Rationale and Design of a Study to Examine Lower Targets for Low-Density Lipoprotein-Cholesterol and Blood Pressure in Coronary Artery Disease Patients

— The Japanese Coronary Artery Disease Study II (JCADII) —

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on behalf of the JCADII Investigators

Background The benefits of coronary risk modification through medication and other methods have been shown in many clinical studies. Recently, aggressive lowering of low-density lipoprotein-cholesterol (LDL-C) has been shown to confer additive benefits in patients with coronary artery disease (CAD). However, it has not been shown in Japanese patients with CAD if multiple aggressive medical interventions for coronary risk factors are beneficial compared with standard regimens, so a prospective, randomized, open-label, blinded-endpoint (PROBE) multicenter study was designed to evaluate whether aggressive lowering of LDL-C and blood pressure in Japanese hypertensive, hypercholesterolemic CAD patients bestows additional benefits compared with regimens based on current Japanese guidelines.

Methods and Results Seventeen hospitals in Japan are participating in the Japanese Coronary Artery Disease II (JCADII) study. Hypertensive and hypercholesterolemic patients who have $\geq 75\%$ stenosis in at least one major coronary artery according to American Heart Association guidelines will be allocated randomly to receive either conventional or aggressive therapy. Standard therapy for hypertension and hypercholesterolemia aims to reduce blood pressure to $<140/90$ mmHg and LDL-C concentration to <100 mg/dl. Aggressive therapy aims for targets of $<120/80$ mmHg and <80 mg/dl, respectively. We plan to recruit 500 patients and follow them up for 3 years. Antihypertensive agents, when used, include the angiotensin receptor blockers candesartan and/or losartan. Antihypercholesterolemic agents, when used, include at least one of the following statins: pravastatin, simvastatin, and atorvastatin.

Conclusion The JCADII study will provide important information concerning medical treatment of coronary risk factors in Japanese patients with CAD (UMIN-ID: UMIN000000571). (Circ J 2008; 72: 515–520)

Key Words: Aggressive therapy; Angiotensin receptor blockers; Coronary artery disease; PROBE study design; Statins

Many epidemiological studies, such as the Framingham study¹ have shown that risk factors for coronary artery disease (CAD) include hypertension, hyperlipidemia, obesity, smoking and diabetes mellitus. Many clinical studies have shown that medical and other forms of coronary risk intervention are effective

in reducing cardiovascular events in the settings of both primary prevention and secondary prevention.^{2–5} Therapeutic guidelines have been devised based on such knowledge, although it is now understood that ethnic differences affect risk factors and outcomes.^{6–8}

For a long period now, Japanese people have adopted Western lifestyles, resulting in their serum lipid concentrations becoming similar to those of Western people.⁹ However, the incidence rate of CAD remains unexpectedly low in Japanese people despite the increase in risk factors.¹⁰ This kind of ethnic difference led us to conduct a large-scale, observational study of Japanese patients with CAD.¹¹ The initial results of the study showed that, although the incidence rate of CAD in the general Japanese population might be lower, the incidence rate of secondary cardiovascular events in patients with CAD is similar to that in Western people.¹²

Recently, the results of several clinical studies showed the additive benefit of multiple medical interventions¹³ and aggressive lowering of low-density lipoprotein-cholesterol (LDL-C)^{14–16} in reducing cardiovascular events. Yet, there have been no studies conducted to measure the effects of

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Table 1 Inclusion Criteria

1. Significant stenosis* in at least one major coronary artery
2. Aged between 20 and 79 years
3. Hyperlipidemia
4. Hypertension
5. Written informed consent obtained from the participant

*Significant stenosis of the coronary artery is defined as $\geq 75\%$ stenosis, according to American Heart Association guidelines.

multiple and aggressive medical interventions for coronary risk factors in Japanese patients with CAD; hence, the Japanese Coronary Artery Disease II (JCADII) study was designed to evaluate the efficacy and safety of such regimens.

Methods

Study Population

Hypertensive and hypercholesterolemic patients of either gender with significant stenosis in at least one major coronary artery are eligible to participate. Significant stenosis of the coronary artery is defined as $\geq 75\%$ stenosis according to American Heart Association guidelines.¹⁷ Diagnosis can be made by either standard coronary angiography or coronary computed tomography angiogram.

The inclusion criteria are: between 20 and 79 years of

age; hypercholesterolemia, defined as a serum total cholesterol concentration of ≥ 220 mg/dl in the past or during current therapy with statins and/or fibrates; hypertension, defined as systolic blood pressure (SBP) of ≥ 140 mmHg and/or diastolic blood pressure (DBP) of ≥ 90 mmHg in the past or during current therapy with antihypertensive agents; and the participant's written informed consent (Table 1).

Exclusion criteria are: known allergic reaction to the study drugs; familial hypercholesterolemia; uncontrolled hypercholesterolemia (serum LDL-C concentration remains ≥ 180 mg/dl despite conventional therapy); uncontrolled hypertension (SBP remains ≥ 180 mmHg and/or DBP ≥ 110 mmHg despite conventional therapy); myocardial infarction or stroke within the past 3 months; secondary hypertension; secondary hyperlipidemia (although diabetes mellitus-induced hyperlipidemia is not excluded); severe valvular disease; uncontrolled severe arrhythmia, such as recurrent ventricular fibrillation or ventricular tachycardia; renal dysfunction, defined as a serum creatinine concentration of ≥ 2.5 mg/dl; hepatic dysfunction, defined as a concentration of alanine aminotransferase or aspartate aminotransferase 3 times the normal upper limit; pregnancy or possible pregnancy; and the decision by the physician in charge that the patient is unsuitable for inclusion (Table 2).

Study Design

The JCADII study is a multicenter, prospective, random-

Table 2 Exclusion Criteria

1. Known allergy to study drugs
2. Familial hypercholesterolemia
3. Uncontrolled severe hypercholesterolemia (low-density lipoprotein cholesterol ≥ 180 mg/dl)
4. Uncontrolled severe hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg)
5. Myocardial infarction or stroke < 3 months before registration
6. Secondary hypertension
7. Secondary hyperlipidemia
8. Severe valvular disease
9. Uncontrolled severe arrhythmia
10. Renal dysfunction (defined as serum creatinine concentration ≥ 2.5 mg/dl)
11. Hepatic dysfunction (defined as an alanine aminotransferase or aspartate aminotransferase 3 times the normal upper limit)
12. Pregnancy or possible pregnancy
13. Decision by the attending physician that the patient is unsuitable for inclusion

Fig 1. Study design. *Any drug can be added except angiotensin receptor blockers not specified in the study, statins not specified in the study and angiotensin-converting enzyme inhibitors. DBP, diastolic blood pressure; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure.

Table 3 Schedule for Data Collection

	Run-in period	Study period (months)							
		0	3	6	12	18	24	30	36
Patient data	M								
Blood pressure	M	M	M	M	M	M	M	M	M
Serum lipid concentrations	M	M	M	M	M	M	M	M	M
Pulse wave pressure		O	O	O	O		O		O
Echocardiography		M	O	O	M		M		M
Other blood tests		M	M	M	M		M		M
Urinary tests		M	M	M	M		M		M

O, optional; M, mandatory.

ized, open-label, blinded-endpoint (PROBE) trial carried out at 17 cardiology centers in Japan. The first patient was enrolled in November 2006, and randomization is expected to end in October 2007. All eligible patients will be allocated randomly to either conventional therapy or aggressive therapy. Randomization is being performed on the basis of the following baseline variables: SBP, serum LDL-C concentration, diabetes mellitus and congestive heart failure. Fig 1 shows the study design.

The therapeutic targets for patients assigned to conventional therapy are an SBP of <140 mmHg and a DBP of <90 mmHg for hypertension, and a serum LDL-C concentration of <100 mg/dl for hypercholesterolemia. If the patient has diabetes mellitus, the therapeutic targets for hypertension are an SBP of <130 mmHg and a DBP of <80 mmHg, according to current Japanese guidelines for hypertension therapy.¹⁸ The therapeutic targets for patients assigned to intensive therapy are an SBP of <120 mmHg and a DBP of <80 mmHg for hypertension, and a serum LDL-C concentration of <80 mg/dl for hypercholesterolemia.

Antihypertensive therapy should include the angiotensin receptor blockers candesartan and/or losartan. Antihypercholesterolemia therapy should include at least one of the following statins: pravastatin, simvastatin and atorvastatin. A no drug regimen is allowed if the targets are met with non-pharmacological therapy. Additional therapy can be used to achieve the target blood pressure and LDL-C concentration, except for angiotensin receptor blockers not specified above, statins not specified above and angiotensin-converting enzyme inhibitors. It is expected that the therapeutic targets for each patient will be achieved within 3 months of randomization.

The schedule for data collection is shown in Table 3. Patient data include the date on which consent was obtained, date of birth, gender, height, weight, history of cardiovascular disease, comorbid diseases, history of smoking, waist circumference, and year and method of coronary angiogram. Blood pressure measurements include both SBP and DBP. Serum lipid concentrations include high-density lipoprotein-cholesterol, triglycerides and LDL-C, where LDL-C is measured by homogeneous assays. Measurement of total cholesterol is not mandatory but data registration is possible and the registered data will be used for later investigations. The measured values of LDL-C are normalized using standard samples sent to each institute. Homogeneous assays of LDL-C measurement were assumed not to vary significantly from the Friedewald calculation method based on studies that showed that LDL-C values obtained by the Friedewald method and homogeneous methods correlate well with each other, in general.^{19,20} Pulse wave pressure is measured at facilities where it is available. Interventricular

septum thickness and ejection fraction are measured by echocardiography. Other blood tests include measurement of white blood cell count, hemoglobin, platelet count, fasting blood glucose, hemoglobin A_{1c} protein (for diabetic patients only), alanine aminotransferase, glutamyl transpeptidase, blood urea nitrogen, uric acid, serum creatinine, creatine kinase, high-sensitive C-reactive protein and B-type natriuretic peptide. Urinary tests include measurements of urinary glucose and protein. It is expected that all patients are followed up for 3 years.

Study Management

The study was initiated by the investigators and is scientifically led by a steering committee consisting of independent researchers and investigators. This committee has full responsibility for the study protocol and publications arising from the study. The committee is granted full access to all data at the study's completion. Data registration is performed through a Web-based interface by each investigator or clinical research coordinator at each facility. All data will be collected in a central data server. An independent monitoring board, which is not involved in the conduct of the trial, will monitor aggregated endpoint summaries and medically serious adverse events on an ongoing basis.

Endpoints

The primary endpoint is a composite of all deaths, non-fatal myocardial infarction, unstable angina pectoris, coronary artery bypass graft operation, non-fatal stroke, non-fatal major vascular diseases and peripheral artery diseases. Secondary endpoints are the occurrence of any primary event; all-cause hospitalization; hospitalization due to congestive heart failure; percutaneous coronary intervention; transient ischemic attack; blood pressure; pulse wave velocity; concentrations of serum lipid, high-sensitive C-reactive protein and B-type natriuretic peptide; left ventricular hypertrophy; and safety.

Sample Size

Sample size calculation is based on the Steno-2 study¹³ and the JCAD study.¹² Steno-2 suggested that at least a 41% risk reduction in cardiovascular events would be achieved in the aggressive therapy group compared with the conventional therapy group. The JCAD study showed that the annual event rate in Japanese patients with CAD is approximately 6%. The MEGA study showed that a moderate 23 mg/dl lowering of LDL-C resulted in 33% reduction of CAD in a low-risk Japanese population. These findings, combined with a detection power of 80% and a 2-sided significance level of 5%, enabled us to calculate that the number of patients needed to detect a significant difference between the

2 groups in 3 years is 244 for each group. Assuming that the dropout rate is 2%, the number of patients needed is 250 for each group.

Analysis

When the study is completed, the primary and secondary endpoints will be analyzed using survival analysis techniques on the basis of time to first event. A comparison of the results for the aggressive therapy group with those for the conventional therapy group will be done with Kaplan–Meier curves and a log-rank test. The non-adjusted hazard ratio of each variable will be calculated using a univariate Cox hazards model. The adjusted hazards ratio of each variable will be calculated using a multivariate Cox hazards model.

Interim analyses will be performed every year after the initiation of the study to evaluate the primary efficacy endpoint for major cardiovascular events and safety. The independent monitoring board may advise early termination of the trial for safety, scientific or ethical reasons.

Ethical Considerations

The Institutional Review Board of each participating institution reviewed and approved the study protocol and other documents. As for informed consent, each attending physician explained the study to each candidate patient, who gave voluntary written informed consent prior to enrolment.

Role of Funding Source

The sponsor of the study has no role in the study design, data collection, data analysis, data interpretation or publication of any articles arising from the study.

Discussion

The incidence rate of CAD in the general Japanese population remains low¹⁰ despite adopting Westernized lifestyles, having similar serum lipid concentrations to those of Western people⁹ and high smoking rates.²¹ Nonetheless, we have shown through analysis of data from a large cohort of CAD patients diagnosed using coronary angiography that the rate of secondary cardiovascular events in Japanese patients with CAD is similar to that in Western people.¹²

Epidemiological studies, such as the Framingham study, established coronary risk factors, such as hypertension, hyperlipidemia, smoking, aging and being male.¹ Many clinical studies have shown that medical interventions to modify coronary risk factors are effective in reducing cardiovascular events in settings of both primary prevention and secondary prevention.^{2–5,22,23}

Therapeutic guidelines have been devised according to the accumulated evidence and are being used in clinical settings. Cardiovascular events increase as the number and extent of risk factors increase. This knowledge led to several clinical studies that evaluated the efficacy and safety of multiple medical interventions for cardiovascular risk factors¹³ or aggressive lowering of LDL-C,^{14–16,24} showing that these approaches confer additive benefits in reducing cardiovascular events.

To the best of our knowledge, there have not been any studies that evaluated the effects of multiple aggressive coronary risk interventions in Japanese patients with CAD. Therefore, the JCADII study was designed to assess the efficacy and safety of aggressive lowering of blood pressure and

LDL-C in patients who have hypertension, hyperlipidemia, and CAD confirmed angiographically or by computed tomography.

As mentioned earlier, several clinical studies have shown that aggressive lowering of LDL-C is effective in the settings of both primary prevention of cardiovascular events⁵ and secondary prevention of cardiovascular events;⁴ be it in the stable phase¹⁵ or in the post-acute event phase.¹⁴ As for evidence in a Japanese population, the only randomized control study on lipid-lowering therapy in Japanese showed that a moderate decrease in LDL-C (23 mg/dl) resulted in a substantial decrease of CAD events.²⁵ An observational study conducted in Japan showed that lowering the LDL-C level below 100 mg/dl in hypercholesterolemic patients is safe and effective in reducing coronary events.²⁶ Additionally, aggressive statin therapy was shown to confer beneficial effects on coronary atherosclerotic lesions compared to usual lipid-lowering therapies.²⁷ These studies suggest that aggressive lowering of LDL-C is safe and might be beneficial in reducing cardiovascular events in the Japanese population.

As for blood pressure lowering, there has long been a debate about the so-called J-curve phenomenon.^{28–30} Theoretically, it can be argued that lowering blood pressure too much, especially DBP, might result in impaired coronary flow, which might reduce even further the coronary flow of CAD patients and result in cardiovascular events. The results of the Hypertension Optimal Treatment study showed that a target DBP of <80 mmHg is safe, and no J-curve effect was observed in the primary prevention of cardiovascular events in hypertensive patients.² The results of the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack trial also showed that achieving an average DBP of <80 mmHg is tolerated well and is effective in reducing major cardiovascular events in high-risk hypertensive patients.³¹ However, not all the patients included in these trials had been rigorously defined as having CAD.

Recently, a subanalysis of the International Verapamil–Trandolapril Study, which was conducted on patients with documented CAD, showed that when the study's participants were categorized into 7 strata according to blood pressure, a J-curve phenomenon was observed.³² However, this result was obtained by post hoc analysis, and, although the background profiles of patients were taken into account when performing statistical analyses, it is not clear whether the worse profile of the lowest blood pressure strata was accounted for appropriately. Although there is scarce direct evidence regarding what level of blood pressure should be attained by medication in elderly Japanese hypertensive patients, an observational study has reported that those in the general population with optimal blood pressure (<120/<80 mmHg) have the lowest risk for cardiovascular disease.³³ Recently, chronic kidney disease is reported to be an independent risk factor for cardiovascular events.³⁴ An observational study conducted in Japan showed that when blood pressure was categorized into 6 levels, those with optimal blood pressure (<120/<80 mmHg) had the lowest risk for developing end stage renal disease,³⁵ suggesting the benefits of lowering blood pressure to this level. To date, there have been no clinical trials that show directly whether aggressively lowering blood pressure in CAD patients is safe and effective in reducing cardiovascular events, and such a study is warranted.

In conclusion, the JCADII study is the first to evaluate whether aggressive lowering of LDL-C and blood pressure

is safe and effective in reducing cardiovascular events in hypertensive, hypercholesterolemic Japanese patients with CAD. The results will add important information regarding the treatment of such patients.

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Appendix 1

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