups according to the following sequence of severity: heart failure, coronary heart disease, and hypertension. We then used a computer-generated list of random numbers to assign patients to receive either valsartan or conventional treatment. We used the minimisation method[25] to adjust for baseline characteristics. Investigators entered all patient data on a secure website. Electronic case report forms were then transferred to the data centre in Kobe. A data management team updated the database every month. All data were kept independently of the funding source.

The primary endpoint was a composite of cardiovascular mortality and morbidity. Components of the endpoint included the following: hospital admissions for stroke or transient ischaemic attack (neurological deficit persisting for less than 24 hours); myocardial infarction (chest pain, ECG-changes, and biomarkers for myocardial necrosis); admission for congestive heart failure (clinical symptoms including dyspnoea, shortness of breath, and peripheral oedema, together with left ventricular dysfunction by echocardiography, according to the guidelines of the American College of Cardiology and American Heart Association [AHA/ACC]); admission because of angina pectoris (diagnosed as ECG changes along with chest discomfort or pain, with documented coronary heart disease according to AHA/ACC guidelines); dissecting aneurysm of the aorta (diagnosed by imaging technique); doubling of serum creatinine; or transition to dialysis. The first of these events to arise in any specific patient was noted as the primary event.

Any component of composite primary endpoint for which a patient could be counted once in each category was treated as a secondary endpoint. Death from any cause was also designated a secondary endpoint. A cardiovascular event was regarded as causal of death on the basis of the judgment of a participating physician, irrespective of the time between the event and death.

Procedures

At enrolment we recorded patients' demographics and baseline characteristics, including sex, age, height, bodyweight, symptoms and signs, and risk factors for cardiovascular disease (smoking, hyperlipidaemia, and diabetes mellitus). We assessed cardiac function, cardiac remodelling, and renal function at baseline and at 6-month intervals. The general clinical laboratory tests were urinalysis (proteinuria); blood chemistry (creatinine, sodium, potassium, total cholesterol, triglyceride, low density lipoprotein cholesterol and high density lipoprotein cholesterol, plasma glucose, and haemoglobin A_{1c}) measured in the fasting state after an overnight 12 h fast; electrocardiography (ECG); echocardiography (left ventricular diastolic dimension, ventricular systolic dimension, ejection fraction, fractional shortening, intraventricular septum, and posterior wall thickness); and chest radiogram. We assessed the quality of life of patients with congestive heart failure with the modified Minnesota living with heart failure and NYHA cardiac functional class scales.[26] Patients could be seen every 2–4 weeks, at least every 6 months for up to 3·5 years. At every visit, a skilled

physician took standard blood pressure measurements, with the patient at rest (5–10 min) in the sitting position, with a validated mercury sphygmomanometer. The mean of three measurements was calculated and recorded. The timing of blood pressure measurement was not constant in relation to patients' intake of medication.

We aimed to control blood pressure in both treatment groups to less than 130/80 mm Hg. Figure 1 shows the phases of treatment in our study protocol. Hypertensive patients in the valsartan group were initially given 80 mg of valsartan orally, once daily in the morning, flexibly adjusted to a dose of 40–160 mg per day, as needed to control blood pressure. Patients with heart failure or coronary heart disease in the valsartan group were started on 40 mg once daily and uptitrated as tolerated. Controls were given either an increased dose of their existing treatment or an additional conventional treatment to achieve the blood pressure goal.

Diagnoses of endpoints were verified automatically by the computer system and by a data monitoring committee consisting of four expert cardiologists from Jikei University. An independent endpoint committee of three members who were not affiliated with the University, all of whom were unaware of treatment allocation, also adjudicated the diagnoses. The endpoint committee reviewed all available documentation, including patient records. Endpoints were confirmed only after agreement from all members of this committee.

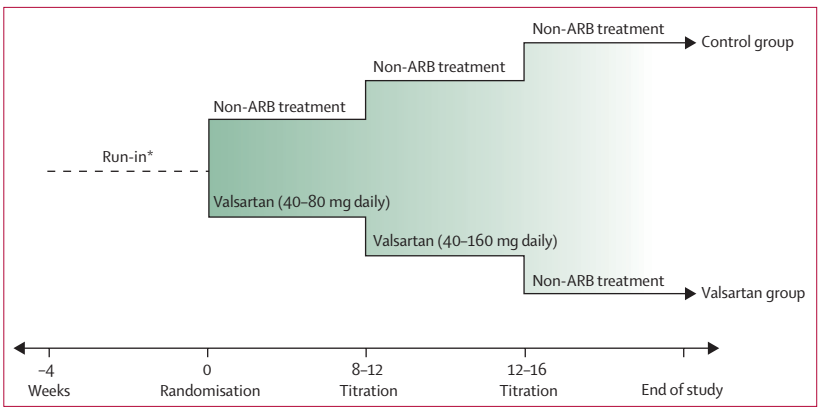

Figure 1: **Schematic of study protocol with treatment phases**
Doses of valsartan were given once daily. ARB=angiotensin receptor blocker. *Both groups given conventional non-ARB treatment.

Statistical analysis

Few epidemiological data about cardiovascular risk profiles in Japan were available. Information about the prognosis of patients treated by specialist doctors at specialised hospitals was especially scarce. Although the cardiovascular event rate in the Japanese population is low, the hospitals participating in our study undertake tertiary care of cardiovascular disease and therefore treat more severely ill patients than those seen in other hospitals. We estimated that the 3-year event rate for cardiac mortality and morbidity for patients with complicated cardiovascular disease would be about 12%. The findings of a retrospective investigation of a few patients under treatment at our participating sites were almost identical to this estimate.

Since our study was event-driven, we calculated that to include 300 primary events, we would need a sample size of at least 3000 patients, followed up for an average of 3 years. We assumed that the valsartan group would achieve a 20% reduction of risk compared with the conventional treatment group, giving our study 80% statistical power and an α error of less than 5% if 10% of patients discontinued treatment or were lost to follow-up.

Analyses were based on intention to treat. The statistical analysis group at Osaka City University, which was independent of the study implementation group and the funding source, did data analyses. We checked that patient characteristics were uniformly distributed between groups, and used Cox's proportional hazard regression analysis to compare the rate of event development. For primary analysis of intergroup differences in endpoints we used inference testing (95% CIs) with significance defined at an α level of less than 5%. Hazard ratios were calculated and adjusted for sex, age, hypercholesterolaemia, diabetes mellitus, smoking, and concomitant antihypertensive treatment with Cox's proportional hazard model. To assess significance, we compared categorical data between groups with the χ^2 test or Fisher's exact test and compared quantitative data between groups with the *t* test or analysis of variance. We compared the total number and rate of adverse events for each group.

Our data safety and monitoring board reviewed effectiveness and safety at regular intervals throughout the study. This board did three interim analyses, with the O'Brien–Fleming method,[27] beginning 6 months after the

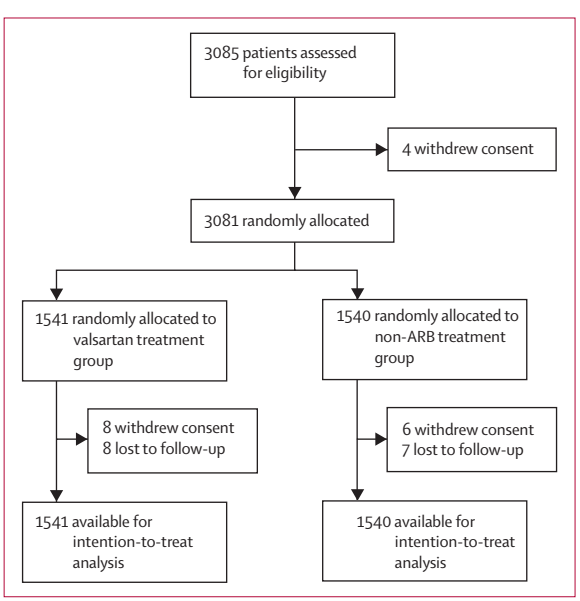

Figure 2: **Trial profile**

	Valsartan treatment group (n=1541)	Non-ARB treatment group (n=1540)
Sex (female)	521 (34%)	517 (34%)
Age (years)	65 (10)	65 (10)
Current smoker	259 (17%)	262 (17%)
Systolic blood pressure (mm Hg)	139·2 (11·4)	138·8 (10·6)
Diastolic blood pressure (mm Hg)	81·4 (10·5)	81·4 (10·8)
Heart rate (beats per min)	71 (11)	72 (11)
Body-mass index (kg/cm^2)	24 (3)	24 (3)
Electrocardiograph (S V1 wave and R V5/V6 wave, mm)	29 (11)	28 (11)
HbA_{1c} (%)	5·6% (1·0%)	5·6% (1·0%)
Total cholesterol (mmol/L)	5·4 (0·9)	5·4 (0·9)
LDL cholesterol (mmol/L)	3·2 (0·8)	3·1 (0·8)
HDL cholesterol (mmol/L)	1·4 (0·4)	1·4 (0·4)
Triglyceride (mmol/L)	1·7 (0·9)	1·7 (1·0)
Fasting plasma glucose (mmol/L)	6·5 (1·9)	6·6 (2·2)
Serum creatinine (μmol/L)	71 (18)	71 (18)
Sodium (mmol/L)	142 (2·5)	142 (2·8)
Potassium (mmol/L)	4·2 (0·4)	4·2 (0·9)
Medical history		
Hypertension	1358 (88%)	1341 (87%)
Coronary heart disease	514 (33%)	522 (34%)
Heart failure	176 (11%)	174 (11%)
Hyperlipidaemia	812 (53%)	813 (53%)
Diabetes mellitus	315 (20%)	314 (20%)

ARB=angiotensin receptor blocker. LDL=low-density lipoprotein. HDL=high-density lipoprotein. Hb=haemoglobin. Data are mean (SD) or number (%).

Table 1: **Baseline characteristics**

last person had been enrolled. In December, 2005, the data safety and monitoring board recommended that the study should be stopped for ethical reasons, because additional valsartan treatment was associated with a reduction in the primary endpoint (p<0·001, adjusted for three interim analyses). This recommendation was endorsed by the executive and steering committees. In January, 2006, all patients were recalled for final visits. Since the event rate was lower and the risk reduction larger than expected, the premature end of the study coincided with the planned duration of follow-up.

Role of the funding source

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 had final responsibility for the decision to submit for publication.

Results

Figure 2 shows the trial profile and table 1 the baseline characteristics for all the 3081 patients who were assigned to treatment. The two treatment groups were well matched for baseline characteristics: all patients were Japanese, with a mean age of 65 years, a mean body-mass index (BMI) of 24 kg/m^2, and a blood pressure of 139/81 mm Hg. About a third were female. Patients were censored at death or at last known visit, with a median follow-up of 3·1 years (SD 0·8, range 1–3·9). In total the study gathered information for 8627 patient years (4326 in the valsartan group and 4321 in the control group). Figure 2 shows that 14 patients (0·5%) withdrew consent after random allocation and 15 patients (0·5%) were lost to follow-up. We obtained complete endpoint information at the end of the study for 3052 patients.

Table 1 shows that, at baseline, blood pressure in both groups combined was at a mean of 139/81 mm Hg (SD 11/11). Throughout the study it fell to 131/77 mm Hg (12/8) in the valsartan group, and 132/78 (11/8) mm Hg in controls. The changes in blood pressure were 8·2/4·7 mm Hg in the valsartan treatment group and 7·2/3·7 mm Hg in controls. At the end of the trial only 122 (4%) of patients in both groups had blood pressure greater than 140/90 mm Hg. 1118 (75%) of patients given valsartan and 1033 (70%) in the control group achieved the target blood pressure of less than 130/80 mm Hg. The Levene test for equality of variances showed no differences between the groups. Blood pressure and heart rate did not differ between the valsartan regimen and the control regimen throughout the trial (table 3, p=0·196 for

	All patients	Valsartan group	Non-ARB treatment group	Patients with hypertension	Patients with coronary heart disease	Patients with heart failure
Calcium-channel blocker	2052 (67%)	1041 (68%)	1011 (66%)	1933 (72%)	626 (60%)	108 (31%)
ACE inhibitor	1073 (35%)	548 (36%)	525 (34%)	979 (36%)	340 (33%)	173 (49%)
β blocker	988 (32%)	486 (32%)	502 (33%)	897 (33%)	342 (33%)	145 (41%)
α blocker	167 (5%)	74 (5%)	93 (6%)	164 (6%)	32 (3%)	13 (4%)
Thiazide	68 (2%)	29 (2%)	39 (3%)	63 (2%)	10 (1%)	13 (4%)
Antialdosterone agent	116 (4%)	52 (3%)	64 (4%)	81 (3%)	31 (3%)	81 (23%)
Other diuretics	243 (8%)	117 (8%)	126 (8%)	170 (6%)	78 (8%)	162 (46%)
Statin	951 (31%)	461 (30%)	490 (32%)	807 (30%)	515 (50%)	58 (17%)
Fibrate	79 (3%)	42 (3%)	37 (2%)	70 (3%)	27 (3%)	5 (1%)

ARB=angiotensin receptor blocker. ACE=angiotensin-converting enzyme.

Table 2: **Medication at baseline**

	Baseline		Month 6		Month 12		Month 24		End of study	
	Valsartan (n=1541)	Control (n=1540)	Valsartan (n=1139)	Control (n=1127)	Valsartan (n=1479)	Control (n=1486)	Valsartan (n=1148)	Control (n=1170)	Valsartan (n=433)	Control (n=454)
Blood pressure										
Mean SBP (mm Hg)	139·2 (11)	138·8 (11)	131·5 (15)	133·6 (13)	130·4 (14)	131·9 (14)	131·9 (14)	132·2 (13)	132·0(14)	132·0 (14)
Mean DBP (mm Hg)	81·4 (11)	81·4 (11)	76·1 (9)	78·2 (10)	76·2 (9)	77·5 (10)	77·1 (9)	77·3 (9)	76·7 (8)	76·6 (9)
Pulse rate (bpm)	71·4 (11)	71·7 (10)	72·0 (10)	72·4(10)	70·9 (10)	70·9 (10)	69·8 (11)	70·0(10)	70·3(10)	71·0 (9)
Medications*										
Valsartan	0	0	0·93	0	0·93	0	0·93	0	0·95	0
ACE inhibitor	0·42	0·48	0·38	0·50	0·38	0·60	0·33	0·56	0·29	0·58
CCB	0·81	0·76	0·79	0·89	0·70	0·87	0·67	0·87	0·67	0·95
βblocker	0·23	0·18	0·22	0·19	0·23	0·21	0·20	0·21	0·20	0·22
All diuretics	0·07	0·07	0·11	0·14	0·07	0·17	0·07	0·20	0·06	0·17
All antihypertensive drugs	1·79	1·79	2·69	2·11	2·55	2·39	2·55	2·39	2·41	2·44

SBP=systolic blood pressure. DBP=diastolic blood pressure. ACE=angiotensin-converting enzyme. CCB=calcium-channel blocker. bpm=beats per minute. *Doses of individual drugs adjusted as fractions of the standard dose of those drugs in Japan. For example, the standard dose of valsartan is 80 mg; if 90% of patients took an average dose that was 110% of this standard dose, the dose-adjusted figure would be 99% (0·9×1·1). For valsartan, the dose-adjusted figure was 95% at the end of the study, representing an average dose of 76 mg.

Table 3: **Patient characteristics and medications throughout the study in the two treatment groups**

	Valsartan group		Non-ARB treatment group		Hazard ratio (95% CI)	p value
	Number of events	Rate per 1000 patient years	Number of events	Rate per 1000 patient years		
Primary endpoint Composite endpoint	92 (6·0%)	21·3	149 (9·7%)	34·5	0·61 (0·47–0·79)	0·0002
Secondary endpoints Stroke or transient ischaemic attack	29 (1·9%)	6·7	48 (3·1%)	11·1	0·60 (0·38–0·95)	0·0280
New or recurrent acute myocardial infection	17 (1·1%)	3·9	19 (1·2%)	4·4	0·90 (0·47–1·74)	0·7545
New occurrence or exacerbation of angina pectoris needing hospitalisation	19 (1·2%)	4·4	53 (3·4%)	12·3	0·35 (0·20–0·58)	0·0001
New occurrence or exacerbation of heart failure needing hospitalisation	19 (1·2%)	4·4	36 (2·3%)	8·3	0·53 (0·31–0·94)	0·0293
Dissecting aneurysm of the aorta	2 (0·1%)	0·5	10 (0·6%)	2·3	0·19 (0·04–0·88)	0·0340
Transition to dialysis, doubling of serum creatinine levels	7 (0·5%)	1·6	8 (0·5%)	1·9	0·93 (0·34–2·61)	0·8966
All-cause mortality	28 (1·8%)	6·5	27 (1·8%)	6·3	1·09 (0·64–1·85)	0·7537
Cardiovascular mortality	9 (0·6%)	2·1	9 (0·6%)	2·1	1·03 (0·41–2·60)	0·9545

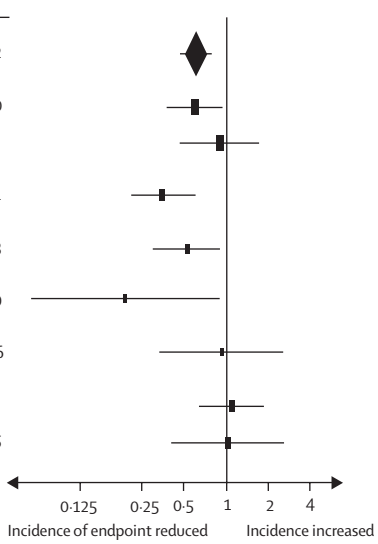

Figure 3: **Effect of treatment on all endpoints**

Hazard ratios are adjusted for sex, age, hypercholesterolaemia, diabetes, smoking, and concomitant antihypertensive treatment. Diamonds and squares indicate the hazard ratio estimate for each type of event; horizontal lines show 95% CIs.

systolic blood pressure and p=0·176 for diastolic blood pressure at end of study).

Table 2 shows patients on medication at baseline: about two-thirds were receiving a calcium antagonist, a third an ACE-inhibitor, another third a β blocker, a tenth a diuretic, and almost a third a statin. A webtable sets out all doses of antihypertenstive medications in more detail. The average additional dose of valsartan was 75 (SD 14) mg per day. Other additional treatments in both groups were mainly calcium-channel blockers, ACE-inhibitors, and β blockers (table 3). The average number of antihypertensive drugs taken during the study was slightly higher in the valsartan group than in controls. However, when doses for all drugs were adjusted to a standard dose, according to Japanese clinical practice, the dose-adjusted numbers of drugs for all treatment groups were identical at the end of the study (table 3). Table 4 shows selected biochemical results.

See Online for webtable

Figure 3 shows that the primary endpoint was recorded in fewer patients given valsartan (92, 6·0%) than in those given additional non-ARB treatment (149, 9·7%); the hazard

	Valsartan treatment group (n=1541)			Non-ARB treatment group (n=1540)			Between-group comparison		Between-group comparison	
	Baseline n=1488	Follow-up visit n=1541	Change	Baseline n=1489	Follow-up visit n=1540	Change	Baseline	p	Mean value at follow-up	p
HbA_{1c} (%)	5·6 (1·0)	5·7(0·9)	0·1(0·5)	5·6 (1·0)	5·7 (0·9)	0·1 (0·5)	−0·01 (−0·08–0·06)	0·8059	−0·01 (−0·08–0·05)	0·6761
Total cholesterol (mmol/L)	5·4 (0·9)	5·2 (0·7)	−0·1 (0·6)	5·4 (0·9)	5·2 (0·1)	−0·1(0·6)	0·02 (−0·04–0·09)	0·4705	0·03 (−0·03–0·08)	0·3208
LDL cholesterol (mmol/L)	3·2 (0·8)	3·1 (0·7)	−0·1 (0·6)	3·1 (0·8)	3·1 (0·7)	−0·1 (0·6)	0·02 (−0·04–0·07)	0·5510	0·03 (−0·02–0·08)	0·2385
HDL cholesterol (mmol/L)	1·4 (0·4)	1·4 (0·3)	−0·02 (0·2)	1·4 (0·4)	1·4 (0·3)	−0·02 (0·2)	−0·01 (−0·04–0·01)	0·3696	−0·01 (−0·04–0·01)	0·3119
Triglyceride (mmol/L)	1·7 (0·9)	1·7 (0·8)	−0·05 (0·3)	1·7 (1·0)	1·6 (0·8)	−0·03 (0·7)	0·04 (−0·02–0·11)	0·2036	0·02 (−0·04–0·08)	0·4747
Fasting plasma glucose (mmol/L)	7·0 (2·1)	7·0 (1·9)	0·05 (1·6)	7·0 (2·2)	7·1 (2·0)	0·1 (1·7)	−0·08 (−0·24–0·07)	0·2968	−0·09 (−0·24–0·05)	0·1839
Serum creatinine (μmol/L)	71 (18)	71 (18)	1·8 (8·9)	71 (18)	71 (18)	1·8 (8·9)	0·35 (−1·1–1·8)	0·6261	0·46 (−1·1–2·0)	0·5560
Sodium (mmol/L)	142 (2·5)	142 (2·0)	0·5 (2·2)	142 (2·8)	142 (1·9)	0·4(2·4)	0·05 (−0·03–0·13)	0·2268	0·07 (0·01–0·13)	0·0228
Potassium (mmol/L)	4·2 (0·4)	4·3(0·3)	0·07 (0·9·)	4·2 (0·9)	4·3(0·3)	0·02(0·9)	−0·01 (−0·02–0·003)	0·1169	0·004 (-0·002–0·01)	0·2207
eGFR (mL/min per 1·73 m2)	88·1 (23)	85·7(22)	−2·4 (10·1·)	88·7 (23)	86·6(22)	−2·2(11·3)	−0·60 (−2·2–1·0)	0·4699	−0·84 (-2·4–0·7)	0·2964

Values are mean (SD). Hb=haemoglobin. eGFR=estimated glomerular filtration rate (normal range of 90–130 mL/min per 1·73 m^2).

Table 4: **Biochemical variables**

ratio was 0·61 (95% CI 0·47–0·79, p=0·0002). This endpoint was a composite of several secondary endpoints (figure 3). The difference in the number of primary endpoints was mainly attributable to reduced frequency of stroke and transient ischaemic attack, angina pectoris, and heart failure. 29 patients given valsartan had stroke or transient ischaemic attack, compared with 48 controls (HR 0·60, 95%CI 0·38–0·95, p=0·028); 19 patients given valsartan had angina pectoris compared with 53 controls (HR 0·35, 95%CI 0·20–0·58, p=0·0001); 19 patients given valsartan had heart failure, compared with 36 controls (HR 0·53, 95%CI 0·31–0·94, p=0·0293); and two patients given valsartan had dissecting aneurysm of the aorta, compared with ten controls (HR 0·19, 95%CI 0·04–0·94, p=0·0293). Mortality, myocardial infarction, or progression of renal disease did not differ between groups.

The event rate curves in figure 4 show that, excluding any of the components of the primary endpoint, the overall significance of the primary endpoint was maintained in all cases. For the endpoint of stroke or transient ischaemic attack, nearly all events were strokes: 25 strokes and four transient ischaemic attacks in the valsartan group, and 43 strokes and five transient ischaemic attacks in the conventional-treatment group.

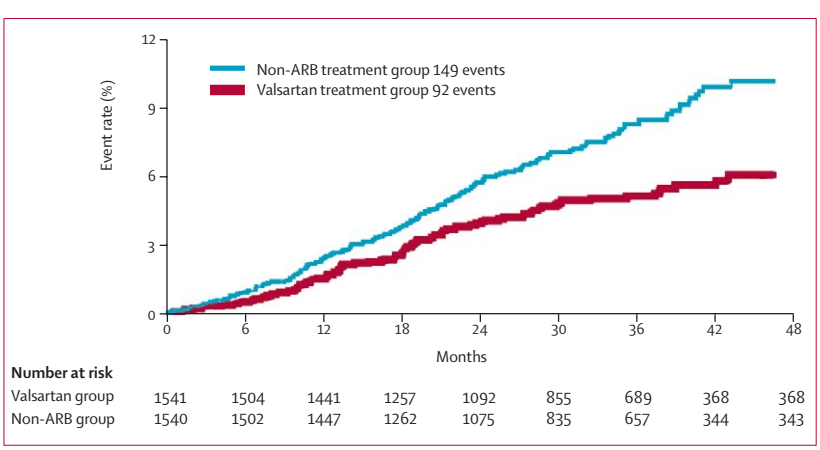

Figure 4: **Kaplan-Meier curves of cumulative frequency of the primary endpoint**

Table 5 shows that only 2·5% of patients reported any adverse event during the study, with no significant difference between treatment groups. The only difference between the groups was a higher incidence of dizziness in the valsartan group, with nine cases compared with three in the control group.

Discussion

Addition of the angiotensin receptor blocker valsartan to standard cardiovascular treatment, compared with an increased dose or number of standard drugs, in Japanese patients with cardiovascular disease, reduced the incidence of the primary composite endpoint, of heart, brain, and kidney complications. The main effect of addition of valsartan was to reduce stroke, angina pectoris, dissecting aortic aneurysm, and heart failure. These benefits were noted despite a short median follow-up of 3·1 years, and were seen across various subgroups (data not shown).

Unfortunately, Asian patients have often been under-represented in cardiovascular trials, including trials of angiotensin receptor blockers. For example, Asians made up 2·8%, 3·5%, and less than 2% of the populations in the Val-HeFT trial,[6] the VALUE trial,[16] and the LIFE trial,[11] respectively. None of these trials included a Japanese centre. One previous study on the effects of the angiotensin receptor blocker candesartan compared with standard treatment in a hypertensive Japanese population[21] had shortcomings such as deficiencies in randomisation and quality control, and large numbers lost to follow-up.

Patients in both treatment groups showed a similar degree of blood pressure control, achieving good control of the same magnitude. Since this was an active-controlled study, we could not ascertain to what degree regression-to-the-mean or placebo effects might have contributed to the result.

The mean dose of valsartan in this study (75 mg) might seem low, but studies in Japanese people have shown that 80 mg of valsartan produced similar antihypertensive effects to those of nifedipine (20 mg)[28] and amlodipine (5 mg).[29] Moreover, because the mean BMI in our study was low (24, compared with the VALUE trial, for which mean BMI was 28),[16] the doses we used would seem sufficient. Doses of all antihypertensive drugs, including valsartan, were based on the guidelines of the Japanese Hypertension Society.[30]

The Kaplan-Meier curves for the primary endpoint diverged early and separated throughout the trial (figure 4), indicating that the response to treatment was early and sustained. The overall reduction in the primary composite endpoint was not driven by any one component, indicating a broad range of benefit—ie, a reduction of the total burden of cardiovascular disease. The effects on myocardial infarction and renal endpoints were neutral. However, event rates for secondary endpoints were low, and these results should not be overinterpreted.

Some further comments are warranted. The reduction in angina with valsartan treatment (65%) was not matched by a similar reduction in myocardial infarction, although some underlying pathophysiological processes would be similar. However, other large-scale trials such as LIFE[11] and VALUE[16] have also failed to show significant differential effects of myocardial infarction with angiotensin receptor blockers compared with other treatments, despite other cardiac benefits. We could speculate that the renin–angiotensin–aldosterone system 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. A possible caveat should be noted: the PROBE design used in our study carries a risk of under-reporting, especially for softer endpoints such as angina. However, we believe that such a scenario would be highly unlikely to account for differences between groups of the magnitude we recorded.

Adverse events (n≥2)	Valsartan	Control group	Total
Cancer or metastasis	7	7	14
Dizziness	9	3	12
Headache	1	1	2
Rashes	2	0	2
Zoster	0	2	2
Stomach discomfort	2	1	3
Palpitations	1	2	3
Liver function	2	1	3
Fracture	1	2	3
Infraconjunctival haemorrhage	0	2	2
Haemoptysis	0	2	2
Dry cough	1	1	2
Elevated serum potassium	2	0	2
Any adverse event	42	36	78
	2·7%	2·3%	2·5%

Table 5: **Adverse events occurring in more than one case**

The reduction in the risk of stroke with added valsartan treatment was consistent with that reported with losartan in the LIFE study.[11] However, we recorded a much lower absolute risk than that reported by LIFE, which is probably related to the lower mean blood pressure in our study population. The stroke endpoint combines both stroke and transient ischaemic attack, but the rates of transient ischaemic attacks were very low in our study. Debate about the degree to which reduction of stroke in the LIFE trial should be attributed to losartan and how much to a lack of stroke benefits in the group given the comparator (atenolol) is unresolved.[31] In our study, atenolol was used in only 5% of patients in each group. In both studies, benefits for stroke reduction were noted at a similar degree of blood pressure control in treatment and control groups.

These findings contrast with the VALUE trial,[11] in which valsartan treatment did not reduce the frequency of strokes compared with amlodipine. In the VALUE trial, blood pressure differed much more between the groups, consistent with the notion that stroke risk is mainly, but not entirely, related to blood pressure, especially in high-risk patients.[32] Any benefits associated with valsartan treatment in the VALUE trial could possibly have been masked by the early differences in blood pressure. The low blood pressures in our study, and the fact that they were similar in both treatment groups, suggest that blood pressure was not a major determinant of outcomes. Furthermore, stroke rates did not cluster early, although any (minor) blood pressure differences were only seen during the first 12 months. The possible benefits of angiotensin receptor blockers indicated in our study are highly relevant to the Japanese population, in which stroke causes four times more mortality and morbidity than does coronary heart disease.[33]

Our study participants represented a range of cardiovascular risk and disease. The range of patients was broader than in most other intervention studies, which have focused on particular stages of cardiovascular disease. Although limiting patient heterogeneity in that regard would have simplified interpretation of the results, such a strategy could also have limited the clinical implications of the findings. The cardiovascular diseases represented in our study population—hypertension, coronary heart disease, and heart failure—are all disorders in which activation of the renin–angiotensin–aldosterone system is thought to play a major part.[22,34]

Some further limitations of our study suggest possibilities for further investigation. First, the use of aortic dissection or peripheral arterial disease as a component of the primary endpoint is uncommon, although not unique to this study. Aortic dissection or lower limb arterial obstruction was reduced in the valsartan group, although the number of events was very low. Since blood pressure was similar between the two treatment groups, the reduced aortic dissection could indicate that valsartan had a beneficial

effect on the aortic wall. Second, neither transition to dialysis nor doubling of creatinine concentrations were associated with cardiovascular benefits from valsartan. These events are standard endpoints in trials to assess the renal protection of angiotensin receptor blockers in diabetic patients with nephropathy.[14,35] However, since numbers of participants with impaired renal function in our study were low, our findings lack sufficient power to draw any conclusions.

A third limitation of our study was that doses of ACE inhibitors given to some patients before the start of our study were low by western standards, although consistent with clinical practice recommendations in Japan. Thus, we have no proof that the renin–angiotensin–aldosterone system had been adequately inhibited before the trial, and we cannot exclude the possibility that the results would have differed in patients who had already been given high doses of ACE inhibitors, or that increasing the ACE inhibitor dose would have provided benefits in these patients. Last, our study was not adequately powered to detect changes in cardiovascular or all-cause mortality and our median follow-up of 3·1 years was short.

Contributors

SM and BD designed the study, wrote the protocol, supervised the implementation of the research, coordinated data collection, wrote the analysis plan, supervised the analyses, interpreted the results, and wrote the report. All members of the steering committee approved the protocol and analysis plan, supervised the study and had input to the report. All authors have seen and approved the final version.

Study organisation

Executive committee

Jikei University School of Medicine—Seibu Mochizuki; *Sahlgrenska University Hospital/Östra*—Bjorn Dahlöf.

Steering committee

Jikei University School of Medicine—Seibu Mochizuki, Mitsuyuki Shimizu, Ikuo Taniguchi, Katsunori Ikewaki, Kenichi Sugimoto, Kazuhiko Ogawa, Tsuneo Mizokami, Takahiro Shibata, Satoru Yoshida, Kenichi Hongo, Hideki Sasaki, Naofumi Aoyama, Hidenori Yagi, Takayuki Ogawa, Syunrou Minami, Fumiko Okazaki, Kiyoshi Kanae, Masayuki Taniguchi, Shingo Seki, Makoto Yoshikawa, Tatsuo Yamazaki, Taku Yamada, Mie Kawai, Hidetoshi Kajiwara, Kenji Noma; *West-Saitama Central Hospital*—Tatsuyuki Onodera; *Tsunan Metropolitan Hospital*—Shinichiro Ishikawa, Yusaku Hayashi; *Fuji City Central Hospital*—Hidefumi Mikawa; *Atsugi Metropolitan Hospital*—Kenichi Maie, Nobunori Tominaga; *Saitama Cardiovascular and Respiratory Centre*—Makoto Muto; *Shonan Hospital*—Noriaki Yoshitake, Hideaki Suzuki; *Oarai-kaigan Hospital*—Osamu Aizawa; *Seki Hospital*—Kiyofumi Suzuki; *Sakuragaoka General Hospital*—Tetsushi Ito.

Endpoint committee

Ehime University—Masatsugu Horiuchi; *Toho University*—Junichi Yamazaki; *Osaka University*—Hiromi Rakugi.

Safety committee

Jikei University School of Medicine—Shigeru Kageyama, Tetsuo Sato, Masato Matsushima, Shigeto Murakami .

Sub-study committee

Jikei University School of Medicine—Mitsuyuki Shimizu, Naoko Tajima, Ikuo Taniguchi, Kiyoshi Kanae, Kazunori Utsunomiya, Kenichi Sugimoto, Katsunori Ikewaki, Satoru Yoshida, Hideaki Kurata.

Writing committee

Jikei University School of Medicine—Seibu Mochizuki, Mitsuyuki Shimizu, Katsunori Ikewaki; *Sahlgrenska University Hospital/Östra*—Björn Dahlöf.

Statistics analysis organisation

Clinical epidemiology, Osaka City University Graduate School—Nobuo Shirahashi.

Investigators

Division of Cardiology, Jikei University School of Medicine—Seibu Mochizuki, Ikuo Taniguchi, Katsunori Ikewaki, Makoto Ohta, Kenichi Sugimoto, Kazuhiko Ogawa, Satoru Yoshida, Takahiro Shibata, Kenichi Hongo, Hideki Sasaki, Teiichi Yamane, Naofumi Aoyama, Makoto Kawai, Hidenori Yagi, Kimiaki Komukai, Takayuki Ogawa, Fumiko Okazaki, Ryuko Anzawa, Taro Date, Sahachiro Nakae, Hisashi Takatsuka, Tadashi Tamura, Tsuneo Mizokami, Osamu Kurusu, Eriko Yokomizo, Yuji Higaki, Hidehiko Kashiwagi, Koichi Marutani, Koshin Mizuniwa, Tomohisa Sakai, Tokuo Kasai, Keiji Iwano, Atsushi Seo; *Division of Diabetes and Endocrinology, Jikei University School of Medicine*—Naoko Tajima, Yoichi Sakamoto, Hideaki Kurata; *Division of Cardiology, Jikei University School of Medicine, Aoto Hospital*—Shingo Seki, Masayuki Taniguchi, Toru Arino, Chikashi Sato, Satoshi Takeda, Hidekazu Miyazaki, Kiyoshi Kanae, Shuji Nakada, Makoto Miyairi, Akihiko Kagami, Kenji Noma, Izuru Nakamura; *Division of Cardiology, Jikei University School of Medicine, Daisan Hospital*—Makoto Yoshikawa, Kazutoshi Takigawa, Keiichi Chin, Yoshiyuki Hashizume, Yoshihisa Shimazu; *Division of Cardiology, Jikei University School of Medicine, Kashiwa Hospital*—Mitsuyuki Shimizu, Taku Yamada, Masafumi Kusaka, Toshio Hasuda, Yoshiki Uehara, Yoshiyuki Azuma, Shinichiro Takizawa, Hiroshi Yoshida, Tomotake Suzuki, Mie Kawai, Hiroyuki Okumura; *Division of Cardiology, Atsugi Municipal Hospital*—Kenichi Maie, Koichi Hashimoto, Takuya Okada, Nobunori Tominaga, Kazuhiro Aoki; *Division of Cardiology, Fuji City Metropolitan Central Hospital*—Hidefumi Mikawa, Hiroshi Takeda, Satoshi Arase, Katsumi Ohnuki, Kosuke Minai; *Division of Cardiology, Sakuragaoka General Hospital*—Takao Shimada, Tetsushi Ito, Ken Nogimura; *Division of Cardiology, West-Saitama Central Hospital*—Tatsuyuki Onodera, Masao Kuwata, Yumi Nishibayashi; *Division of Cardiology, Saitama Cardiovascular and Respiratory Centre*—Makoto Muto, Tetsuya Ishikawa, Hiroshi Sakamoto, Tetsushi Tsurusaki, Satoru Onoda; *Division of Cardiology, Shonan Hospital*—Noriaki Yoshitake, Hideaki Suzuki, Kunihiko Abe; *Division of Cardiology, Oarai-kaigan Hospital*—Osamu Aizawa, Takehiko Izumi, Kazuaki Horikoshi, Shunichi Tamura; *Division of Cardiology, Machida Metropolitan Hospital*—Syunrou Minami, Satoshi Imamoto, Akimasa Matsuyama; *Division of Cardiology, Seki Hospital*—Kiyofumi Suzuki, Takashi Ito, Jun Koga, Mamoru Kunou; *Division of Cardiology, Tsunan Metropolitan Hospital*—Shinichiro Ishikawa, Yusaku Hayashi; *Division of Cardiology, Tokyo Musashino Hospital*—Takuya Sakamoto, Akihisa Tomaru; *Division of Cardiology, Kanoiwa Metropolitan Hospital*—Takeshi Sato; *Division of Cardiology, Shonan Memorial Hospital*—Hisao Nakamura; *Division of Cardiology, Mitaka Hospital*—Tatsuo Yamazaki; *Division of Cardiology, Higashiyama Takeda Hospital*—Izuru Masuda; *Division of Cardiology, Sagamino Central Hospital*—Takaaki Iwai; *Division of Cardiology, Seirei-Mikatagahara*—Sousuke Miyazawa, Hideki Kajiwara, Tohru Sugiura.

Conflict of interest statement

SM has received lecture fees from Novartis and Daiichi-Sankyo; BD has served as a consultant for and received lecture fees from Boehringer-Ingelheim, Novartis, Merck, and Pfizer and lecture fees from Servier and Astra; MS has received lecture fees from Shionogi; KI has served as a consultant for Japan Tobacco and received lecture fees from Kissei, Sankyo, Astellas, Kowa, and Novartis; NT has served as a consultant for Eli Lilly, Novo Nordisk Pharma, Sanofi-Aventis, and Takeda, and received lecture fees from Astellas, Banyu, Dainippon Sumitomo, Novartis, and Sankyo. None of the other authors had any potential conflict of interest.

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