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Design and Baseline Characteristics of a Study of Primary Prevention of Coronary Events With Pravastatin Among Japanese With Mildly Elevated Cholesterol Levels

Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study Group

Background Although cholesterol management reportedly reduces fatal and non-fatal coronary heart disease (CHD) events in subjects with or without evident atherosclerotic disease, it is still uncertain whether these benefits extend to Japanese.

Methods and Results The study group comprised 8,009 subjects with mildly elevated total cholesterol who were randomized to treatment with 10–20 mg pravastatin plus diet (2,691 women, 1,267 men) or diet alone (2,758 women, 1,293 men). The groups were extremely well balanced with respect to baseline demographics and risk factors such as blood pressure and plasma lipids. Over a 5-year period of follow-up, the primary end-points will be a composite of fatal and non-fatal coronary events. Secondary end-points will include stroke and transient ischemic attack, all cardiovascular events and total mortality.

Conclusions The 2 groups will be followed up until the end of March 2004 and end-points will be analyzed by full analysis set. (*Circ J* 2004; **68:** 860–867)

Key Words: Cholesterol; Coronary heart disease; Pravastatin; Primary prevention

Since the development of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) in 1989, their strong efficacy in lowering blood cholesterol was first noted in the early 1990s[1,2] and it became clear that evidence was needed to confirm their effects on the atherosclerotic process.

Previous studies have consistently shown a slowing of lesion progression, but there was little actual differences in stenosis compared with a placebo group![1–3] However, key pieces of evidence were still missing: to what extent would the vascular benefit translate into reduced risk for clinical events and would substantial lipid lowering be safe.

Cholesterol-lowering therapy has been shown to reduce fatal and nonfatal coronary heart disease (CHD) events in Caucasian subjects with or without coronary disease![4–9] but it is still uncertain whether these benefits extend to Japanese. Compared with Caucasians, Japanese have some characteristics that might modify treatment effects, such as a much lower age-standardized death rate from CHD![10] a higher proportion of hemorrhagic stroke![10] overall lower blood cholesterol concentration![11] a diet that typically contains less saturated fat and cholesterol intake![11] and relatively small physical stature.

A large-scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy has been conducted in Japanese patients with hypercholesterolemia, but without a control group![12,13] Thus, a randomized study was designed to compare the effect on pravastatin plus diet with diet alone for the prevention of major CHD events in Japanese men and women without clinically evident atherosclerotic cardiovascular disease and with mildly elevated total cholesterol levels. This study will be the largest long-term controlled study yet conducted among Orientals in Asia.

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Members of the MEGA Study Group are shown in Appendix 2.

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Methods

Subjects

Between 1994 and 1999, a total of 15,210 subjects were temporarily registered in 924 hospitals throughout Japan based on their age, gender and cholesterol concentration, which was determined by the relevant institutions. The relatively long period for registration was required because of alterations to the rules for post-marketing surveys and the immature infra-structure of the trial's organization. After registration, participants were instructed to adhere to the dietary advice, which was based on the National Cholesterol Education Program (NCEP) Step I diet.[14]

After at least a 4-week washout period during which subjects were encouraged to comply with the low fat and low cholesterol diet, blood cholesterol was determined by a standardized procedure on 2 or 3 occasions over 12 weeks. The baseline cholesterol was estimated as the average of these measurements and for entry to the study was required to be 220–270 mg/dl. Of the total cohort, 8,214 subjects met the inclusion criterion. Eligible subjects included men aged 40–70 years, and post-menopausal women up to 70 years of age. Exclusion criteria included familial hypercholesterolemia; a history of angina pectoris, myocardial infarction, coronary artery bypass graft surgery or percutaneous coronary intervention; electrocardiographic abnormalities consistent with myocardial ischemia; a history of peripheral arterial disease, stroke or transient ischemic

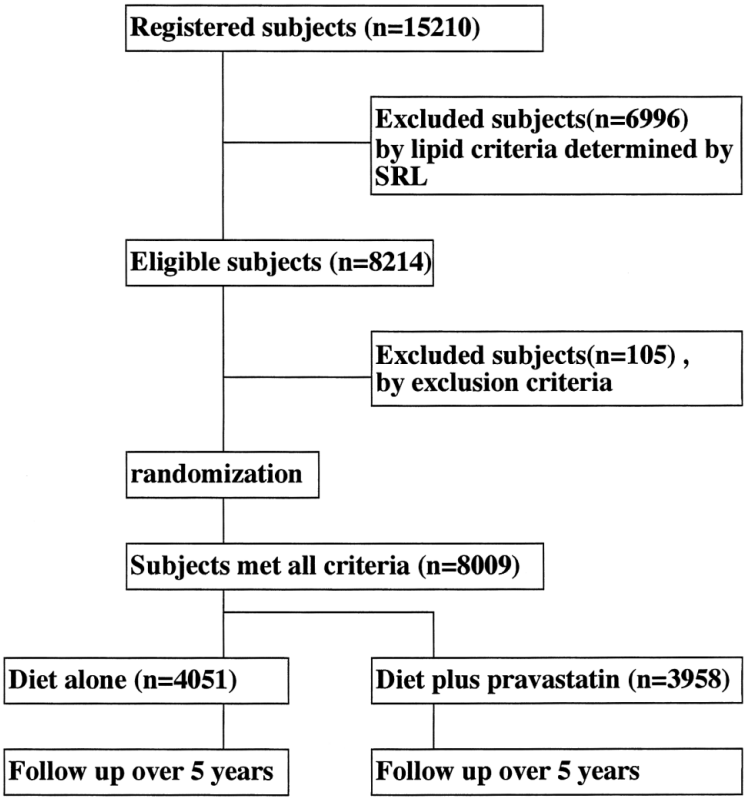

Fig 1. Flow diagram of participants.

attack; a diagnosis of congenital or rheumatic heart disease; chronic atrial fibrillation; current diagnosis of malignancy; severe liver (chronic active hepatitis and cirrhosis) or renal (creatinine ≥4 mg/dl) disease; poorly controlled hypertension or diabetes mellitus; secondary hyperlipidemia; current use of oral or parenteral corticosteroids; and other conditions at the discretion of the individual physician.

After exclusions, 8,009 subjects who still met all the criteria and who provided written informed consent were randomized to treatment with either diet alone or diet plus pravastatin (10–20 mg/day, the particular dose needed to decrease total cholesterol to less than 220 mg/dl) in an open-label, parallel-group design (Fig 1).

Study Management and Follow-up

It is planned that subjects will be followed up over 5 years. The subjects will be seen at 3–6 month intervals and at each visit dietary advice will be reinforced and fasting plasma lipids measured. Compliance with the dietary or drug regimen will be checked at every visit and the subjects' responses to a questionnaire, which will be given in every dietary practicing meeting, will be collected. An electrocardiogram (ECG) will be recorded annually.

Other treatments, both for cardiovascular and non-cardiovascular conditions, will be at the discretion of the patients' primary physicians and this includes commencement of lipid-lowering therapy other than with statins in those subjects randomized to diet alone, if this is considered appropriate.

An independent Data and Safety Monitoring Committee reviews study progress at periodic intervals from the ethical, safety and efficacy stand points, and is responsible for taking appropriate action if the data suggest that there may be an unacceptable risk to the subjects in the study. The stopping rule will be blinded for all participating physicians and members of steering committee.

Administrative, clinical and data management are performed by a contract research organization that is independent of the sponsors.

Laboratory Methods

All lipid values are measured centrally at the Special Reference Laboratory (SRL, Hachioji, Tokyo), which is certified for major lipid measurements by the Center for Disease Control, Atlanta, Georgia, USA. Total serum cholesterol and triglyceride (TG) concentrations are determined enzymatically[15] Low-density lipoprotein (LDL) cholesterol is calculated according to the formula described by Friedewald et al[16] using high-density lipoprotein (HDL) cholesterol values measured with a homogeneous assay from Daiichi Chemical Co (Tokyo). If the serum TG concentration is greater than >300 mg/dl, the LDL cholesterol is determined by direct assay kit (Cholestest LDL, Daiichi Pure Chemicals, Tokyo, Japan). Lipoprotein(a) (Lp(a)) is also measured annually by an antihuman Lp(a) monoclonal antibody-coated latex assay kit [Lp(a) Latex 'DAIICHI', Daiichi Pure Chemicals]. Hemoglobin A1c is measured by Hi-AUTO A1c kit of the HA-8150 series (Arkray Co Kyoto, Japan).

All other laboratory parameters are determined routinely by automated analyzers in each participating hospital.

Endpoints

The primary endpoint of the study is a composite of major CHD events, comprising fatal or nonfatal myocardial infarction, sudden cardiac death, development of unstable angina and coronary revascularization procedures, either coronary artery bypass grafting or percutaneous coronary intervention.

Secondary endpoints include cerebral infarction, cerebral

Table 1 Baseline Characteristics of the Study Subjects With High Cholesterol

	Diet (n=4,051)	*Diet plus pravastatin (n=3,958)*
Men aged 39–71 years (%)	*1,293 (50.5)*	*1,267 (49.5)*
Women aged 37–74 years (%)	*2,758 (50.6)*	*2,691 (49.4)*
Age, mean (SD) years	*59 (7)*	*59 (7)*
Men	*55.2*	*55*
Women	*59.8*	*59.6*
≥65 years (%)		
Men	*224 (17.3)*	*210 (16.6)*
Women	*720 (26.1)*	*695 (25.8)*
Height, mean (SD), cm	*156.6 (8)*	*156.6 (8)*
Weight, mean (SD), kg	*58.6 (10)*	*58.7 (10)*
Body mass index, mean (SD), kg/m²	*23.8 (3)*	*23.9 (3)*
Current smoker (%)	*595 (14.9)*	*618 (16.0)*
Major complications (%)		
Hypertension	*1,647 (41.2)*	*1,574 (40.6)*
Diabetes	*810 (20.3)*	*779 (20.1)*
Liver disease	*274 (6.9)*	*264 (6.8)*
Renal disease	*85 (2.1)*	*62 (1.6)*
Plasma lipid concentrations		
TC, mean (SD), mg/dl	*242.5 (12.1)*	*242.6 (12.0)*
LDL-C, mean (SD), mg/dl	*155.6 (18.6)*	*156.2 (18.2)*
HDL-C, mean (SD), mg/dl	*57.4 (15.1)*	*57.3 (14.8)*
TG, median, mg/dl	*128*	*128*
Lp(a), median, mg/dl	*15*	*15*
Blood pressure, mean (SD), mmHg		
Systolic	*132.5 (16.7)*	*132.0 (16.8)*
Diastolic	*78.9 (10)*	*78.5 (10)*
Blood glucose, mean (SD), mg/dl	*109.0 (31.8)*	*109.1 (32.1)*
HemoglobinA1c, mean (SD) %	*5.9 (1.2)*	*5.9 (1.2)*

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; Lp(a), lipoprotein(a).

hemorrhage, transient ischemic attack, all cardiovascular events, and total mortality, as listed in Appendix 1.

Tertiary endpoints include tolerability and safety parameters, noncardiovascular mortality, fatal and non-fatal cancer, and the relationship between CHD event rates and baseline concentrations and changes in lipid parameters.

Reports of the major endpoints are reviewed and classified by an Endpoint Committee.

Statistical Analysis

Endpoints will be analyzed mainly on full analysis set and according to treatment actually received (per protocol). A log-rank test will be used to assess the effect of therapy on the rate of primary endpoint events. Analyses of relative reductions in risk resulting from statin treatment are to be calculated using the Cox proportional hazards regression model. Cumulative incidence of events and interval estimates are to be calculated using the Kaplan-Meier method.

One-sided probability values of <0.05 will be considered to indicate a statistically significant difference.

Power Calculations The CHD morbidity and mortality in the general Japanese population is estimated at 5.3/1,000 person years![17]

The following assumptions are also made: an annual CHD death for all males aged 40–70 years of 0.9/1,000;[18] annual rates of major nonfatal CHD events twice that of CHD deaths; a combined incidence of fatal and nonfatal CHD events in those with total cholesterol of 220 mg/dl or more, twice that of the general population (therefore in this study cohort a combined incidence of approximately 5.6/1,000 per year); decrease in rates of the composite CHD endpoint of 10% in the group randomized to diet and 40% in the group randomized to diet plus statin. Also, an assumed 20% drop-in to treatment in these randomized to diet alone or drop-out in these randomized to also receive statin, randomization of 8,000 subjects has 80% power with α=0.10 (two-sided).

Results

Baseline Characteristics

Recruitment commenced in March, 1994 and concluded in September 1999. At that time, 8,009 participants were randomized to treatment with diet alone (2,758 women, 1,293 men) or with pravastatin plus diet (2,691 women, 1,267 men) (Table 1). The groups were extremely well balanced with respect to the baseline demographics and risk factors. The difference in diastolic blood pressure was small in absolute terms.

Combined mean lipid parameters included the mean (SD) total cholesterol 242.6 (12) mg/dl; mean (SD) LDL-cholesterol 156.9 (18) mg/dl; mean (SD) HDL-cholesterol 57.3 (15) mg/dl; median TG 128 mg/dl; and median lipoprotein(a) 15 mg/dl.

Discussion

Compelling epidemiological data have related serum cholesterol concentrations to the risk of CHD events in both Western populations[19] and in a cross-sectional study in Japan.[20] However, there has been considerable controversy concerning both the benefits and, to a lesser extent, the safety of cholesterol-lowering therapy, partly because prior to the availability of the 3-hydroxymethyl-3-glutaryl coenzyme A (HMG CoA) reductase inhibitors, trials had tested interventions that only lowered cholesterol by approxi-

mately 10%.

Although recently published large-scale trials have demonstrated both the benefits and safety of the HMG CoA reductase inhibitors in Western populations either known to have CHD[4–6] or without known CHD[8,9] it is important that such studies are also undertaken in different populations such as in Japan. Atherothrombotic disease results from the interaction between many genes and a variety of environmental factors including those that influence cholesterol concentrations. Migration studies have shown changes in the levels of CHD risk factors, including serum cholesterol, in Japanese who have migrated from their homeland to Hawaii and mainland United States.[21] In Japan, the rates and types of cardiovascular endpoints differ to those in Caucasian populations, reflecting possible genetic as well as environmental differences.

Not only might the effects of HMG CoA reductase inhibitors on CHD endpoints differ in Japan, but the present study will provide important data on the effects of pravastatin on both non-hemorrhagic and hemorrhagic stroke, the rates of which are relatively high in Japan, perhaps related to the high prevalence of hypertension. An overview of population studies has shown no association between serum cholesterol concentrations and strokes rates, when adjusted for known risk factors including age, blood pressure and cardiac disease;[22] although other studies in both the USA[23] and Asian populations;[22,24] which considered stroke by subtype, have shown a continuous positive relation between cholesterol concentrations and non-hemorrhagic stroke, and a possible increase in the rates of hemorrhagic stroke in association with low serum cholesterol concentrations. The latter may be a more common occurrence in those with hypertension;[23] which highlights the importance of the present study in this cohort in which more than 40% of the subjects had a history of hypertension at baseline.

The baseline cholesterol concentrations and other risk factors of the cohort in the present trial make them suitably representative for a study of the effects of an HMG CoA reductase inhibitor in Japanese. The mean baseline total cholesterol of 242.6 mg/dl lies between those in the WOSCOPS[8] and the AFCAPS/TexCAPS;[9] and the range is typical of cholesterol concentrations in Japanese who develop CHD. Patients with familial hypercholesterolemia frequently have total cholesterol levels greater than 270 mg/dl, and generally would have been excluded from this study.

As already noted, 40% of the cohort has a history of hypertension at baseline and approximately 20% have self-reported diabetes mellitus. Smoking rates of 15–16% are relatively high despite the large number of female subjects. Therefore, over half of the subjects have other CHD risk factors, the pattern of which differs from the baseline characteristics in the previous major primary prevention trials of HMG CoA reductase inhibitors[8,9]

A total of 68% of participants in the study are females, which reflects the frequent occurrence of elevated cholesterol concentrations in Japanese women, and is an important feature of the present study because in the past they have either been excluded[8] or notably underrepresented in other primary prevention[9] as well as secondary prevention studies[4–6] of the HMG CoA reductase inhibitors.

The dosage of pravastatin that is being used in this trial, 10–20 mg/day, differs from the higher dose of 40 mg/day employed in the other major studies.[5,6,8] Approval could not be obtained to administer a fixed dose (20 mg) of pravastatin, but the dose range being tested reflects usual clinical prescribing practice in Japan and has been shown to achieve approximately 20% reduction in total cholesterol and 25% for LDL-cholesterol reduction in this population;[25] similar to that found in the other studies with a 40 mg daily dose of the agent[6,26,27]

Finally, the study design allows for commencement of lipid-lowering therapy with an HMG CoA reductase inhibitor during trial follow-up by a treating physician if this is considered indicated, which overcomes any ethical dilemmas in continuing the trial, as has been described previously.[28]

In summary, this is the largest controlled study yet conducted among Orientals in Asia. The difficulties in mounting such a study are reflected by the need for an open rather than blinded design, because Japanese are uncomfortable with a placebo-control design. However any bias that might have been introduced will be minimized because an independent Data and Safety Monitoring Committee will oversee progress in the study, and analyses will be performed by a group that is independent of the Steering Committee and investigators. Therefore the study is still able to provide very important new information on the effects of an HMG CoA reductase inhibitor in an Oriental population with a predominance of women.

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Appendix 1

All endpoints will be adjudicated by the Endpoint Committee and major endpoints are defined as follows.

1. Definite fatal and nonfatal myocardial infarction (1 or more of the following criteria must be met):
   (a) Diagnostic ECG at the time of the event.
   (b) Ischemic cardiac pain (and/or unexplained acute left ventricular failure) and diagnostic enzymes.
   (c) Ischemic cardiac pain and/or unexplained acute left ventricular failure with both equivocal enzymes and equivocal ECG.
   (d) Diagnostic enzymes and equivocal ECG.
   (e) Angiographic evidence of occlusion of a major artery with appropriate ventriculographic wall motion abnormality where previous angiogram since randomization showed no such abnormality.
   (f) Postmortem examination.
2. Angina pectoris (stable or unstable, both of the following criteria must be met):
   (a) Ischemic cardiac pain, relieved by nitrates.
   (b) Equivocal ECG.
3. Ischemic stroke (1 of the following conditions must be met):
   (a) Rapid onset of focal neurologic deficit lasting at least 24 h or leading to death plus evidence from neuroimaging (computed tomography or magnetic resonance imaging) showing cerebral/cerebellar infarction or no abnormality, or postmortem examination showing cerebral and/or cerebellar infarction).
   (b) Rapid onset of global neurologic deficit (eg, coma) lasting at least 24 h or leading to death plus evidence from neuroimaging showing infarction, or postmortem examination showing infarction.
   (c) Focal neurologic deficit (mode of onset uncertain) lasting at least 24 h or leading to death plus evidence from neuroimaging showing infarction, or postmortem examination showing infarction.
4. Primary intracerebral hemorrhage (1 of the following conditions must be met):
   (a) Rapid onset of focal neurologic deficit lasting at least 24 h or leading to death, plus neuroimaging or postmortem examination showing primary intracerebral and/or cerebellar hemorrhage.
   (b) Rapid onset of global neurologic deficit (eg, coma) lasting at least 24 h or leading to death, plus evidence from neuroimaging or postmortem examination showing primary intracerebral and cerebellar hemorrhage.
   (c) Focal neurologic deficit (mode of onset uncertain) lasting at least 24 h or leading to death, plus evidence from neuroimaging or postmortem examination showing primary intracerebral and/or cerebellar hemorrhage.
5. Transient ischemic attack:
   (a) Rapid onset of focal neurologic deficit or loss of monocular function lasting less than 24 h.
   (b) Negative neuroimaging.
6. ASO (atherosclerosis obliterans):
   (a) At least Fontaine Classification Ⅱ.
   (b) Less than 0.9 (ankle brachial presssure index).
   (c) Positive vascular imaging.

Appendix 2

Steering Committee: Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Saito Y, Toyota T, Nakaya N, Nishimoto S, Yamamoto A, Muranaka M.
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Kitakanto Koshinetsu District (198): Aizawa T, Aizawa Y*, Akutsu H, Akutsu T, Ando T, Aoyagi K, Arai K, Arakawa M*, Arisaka H, Banba N, Fujieda K, Fujiwara H, Fujiwara Y, Fukuuchi Y*, Furuno I, Gejyo F*, Godo M, Goto K, Goto M, Hama H, Handa Y, Hatano T, Hattori N, Hayashi K, Hayashi T, Hayata H, Hirahara K, Hirayama K, Hirayama S, Hirono O, Hoshiyama M, Ichikawa S, Iijima H, Inomata A, Inoue K, Ishihara M, Ishikawa M, Ishikawa M, Ishikawa M, Ishikawa S, Ishikawa Y, Ito N, Ito Y, Iwamae S, Iwasaki S, Kado S, Kageyama Y, Kakishita H, Kamei T, Kamiyama K, Kanazawa H, Kaneko T, Kasai G, Kasai K*, Kase H, Kato T, Katsura Y, Kawada K, Kawai H, Kawai Y, Kawakami Y, Kawashima S, Kawauchi A, Kayanuma K, Kimura Y, Kobayashi K, Kobayashi T, Komori S, Komuro F, Koro T, Koshizuka M, Koyama A*, Koyata H, Kurabayashi T, Kurihara M, Kuroda H, Machida M, Maeda K, Matsumoto R, Matsumura M, Matsushima T, Matsushita H, Mimura A, Miyajima S, Miyazaki M, Mizutani M, Mori K, Mori M*, Mori Y, Morita E, Morohashi H, Motohashi S, Murakami Y, Murata M, Murayama J, Murayama N, Murayama Y, Nagai A, Nagai T, Nagano T, Nagase S,

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