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ORIGINAL ARTICLE

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

T Sawada[1], T Takahashi[1], H Yamada[1], B Dahlöf[2] and H Matsubara[1], for the KYOTO HEART Study Group

[1]*Department of Cardiovascular Medicine, Kyoto Prefectural University School of Medicine, Kyoto, Japan and* [2]*Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden*

It remains to be determined whether the evidence in Western countries for blockade of the renin–angiotensin System in cardiovascular diseases could be directly applied to East Asian races including the Japanese population as a long-term strategy. The KYOTO HEART Study (KHS) is designed to investigate the add-on effect of valsartan versus conventional anti-hypertensive treatment on cardiovascular morbidity and mortality in Japanese hypertensive patients with uncontrolled blood pressure and with high cardiovascular risk. Over 3000 high-risk Japanese patients with uncontrolled hypertension were randomised to receive either additional treatment with valsartan or conventional non-angiotensin receptor blocker therapies, and the follow-up period will be at least 3 years. The primary end point is a composite of defined cardio- or cerebro-vascular events. Secondary end points include all causes of mortality, worsening of cardiac function, new onset or worsening of arrhythmias or diabetes mellitus. The KHS will provide new evidence for the management of blood pressure in hypertensive patients with high risk.
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Introduction

Hypertension is the most prevalent cardiovascular disease in the world and a major public health issue.[1] Cardiovascular disease is the leading cause of mortality worldwide[2] and is expected to increase with the general ageing of the world's population. The goal of anti-hypertensive therapy is to reduce the incidence of blood pressure-related morbid events and cardiovascular mortality.

The heart is an important target organ of hypertension. Continuous high blood pressure is associated with left ventricular hypertrophy and increases the burden of coronary artery disease (CAD). These forms of damage may result in congestive heart failure, CAD manifestations, arrhythmias and sudden cardiac death. The event rates of cardiovascular disease in Japan differ from those in Europe and the United States. Mortality from CAD in Japan is one-third of that in the United States, and mortality from cerebrovascular disease in Japan is ~1.5 times higher than that in the United States.[3] Hypertension is the most common cause of CAD and heart failure in Japan, and cerebrovascular disease is even more prevalent in the Japanese population than in Western societies.[4] The percentage of cerebral bleeding is two or three times greater than in Caucasian people in Europe and in the United States, and cerebral infarction is mostly caused by lacunar type ischaemic stroke owing to hypertensive small vessel disease.[5] The incidence of athero-thrombotic infarction or cardio-embolic infarction is currently increasing in Japan, and the dominant pathogenetic factor for stroke is changing from small arterial disease to large arterial disease in Japanese hypertensive patients. These differences may be partly explained by differences in the lifestyle of Japanese and Western populations,

Correspondence: Dr T Sawada, Department of Cardiovascular Medicine, Kyoto Prefectural University School of Medicine, Kajiicho 465, Kamigyoku, Kyoto 602-8566, Japan.
E-mail: tsawada@koto.kpu-m.ac.jp
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which are reflected in body mass index (mean BMI: 23–25 and 28–30 kg/m^2, respectively).[6,7] Most of mortality–morbidity trials have been carried out in Western country, in which none or only a minority of East Asian patients were included. Owing to the paucity of large-scale trials in East Asian people, it remains to be determined whether the results from similar clinical trials in Western societies are internationally applicable to East Asian races or the Japanese population, or whether genetic background can cause different pharmacokinetic and pharmacodynamic responses to the same drug.

The renin–angiotensin system (RAS) has a major physiological function in the homoeostasis of blood pressure, electrolytes and fluid balance, and circulatory blood volume.[8] However, chronic activation of RAS contributes to the development of hypertension or cardiovascular target organ damage, ultimately leading to the manifestation of cardiovascular disease.[9] Numerous trials have investigated the benefits of angiotensin-converting enzyme (ACE) inhibitors; the Heart Outcomes Prevention Evaluation Study reported that ACE inhibitors significantly reduced the rates of death, myocardial infarction and stroke in high-risk patients.[10] The beneficial effect observed was probably in some part independent of ramipril-mediated blood pressure lowering actions, and the direct participation of RAS in cardiovascular events was strongly suggested. Another important study investigating the benefit of RAS-blockade in hypertension, in this case with an angiotensin receptor blocker (ARB), was the Losartan Intervention For Endpoint reduction in hypertension study, where losartan-based anti-hypertensive therapy prevented more cardiovascular morbidity and death, and in particular stroke, than an atenolol-based regimen despite similar blood pressure control.[11] The anti-inflammatory properties of ARBs have been reported in hypertensive patients,[12,13] which may contribute to the beneficial action of ARBs beside the anti-hypertensive effects. Very recently, it was shown that the ARB telmisartan is equivalent to ramipril in preventing vascular events in patients with cardiovascular diseases or high-risk diabetes.[14] It is beyond the scope of this introduction to review all the studies showing beneficial effects on cardiovascular outcomes from blocking the RAS, in particular with ARBs, in various stages of the cardiovascular continuum.[15] It is important though to point out that all these studies with a few exceptions have included at maximum a few percentage of Asian patients in general and very few Japanese patients in particular.

The Jikei Heart Study was designed to examine whether the addition of valsartan to conventional cardiovascular treatment is effective in Japanese hypertensive patients with cardiovascular diseases along the whole cardiovascular continuum.[16] The JIKEI Heart study demonstrated a preventive action of valsartan, added to excellent blood pressure control, on major cardiovascular events and in particular the incidences of stroke, heart failure and coronary artery events. In contrast, the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) anti-hypertensive study reported that candesartan-based and amlodipine-based regimens produced no statistical differences between therapies on stroke or cardiovascular events in high-risk Japanese hypertensive patients.[17] The KYOTO HEART Study (KHS) will be important to solve this apparent controversy.

A new guideline on metabolic syndrome has been introduced very recently in Japan. When the patients have hypertension, the definition of metabolic syndrome is made from abdominal obesity plus either dyslipidemia or glucose intolerance, or both. Nevertheless, it remains to be determined how ARBs affect cardiovascular morbid events and mortality in hypertensive patients with metabolic syndrome. The KHS was also designed to examine whether valsartan added to conventional anti-hypertensive treatment influences the cardiovascular events in the hypertensive patients with the metabolic syndrome as well as how it improves the morbidity and mortality in other high-risk Japanese patients with uncontrolled hypertension.

Methods

Study design

The KHS is a multi-centre (31 hospitals), Prospective, Randomised, Open-labeled, Blinded Endpoints (PROBE),[18] two-arm parallel treatment group comparison with a response-dependent dose titration scheme.

Study objectives

The objective of KHS is to assess the add-on effect of valsartan, an ARB, on top of conventional anti-hypertensive treatment in uncontrolled hypertensive patients with cardiovascular disease or at least one additional risk factor indicating high-risk with respect to cardiovascular morbidity and mortality, compared with titration by non-ARB therapy.

Patient population

The eligible population consists of Japanese hypertensive patients (men and women, $\geqslant$20 years old) whose blood pressures have been uncontrolled for at least 4 weeks. Uncontrolled hypertension was defined as a mean sitting systolic blood pressure $\geqslant$140 mm Hg, and/or a mean sitting diastolic blood pressure $\geqslant$90 mm Hg in the outpatient clinic. Skilled physicians took standard blood pressure measurements with patients at rest (5–10 min) in the sitting position with a validated mercury sphygmomanometer in accordance with the guidelines proposed by the Japanese Society of Hypertension.[19] The mean of $\geqslant$3 consecutive blood pressure

measurements was calculated and recorded. The timing of blood pressure measurement was not constant in relation to patients' intake of medication. When patients were already treated for hypertension, anti-hypertensive drugs other than ARB were administered for the first 4 weeks and then if still uncontrolled ($\geqslant$140/90), they were considered as candidates for the study. Uncontrolled hypertensive patients treated with ACE inhibitors before randomisation could also participate in this study. Uncontrolled hypertensive patients who had been treated with ARB, but were not treated with ARB within 4 weeks before randomisation, could participate in this study.

When these uncontrolled hypertensive patients had at least one of CAD signs (angina pectoris or a history of myocardial infarction >6 months before the screening), cerebrovascular diseases (a history of stroke or transient ischaemic attack >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 cardiovascular risk factors mentioned below, they were randomised into the trial. The cardiovascular risk factors included type II diabetes mellitus (defined as fasting plasma glucose $\geqslant$126 mg per 100 ml, causal blood glucose $\geqslant$200 mg per 100 ml, glycosylated hemoglobin (HbA1c) $\geqslant$6.5%, and/or plasma glucose 2 h after 75 g glucose load $\geqslant$200 mg per 100 ml or current treatment with anti-diabetic agents), current smoking, lipid metabolism abnormality (defined as low-density lipoprotein cholesterol $\geqslant$140 mg per 100 ml, and/or triglyceride $\geqslant$150 mg per 100 ml or current treatment with anti-dyslipidemia agents), obesity (defined as body mass index $\geqslant$25 kg/m^2) and/or left ventricular hypertrophy defined by the electrocardiogram (ECG), centrally read at a core-lab.[20]

Exclusion criteria

The exclusion criteria were set as follows: (1) malignant or secondary hypertension; (2) pregnant women or women of childbearing potential; (3) history of worsening heart failure, unstable angina, myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within the preceding 6 months; (4) arrhythmia needing to be treated or accompanied with symptoms including second or third degree atrioventricular block; (5) renal impairment (serum creatinine level >3.0 mg per 100 ml); (6) hepatic impairment (hepatic failure, cirrhosis, etc.); (7) history of cerebral infarction, cerebral haemorrhage or transient ischaemic attack within the past 6 months; (8) allergy of potential clinical concern; (9) electrolyte abnormality (remarkable change in sodium or potassium); (10) history of malignant tumour including leukaemia and lymphoma; and (11) patients who were unwilling or unable to comply with the trial protocol.

Informed consent

The protocol was approved by the Ethics Committee at each participating centre. At the first clinic visit, the trial objectives, study design, and the risks and benefits of study participation were explained carefully to each patient, and subsequently written and signed informed consent was obtained.

Study procedures

The titration schedule of the study is shown in Figure 1. After confirming the eligibility for patient's enrolment into this study, patients were randomised in accordance with the minimisation method,[21] which consisted of eight factors (age, gender, dyslipidemia, 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 add-on treatment group. For the valsartan add-on group, valsartan 80 mg once daily was administered in the morning to the patient as an initial dose and flexibly adjusted to a dose of 40–80 mg per day as needed to control blood pressure. The dose of valsartan was doubled after 4 weeks if the initial dose did not achieve the target blood pressure of less than 140 mm Hg for systolic blood pressure and 90 mm Hg for diastolic blood pressure (in hypertensive patients with diabetes or renal disease, target blood pressure was set to less than 130 mm Hg for systolic blood pressure and 80 mm Hg for diastolic blood pressure.) After 8 weeks an additional administration of other anti-hypertensive drugs with flexible dosing regimen other than ARB and ACE inhibitors was allowed if necessary. In contrast, for the conventional treatment group, the conventional treatment with anti-hypertensive drugs other than ARB and ACE inhibitors were provided for the patients to reach the common goal of blood pressure control. Periodical follow-up was implemented every 6 months after setting the sustainable dose.

Randomisation was automatically executed by the host computer and all the data recorded at each centre was managed centrally at the independent data centre in Kobe, Japan. Randomisation and data management were managed by the wide area network using a secure server.

Investigative measurements

Background data such as sex, age, height, body weight, signs and symptoms, and risk factors were recorded during the enrolment period. The following general clinical laboratory tests were carried out at baseline and every 6 months. (1) Urinalysis (proteinuria and urinary occult blood); (2) blood chemistry tests (serum creatinine, Na, K, triglyceride,

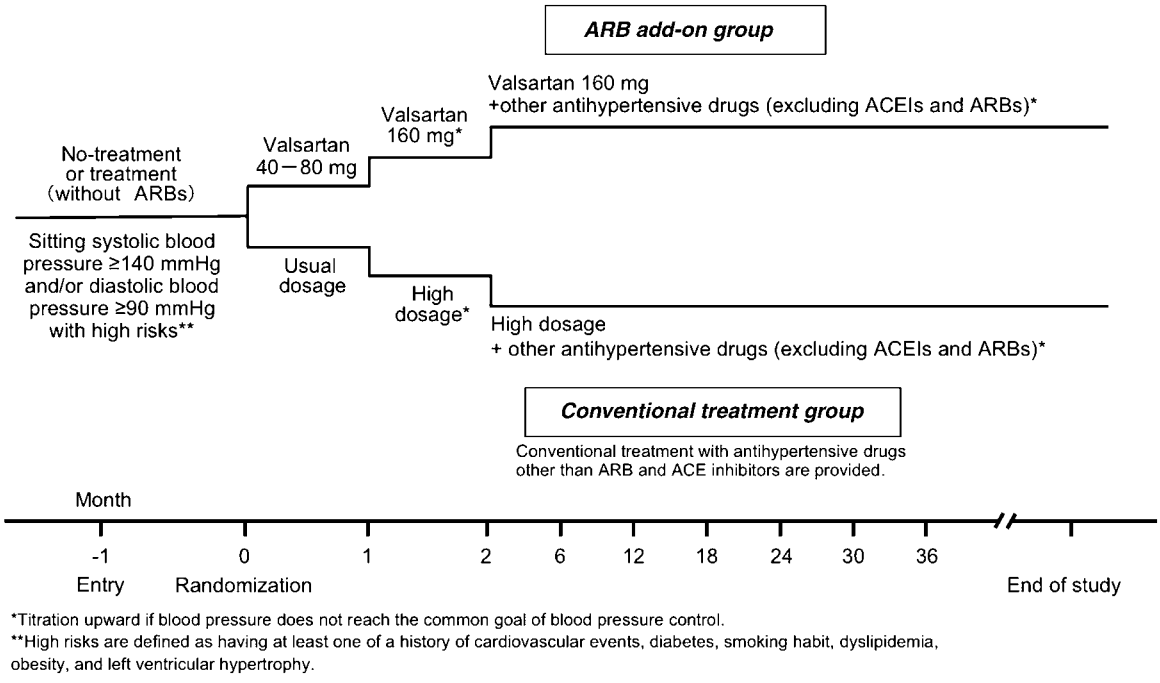

Figure 1 Titration schedule for the KYOTO HEART Study.

low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting blood sugar, HbA1C, uric acid, blood urea nitrogen, and white blood cell count; (3) ECG central reading in a core laboratory in Kyoto Prefectural University Hospital; (4) echocardiogram (examined every year, left ventricular diastolic dimension, left ventricular systolic dimension, ejection fraction, functional shortening, interventricular septum, posterior wall, isovolumic relaxation time, the ratio of early ventricular filling (E) to atrial contraction (A) velocity, deceleration time, and left ventricular weight;[22] and (5) chest X-ray (cardiothoracic ratio). In addition, the brain natriuretic peptide (BNP) and aldosterone levels were measured in patients related to the progression of cardiovascular diseases every year. The oral glucose tolerance test (OGTT) was implemented in patients showing the impaired fasting glucose stage (110⩽ fasting glucose level <126 mg per 100 ml), and the patients who had impaired glucose tolerance (IGT: 140⩽ glucose level 2 h after OGTT <200) was checked by OGTT test every year. Additional Holter ECG measurements were implemented every year in patients who were already diagnosed by Holter ECG to have paroxysmal atrial fibrillation.

Evaluation outcomes

The primary end point was a composite of cardio- and cerebro-vascular events. Components of the end point include the following: stroke (diagnosed by imaging technique), new or recurrent transient ischaemic attack (neurological deficit persisting for less than 24 h), new or recurrent acute myocardial infarction (ECG-change and biomarkers for myocardial infarction), new occurrence or exacerbation of 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 Heart Association and American College of Cardiology (AHA/ACC), new occurrence or exacerbation of angina pectoris (ECG changes with documented CAD according to AHA/ACC guidelines), dissecting aneurysm of the aorta (diagnosed by imaging technique), lower limb arterial obstruction (ankle brachial pressure index and imaging technique), emergency thrombosis, transition to dialysis or doubling of serum creatinine levels. The first of these to occur in a specific patient was classified as an event and to be counted as the primary end point. The following were set as the secondary end points: all causes of mortality, worsening of cardiac function (clinical symptoms together with left ventricular dysfunction by echocardiography), new occurrence or exacerbation of arrhythmias (diagnosed by Holter ECG), new occurrence or exacerbation of diabetes mellitus or impaired glucose tolerance (according to the guidelines of American Diabetes Association), or uncontrolled blood pressure. Any component of composite primary end point for which a patient could be counted once in each category was treated as a secondary end point. Data from any cause was also designated a second end point. The end points reported will be reviewed and settled by the independent Endpoint Committee. The study was registered at http://clinicaltrials.gov/ with the identification number NCT00149227.

Statistical analysis
On the basis of results of large end point studies conducted overseas in high-risk hypertensive patients, the number of patients to be enroled was calculated 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 clinically significant between-group differences with a two tailed 5% statistical significant level.

Very limited epidemiological data about cardiovascular risk profiles in Japan are available. Information about the prognosis of patients treated by specialist doctors at specialised hospitals is particularly scarce. Although the cardiovascular event rate in the Japanese population is low, the hospitals participating in this study undertake the tertiary care of cardiovascular disease; therefore, they treat more severely ill patients than those seen in other hospitals. On the basis of the prevalence of cardiovascular disease in the Japanese cohort,[4] it was estimated that the 3-year event rate for cardiac mortality and morbidity for patients with complicated cardiovascular disease would be approximately 12%. The findings of a retrospective investigation of few patients under treatment at the participating sites were almost identical to this estimate. However, as this study was end point-driven, the duration of the study was determined by the accumulated number of patients with a primary end point ($n = 325$ patients).

Analyses will also be made by an independent Statistical Analysis Organization based on the intention-to-treat approach and time to first event in accordance with the principle of harmonised tripartite guideline 'Statistical Principles for Clinical Trials' developed by International Conference on Harmonisation (ICH). All randomised patients were included in the analysis. Patient characteristics, corresponding to data characteristics, were checked for uniform distribution among the various groups. Cox's proportional hazard regression analysis was used for comparing the event rate between the two medical treatment groups.

Subgroup analysis
Clinical trials evaluate treatment effects predefined as primary and secondary end points in the study design. However, *post-hoc* subgroup analyses are frequently added for the reason of the study outcome, cost-effectiveness and other intentions. Recently, guidelines for reporting subgroup analysis have been reported.[23] In the KHS, the subgroup analysis committee also indicated the detailed planning in the primary end point report; the subanalyses were deliberately planned for cardiovascular events compared with the number of risk factors, the achievement rate of blood pressure control, systolic/diastolic parameters using ultrasound echocardiogram, and the efficacy of valsartan with/without diabetes and with/without metabolic syndrome.

Study period
Recruitment began in January 2004 and follow-up is calculated to go on until 2010 or to a time point when the pre-determined number of patients with a primary end point has been reached, unless there is a decision for discontinuation of this trial ratified by the Steering Committee by recommendation from the Data and Safety Monitoring Board.

Discussion

Earlier large-scaled clinical trials were mainly targeted for white and black races, and only a few studies reported the morbidity and mortality of anti-hypertensive treatment for East Asian races. Japan is one among the countries where people live the longest in the world, and the average life span is 79 years in men and 85.8 years in women in 2007, and these values are increasing. The incidence of stroke was relatively higher than that of CAD in Japanese hypertensive patients. The percentage of cerebral bleeding was two or three times greater than in Europe and the United States, and cerebral infarction was mostly caused by lacunar-type ischaemic strokes owing to hypertensive small vessel disease.[5]

Differences in genetic inheritance among the races, life-style, public health insurance and free access system to hospitals might contribute to the excellent longevity in Japan. However, the ratio of the elderly will reach one-fourth of the population in 2020, and the fatty food intake, obesity and high rate of smoking have been increasing the incidence of high-risk hypertension. Although a new guideline on metabolic syndrome has been introduced very recently, few studies have reported whether ARBs significantly affect cardiovascular events and mortality in hypertensive patients with metabolic syndrome. When patients have hypertension, the definition of metabolic syndrome is made when the patients also have abdominal obesity plus either dyslipidemia or glucose intolerance, or both. The KHS is a clinical trial designed from PROBE and wide area network, and is first designed to evaluate whether the addition of valsartan to conventional anti-hypertensive treatment to improve blood pressure control influences the cardiovascular outcome in Japanese high-risk hypertensive patients with or without metabolic syndrome. This study will also have the power to address the additional benefits of valsartan, which are not related to blood pressure lowering effects. The KHS is expected to provide benefits beyond the anti-hypertensive effects of ARBs for hypertensive patients in East Asia with metabolic syndrome or high-risk. The KHS will furthermore settle the issue whether the discrepancy between the outcomes of the JIKEI Heart and CASE-J

studies is related to molecule specific differences between ARBs or related to different study designs.

The study is ongoing and the first patient was randomised January 2004. There are currently 3042 patients in the study.

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Appendix

Organisation and data management

Matsubara H supervises the KYOTO HEART Study (KHS) as the chief investigator, and several staff have been appointed by the chief investigator to support the management of the study as representatives of the KHS group secretariat. The KHS is administered by the Steering Committee, which is composed of academic leaders appointed by the chief investigator. The role of the Steering Committee is to supervise the overall execution of the study.

In the KHS, the Data and Safety Monitoring Board (DSMB), the Endpoint Committee and the Safety Committee are organised independently from the study group and each organisation consists of three external experts. The DSMB members are blinded to the allocation of drug treatment groups, meet periodically, have a stopping guideline for terminating the trial prematurely and make recommendations to the Steering Committee about the ethical aspects of trial continuation by evaluating each case of possible adverse events. This study will finish when the number of primary endpoints reaches the hypothesis after the end of enrolment. The DSMB will review the effectiveness and safety of the study at regular intervals. This board executes three interim analyses, with the O'Brien–Fleming method. Yagi K, who is a chief biostatistician at the Louis Pasteur Center for Medical Research, Kyoto, Japan, appointed the DSMB members consisting of two physicians who are independent of the study. The Endpoint Committee and the Safety Committee are blinded to the allocation of drug treatment groups and the results of the study, and are managed separately from investigators and biostatisticians. The Safety Committee has the role to oversee the welfare of patients enroled in the trial from the ethical point of view. In addition, the Substudy committee is organised according to the agreement of the Steering Committee. Investigators are blinded to the allocation of drug treatment groups and the results of the study until the discontinuation report from the DSMB or the final report of the study data analysis is announced.

Data collection and management, and allocation for drug treatment groups are conducted by the automatic electronic data-capturing system using the wide area network with a secure server managed by the data centre in Kobe, which is independent of the study implementation group. The statistical analysis of the data is performed by the biostatisticians at the Louis Pasteur Center for Medical Research, Kyoto, Japan, who are blinded to the allocation of drug treatment groups and independent of the study implementation group and the funding source. The Data monitoring team periodically visits randomly selected investigators to check the suitability between the hospital data and the input data presented by internet network system.

Executive committee

H Matsubara, Department of Cardiovascular Medicine, Kyoto Prefectural University of Medicine is the study chairman. B Dahlöf, 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 Sawada (Main Steering Committee Member), T Shirayama, Y Mori, M Okigaki, A Matsumuro, H Yamada, Y Tsutsumi, M Matoba, T Takahashi, H Shiraishi, K Ikeda, T Nakamura and T Yamada; National Hospital Organization Maizuru Medical Center—S Hirano; National Hospital Organization Shiga Hospital—A Azuma; Kyoto Prefectural Yosanoumi Hospital—S Kimura; Akashi Municipal Hospital—S Sasaki; Ayabe City Hospital—K Shiga; Omihachiman Community Medical Center—K Maki; Kyoto City Hospital—K Furukawa; Kumihama Hospital—S Okuda; Nantan General Hospital—Y Kajita; Fukuchiyama City Hospital—M Nishio; Kyoto First Red Cross Hospital—Y Kohno; Kyoto Second Red Cross Hospital—M Kitamura; Maizuru Red Cross Hospital—K Nishida; Saiseikai Kyoto Hospital—Y Yamahara; Saiseikai Shiga Hospital—T Nakamura; Uji Hospital—S Sawada; Gakkentoshi Hospital—R Sakai; Kameoka Municipal Hospital—T Kuriyama; Kyoto Kizugawa Hospital—H Miyanaga; Kyoto Interdisciplinary Institute Hospital of Community Medicine—T Kitani; Social Insurance Kyoto Hospital—H Haruyama; Shakaihoken Kobe Central Hospital—A Nishio; Kouseikai Takeda Hospital—N Kinoshita; Aijyukai Dohjin Hospital—S Inagaki; Matsushita Memorial Hospital—H Sugihara; Aiseikai Yamashina Hospital—M Katamura; Midorigaoka Hospital—T Hachiya; Asahi University Murakami Memorial Hospital—S Kato; Meiji University of Oriental Medicine Hospital—K Ohtsuki.

Endpoint committee

J Higaki, Department of Integrated Medicine and Informatics, Ehime University Graduate School of Medicine, Shitsukawa, Japan; S Kim-Mitsuyama, Department of Pharmacology and Molecular Therapeutics, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; T Ichiki, Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan.

Safety committee

M Kitakaze, Department of Cardiovascular Medicine, National Cardiovascular Center, Osaka, Japan; T Sugiura, Department of Clinical Laboratory Medicine, Kochi Medical School, Kochi University, Kochi, Japan; H Rakugi, Department of Geriatric

Medicine, Osaka University Graduate School of Medicine, Suita, Japan.

Data and safety monitoring board
K Yagi, Louis Pasteur Center for Medical Research, Kyoto, Japan; K Kanda, Department of Cardiovascular surgery, Division of Surgery, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan; C Sakakura, Department of Digestive Surgery, Division of Surgery, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan.

Statistical analysis organization
K Yagi, Louis Pasteur Center for Medical Research, Kyoto, Japan; Nobuo Shirahashi, Department of Preventive Medicine and Environmental Health, Osaka City University Medical School, Osaka, Japan.

Data monitoring board
M Miki, Kyoto Prefectural University School of Medicine, Kyoto, Japan; S Toyoda, Kyoto Prefectural University School of Medicine, Kyoto, Japan.