Circ J 2002; **66:** 1087 – 1095

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

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

Masunori Matsuzaki, MD; Toru Kita, MD*; Hiroshi Mabuchi, MD**; Yuji Matsuzawa, MD†; Noriaki Nakaya, MD††; Shinichi Oikawa, MD‡; Yasushi Saito, MD‡‡; Jun Sasaki, MD§; Kazuaki Shimamoto, MD§§; Hiroshige Itakura, MD¶, ¶¶ and the J-LIT Study Group

Hyperlipidemia is a well-established risk factor for primary coronary heart disease (CHD). Although simvastatin is known to lower serum lipid concentrations, the protective effect of such lipid-lowering therapy against primary CHD has not been established in Japanese patients with hypercholesterolemia. The Japan Lipid Intervention Trial was a 6-year, nationwide cohort study of 47,294 patients treated with open-labeled simvastatin (5–10 mg/day) and monitored by physicians under standard clinical conditions. The aim of the study was to determine the relationship between the occurrence of CHD and the serum lipid concentrations during low-dose simvastatin treatment. Simvastatin reduced serum concentrations of total cholesterol (TC), low-density lipoprotein- cholesterol (LDL-C) and triglyceride (TG), by 18.4%, 26.8% and 16.1% on average, respectively, during the treatment period. The risk of coronary events was higher when the average TC concentration was ≥240 mg/dl and the average LDL-C concentration was ≥160 mg/dl. The incidence of coronary events increased in the patients with TG concentration ≥300 mg/dl compared with patients with TG concentration <150 mg/dl. The high-density lipoprotein cholesterol (HDL-C) inversely correlated with the risk of coronary events. The J-curve association was observed between average TC or LDL-C concentrations and total mortality. Malignancy was the most prevalent cause of death. The health of patients should be monitored closely when there is a remarkable decrease in TC and LDL-C concentrations with low-dose statin. A reasonable strategy to prevent coronary events in Japanese hypercholesterolemic patients without prior CHD under low-dose statin treatment might be regulating the serum lipid concentrations to at least <240 mg/dl for TC, <160 mg/dl for LDL-C, <300 mg/dl for TG, and >40 mg/dl for HDL-C. (*Circ J* 2002; **66:** 1087 – 1095)

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

Hypercholesterolemia is a known and significant risk factor for the development of coronary heart disease (CHD) and death[1] Epidemiologic studies from Western countries, such as the Framingham Study,[2] have established that a high concentration of serum cholesterol confers a high risk of CHD. The incidence of CHD in the Japanese population is relatively lower than that reported in the Western countries.[3–5] Cholesterol-lowering therapy with resins and fibrates has been shown to reduce the risk of CHD.[6–8] Recent primary and secondary prevention studies have indicated that statins also reduce the incidence of CHD.[9–13] The mechanism of statin action is selective inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes a rate-limiting step of cholesterol synthesis,[14] and as a consequence, reduces the serum total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) concentrations.[15]

Statins are now the most widely prescribed drugs worldwide and are established as the first-line treatment for hyperlipidemia. Although cholesterol-lowering therapy is also prescribed widely for Japanese patients with hypercholesterolemia, the relationship between serum lipid concentrations and the incidence of CHD under low-dose statin treatment has not been completely elucidated. The

(Received May 27, 2002; revised manuscript received August 8, 2002; accepted August 23, 2002)

*Yamaguchi University Graduate School of Medicine, Ube, *Kyoto University Graduate School of Medicine, Kyoto, **Kanazawa University Graduate School of Medicine, Kanazawa, †Osaka University Graduate School of Medicine, Suita, ††Fussa general hospital, Fussa, ‡Nippon Medical School, Tokyo, ‡‡Chiba University Graduate School of Medicine, Chiba, §International University Graduate School of Health and Welfare, Fukuoka, §§Sapporo Medical University School of Medicine, Sapporo and ¶Ibaraki Christian University, Hitachi, Japan and ¶¶Chairman of Central Committee.*

Mailing address: Masunori Matsuzaki, MD, Department of Cardiovascular Medicine, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-kogushi, Ube, Yamaguchi 755-8550, Japan. E-mail: masunori@yamaguchi-u.ac.jp

Table 1 Baseline Characteristics of the Population in the Primary Prevention Cohort Study

					TC during treatment (mg/dl)	
	<160	160–179	180–199	200–219	220–239	240–259
n	461	2,065	7,233	12,494	10,671	5,380
Male gender (%)	61.6	43.5	33.8	30.7	29.8	27.8
Age (years)	57.4±8.8	59.0±8.0	58.9±7.6	58.2±7.7	57.6±7.8	56.7±7.9
Obesity (%)	37.0	36.5	33.2	33.0	33.1	34.4
Hypertension (%)	52.5	57.3	53.8	48.3	42.5	39.1
Diabetes mellitus (%)	20.8	20.2	17.2	14.7	13.4	13.6
Cerebrovascular disease (%)	6.3	5.6	4.3	3.0	2.3	2.0
Renal disease (%)	4.8	2.6	2.4	1.9	1.7	1.9
Hepatic disease (%)	16.5	11.1	8.0	7.7	7.1	8.0
ECG abnormality (%)	18.0	17.8	14.7	12.9	11.7	11.8
Family history of CHD (%)	5.0	3.8	4.5	4.4	4.5	5.2
Smoking habit (%)	31.2	21.2	16.7	15.2	15.6	16.3
Alcohol consumption (%)	44.9	32.9	28.7	28.0	28.7	27.8
TC (mg/dl)	253±40	252±24	256±22	264±34	272±28	282±30
LDL-C (mg/dl)	165±34	167±26	171±26	177±28	185±30	193±33
TG (mg/dl)	263±270	211±188	185±140	183±132	192±159	205±174
HDL-C (mg/dl)	45.6±13.5	48.8±13.8	52.1±14.6	53.2±14.8	53.7±15.1	54.0±15.5

TC, total cholesterol; Obesity, body mass index ≥25 kg/m²; 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.

Japan Lipid Intervention Trial (J-LIT) is the first nationwide study conducted to determine the relationship between serum lipid concentration and the development of CHD under low-dose simvastatin treatment. In order to evaluate this relationship, we used a surveillance study under common medical practice.

We have already reported that the serum lipid concentrations in Japanese patients with hypercholesterolemia are well-controlled by low-dose simvastatin (initial dose, 5–10 mg/day),[16] and in the present study, we examined how serum cholesterol concentrations relate to the incidence of CHD and overall mortality in a large number of these patients who did not have a history of CHD.

Methods

Subjects

The J-LIT study enrolled 52,421 patients with a serum TC concentration ≥220 mg/dl; men aged 35–70 years and postmenopausal women under 70 years of age who were selected from throughout Japan. Patients who had been treated with a lipid lowering agent, were screened for eligibility after a washout period of at least 4 weeks; the washout period was at least 12 weeks for patients previously treated with probucol. Exclusion criteria included a recent acute myocardial infarction (MI) or stroke (≤1 month), uncontrolled diabetes mellitus, serious concomitant hepatic or renal disease, secondary hypercholesterolemia, malignancy or any other illness with a poor prognosis. Patients without documented CHD (ICD[17] codes: I20 to I25) or a history of any coronary intervention at the time of enrollment were assigned to the primary prevention cohort.

Study Design

The design of the J-LIT study has been described previously,[16] but in brief it involved 6,500 general practitioners throughout Japan. During the screening period, body weight and blood pressure were determined and fasting serum lipid profiles were measured twice at monthly intervals at the local recruiting sites. Indicators of hepatic and renal function were assessed, and an electrocardiogram (ECG) was recorded. Patients were treated with open-labeled simvastatin at a dose of 5–10 mg/day and all patients, including those who discontinued simvastatin for any reason, were monitored for 6 years. Their lipid concentrations, adverse events, and CHD-related events were recorded. Cholesterol concentrations were determined locally in study institutions. The inter-hospital differences were assessed twice in 1996 and 1999 using standards distributed to sampled institutions throughout the country, and no inter-hospital differences in measurement of cholesterol were found. Dietary changes and exercise therapy for hyperlipidemia were recommended to the patients by the investigators. Additional lipid-lowering agents were allowed only when the serum TC concentration did not respond adequately to simvastatin alone. No restrictions were placed on the administration of medical treatment for complications. The LDL-C concentration in patients with a serum triglyceride (TG) concentration ≤400 mg/dl was calculated using the Friedewald formula.[18] Body weight, blood pressure, and the serum lipid concentrations were measured every 6 months after enrollment and patients were asked about drug compliance, number of cigarettes smoked, alcohol consumption, and amount of exercise. Every 12 months, hepatic and renal functions were monitored and an ECG was recorded.

The primary end-points of the study were major coronary events, such as acute MI or sudden cardiac death. The secondary end-points were the occurrence of other cardiovascular events, such as the onset of angina pectoris, and death from any cause. All CHD-related events and deaths that occurred during the study period were reviewed and determined by the Endpoint Classification Committee. The adverse drug reactions (ADRs) were evaluated by the Adverse Event Subcommittee. Each patient was informed of the study purpose, as well as drug efficacy and the need for long-term treatment. Written informed consent was not obtained from the patients because a commercially available simvastatin preparation was used for the open-labeled study.

Statistical Analysis

All data, including those obtained after the termination of

260–279 2,110	≥280 1,387	p value	Total 41,801
30.2	32.4	*	31.6
56.1±8.0	54.6±8.2	*	57.8±7.8
35.2	36.2		33.7
35.6	33.0	*	45.9
16.0	17.5	*	15.2
2.4	1.7	*	3.0
2.4	3.0		2.1
8.0	8.9	*	8.0
10.9	11.8	*	12.9
7.1	7.9	*	4.8
17.8	20.0	*	16.5
29.5	30.9	*	28.9
294±39	322±57	*	270±34
203±38	233±59	*	182±33
222±254	256±317		195±169
53.7±15.8	52.0±17.2	*	52.9±15.1

simvastatin therapy were analyzed. For baseline characteristics, the patients were divided into 8 subgroups based on their average serum TC concentration during the treatment. The average lipid concentrations were calculated using the data obtained throughout the study period. The data for lipid concentrations acquired after the onset of disease other than a primary or secondary end-point were excluded. For analysis of baseline patient age and lipid profiles, continuous variables within and between subgroup were assessed using analysis of variance by trend test. For analysis of baseline characteristics determined by categorical outcomes, differences between groups were compared using the Mantel-Haenszel test. Patients were classified into 3–8 subgroups based on the average lipid concentrations during treatment. TC, TG, LDL-C, and high-density lipoprotein cholesterol (HDL-C) concentrations and the ratio of LDL-C/HDL-C were classified into discrete intervals of 20, 150, 20, 10 mg/dl and 0.5, respectively. Reference categories were set for the subgroups, according to the guidelines,[19] of normal ranges with an upper limit of 220 mg/dl for TC, 150 mg/dl for TG, 140 mg/dl for LDL-C and with the lower limit of 40 mg/dl for HDL-C. The reference category for the ratio of LDL-C/HDL-C was set on the subgroup with 2.0–2.4. We calculated the relative risks, with 95% confidence intervals (CI) for each end-point of each subgroup relative to the reference category, using the Cox proportional-hazards model[20] with adjustment for gender and age at baseline (as a continuous variable), hypertension, diabetes mellitus, and smoking habit. We excluded 559 patients from this analysis because information about their smoking habits was not available. In addition, the effects on each baseline characteristic at each end-point were assessed, except for the effect of age, which was not adjusted because it was treated as a continuous variable. Data are expressed as the average ± SD. For all statistical analyses, $p<0.05$ was considered to be significant. All statistical calculations were performed using the SAS software (V.6.12, SAS Institute Inc, Cary, NC, USA).

Results

Follow-up

A total of 47,294 of the 52,421 patients enrolled in the J-LIT study, were eligible for the primary prevention cohort, and the remaining 5,127 patients who had a history of CHD were enrolled in the secondary prevention cohort, and the clinical characteristics of which are reported elsewhere![6] In the present study, data collected from 42,360 patients were analyzed and data from 4,934 patients were excluded for the following reasons: lack of follow-up data (932 patients), violation of inclusion/exclusion criteria (63 patients), unwillingness to participate (6 patients), and incomplete covariance (3,933 patients). Of the study patients, 31,766 were followed up by the investigators through to the end of the 6th year (average length of follow up, 5.39 years per subject). For the analysis of the baseline characteristics, patients were stratified according to their serum TC concentrations during treatment with every 20 mg/dl. In the analysis with the trend test, a trend in the relationship between average serum total cholesterol concentration during treatment and the baseline characteristics of patients was observed. The percentage of male patients, age, incidence of hypertension, diabetes mellitus, cerebrovascular disease, hepatic disease and abnormal ECG, percentage of patients with a family history of CHD, smoking and drinking increased as average serum total cholesterol concentration during treatment decreased (Table 1). The incidence of obesity and renal disease was similar in all groups. The decrease in average serum TC concentration during treatment was proportional to the patients' baseline concentrations of TC, LDL-C and HDL-C.

Table 2 Adverse Drug Reaction During the 6-Year Simvastatin Therapy

	No. of patients	Incidence rate (%)
Hepatic	450	0.97
Musculoskeletal	388	0.84
Digestive	256	0.55
Body as a whole; general	178	0.38
Skin	166	0.36
Kidney	82	0.18
Mental and nervous system	80	0.17
Blood	56	0.12
Laboratory test abnormal	59	0.13
Miscellaneous	19	0.04

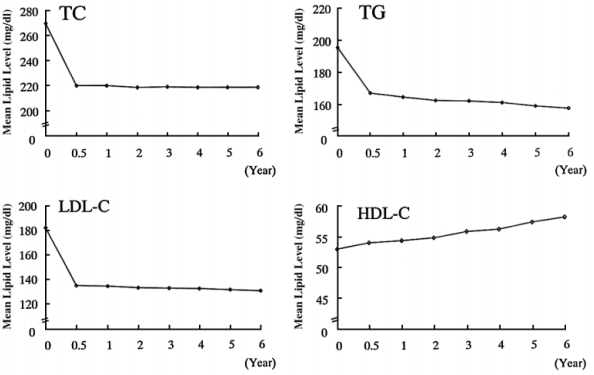

Fig 1. Sequential changes in serum lipid concentrations in patients maintained on low-dose simvastatin.

Safety

Simvastatin was well tolerated: ADRs were reported in 1,478 patients (2,194 events) for an overall ADR frequency of 3.2% over 6 years (Table 2). The most frequently ob-

Table 3 Incidence of Coronary Heart Disease in Patients With Hypercholesterolemia Receiving Low-Dose Simvastatin for 6-Years

	No. of patients	*Incidence rate (/1,000 patients-year)*
Primary end point (coronary events)	*209*	*0.91*
MI (nonfatal)	*147*	*0.64*
MI (fatal)	*51*	*0.22*
Cardiac sudden death	*11*	*0.05*
Secondary end point	*146*	*0.64*
Angina pectoris (definite)	*146*	*0.64*
Total	*355*	*1.55*

MI, myocardial infarction.

Table 4 Risk of Coronary Events and Lipids Concentration During the 6-Year Treatment Study of Low-Dose Simvastatin

	Study population	*No. of events*	*Relative risk*	*95% confidence intervals*	*p value*
TC (mg/dl)					
<180	*2,526*	*14*	*1.29*	*(0.70–2.38)*	*0.241*
180–199	*7,233*	*36*	*1.38*	*(0.88–2.16)*	*0.16*
200–219	*12,494*	*40*	*1.00*		
220–239	*10,671*	*45*	*1.47*	*(0.96–2.25)*	*0.08*
240–259	*5,380*	*37*	*2.63*	*(1.68–4.12)*	*<0.001*
≥260	*3,497*	*35*	*4.03*	*(2.55–6.38)*	*<0.001*
LDL-C (mg/dl)					
<100	*4,025*	*14*	*0.74*	*(0.40–1.35)*	*0.32*
100–119	*9,376*	*38*	*1.03*	*(0.67–1.59)*	*0.89*
120–139	*12,622*	*44*	*1.00*		
140–159	*9,089*	*41*	*1.45*	*(0.95–2.22)*	*0.09*
160–179	*3,931*	*29*	*2.59*	*(1.62–4.15)*	*<0.001*
≥180	*2,367*	*34*	*5.71*	*(3.64–8.97)*	*<0.001*
TG (mg/dl)					
<150	*23,140*	*88*	*1.00*		
150–299	*16,060*	*91*	*1.26*	*(0.93–1.69)*	*0.13*
≥300	*2,577*	*28*	*2.16*	*(1.38–3.37)*	*<0.001*
HDL-C (mg/dl)					
<40	*4,161*	*47*	*1.45*	*(1.01–2.07)*	*<0.05*
40–49	*11,897*	*85*	*1.00*		
50–59	*12,522*	*51*	*0.63*	*(0.44–0.89)*	*<0.01*
≥60	*13,221*	*24*	*0.30*	*(0.19–0.48)*	*<0.001*
LDL-C/HDL-C					
<2.0	*10,808*	*23*	*0.67*	*(0.39–1.14)*	*0.14*
2.0–2.4	*10,197*	*32*	*1.00*		
2.5–2.9	*8,949*	*33*	*1.21*	*(0.74–1.96)*	*0.45*
3.0–3.4	*5,730*	*44*	*2.54*	*(1.61–4.00)*	*<0.001*
≥3.5	*5,726*	*68*	*4.02*	*(2.63–6.13)*	*<0.001*

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

served ADR was hepatic dysfunction and 760 events occurred in 450 subjects for an incidence of 0.97%. The incidence of musculoskeletal and digestive ADRs were 0.84 and 0.55%, respectively. Rhabdomyolysis was not observed in any patients for the entire 6 years of this study.

Changes in Serum Lipid Concentrations With Simvastatin

The average serum concentrations of TC, TG, and LDL-C decreased from their average baseline concentrations of 270 to 221, 196 to 167, and 182 to 132 mg/dl, respectively, after 6 months of treatment, and these concentrations were well maintained during the 6 years (Fig 1). The average lipid concentrations during the treatment for TC, TG and LDL-C were 220 mg/dl, 164 mg/dl and 134 mg/dl, respectively. The average serum HDL-C concentration increased from a baseline of 52.9 mg/dl to 54.0 mg/dl after 6 months of treatment, and continued to further increase to 58.1 mg/dl at the 6th year. The average percent changes in the TC, LDL-C, TG and HDL-C concentrations during the treatment period were –18.4±10.3%, –26.8±15.0%, –16.1±42.5%, and +4.5±29.8%, respectively.

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

Coronary events occurred in 209 patients during the course of the study with a rate of incidence of 0.91 events per 1,000 patients-year (Table 3). Fatal MI occurred in 51 patients, non-fatal MI in 147 patients, and sudden cardiac death in 11 patients. Unequivocal angina pectoris (secondary end-point) developed in 146 patients.

The average serum concentrations of TC and LDL-C were closely related to the risk of coronary events for 6 years (Table 4). The risk of coronary events was higher in patients whose TC concentration was ≥240 mg/dl, compared with those whose TC concentrations were between 200 and 219 mg/dl (the reference category). Likewise, in

patients with a LDL-C concentration ≥160 mg/dl, the risk of coronary events was higher than in those with a concentration between 120 and 139 mg/dl (the reference category). A group of patients with an average TG concentration ≥300 mg/dl had a higher incidence of coronary events than the group with an average TG concentration <150 mg/dl. In contrast, the average serum HDL-C concentration was inversely related to the risk of coronary events. The incidence of coronary events was lower in patients with an average HDL-C concentration ≥50 mg/dl and higher in those with an average HDL-C concentration <40 mg/dl compared with patients whose HDL-C concentration was between 40 and 49 mg/dl. The incidence of coronary events and the average lipid concentrations during the treatment were found to be strongly related because each 10 mg/dl decrease in the TC, LDL-C and TG concentrations and each 10 mg/dl increase in the HDL-C concentration reduced the risk of coronary events by 11.3%, 15.8%, 1.2%, and 37.5%, respectively. In comparison, the incidence of coronary events was less correlated with the baseline concentrations of TC, LDL-C and HDL-C because a 10 mg/dl decrease in baseline serum TC, LDL-C, and TG concentrations and 10 mg/dl increase in baseline serum HDL-C concentration reduced the risk of coronary events by a mere 1.5%, 7.3%, 0.1%, and 21.6%, respectively.

Relationship Between the Risk of Coronary Events and Baseline Patient Characteristics (Fig 2)

The risk of coronary events was analyzed using multiple regression. Male patients had a higher risk, with a relative risk of 2.29 compared with female patients. Age correlated with the incidence of coronary events: coronary events occurred more often in patients with aged 60 years or more than in patients younger than 60 years old. Hypertension, diabetes mellitus, ECG abnormalities, cerebrovascular disease, a family history of CHD and a smoking habit were also risk factors for coronary events. In contrast, patients' alcohol consumption reduced the risk for coronary events; the average consumption was approximately 38 g/day per patient (measured as absolute alcohol).

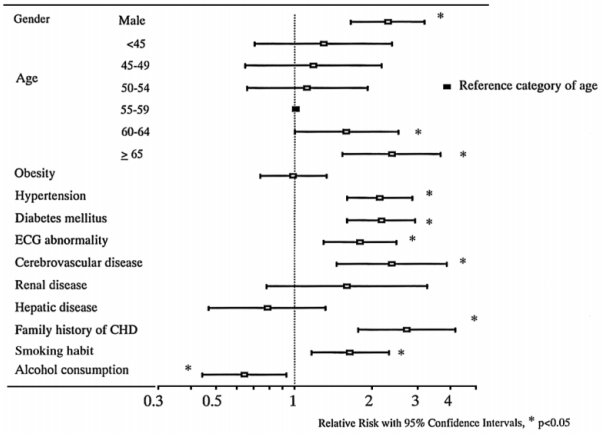

Fig 2. Relationship between the relative risk of coronary events and baseline characteristics of patients maintained on low-dose simvastatin. Bars express the relative risk with a 95% confidence interval. Obesity, body mass index ≥25 kg/m^2.

Relationship Between the Relative Risk of Overall Mortality and Lipid Concentrations

During the study period, 844 patients died (3.69 deaths

Table 5 Relative Risk of Death and Serum Lipid Concentrations During Treatment of Hypercholesterolemia With Low-Dose Simvastatin

	Study population	*No. of events*	*Relative risk*	*95% confidence intervals*	*p value*
TC (mg/dl)					
<160	*461*	*28*	*2.76*	*(1.86–4.10)*	*<0.001*
160–179	*2,065*	*77*	*1.72*	*(1.33–2.23)*	*<0.001*
180–199	*7,233*	*161*	*1.13*	*(0.92–1.38)*	*0.25*
200–219	*12,494*	*222*	*1.00*		
220–239	*10,671*	*178*	*1.03*	*(0.84–1.25)*	*0.79*
240–259	*5,380*	*79*	*1.01*	*(0.78–1.30)*	*0.95*
260–279	*2,110*	*49*	*1.68*	*(1.23–2.28)*	*<0.01*
≥ 280	*1,387*	*43*	*2.58*	*(1.85–3.58)*	*<0.001*
LDL-C (mg/dl)					
<80	*839*	*30*	*1.72*	*(1.17–2.53)*	*<0.01*
80–99	*3,186*	*76*	*1.16*	*(0.90–1.51)*	*0.26*
100–119	*9,376*	*211*	*1.20*	*(0.99–1.44)*	*0.07*
120–139	*12,622*	*219*	*1.00*		
140–159	*9,089*	*154*	*1.07*	*(0.87–1.31)*	*0.54*
160–179	*3,931*	*75*	*1.32*	*(1.02–1.72)*	*<0.05*
180–199	*1,403*	*25*	*1.37*	*(0.90–2.07)*	*0.14*
≥ 200	*964*	*33*	*2.92*	*(2.03–4.22)*	*<0.001*
TG (mg/dl)					
<150	*23,140*	*425*	*1.00*		
150–299	*16,060*	*353*	*1.13*	*(0.98–1.31)*	*0.09*
≥ 300	*2,577*	*58*	*1.29*	*(0.97–1.70)*	*0.08*
HDL-C (mg/dl)					
<40	*4,161*	*135*	*1.30*	*(1.06–1.60)*	*<0.05*
40–49	*11,897*	*286*	*1.00*		
50–59	*12,521*	*217*	*0.75*	*(0.63–0.90)*	*<0.01*
60–69	*7,536*	*94*	*0.55*	*(0.44–0.70)*	*<0.001*
≥ 70	*5,686*	*105*	*0.84*	*(0.67–1.05)*	*0.13*

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

Table 6 Causes of Death and Total Cholesterol (TC) Concentration of Patients Treated With Low-Dose Simvastatin for 6-Year

	TC (mg/dl)	Study population	No. of deaths	Relative risk	95% confidence intervals	p value
Cardiac	Subtotal	41,801	83			
	<160	461	4	6.23	(1.99–19.52)	<0.01
	160–179	2,065	5	1.83	(0.64–5.23)	0.26
	180–199	7,233	15	1.82	(0.85–3.89)	0.12
	200–219	12,494	12	1.00		
	220–239	10,671	16	1.80	(0.85–3.81)	0.12
	240–259	5,380	16	4.04	(1.91–8.56)	<0.001
	260–279	2,110	6	3.96	(1.48–10.58)	<0.01
	>280	1,387	9	10.67	(4.45–25.54)	<0.001
Cerebrovascular /other vascular	Subtotal	41,801	188			
	<160	461	4	1.48	(0.54–4.11)	0.45
	160–179	2,065	16	1.34	(0.77–2.33)	0.31
	180–199	7,233	35	0.92	(0.60–1.40)	0.70
	200–219	12,494	58	1.00		
	220–239	10,671	36	0.81	(0.53–1.22)	0.31
	240–259	5,380	21	1.04	(0.63–1.71)	0.89
	260–279	2,110	8	1.03	(0.49–2.17)	0.93
	>280	1,387	10	2.25	(1.14–4.41)	<0.05
Malignancy	Subtotal	41,801	313			
	<160	461	12	3.16	(1.72–5.81)	<0.001
	160–179	2,065	31	1.85	(1.22–2.80)	<0.01
	180–199	7,233	61	1.13	(0.81–1.57)	0.47
	200–219	12,494	86	1.00		
	220–239	10,671	77	1.13	(0.83–1.54)	0.43
	240–259	5,380	22	0.72	(0.45–1.15)	0.17
	260–279	2,110	16	1.42	(0.83–2.42)	0.20
	>280	1,387	8	1.24	(0.60–2.57)	0.56
Accident/suicide	Subtotal	41,801	72			
	<160	461	3	2.87	(0.86–9.64)	0.09
	160–179	2,065	3	0.67	(0.20–2.22)	0.51
	180–199	7,233	12	0.82	(0.41–1.64)	0.57
	200–219	12,494	24	1.00		
	220–239	10,671	14	0.72	(0.37–1.39)	0.32
	240–259	5,380	8	0.88	(0.39–1.96)	0.75
	260–279	2,110	3	0.87	(0.26–2.90)	0.82
	>280	1,387	5	2.40	(0.91–6.36)	0.08
Others	Subtotal	41,801	181			
	<160	461	5	2.67	(1.05–6.80)	<0.05
	160–179	2,065	22	2.59	(1.54–4.36)	<0.001
	180–199	7,233	38	1.40	(0.90–2.17)	0.14
	200–219	12,494	42	1.00		
	220–239	10,671	35	1.07	(0.68–1.68)	0.77
	240–259	5,380	12	0.81	(0.43–1.54)	0.52
	260–279	2,110	16	2.92	(1.64–5.21)	<0.001
	>280	1,387	11	3.61	(1.85–7.04)	<0.001
Total deaths	Subtotal	41,801	837			

per 1,000 patients-year). The J-curve was observed between average TC concentration and total mortality (Table 5): the relative risk of death was higher in patients with a TC concentration <180 mg/dl or ≥260 mg/dl compared with the other groups. A similar pattern was observed between average LDL-C concentration and total mortality. Significantly lower total mortality was observed in patients with an average HDL-C concentration between 50 and 69 mg/dl, whereas there was higher mortality in patients with a HDL-C concentration <40 mg/dl compared with those whose average HDL-C concentration was between 40 and 49 mg/dl. There was no significant relationship between average TG concentration and total mortality. Of the 41,801 patients evaluated, 461 (1.1%) had an average TC concentration <160 mg/dl (40.2% reduction) during the treatment. Among the highly responsive population of patients to low-dose simvastatin therapy, 28 patients died at an average of 3.30±1.59 years after starting the treatment and of them, 12 died from malignancy (4 cases of gastric cancer, the highest, and 2 cases of lung cancer). Malignancy was the most common cause of death in most TC subgroups, followed by cerebrovascular diseases 1 other vascular diseases (Table 6). Death from cardiac disease occurred in 83 of 41,801 patients, including 51 who died from MI, 11 from sudden cardiac death, and 21 from other cardiac diseases. There was no obvious correlation between the relative risk of accident/suicide and serum TC concentration.

Relationship Between the Relative Risk of Death and Baseline Patient Characteristics

The relative risk of death was analyzed using multiple regression (Fig 3). Male patients had higher risk of death compared with female patients, and the incidence of death increased with age. Obesity did not correlate with the risk of death. Hypertension, diabetes mellitus, ECG abnormalities, cerebrovascular disease, and renal and hepatic diseases

also were risk factors for death. A smoking habit tended to increase the risk of death, but not significantly. Alcohol consumption reduced the risk of death.

Discussion

The J-LIT, a long-term prospective cohort study on the use of simvastatin, is the first epidemiological study in Japan to demonstrate a relationship between serum lipid concentrations and the incidence of primary onset of CHD or total mortality in Japanese patients with hypercholesterolemia and low-dose statin administration.

The overall frequency of ADRs during the simvastatin treatment was 3.2% over 6 years, which suggests that simvastatin is safe and well-tolerated.

After 6 months of treatment, the serum concentrations of TC and LDL-C had changed to 18.4% and 26.8% below baseline, respectively, and these concentrations were maintained throughout the 6 years of the study, however the concentration of HDL-C continued to increase during the treatment period.

The incidence of coronary events in Japanese patients without prior CHD in this study was 0.91 events per 1,000 patients-year, much lower than in Western countries[21–22] Since the relative risk of coronary events in men was 2.3 times higher than in women, and two-thirds of the patients enrolled in the J-LIT study were women, this low male/female ratio may have contributed to the overall low incidence of coronary events.

In the J-LIT study, patients with average TC concentration ≥240 mg/dl developed coronary events more frequently than those with a concentration <240 mg/dl during simvastatin (5–10 mg/day) treatment. The incidence of MI significantly increased when the TC concentration rose above 220 mg/dl in the Framingham Study[2] and a correlation between serum cholesterol and the risk of MI was also reported in an Okinawan population[23] The reason for having more coronary events at a TC concentration ≥240 mg/dl in the J-LIT study, not ≥220 mg/dl as in the Framingham study, could be simvastatin's anti-atherosclerotic effect, which is presumed to be the result of its pleiotropic actions on coronary vessels. It has been reported that simvastatin inhibits smooth muscle cell migration[24] and inflammatory reactions;[25] and improves the responsiveness of endothelium cells to the factors influencing blood vessels[26]

It is well documented that an elevated LDL-C concentration is an independent risk factor for CHD and death[1] When the J-LIT subgroups were divided on the basis of a constant interval of serum lipid concentration, the average serum concentration of LDL-C closely correlated with the risk of coronary events, whereas the concentration of HDL-C was inversely correlated. Coronary events did not occur in any of the 871 patients (4,633 patient-years) whose baseline HDL-C concentration was ≥90 mg/dl, and an increase in the HDL-C concentration as a result of statin treatment may prevent CHD[27,28] We observed an average reduction of LDL-C concentration of 48 mg/dl below baseline during 6 years of simvastatin treatment, and an increase in HDL-C concentration by 5.2 mg/dl. Using these combined changes in lipid concentrations and previously calculated rate of reduction in coronary events of 15.8% per 10 mg/dl reduction in LDL-C and 37.5% per 10 mg/dl increase in HDL-C, 66% reduction in coronary events during the treatment was predicted.

TG concentration was not a strong risk factor for coronary events in the present study and others have reported that the relationship between the TG concentration and the incidence of MI is greatly affected by the serum TC and HDL-C concentrations of the patient[29,30] In a recent epidemiological study, a close relationship between the concentration of serum TG and coronary events was reported in Japanese patients;[31] thus further examination is needed to clarify the relationship.

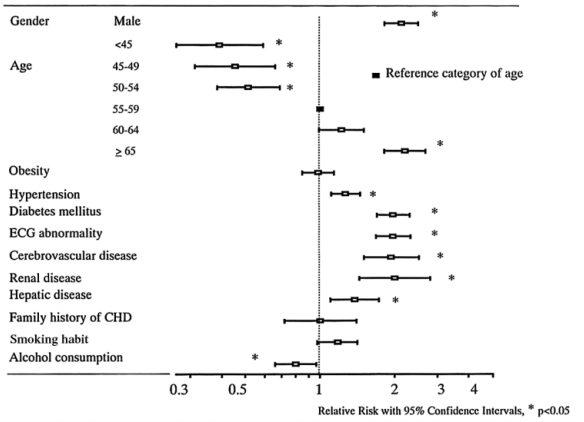

Fig 3. Relationship between the relative risk of death and baseline characteristics of patients maintained on low-dose simvastatin. Bars express the relative risk with a 95% confidence interval. Obesity, body mass index ≥25 kg/m^2.

We also analyzed the risk of coronary events in 8 subgroups divided by equal number of subjects (approx. 5,200 patients in each group), in addition to the average concentrations of serum lipids during the study. The occurrence of coronary events in relation to the lipid concentrations in this analysis was similar with the result from the subgroups divided by constant interval of serum lipid concentrations. The correlation between the incidence of coronary events and the baseline concentrations of TC, LDL-C or HDL-C was weak in the present study. In another clinical intervention trial, a 6-month simvastatin regimen prevented the occurrence of MI, which was more closely correlated with average TC concentration during treatment rather than the baseline lipid concentrations;[8] and our present result is consistent with that finding.

The risk factors for coronary events, other than the average serum lipid concentrations, were male gender, age, hypertension, diabetes mellitus, ECG abnormality, cerebrovascular disease, a family history of CHD and smoking. Numerous epidemiologic studies have documented that hypertension, diabetes mellitus and smoking are risk factors for MI[32–44] To minimize the risk of coronary events, eliminating those risk factors as well as normalizing the lipid concentrations is important, especially for patients with hypertension or diabetes mellitus. Alcohol consumption was a negative risk factor for coronary events and that finding was noted in other several epidemiologic studies[45–49]

In a minority of patients with exceptional lowering of the TC concentration (<160 mg/dl) by low-dose simvastatin therapy, the relative risk of death was similar to the group of patients in which the treatment had little effect on patient TC concentration ≥280 mg/dl. The J-curve was observed between TC or LDL-C concentrations and total mortality: the relative risk of death was higher in patients with a TC concentration <180 mg/dl or ≥260 mg/dl compared with the other patient group. The patients with an exceptionally low

TC concentration, the so-called 'hyper-responders' to simvastatin, had a higher relative risk of death from malignancy than in the other patient groups. Almost all patients in this group showed a marked decrease in TC concentrations at 6 months after starting the treatment and maintained the same concentration throughout the study period, therefore the exceptionally low TC concentration may have been caused by underlying diseases that were responsible for the patient's death. It is still unclear why those hyperresponsive patients responded to simvastatin so remarkably, but the effect should be noted. The 1990 National Heart, Lung, and Blood Institute Conference on Low Blood Cholesterol reported a U-shaped association between serum cholesterol concentration and death based on data from cohort studies[50] and it was concluded that the cause of the higher death rates in those with a TC concentration <160 mg/dl was probably a mixed bag of mechanisms that had yet to be clarified. The PROCAM[51] and MRFIT[52] studies also observed an association between low TC concentration and malignancy. The data of the J-LIT study were obtained from observations during low dose simvastatin (5 mg/day) treatment in which the average serum TC concentration of patients was 270 mg/dl at baseline and decreased to 220 mg/dl during the treatment. On the other hand, the PROCAM and MRFIT were epidemiological studies and therefore we cannot directly compare our results with those studies. Further analysis is necessary to elucidate why the hyper-responders had an increased risk of death; their baseline characteristics will be described and discussed in detail in the future. Nevertheless, the health of patients who show a remarkable decrease in TC or LDL-C concentration with low-dose statin therapy should be monitored closely.

The present study demonstrates a relationship between serum lipid concentrations and the incidence of coronary events in Japanese patients with hypercholesterolemia under low-dose simvastatin treatment. A reasonable strategy to prevent coronary events in Japanese hypercholesterolemic patients without prior CHD under low-dose statin treatment might be to regulate the serum lipid concentrations to at least <240 mg/dl for TC, <160 mg/dl for LDL-C and <300 mg/dl for TG and >40 mg/dl for HDL-C. The relationship between the relative risk of death and the concentrations of the different lipids requires further study.

Study Limitation

Although we have named this study 'The Japan Lipid Intervention Trial', in reality it was a cohort and observational study rather than an intervention study.

Acknowledgments

Authors 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 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. 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; **13:** 141–154.
4. Sekikawa A, Satoh T, Hayakawa T, Ueshima H, Kuller LH. Coronary heart disease mortality among men aged 35–44 years by prefecture in Japan in 1995–1999 compared with that among white men aged 35–44 by state in the United States in 1995–1998: Vital statistics data in recent birth cohort. *Jpn Circ J* 2001; **65:** 887–892.
5. 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.
6. The Lipid Research Clinics Coronary Primary Prevention Trial. Results I: Reduction in incidence of coronary heart disease. *JAMA* 1984; **251:** 351–364.
7. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317:** 1237–1245.
8. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate: Report from the Committee of Principal Investigators. *Br Heart J* 1978; **40:** 1069–1118.
9. 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.
10. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia: West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; **333:** 1301–1307.
11. 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.
12. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS /TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; **279:** 1615–1622.
13. 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.
14. Alberts AW, Chen J, Kuron G, Hunt V, Huff J, Hoffman C, et al. Mevinolin: A highly potent competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase and a cholesterol-lowering agent. *Proc Natl Acad Sci USA* 1980; **77:** 3957–3961.
15. Todd PA, Goa KL. Simvastatin: A review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. *Drugs* 1990; **40:** 583–607.
16. 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.
17. International Statistical Classification of Diseases and Related Health Problems, Vol. 1, 10th Revision. Geneva: World Health Organization, 1992; 471–513.
18. Friedwald WT, Levy RI, Fredrickson DS. Estimation of the level of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18:** 499–502.
19. Investigating Committee on Guidelines for Diagnosis and Treatment of Hyperlipidemias, Japan Atherosclerosis Society. Guidelines for diagnosis and treatment of hyperlipidemia in adults. *Jpn J Atheroscler* 1997; **25:** 1–34.
20. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc* 1972; **B34:** 187–220.
21. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations: Monitoring trends and determinants in cardiovascular disease. *Lancet* 1999; **353:** 1547–1547.
22. Menotti A, Blackburn H, Seccareccia F, Kromhout D, Nissinen A, Aravanis C, et al. The relation of chronic diseases to all-cause mortality risk: The Seven Countries Study. *Ann Med* 1997; **29:** 135–141.

23. 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.
24. Hidaka Y, Eda T, Yonemoto M, Kamei T. Inhibition of cultured vascular smooth muscle cell migration by simvastatin (MK-733). *Atherosclerosis* 1992; **95:** 87–94.
25. Strandberg TE, Vanhanen H, Tikkanen MJ. Effect of statins on C-reactive protein in patients with coronary artery disease. *Lancet* 1999; **353:** 118–119.
26. O'Driscoll G, Green D, Taylor RR. Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month. *Circulation* 1997; **95:** 1126–1131.
27. Boden WE. High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: Assessing the data from Framingham to the Veterans Affairs High-Density Lipoprotein Intervention Trial. *Am J Cardiol* 2000; **86:** 19L–22L.
28. 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.
29. Austin MA. Plasma triglyceride as a risk factor for coronary heart disease: The epidemiologic evidence and beyond. *Am J Epidemiol* 1989; **129:** 249–259.
30. Assmann G, Schulte H, Funke H, von Eckardstein A. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. *Eur Heart J* 1998; **19:** M8–M14.
31. Iso H, Naito Y, Sato S, Kitamura A, Okamura T, Sankai T, et al. Serum triglycerides and risk of coronary heart disease among Japanese men and women. *Am J Epidemiol* 2001; **153:** 490–499.
32. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997; **157:** 2413–2446.
33. 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.
34. 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.
35. Borch-Johnsen K, Kreiner S. Proteinuria: Value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. *BMJ* 1987; **294:** 1651–1654.
36. Krolewski AS, Kosinski EJ, Warram JH, Leland OS, Busick EJ, 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.
37. 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.
38. 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.
39. US Department of Health and Human Services. Cardiovascular disease: The health consequences of smoking. DHHS Publication No. (PHS) 84-5024. Washington DC: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on smoking and Health, 1983.
40. US Department of Health and Human Services. Reducing the health consequences of smoking, 25 years of progress: A report of the Surgeon General. DHHS Publication No. (CDC) 89-8411. Washington DC: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1989.
41. Willett WC, Green A, Stampfer MJ, Speizer FE, Colditz GA, Rosner B, et al. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med* 1987; **317:** 1303–1309.
42. Kannel WB, Neaton JD, Wentworth D, Thomas HE, Stamler J, Hulley SB, et al. Overall and coronary heart disease mortality rates in relation to major risk factors in 325,348 men screened for the MRFIT (Multiple Risk Factor Intervention Trial). *Am Heart J* 1986; **112:** 825–836.
43. LaCroix AZ, Lang J, Scherr P, Wallace RB, Cornoni-Huntley J, Berkman L, et al. Smoking and mortality among older men and women in three communities. *N Engl J Med* 1991; **324:** 619–625.
44. Jonas MA, Oates JA, Ockene JK, Hennekens CH. Statement on smoking and cardiovascular disease for health care professionals: American Heart Association. *Circulation* 1992; **86:** 1664–1669.
45. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. *N Engl J Med* 1988; **319:** 267–273.
46. Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, et al. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet* 1991; **338:** 464–468.
47. Kitamura A, Iso H, Sankai T, Naito Y, Sato S, Kiyama M, et al. Alcohol intake and premature coronary heart disease in urban Japanese men. *Am J Epidemiol* 1998; **147:** 59–65.
48. Solomon CG, Hu FB, Stampfer MJ, Colditz GA, Speizer FE, Rimm EB, et al. Moderate alcohol consumption and risk of coronary heart disease among women with type 2 diabetes mellitus. *Circulation* 2000; **102:** 494–499.
49. Ajani UA, Gaziano JM, Lotufo PA, Liu S, Hennekens CH, Buring JE, et al. Alcohol consumption and risk of coronary heart disease by diabetes status. *Circulation* 2000; **102:** 500–505.
50. Hulley SB, Walsh JM, Newman TB. Health policy on blood cholesterol: Time to change directions. *Circulation* 1992; **86:** 1026–1029.
51. Cullen P, Schulte H, Assmann G. The Munster Heart Study (PROCAM): Total mortality in middle-aged men is increased at low total and LDL cholesterol concentrations in smokers but not in non-smokers. *Circulation* 1997; **96:** 2128–2136.
52. Sherwin RW, Wentworth DN, Cutler JA, Hulley SB, Kuller LH, Stamler J. Serum cholesterol levels and cancer mortality in 361,662 men screened for the Multiple Risk Factor Intervention Trial. *JAMA* 1987; **257:** 943–948.