Circ J 2002; **66:** 1096 – 1100

Large Scale Cohort Study of the Relationship Between Serum Cholesterol Concentration and Coronary Events With Low-Dose Simvastatin Therapy in Japanese Patients With Hypercholesterolemia and Coronary Heart Disease

—— Secondary Prevention Cohort Study of the Japan Lipid Intervention Trial (J-LIT) ——

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Hyperlipidemia is primarily implicated in the progression of coronary heart disease (CHD) and its treatment is essential for patients with a history of CHD. Statins such as simvastatin, the lipid-lowering agents, are well-known for their ability to normalize patient's serum lipid levels. The Japan Lipid Intervention Trial study of simvastatin is the first nationwide investigation of the relationship between serum lipid levels and the development of CHD in Japanese patients with hypercholesterolemia. Of 5,127 patients, exclusively with a history of documented CHD at enrollment, 4,673 were treated with open-labeled simvastatin at an initial dose of 5–10 mg/day and were monitored for 6 years. The risk of coronary events tended to be higher in patients with a serum total cholesterol (TC) ≥240 mg/dl compared with total cholesterol <240 mg/dl. The concentration of low-density lipoprotein cholesterol (LDL-C) positively correlated and that of high-density lipoprotein cholesterol (HDL-C) inversely correlated with the risk of CHD. Each 10 mg/dl decrease in LDL-C and each 10 mg/dl increase in HDL-C concentration reduced the risk of CHD by 8.0% (95% confidence interval 3.8–12.0) and 28.3% (95% CI 13.9–40.3), respectively. A reasonable therapeutic strategy to reduce CHD progression in patients with prior CHD under low-dose statin treatment might be regulating the serum LDL-C concentration to at least <120 mg/dl and HDL-C >40 mg/dl, respectively. (*Circ J* 2002; **66:** 1096 – 1100)

Key Words: Cholesterol-lowering medication; Coronary heart disease; Hyperlipidemia; Longitudinal study; Risk factors; Simvastatin

Hypercholesterolemia is an independent risk factor that contributes to the incidence of coronary heart disease (CHD) and death[1–4] The risk of CHD-related events are 5–7-fold higher in patients with atherosclerostic diseases than in those without them, and reducing the total cholesterol (TC) concentration is an important therapeutic goal[5–8] Statins, including simvastatin, are known to selectively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes a rate-limiting step in the cholesterol biosynthetic pathway[9] and, in turn, to reduce the concentrations of TC and low-density lipoprotein-cholesterol (LDL-C). The Scandinavian Simvastatin Survival Study (4S) showed that simvastatin significantly reduced the mortality of patients with CHD[5]

In Japan, cholesterol-lowering therapy is widely prescribed for patients with hypercholesterolemia, but its effect on the incidence of CHD has not been well established. Lifestyle factors, such as diet and exercise, have a strong influence on the progression of CHD and although the incidence of CHD in Japan is far lower than in Western countries[5,10,11] it may increase as the lifestyle becomes more westernized (eg, increased intake of animal fats and proteins[12]) and the aged population increases in Japan[13]

The Japan Lipid Intervention Trial (J-LIT) is the first nationwide cohort study involving a large number of patients with hypercholesterolemia under ordinary clinical care with the goal of investigating the relationship between lipid levels and the incidence of CHD. The primary object of this report is to analyze the relationship between serum

(Received May 27, 2002; revised manuscript received August 8, 2002; accepted August 23, 2002)
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lipid concentrations and the incidence of CHD under low-dose simvastatin treatment in subjects with a history of CHD. We adopted a surveillance model for the study because patients already had a history of coronary disease and thus placebo control was not possible for ethical and feasibility reasons.

Simvastatin reduces the serum TC and LDL-C concentrations and increases high-density lipoprotein cholesterol (HDL-C) concentration in patients with hypercholesterolemia, and without a history of CHD, and a relationship exists between the serum lipid concentrations and the relative risk of coronary events.[14] In this report, we examine the relationship between serum lipid concentrations and the incidence of coronary events under low-dose simvastatin treatment in patients with previous CHD.

Methods

Study Design

The design of the J-LIT study has been described previously;[15] but briefly this study involved 6,500 general practitioners throughout Japan and enrolled 52,421 patients; men aged 35–70 years and postmenopausal women aged under 70 years, with a TC concentration ≥220 mg/dl. Of those enrolled, patients with documented CHD[16] (ICD codes I 20 to I 25 and a history of coronary intervention) at the time of enrollment were selected for the secondary prevention cohort study. Exclusion criteria included a recent acute myocardial infarction (MI) or stroke within the past month, uncontrolled diabetes mellitus, serious concomitant hepatic or renal disease, secondary hypercholesterolemia, malignancy or any illness with a poor prognosis. Patients were selected from throughout Japan and received open-labeled simvastatin 5–10 mg/day for 6 years. The lipid concentration, adverse events and CHD-related events were monitored. Another lipid-lowering agent was permitted if the serum TC concentration did not respond adequately to simvastatin alone. The primary endpoints were coronary events, including acute MI[17] and sudden cardiac death. The secondary endpoints were other cardiac events such as deterioration of angina pectoris indicated by hospitalization or the requirement for coronary intervention. All CHD events during the study period were assessed by the Endpoint Classification Committee. Each patient was informed of the study purpose, as well as drug efficacy and the need for long-term treatment.

Statistical Analysis

For baseline patient characteristics, the study group was divided into 5 subgroups based on the average serum TC concentration during the treatment. The relationship between baseline characteristics and average TC concentration during treatment was analyzed with a trend test. For risk of coronary events, patients were stratified according to average lipid concentrations (TC, LDL-C, triglyceride (TG) and HDL-C) during the treatment period and according to the ratio of LDL-C/HDL-C during that time. Relative risks with a 95% confidence interval (CI) for the primary and secondary endpoints were calculated using the Cox proportional-hazard model[18] with adjustment for baseline characteristics (gender, age, hypertension, diabetes mellitus, smoking habit, and a history of MI). We excluded 74 patients because data on their smoking habit was not available. Continuous data are expressed as average ± SD. For all statistical analysis, $p<0.05$ was considered significant. All statistical calculations were performed using SAS software (V.6.12, SAS Institute Inc, Cary, NC, USA).

Results

Follow-up

Of the 52,421 patients enrolled, 5,127 were screened for the secondary prevention cohort study.[15] In the present study, data collected from 4,673 patients were analyzed and data from 454 patients were excluded for the following reasons: lack of follow-up data (93), violation of inclusion/exclusion criteria (5), unwillingness to participate (1), and incomplete covariance (355). The average length of follow-up was 5.3 years per subject and after 6 years there were 3,348 patients remained. In 6 years, 203 patients died.

Table 1 Baseline Characteristics in the Subgroups of Patients Classified by Serum Total Cholesterol (TC) Concentration During Simvastatin Treatment

	TC (mg/dl)						
	<180	*180–199*	*200–219*	*220–239*	*≥240*	*p value*	*Total*
n	*491*	*1,095*	*1,351*	*946*	*716*		*4,599*
Male gender (%)	*60.9*	*46.5*	*40.3*	*36.7*	*33.9*	*	*42.2*
Age (years)	*60.9±6.6*	*60.7±6.9*	*60.2±6.9*	*59.8±7.0*	*58.9±7.5*	*	*60.1±7.0*
Obesity (%)	*38.4*	*35.8*	*33.9*	*38.9*	*41.9*	*	*37.1*
Hypertension (%)	*49.3*	*48.7*	*46.0*	*47.4*	*47.3*		*47.5*
Diabetes mellitus (%)	*22.4*	*18.4*	*15.9*	*16.3*	*22.9*		*18.4*
Cerebrovascular disease (%)	*4.5*	*3.3*	*3.3*	*3.9*	*4.5*		*3.7*
Renal disease (%)	*3.9*	*3.6*	*1.6*	*1.7*	*2.7*	*	*2.5*
Hepatic disease (%)	*7.5*	*7.1*	*6.7*	*7.5*	*8.7*		*7.3*
History of MI (%)	*39.3*	*26.7*	*21.8*	*21.2*	*19.8*	*	*24.4*
ECG abnormality (%)	*69.7*	*71.5*	*69.7*	*70.1*	*73.3*		*70.8*
Family history of CHD (%)	*11.2*	*9.4*	*9.2*	*10.1*	*12.2*		*10.1*
Smoking habit (%)	*23.2*	*16.7*	*15.9*	*14.7*	*18.0*	*	*17.0*
Alcohol consumption (%)	*39.0*	*33.4*	*30.6*	*30.6*	*28.7*	*	*31.9*
TC (mg/dl)	*249±22*	*255±23*	*261±24*	*271±31*	*290±38*	*	*265±30*
LDL-C (mg/dl)	*168±23*	*170±26*	*176±28*	*183±33*	*202±40*	*	*179±32*
TG (mg/dl)	*194±183*	*186±118*	*183±116*	*204±151*	*216±180*	*	*194±144*
HDL-C (mg/dl)	*47.1±13.3*	*50.3±14.4*	*51.6±15.1*	*51.3±15.2*	*51.6±15.6*	*	*50.7±14.9*

*Obesity, body mass index ≥25 kg/m²; MI, myocardial infarction; CHD, coronary heart disease; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides. p value for trend test, *<0.05.*

The relationships between baseline patient characteristics and average serum TC concentration were analyzed with a trend test when patients were grouped according to their average serum TC concentration during treatment. The percentage of male patients, age, incidence of renal disease, and percentage of smokers and drinkers at baseline decreased proportionally as the average serum TC concentration increased. On the other hand, the percentage of obesity increased as the average serum TC concentration increased (Table 1).

Changes in Serum Lipid Levels With Simvastatin

Serum concentrations of TC, LDL-C and TG decreased significantly from baseline (265, 179 and 194 mg/dl, respectively) to 213 (19.6%), 130 (27.3%), and 167 (13.9%) mg/dl, respectively, after 6 months of treatment. Those concentrations were well-controlled for 6 years and were reduced to 211, 125, and 154 mg/dl, respectively, at the end of the study (Fig 1). The mean serum HDL-C concentration increased from 50.7 mg/dl (pretreatment) to 51.8 mg/dl after 6 months of treatment, and gradually increased to 56.1 mg/dl after 6 years of treatment. Over the course of the study, the average reductions in serum TC, LDL-C, and TG concentrations were 19.8±10.5%, 28.6±15.6%, and 15.9±40.1%, respectively, and the average increase in the serum HDL-C concentration was 4.7±25.0%.

Relationship Between the Risk of Coronary Events and Lipid Concentrations During Treatment

During the 6 years of treatment, 110 patients developed coronary events (primary endpoint), and the rate of incidence was 4.45 events per 1,000 patients-year (Table 2):

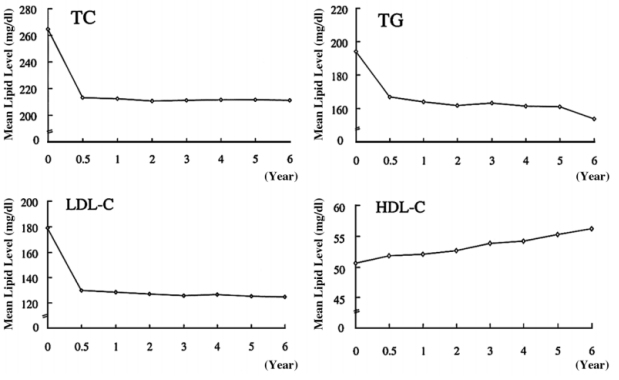

Fig 1. Sequential changes in serum lipid levels in hypercholesterolemic patients with a history of CHD who were maintained on low-dose simvastatin.

non-fatal MI (67 patients), fatal MI (38 patients), and sudden cardiac death (5 patients). Deterioration of angina pectoris (secondary endpoint) occurred in 95 patients. Overall, coronary heart disease occurred in 205 patients and the rate was 8.29 per 1,000 patients-year.

The risk of coronary events was a function of the average LDL-C concentration and inversely related to that of HDL-C during treatment (Table 3). No correlation existed between the relative risk of coronary events and the TC concentration in patients with TC concentration <240 mg/dl. However, the relative risk increased in patients whose average TC concentration was ≥240 mg/dl. The average TG concentration did not correlate with the risk of coronary events. Patients with an HDL-C concentration <40 mg/dl had a higher risk of coronary events compared with those who had a HDL-C concentration from 40 to 49 mg/dl. The risk of coronary events was lower in patients with HDL-C concentration ≥60 mg/dl than in patients with a concentration of 40–49 mg/dl. Each 10 mg/dl decrease in LDL-C and each 10 mg/dl increase in HDL-C lowered the relative risk of coronary events by 8.0% (95% confidence interval 3.8–12.0) and 28.3% (95% CI 13.9–40.3), respectively.

Relationship Between the Risk of Coronary Events and Baseline Patient Characteristics

Of the baseline characteristics, male patients had a higher risk for coronary events, with a relative risk of 2.61, compared with female patients (Fig 2). Age and obesity (body mass index ≥25 kg/m^2) did not affect the incidence of coronary events. Diabetes mellitus and a history of MI (relative risk, 2.76) increased the incidence of coronary events as well as smoking (relative risk, 1.41; p=0.133). Alcohol consumption decreased the risk and possibly protected patients. Hypertension did not affect the risk of coronary events and although renal disease tended to increase the risk, it was not statistically significant.

Discussion

The present study monitored 5,127 patients with hypercholesterolemia and a previous history of CHD for 6 years to examine the relation between serum lipid concentrations and the recurrence of coronary events. Patients were maintained on low-dose simvastatin (5–10 mg/day) under ordinary clinical care. The accumulated treatment term was approximately 24,747 patients-year. After 6 months of treatment, the serum concentrations of TC and LDL-C were lower than the baseline values, and the HDL-C concentration was higher. HDL-C concentration continued to increase during the study period. This pattern of changes in lipid concentrations during treatment was similar in that

Table 2 Incidence of Coronary Heart Disease (CHD) in Patients With Hypercholesterolemia and a History of CHD During the 6-Year Low-Dose Simvastatin Treatment Study

	No. of patients	*Incidence rate (/1,000 patients-year)*
Primary end point (coronary events)	*110*	*4.45*
MI (nonfatal)	*67*	*2.71*
MI (fatal)	*38*	*1.54*
Cardiac sudden death	*5*	*0.20*
Secondary end point	*95*	*3.84*
Angina pectoris (definite)	*95*	*3.84*
Total	*205*	*8.29*

MI, myocardial infarction.

Table 3 Risk of Coronary Events and Serum Lipids Concentration During the 6-Year Low-Dose Simvastatin Treatment Study in Patients With Hypercholesterolemia

	Study population	No. of events	Relative risk	95% CI	p value
TC (mg/dl)					
<180	*491*	*11*	*0.68*	*(0.34–1.38)*	*0.29*
180–199	*1,095*	*27*	*1.00*		
200–219	*1,351*	*26*	*0.91*	*(0.53–1.56)*	*0.72*
220–239	*946*	*20*	*1.07*	*(0.60–1.92)*	*0.81*
≥240	*716*	*21*	*1.65*	*(0.92–2.94)*	*0.09*
LDL-C (mg/dl)					
<100	*643*	*9*	*0.70*	*(0.32–1.54)*	*0.38*
100–119	*1,237*	*21*	*1.00*		
120–139	*1,362*	*34*	*1.61*	*(0.94–2.78)*	*0.08*
140–159	*789*	*21*	*1.95*	*(1.06–3.58)*	*<0.05*
≥160	*534*	*17*	*2.27*	*(1.19–4.32)*	*<0.05*
TG (mg/dl)					
<100	*854*	*21*	*1.36*	*(0.78–2.37)*	*0.28*
100–149	*1,611*	*31*	*1.00*		
150–249	*1,628*	*41*	*1.16*	*(0.73–1.86)*	*0.53*
≥250	*504*	*12*	*1.03*	*(0.53–2.03)*	*0.93*
HDL-C (mg/dl)					
<40	*669*	*32*	*1.60*	*(0.99–2.58)*	*0.06*
40–49	*1,417*	*36*	*1.00*		
50–59	*1,261*	*24*	*0.87*	*(0.52–1.47)*	*0.61*
≥60	*1,252*	*13*	*0.58*	*(0.31–1.11)*	*0.09*
LDL-C/HDL-C					
<2.0	*1,241*	*11*	*0.75*	*(0.34–1.63)*	*0.47*
2.0–2.4	*1,120*	*15*	*1.00*		
2.5–2.9	*898*	*26*	*2.18*	*(1.15–4.11)*	*<0.05*
3.0–3.4	*655*	*22*	*2.40*	*(1.24–4.62)*	*<0.01*
≥3.5	*651*	*28*	*3.05*	*(1.63–5.72)*	*<0.001*

CI, confidence intervals; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol.

observed in patients without a previous history of CHD![14]

During the 6 years of treatment, 110 patients developed CHD and the incidence of recurrent CHD was 4.45 events per 1,000 patients-years. We found in our primary prevention cohort study that the serum TC and LDL-C concentrations positively correlated and that of serum HDL-C inversely correlated with the risk of CHD in patients without a history of CHD![14] In the primary prevention cohort study, 209 patients developed coronary events, including fatal MI (51 patients), non-fatal MI (147 patients) and sudden cardiac death (11 patients). The incidence of coronary events in patients with a history of CHD was 5-fold higher than in patients without the history; the incidence was 4.45 per 1,000 patients-year for those with a history of CHD and 0.91 in patients without CHD.

Early studies established that an elevated TC concentration was an independent risk factor for CHD and death![1–4] However, in the present study, patients with a TC concentration ≥240 mg/dl developed CHD more often than patients with TC <240 mg/dl. The relationship between the TC concentration and the risk of coronary events was less clear wheres there was a strong relationship between the risk of coronary events and the LDL-C or HDL-C concentration. The serum LDL-C concentration positively correlated and serum HDL-C inversely correlated with the incidence of coronary events. The observation in TC concentration may be the result of opposite effects on coronary events influenced by the 2 lipoprotein-cholesterol components of TC because it has been established that LDL-C is a risk factor and HDL-C is, inversely, a negative risk factor for CHD?[2,19,20] In our previous primary prevention cohort study, TG concentration was a risk factor for coronary events, although the association was not strong. In the present study, serum TG concentration was not a risk factor for coronary events. The LDL-C/HDL-C ratio proportionally correlated with the incidence of coronary events, which was consistent with data from the primary prevention cohort study![14] The present results suggest that monitoring TC, LDL-C and HDL-C concentrations is crucial in the prevention of CHD progression. We also analyzed the risk of coronary events in 5 subgroups divided by equal number of subjects (about 920 patients in each group) along the average concentration of serum lipids during the study. The

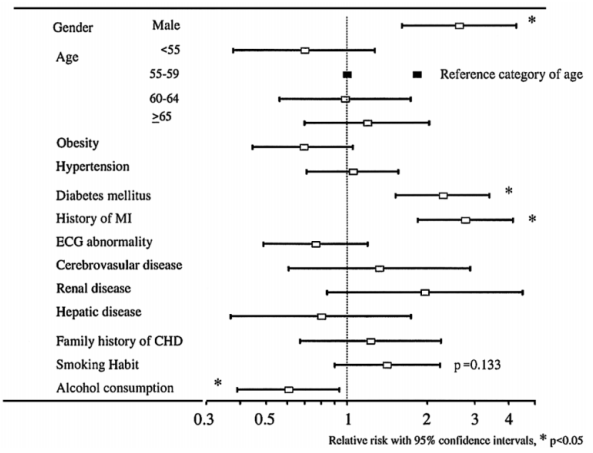

Fig 2. Correlation between the risk of coronary events and baseline characteristics of patients with a history of CHD treated by simvastatin therapy. Bars express the relative risk with 95% confidence intervals. *p<0.05. ECG, electrocardiogram; MI, myocardial infarction; Obesity, body mass index ≥25 kg/m^2.

occurrence of coronary events in relation to lipid concentration in this analysis was confirmed to be similar with the results obtained when subgroups were divided by a constant interval of serum lipid concentrations.

Other risk factors for coronary events included male patients, history of MI, diabetes mellitus, and smoking. Hypertension was not a risk factor in this study, probably because of stricter management of patient blood pressure. To elucidate further, analysis of the relationship between coronary events and patient blood pressure during treatment would be necessary. For patients who have any of these risk factors, especially diabetes mellitus, normalizing the lipid concentrations is important.[21–26]

Because the J-LIT study was conducted under the usual clinical conditions in a target population of patients throughout Japan, our findings can be reasonably extrapolated to the general Japanese population. We conclude from the data that serum choresterol concentrations relate to the incidence of coronary events in hypercholesterolemic patients under low-dose simvastatin treatment. A reasonable treatment strategy to prevent coronary events in Japanese hypercholesterolemic patients with prior CHD under low-dose statin might be regulating the serum lipid concentration to at least less than 120 mg/dl for LDL-C and more than 40 mg/dl for HDL-C.

Acknowledgments

We are grateful to Dr Heizo Tanaka, National Institute of Health and Nutrition, for expert statistical analysis of the data. This study was supported in part by a grant from the Banyu Pharmaceutical Co, Ltd, Tokyo, Japan.

References

1. National Cholesterol Education Program. Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994; **89:** 1333–1445.
2. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels: The Framingham Study. *JAMA* 1986; **256:** 2835–2838.
3. Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986; **256:** 2823–2828.
4. Keys A, Menotti A, Aravanis C, Blackburn H, Djordevic BS, Buzina R, et al. The Seven Countries Study: 2,289 deaths in 15 years. *Prev Med* 1984; **2:** 141–154.
5. Pedersen TR, Wilhelmsen L, Faergeman O, Strandberg TE, Thorgeirsson G, Troedsson L, et al. and Scandinavian Simvastatin Survival Study Group: Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344:** 1383–1389.
6. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels: Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996; **335:** 1001–1009.
7. Tonkin A, Aylward P, Colquhoun D, Glasziou P, Harris P, Hunt D, et al. and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels: The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998; **339:** 1349–1357.
8. Sugimoto K, Chikamori T, Kitaoka H, Furuno T, Seo H, Takata J, et al. Efficacy of cholesterol lowering therapy on the prognosis of Japanese patients with coronary heart disease. *J Noninvasive Cardiol* 1999; **3:** 86–90.
9. Todd PA, Goa KL. Simvastatin: A review of its pharmacological properties and therapeutic potential in hypercholesterolemia. *Drugs* 1990; **40:** 584–607.
10. Kodama K, Sasaki H, Shimizu Y. Trend of coronary heart disease and its relationship to risk factors in a Japanese population: A 26-year follow-up, Hiroshima/Nagasaki study. *Jpn Circ J* 1990; **54:** 414–421.
11. Wakugami K, Iseki K, Kimura Y, Okumura K, Ikemiya Y, Muratani H, et al. Relationship between serum cholesterol and the risk of acute myocardial infarction in a screened cohort in Okinawa, Japan. *Jpn Circ J* 1998; **62:** 7–14.
12. Okayama A, Ueshima H, Marmot MG, Nakamura M, Kita Y, Yamakawa M. Changes in total serum cholesterol and other risk factors for cardiovascular disease in Japan 1980–1989. *Int J Epidemiol* 1993; **22:** 1038–1047.
13. Investigating Committee on Guidelines for Diagnosis and Treatment of Hyperlipidemias, Japan Atherosclerosis Society. Guidelines for diagnosis and treatment of hyperlipidemias in adults. *Jpn J Atheroscler* 1997; **25:** 1–34.
14. Matsuzaki M, Kita T, Mabuchi H, Matsuzawa Y, Nakaya, N, Oikawa S, et al. and the J-LIT Study Group. Large scale cohort study on the relationship between serum cholesterol concentration and coronary events under low-dose simvastatin therapy in Japanese patients with hypercholesterolemia: Primary Prevention Study of the Japan Lipid Intervention Trial (J-LIT). *Circ J* 2002; 66 (accepted for publication).
15. Matsuzawa Y, Itakura H, Kita T, Mabuchi H, Matsuzaki M, Nakaya N, et al. and the J-LIT Study Group: Design and baseline characteristics of a cohort study in Japanese patients with hypercholesterolemia: The Japan Lipid Intervention Trial (J-LIT). *Curr Ther Res* 2000; **61:** 219–243.
16. International Statistical Classification of Diseases and Related Health Problems, Vol. 1, 10th Revision. Geneva: World Health Organization, 1992; 471–513.
17. WHO MONICA Project. MONICA Manual, revised edn. Geneva: Cardiovascular Disease Unit, WHO, 1990.
18. Cox DR. Regression methods of life tables (with discussion). *JR Stat Soc* 1972; **B34:** 187–220.
19. Miwa K, Nakagawa K. Risk factors that discriminate 'high-risk' from 'low-risk' Japanese patients with coronary artery disease. *Jpn Circ J* 2000; **64:** 825–830.
20. Saku K, Zhang B, Liu R, Shirai K, Arakawa K. Associations among serum lipoprotein(a) levels, apolipoprotein(a) phenotypes, and myocardial infarction in patients with extremely low and high levels of serum lipoprotein(a). *Jpn Circ J* 1999; **63:** 659–665.
21. Jarrett RJ, McCartney P, Keen H. The Bedford survey: Ten year mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycaemic controls and risk indices for coronary heart disease in borderline diabetics. *Diabetologia* 1982; **22:** 79–84.
22. Butler WJ, Ostrander LD Jr, Carman WJ, Lamphiear DE. Mortality from coronary heart disease in the Tecumseh study: Long-term effect of diabetes mellitus, glucose tolerance and other risk factors. *Am J Epidemiol* 1985; **121:** 541–547.
23. Borch-Johnsen K, Kreiner S. Proteinuria: Value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. *BMJ* 1987; **294:** 1651–1654.
24. Krolewski AS, Kosinski EJ, Warram JH, Leland OS, Busick KJ, Asmal AC, et al. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. *Am J Cardiol* 1987; **59:** 750–755.
25. Jarrett RJ, Shipley MJ. Type 2 (non-insulin-dependent) diabetes mellitus and cardiovascular disease: Putative association via common antecedents: Further evidence from the Whitehall Study. *Diabetologia* 1988; **31:** 737–740.
26. Morrish NJ, Stevens LK, Head J, Fuller JH, Jarrett RJ, Keen H. A prospective study of mortality among middle-aged diabetic patients (the London Cohort of the WHO Multinational Study of Vascular Disease in Diabetics). II: Associated risk factors. *Diabetologia* 1990; **33:** 542–548.