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![4]

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![4] 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![4] 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

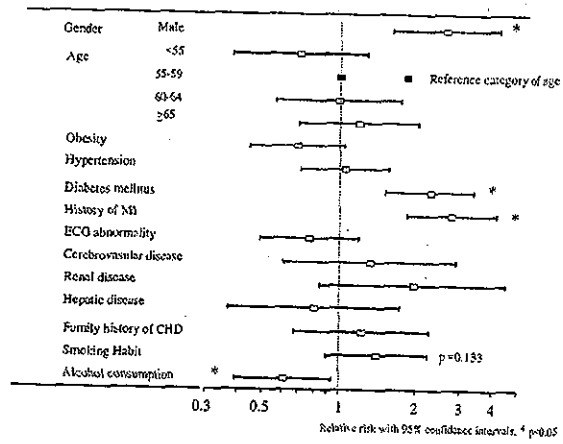

Fig 2. Correlation between the risk of coronary events and baseline characteristics of patients with a history of CHD treated by simvastatin therapy. Bars express the relative risk with 95% confidence intervals. *p<0.05. ECG, electrocardiogram; MI, myocardial infarction; Obesity, body mass index ≥25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

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Circ J 2003; **67**: 287–294

Sustained Reduction of Serum Cholesterol in Low-Dose 6-Year Simvastatin Treatment With Minimum Side Effects in 51,321 Japanese Hypercholesterolemic Patients

—— Implication of the J-LIT Study, a Large Scale Nationwide Cohort Study ——

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

The Japan Lipid Intervention Trial (J-LIT) study, a nationwide cohort study utilizing the clinical practice of general physicians, was designed to clarify the relationship between the incidence of coronary heart disease and serum lipid concentrations during simvastatin therapy, as well as the safety of the therapy, in a large number of Japanese hypercholesterolemic patients. All the enrolled patients were treated with simvastatin. The current study analyzed the lipid lowering effect and safety of the low-dose simvastatin therapy used in the J-LIT study. Open-labeled simvastatin was given to 51,321 patients at an initial dose of mostly 5 mg/day. After 6 months of the treatment, the average serum total cholesterol (TC) and low density lipoprotein-cholesterol concentrations in all the patients followed up were reduced by 18.3% and 26.0%, respectively, and that of high density lipoprotein-cholesterol increased 2.3% on average. These concentrations were well maintained throughout the 6-year treatment period. A minority of patients (1.4%) unexpectedly had a remarkable reduction in TC concentration by more than 40%. Hyper-responders, even to low-dose statin, were found for the first time in this large-scale and long-term investigation. Overall adverse drug reactions occurred in 3.3% of subjects during the 6-year treatment, the major events being hepatic and musculoskeletal disorders, of which the incidence was less than 1%. Low-dose simvastatin therapy of 5 mg/day effectively controlled the serum TC concentration by reducing it by approximately 20% on average in hypercholesterolemic Japanese patients, a reduction that corresponds to the effect of simvastatin 20 mg/day in Western studies. In addition, the low incidence of drug-related adverse events in this study may be also related to the low dosage of simvastatin. (*Circ J* 2003; **67**: 287–294)

Key Words: Cholesterol-lowering medication; Cohort study; Drug tolerance; Safety; Simvastatin

The Japan Lipid Intervention Trial (J-LIT) study was the first nationwide cohort study conducted to elucidate the relationship between serum lipid concentrations and the incidence of coronary heart disease (CHD), and was designed to reflect ordinary clinical practice for lipid lowering therapy in Japan[1] In order to maintain patient compliance under these conditions, it was essential for simvastatin to be administered to all patients, and we believed that by analyzing a large amount of clinical data for the correlation between the serum lipid concentrations and prevalence of coronary events under simvastatin treatment, the possible benefit of lipid lowering therapy in prevention of coronary events would be elucidated even without the use of placebo. Our study design was compatible with the ethical standards of the Declaration of Helsinki, which was revised on October 2000 to include the conditions for the use of a placebo control group. Therefore, the present protocol may be a practical method for the confirmation of the effectiveness and safety of other widely used drugs.

There have been a number of epidemiological studies in Western countries that have demonstrated a close relationship between the concentration of serum cholesterol and the incidence of CHD, the most well known being the Framingham study conducted in the USA[2] In those studies, patients with lower serum cholesterol concentrations had a reduced risk of CHD. In the past, cholesterol-lowering treatments using resins[3] and fibrates[4,5] were reported to reduce the risk of CHD. Recently, statins, including simvastatin, were found to selectively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway, and reduce the serum total cholesterol (TC) and low density lipoprotein-cholesterol (LDL-C) concentrations[6] In

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*Osaka University Graduate School of Medicine, Osaka; *Kyoto University Graduate School of Medicine, Kyoto; **Kanazawa University Graduate School of Medicine, Kanazawa; †Yamaguchi University Graduate School of Medicine, Ube; ††Fussa General Hospital, Tokyo; ‡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, Ibaraki, Japan*

Mailing address: Yuji Matsuzawa, MD, Department of Internal Medicine and Molecular Science, Osaka University Graduate School of Medicine 2-2 B-5, Yamadaoka, Suita, Osaka 565-0871, Japan

Table 1 Demographics and Clinical Characteristics of Japanese Hypercholesterolemic Patients Receiving Long-Term, Low-Dose Simvastatin

Total (N=52,421)	
Age (years)	*57.9±7.9*
Male, no. (%)	*17,424 (33.2)*
BMI	*24.0±3.2*
Blood pressure (mmHg)	
Systolic	*139±19*
Diastolic	*82±11*
Hospitalization (%)	*0.8*
Hypertension (%)	*45.2*
Diabetes mellitus (%)	*15.4*
Obesity (%)	
BMI ≥25	*32.0*
BMI ≥30	*3.7*
ECG abnormality (%)	*18.4*
Family history of CHD (%)	*5.2*
Current smoker (%)	*16.6*
Male (%)	*41.9*
Ex-smoker (%)	*4.5*
Renal disorder (%)	*2.2*
Hepatic disorder (%)	*8.0*
Coronary heart disease (%)	*9.8*
Cerebrovascular disease (%)	*3.0*
Alcohol consumption (%)	*29.1*
Male (%)	*70.7*
FH (%)	*2.6*
Serum cholesterol level (mg/dl)	
TC	*269±34*
HDL-C	*52.6±15.1*
LDL-C	*182±34*
Triglyceride (mg/dl)	*196±169*
Atherogenic index (TC/HDL-C)	*5.6±1.9*

BMI, body mass index; CHD, coronary heart disease; FH, familial hypercholesterolemia; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Data are presented as the mean±SD.

the Scandinavian Simvastatin Survival Study (4S), simvastatin significantly reduced the mortality of patients with hypercholesterolemia[7] and other statins have also been reported to reduce the incidence of CHD[8–11]

The dose of statins prescribed in Japan is lower than that in Western countries; for example, the daily dose of simvastatin approved in Japan is 5–10 mg in contrast to 20–40 mg in Western countries[12] The present study examined the safety and drug tolerance, as well as the efficacy of long-term treatment, of relatively low dose simvastatin in Japanese hypercholesterolemic patients.

Methods

Patient Selection

In the J-LIT study, 54,203 Japanese hypercholesterolemic (TC ≥220 mg/dl) patients were screened from November 1992 through June 1993 by 6,511 investigators, almost all of whom were general practitioners, at 5,289 institutions from all 47 prefectures in Japan. Of those patients, 52,421 study subjects (17,424 men aged 35–70 years and 34,997 postmenopausal women) under 70 years of age were recruited and of them, 47,294 were eligible as the primary prevention cohort, and the remaining 5,127 patients with a history of CHD were enrolled as the secondary prevention cohort. Patients who had previously been treated with lipid-lowering agents were screened for eligibility after a washout period of at least 4 weeks, and the washout period was at least 12 weeks for those previously treated with probucol. Exclusion criteria included a recent (≤1 month) history of myocardial infarction (MI) or stroke, a history of severe MI or stroke, uncontrolled diabetes mellitus, serious concurrent hepatic or renal disease, secondary hypercholesterolemia, malignant disease, or other illness with a poor prognosis.

Study Design

The design of the J-LIT study has been reported previously in detail[1] During the screening period at the local recruiting site, body weight and blood pressure were determined, and fasting serum lipid profiles were measured twice consecutively. Every 6 months after enrollment, body weight, blood pressure, and serum lipid concentrations were measured and drug compliance, number of cigarettes smoked (none, 1–10, 11–19 or ≥20 per day), alcohol consumption (none, <25, 25–49 or ≥50 g/day) and amount of exercise (none, occasional, frequent or every day) were recorded. Hepatic and renal functions were assessed and an electrocardiogram was obtained every 12 months. Every patient started treatment with open-labeled simvastatin 5–10 mg/day, and lipid concentrations, adverse events and CHD events were monitored for 6 years. Diet and exercise therapies for hyperlipidemia were recommended by the investigators. Other lipid-lowering agents were added only when the investigator considered that the patient's serum TC concentration had not responded adequately to simvas-

Table 2 Sequential Changes of Treatment Profiles in Cholesterol-Lowering Therapy During 6 Years Follow-up

	Year						
	0	*1*	*2*	*3*	*4*	*5*	*6*
Simvastatin							
5 mg monotherapy	*n=48,428*	*39,519*	*32,900*	*28,981*	*25,461*	*22,823*	*20,518*
10 mg monotherapy	*1,729*	*2,081*	*2,069*	*2,025*	*1,966*	*1,812*	*1,668*
Other monotherapy	*1*	*168*	*249*	*293*	*295*	*261*	*229*
Simvastatin monotherapy total	*50,158*	*41,768*	*35,218*	*31,299*	*27,722*	*24,896*	*22,415*
Simvastatin + other lipid-lowering agent	*1,163*	*1,688*	*1,968*	*2,133*	*1,993*	*1,813*	*1,845*
Other lipid-lowering agent	*0*	*56*	*235*	*463*	*509*	*525*	*814*
No or Unknown medication	*0*	*6,576*	*10,419*	*11,655*	*12,074*	*12,190*	*11,821*
Total	*51,321*	*50,088*	*47,840*	*45,550*	*42,298*	*39,424*	*36,895*
Simvastatin total	*51,321*	*43,456*	*37,186*	*33,432*	*29,715*	*26,709*	*24,260*
5 mg (%)	*49,495 (96.4)*	*40,946 (94.2)*	*34,561 (92.9)*	*30,694 (91.8)*	*27,065 (91.1)*	*24,246 (90.8)*	*21,994 (90.7)*
10 mg (%)	*1,825 (3.6)*	*2,332 (5.4)*	*2,365 (6.4)*	*2,422 (7.2)*	*2,334 (7.9)*	*2,183 (8.2)*	*2,018 (8.3)*
Other (%)	*1 (0.0)*	*178 (0.4)*	*260 (0.7)*	*316 (0.9)*	*316 (1.1)*	*280 (1.0)*	*248 (1.0)*

tatin monotherapy. No restrictions were placed on treatments for other medical conditions. The LDL-C concentration in patients with serum triglyceride (TG) concentrations under 400 mg/dl was calculated using the Friedewald formula[13] At the beginning of this study, each patient was informed of the study purpose and was given information on drug efficacy and the need for long-term treatment.

Examination of Adverse Events

All adverse events were graded by the collaborating investigators according to the direct relation to simvastatin as definite, possible, unclear or not, as judged from the available information. All simvastatin-related adverse events were pooled and described as adverse drug reactions (ADRs). Cases of patient death were evaluated by the Endpoint Classification Committee, and all adverse events were reviewed by the Adverse Event Subcommittee, which consisted of 3 specialists who were not part of the J-LIT study group. The adverse events, such as hepatic dysfunction (aspartate aminotransferase (AST) ≥80 IU/L, alanine aminotransferase (ALT) ≥80 IU/L, γ-glutamyl transpeptidase (γ-GTP) ≥100 IU/L, or a diagnosis of hepatobiliary disorder), thrombocytopenia (platelets <100,000/mm^3, presence of purpura or pancytopenia), musculoskeletal disorder (rhabdomyolysis, elevated creatine kinase (CK) concentration (≥1,000 IU/L) and elevated creatine kinase concentration (≥600 IU/L) with muscle symptoms), and other serious adverse events, were reviewed in detail. Hepatitis was diagnosed as AST or ALT ≥120 IU/L, or γ-GTP ≥150 IU/L with abnormal AST or ALT (≥80) as judged by an investigator, rhabdomyolysis as CK ≥10,000 IU/L with muscular symptoms, and myopathy as muscle symptoms (malaise, muscular pain or cramp) with CK ≥1,900 IU/L in men or ≥1,500 IU/L in women.

Statistical Analysis

Differences between groups in baseline characteristics were compared using the unpaired t-test or the chi-square test. Results are expressed as mean±SD, and differences were considered statistically significant at $p<0.05$. Continuous variables within and between subgroups were assessed using the paired or unpaired t-test, or trend test. Analysis of covariance was used for this purpose when a significance in between-group incompatibility existed at baseline. Differences in categorical data between groups were compared using the chi-square test. Patients who received at least one dose of simvastatin during the trial was included in the analysis of adverse events. All statistical calculations were performed using SAS software (version 6.12, SAS Institute, Inc, Cary, NC, USA).

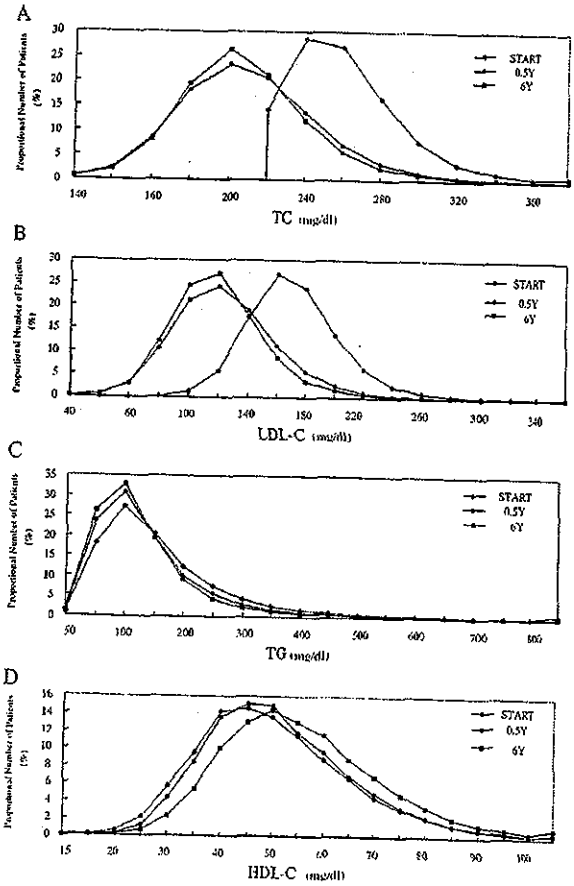

Fig 1. Distribution of proportional number of patients by serum lipid concentration at baseline, after 6 months and 6 years of low-dose simvastatin therapy. (A) Total cholesterol, (B) LDL-C, (C) triglyceride and (D) HDL-C.

Results

Patient Follow-up

The patients' clinical characteristics have been described before[1] and the baseline characteristics of the current 52,421 cohort members are summarized in Table 1. The average age was 57.9 years and 33% were male. After enrollment, 1,100 patients were excluded for the following reasons: violation of initial dosage (68 patients), missing follow-up data (1,025 patients) and unwillingness to participate (7 patients). Sequential changes in the treatment profile of the different cholesterol-lowering therapies during the 6 years of follow-up is summarized in Table 2. Of 51,321 patients, the majority (96.4%) received the most common starting dose of simvastatin 5 mg/day, and only

Table 3 Sequential Changes in Lipid Concentrations During Simvastatin Treatment

	Baseline (mg/dl)	*6 months*		*6 years*	
		(mg/dl)	*(%)*	*(mg/dl)*	*(%)*
TC	*269±34*	*220±37**	*(−18.3)*	*217±34**	*(−19.3)*
LDL-C	*182±33*	*135±35**	*(−26.0)*	*129±32**	*(−28.9)*
TG	*196±169*	*167±126**	*(−14.7)*	*155±103**	*(−21.0)*
HDL-C	*52.6±15.1*	*53.8±14.8**	*(2.3)*	*58.1±15.7**	*(10.5)*

Data are presented as the mean±SD.
**p<0.0001 vs Baseline.*

Table 4 Percent Change in TC and Number of Patients With Adverse Drug Reactions in the Hypercholesterolemic Patients Receiving Long-Term, Low-Dose Simvastatin Therapy

	Reduction in TC (%)						
	>40	31–40	21–30	11–20	≤10	Lipid data missing	Total
All ADRs*	24 (3.29)	146 (3.16)	427 (2.70)	458 (2.73)	282 (3.04)	333	1,670
Hepatic*	8 (1.10)	57 (1.23)	148 (0.94)	147 (0.88)	81 (0.87)	59	500
Musculoskeletal*	10 (1.37)	50 (1.08)	126 (0.80)	138 (0.82)	70 (0.75)	45	439
Digestive*	4 (0.55)	8 (0.17)	47 (0.30)	65 (0.39)	66 (0.71)	101	291
Skin*	0 (0.00)	12 (0.26)	40 (0.25)	44 (0.26)	30 (0.32)	59	185
Total no. of patients (%)	729 (1.4)	4,618 (9.0)	15,827 (30.8)	16,780 (32.7)	9,279 (18.1)	4,088 (8.0)	51,321 (100)

*No. of incodence (%), described in Tables 6–8.

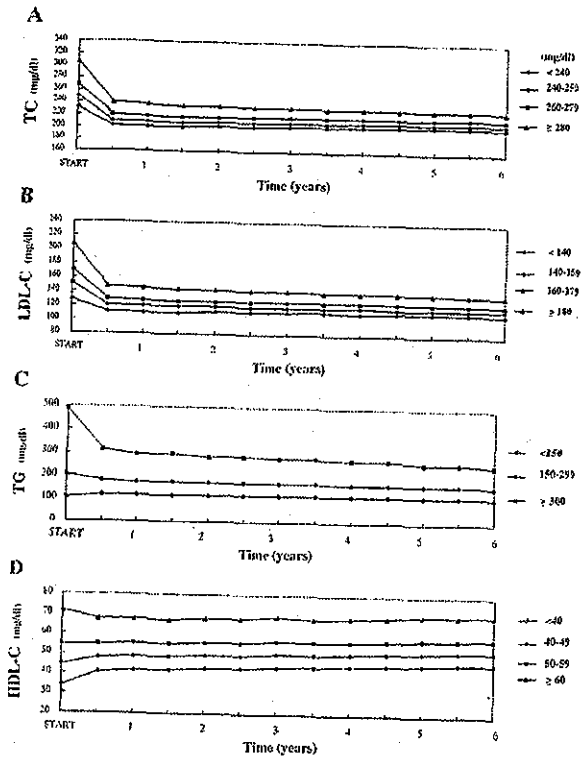

Fig 2. Sequential changes in the serum lipid concentrations as a function of the duration of simvastatin treatment for groups of patients categorized by their baseline lipid concentrations. (A) Total cholesterol, (B) LDL-C, (C) triglyceride, (D) HDL-C.

3.6% (1,825 patients) started at 10 mg/day, with 1 patient starting at 7.5 mg/day. At the 6th year, 36,895 patients remained in the study. The average follow-up period was 5.3±1.4 years (0.5–6.0 years). At the 6th year, 20,518 patients had received simvastatin 5 mg/day alone, 1,668 patients had received simvastatin 10 mg/day alone, 1,845 patients had received other lipid-lowering drugs in addition to simvastatin and 814 patients had received other lipid-lowering drugs. The ratio of patients treated with simvastatin 10 mg/day to those on 5 mg/day slightly increased during the course of treatment, nonetheless, more than 90% of patients remained on 5 mg/day for 6 years. The cumulative treatment term was 174,769 patient-years and the average term of drug treatment was 3.41 years per patient.

Changes in Serum Lipid Concentrations

After 6 months of treatment, the distribution curve of patient number by serum TC and LDL-C concentrations shifted lower in comparison with the baseline in all the patients followed up (Fig 1). The average reduction in serum TC and LDL-C was 18.3% and 26%, respectively, after 6 months, and these concentrations were maintained during the 6-year treatment period (Table 3). After 6 years of treatment, TC and LDL-C concentrations were reduced by 19.3 and 28.9%, respectively, although a minority (1.4%) had an unexpectedly remarkable reduction by more than 40% in serum TC concentration (Table 4). That group had 1.7-fold more men and 4.4-fold higher incidence of complications of renal disease, 2.2-fold of hepatic disease and 1.8-fold of diabetes mellitus when compared with the group of patients with a 10-20% reduction in TC concentration. In the contrast, the serum high density lipoprotein-cholesterol (HDL-C) concentration increased on average by 2.3% after 6 months of treatment, and kept gradually increasing throughout the treatment period up to 10.5% by the 6th year. Although no change in the serum TG distribution pattern was observed, the average value decreased by 14.7% at the 6th month and by 21 % during the 6-year treatment period in comparison with baseline.

The time course of the effect of treatment on lipid concentrations can be seen when the patient groups are stratified by their baseline lipid concentrations (Fig 2). The serum TC and LDL-C concentrations decreased with the treatment in all groups, but the reduction was greater in the patients with a higher baseline TC or LDL-C concentration (Table 5). The mean concentration of serum HDL-C increased after 6 months of the treatment and continued to increase during the treatment period. The serum HDL-C concentration after 6 years of treatment did not change in patients whose baseline HDL-C was 60 mg/dl or more, but in those with a baseline concentration less than 60 mg/dl the increase in serum HDL-C after the treatment was greater as the baseline concentration decreased. The serum TG concentrations decreased markedly in patients with a higher baseline TG concentration, particularly in patients with the highest range of concentrations (TG ≥300 mg/dl) for whom the reduction was 41.4% of the baseline. On the other hand, the TG concentration increased slightly in the group with a low baseline TG concentration.

Clinical Adverse Effects

Overall, treatment with simvastatin was well tolerated. ADRs were reported in 1,670 patients (2,470 events), and the overall frequency of ADRs during the treatment for 6 years was 3.3% of subjects (Table 4). The incidence of ADRs is demonstrated with the patient groups stratified by the reduction in serum TC concentration during the treatment (Fig 3, Table 4). There was no significant difference in the incidence of ADRs in these groups, except in the patients with less than 10 % decrease in TC concentration

Table 5 Baseline Serum Lipid Concentration and Percent Changes at 6 Years With Low-Dose Simvastatin Therapy in Japanese Hypercholesterolemic Patients

Baseline serum lipid concentration (mg/dl)	*n*	*% changes*	*p value for trend test*
TC			
<240	*2,836*	*-12.0±12.8*	
240–259	*6,059*	*-16.5±11.7*	
260–279	*5,771*	*-19.4±11.2*	
≥280	*6,404*	*-24.4±11.7*	
			<0.001
LDL-C			
<140	*1,193*	*-13.5±22.2*	
140–159	*3,134*	*-21.9±17.9*	
160–179	*4,918*	*-26.8±16.1*	
≥180	*9,129*	*-33.3±14.6*	
			<0.001
TG			
<150	*9,960*	*17.3±55.7*	
150–299	*8,352*	*-17.6±40.1*	
≥300	*2,500*	*-41.4±35.9*	
			<0.001
HDL-C			
<40	*3,322*	*40.7±61.8*	
40–49	*5,684*	*18.0±24.6*	
50–59	*5,055*	*8.3±21.4*	
≥60	*5,692*	*-0.4±20.9*	
			<0.001

% changes are presented as the mean±SD.

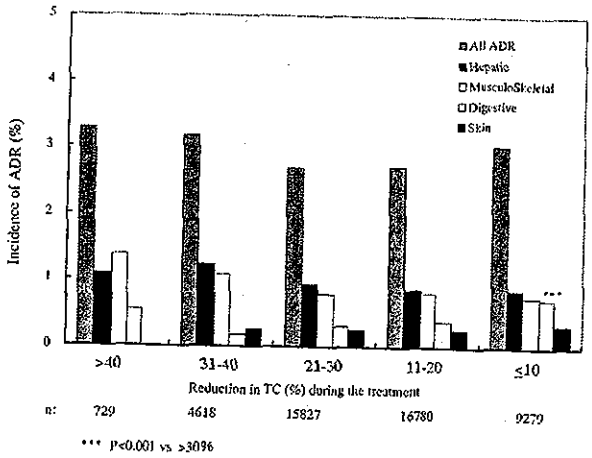

Fig3. Incidence of adverse drug reactions in long-term, low-dose simvastatin therapy as a function of the change in the total cholesterol concentration during the treatment.

who showed an increase in the incidence of digestive ADRs. The incidence of musculoskeletal ADRs had a tendency to increase slightly in proportion to the reduction of TC concentration, and the added incidence in the group of patients with a greater than 30% decrease in serum TC concentration was significantly higher when compared to the group with a 20–30% decrease.

The ADRs summarized by different organ system are shown in Table 6. The most frequently observed ADRs were hepatic disorders in 500 cases (838 events) with an incidence of 0.97%. Of these, 411 cases (82%) represented abnormal laboratory values without clinical significance (Table7). Hepatitis occurred in 80 patients with an incidence of 0.16%. There were 3 cases of elevated AST and/or ALT greater than 500 IU/L. The severity of hepatic disorders was mild in 421 cases, and moderate in 79 cases. None

Table 6 Summary of Adverse Drug Reactions (ADRs) in Hypercholesterolemic Japanese Patients on Long-Term, Low-Dose Simvastatin Therapy

ADR	*n (no. of patients)*
Hepatic (described in Table 7)	*838 (500)*
Musculoskeletal (described in Table 8)	*492 (439)*
Digestive	*352 (291)*
Abdominal symptoms	*187*
Diarrhea	*45*
Nausea	*31*
Anorexia	*27*
Miscellaneous	*62*
Generalized	*220 (200)*
Malaise	*49*
Headache	*39*
Dizziness	*38*
Weakness	*29*
Miscellaneous	*65*
Skin	*190 (185)*
Rash	*131*
Pruritus	*47*
Miscellaneous	*12*
Kidney	*108 (96)*
BUN increased	*39*
Hematuria	*20*
Miscellaneous	*49*
Neurological	*101 (93)*
Sleep disorder	*25*
Numbness	*23*
Miscellaneous	*53*
Blood	*71 (62)*
Anemia	*27*
Miscellaneous	*44*
Laboratory test abnormality	*71 (67)*
Uric acid increased	*26*
Miscellaneous	*45*
Miscellaneous	*27 (26)*

of the cases was considered serious by the Adverse Event Subcommittee. The second most common ADRs were musculoskeletal disorders (439 cases, 492 events), which

Table 7 Hepatic Disorders as Adverse Drug Reaction (ADR) in Hypercholesterolemic Japanese Patients on Long-Term, Low-Dose Simvastatin Therapy

ADR	Mild	Moderate	Serious	Total
Hepatitis	9	71	0	80
Fatty Liver	20	7	0	27
Cholelithiasis	1	0	0	1
Liver function test abnormality	408	3	0	411
AST increased	206	2	0	208
ALT increased	232	1	0	233
γ-GTP increased	115	2	0	117
ALP increased	48	0	0	48
LDH increased	83	0	0	83
Bilirubin increased	16	0	0	16
Miscellaneous	25	0	0	25
Total	755	83	0	838
No. of patients	421	79	0	500

AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyltranspeptidase, ALP, alkaline phosphatase; LDH, lactate dehydrogenase.
Serious = life-threatening condition, Moderate = requiring medical treatment or discontinuation of simvastatin treatment, Mild = others.

Table 8 Musculoskeletal Disorders as Adverse Drug Reaction (ADR) in Hypercholesterolemic Japanese Patients on Long-Term, Low-Dose Simvastatin Therapy

ADR	Total (with elevated CK)
Rhabdomyolysis	0
Myopathy	4 (4)
Myalgia	97 (32)
Muscle cramp	36 (9)
Muscle atrophy	1 (0)
Arthralgia	8 (1)
Myoglobin increased	2 (1)
Elevated CK (IU/L)	
≥1,900 (Men), ≥1,500 (Women)	2
≥1,000	21
≥600 with symptoms	18
Other	303
Total	492
No. of patients	439

CK, creatine phosphokinase.

occurred with incidence of 0.86% (Table 8). Among them, 344 events had an elevated CK concentration; 6 patients showed a 10-fold increase of the normal values and 4 patients were considered to have myopathy because of the occurrence of pathognomonic symptoms. There was no case of rhabdomyolysis as defined by the ADR assessment subcommittee as CK greater than 10,000 IU/L with muscular symptoms. The significant increase of musculoskeletal ADRs that accompanies treatment with fibrate agents was not observed. Among the digestive adverse reactions, abdominal symptoms were reported in 187 cases (0.36%) and for skin reactions, a rash developed in 131 cases (0.26%) (Table 6). Twenty five patients had a sleep disorder (0.05%).

Information for 10 patients who died or were hospitalized because of simvastatin-related adverse events is summarized in Table 9. One death was caused by thrombocytopenia in the 3rd month of the treatment. That patient received 9 drugs concomitant to the simvastatin, and the platelet count had not been determined prior to or at the start of simvastatin therapy. The platelet count was less than 10,000/μL after 3 months of the therapy, and the patient died 5 days after the finding of thrombocytopenia, which the reporting physician did not considered to be related to the simvastatin. However, the relationship of thrombocytopenia to simvastatin could not be denied. Of 9 patients requiring hospitalization from possible serious ADRs, 3 had thrombocytopenia.

The frequency of overall ADRs was 9.6 cases per 1,000 patients-year and that of death and hospitalization was 57 cases per 1,000,000 patients-year.

Discussion

The J-LIT study is the first prospective cohort study to successfully establish a correlation between serum lipid concentrations and the incidence of CHD in Japanese hypercholesterolemic patients. In this study, low-dose simvastatin (mostly 5 mg/day) administered for 6 years effectively reduced serum TC and LDL-C concentrations, and increased the HDL-C concentration, in Japanese subjects with hypercholesterolemia and the treatment was safe and well tolerated. The number of participating subjects was approximately 50,000 and the total study period of 6 years simulated long-term simvastatin treatment for patients with hypercholesterolemia. A study without placebo control was required to obtain information of the safety and efficacy of simvastatin in Japanese patients for following reasons. First, this long-term and large-scale study was only possible through ordinary standard clinical practices in Japan. Under those conditions, administering simvastatin to every subject was critical to ensure the compliance of patients, because the availability of the well established health insurance to every Japanese patient without exception meant that this study provided no additional financial incentive to the participants. Second, statins are already a proven effective treatment for hypercholesterolemia and it was difficult to convince physicians and patients to participate if the lives of the hypercholesterolemic patients in the placebo group would be compromised because of the possible consequences of coronary events. In this regard, the study plan is in agreement with the October 2000 revised Declaration of Helsinki and could be a practical method for assessing the effectiveness and safety of other widely used drugs with life saving effects.

Hypercholesterolemia has been identified as a major risk factor for CHD[1,14] and previous studies have demonstrated that cholesterol-lowering medication can reduce the risk of CHD[2-10] or death[6] Of those medications, simvastatin, which

Table 9 Summary of Death and Hospitalization in Hypercholesterolemic Japanese Patients Receiving Long-Term, Low-Dose Simvastatin Therapy

ADR	*Sex*	*Age (years)*	*Month of treatment*	*Details*
Thrombocytopemia	*M*	*56*	*3*	**Platelet <1.0×10⁴/μL Death 5 days after emergency hospitalization.*
Thrombocytopenia	*F*	*59*	*30*	**Platelet <2.0×10⁴/μL Simvastatin discontinued, recovery after hospitalization.*
Thrombocytopenia	*F*	*51*	*31*	**Platelet <7.5×10⁴/μL, Not recovered with discontinuation of simvastatin, hospitalization.*
Aplastic anemia	*F*	*62*	*52*	*Subcutaneous hemorrhage continued after cassation of simvastatin. Hospitalization. Simvastatin resumed.*
Myalgia	*F*	*56*	*31*	*CK 1,402 IU/L. Hospitalization because of continued thigh muscle pain.*
Renal failure	*M*	*61*	*2*	*CK 865 IU/L. Dialysis.*
Vertigo, nausea	*F*	*51*	*2*	*Hospitalization because of severe vertigo and nausea. CT normal. Symptoms improved in 1 week after sodium bicarbonate infusion.*
Dizziness	*F*	*66*	*40*	*Hospitalization because of difficulty walking with dizziness. Recovered in 1 month.*
Pancreatitis	*M*	*56*	*53*	*Hospitalization because of vomiting and epigastric pain. Diagnosis stage 4 pancreatitis. Pancreatitis improved after treatment with camostat mesilate.*
Fever, vomiting, diarrhea, Creatinine·BUN ↑	*F*	*66*	*49*	*Hospitalization with fever, vomiting, diarrhea and creatinine·BUN increase. Details unknown.*

**No data for baseline platelet count.*

is a powerful drug for normalizing serum lipid concentrations, is one of the most widely prescribed statins in the world.[5] A comparable long-term large-scale study of simvastatin conducted in a Western country was the 4S study in which the effect of 20–40 mg/day of simvastatin in hypercholesterolemic subjects was examined for 5.4 years on average.[7] In Japan, the recommended starting dose is 5 mg/day, which is 1/4 of the dose used in Western countries,[12] and during the initial 6-month simvastatin treatment period, the serum concentrations of TC and LDL-C decreased 18.3% and 26.0% of their baseline values, respectively. The magnitude of the reductions was similar to those observed in higher dose simvastatin studies performed in Western countries, such as the 4S study. However, the reasons why Japanese patients responded differently from those in Western countries are not clear. We speculate that differences in patient susceptibility to simvastatin because of differences in intrinsic metabolism and/or the nature of dietary intake or genetic factors in both populations could account for the dose difference. In particular, the difference may be related to dietary differences, because there seems to be basically no difference in the pharmacokinetics of the drug and the effect of simvastatin on the reduction of LDL-C has been enhanced by lower fat diet.[15,16] Treatment with low-dose statin in combination with a low-fat diet might benefit patients in Western countries. With the recent progress in understanding the genetic factors associated with hyperlipidemia, the genetic characteristics of both populations that contribute to the difference in dosage may be clarified in the near future.

A minority(1.4%) of the present patient population had an exceptional reduction of serum TC (>40%) with the low dose of simvastatin, and this is the first time such a phenomenon has been documented. That group of patients had more male subjects and a higher incidence of complications of renal disease, hepatic disease and diabetes mellitus when compared with the group of patients whose TC concentration was reduced by 10–20%. In the past, cancer was suggested as a possible cause of hypocholesterolemia,[17] but the reduction reported here may have included other causes. Hyper-responders have an increased risk of death,[19] so patients who show a remarkable decrease in TC or LDL-C concentration with low-dose statin therapy should be monitored closely. We will report on these hyper-responders in detail in another paper.

Patients with hypercholesterolemia require long-term treatment to normalize and maintain their cholesterol concentration, but because these patients frequently have concomitant medical conditions, such as hypertension, diabetes mellitus, and cardiac disease, they are usually treated with multiple medications. Hence, in the selection of cholesterol-lowering drug, safety is an important consideration for daily clinical care.

The well-known ADRs of statins are rhabdomyolysis and hepatitis. Serious cases of rhabdomyolysis have been reported in Western countries, especially with concomitant treatment with substrates or inhibitors of cytochrome P450 3A4 enzyme, such as cyclosporin A and itraconazole. Generally, close monitoring of the patient for rhabdomyolysis is recommended strongly when statins are prescribed. Although there were 4 cases of myopathy with CK elevation in this study, the ADR assessment subcommittee judged that there were no cases of rhabdomyolysis (CK ≥10,000 IU/L with muscular symptoms), which may have been because there was early detection of symptoms and abnormal CK values of patients receiving simvastatin and countermeasures were taken by the physicians who were aware of the risk of musculoskeletal ADRs. In the 4S study, there was a case of rhabdomyolysis that was relieved by discontinuation of simvastatin. The incidence of musculoskeletal ADRs increased in proportion with the magnitude of the increased TC lowering effect, which suggests that the pathophysiology of this ADR is related to the biochemical mechanism of the cholesterol-lowering effect of the drug.

Hepatitis occurred only in 0.16% of the patients in the present study, and none of the cases was serious, which may also be a result of the careful patient monitoring by the physicians. Following the safety information on the drug is critical for the prevention of ADRs.

Thrombocytopenia is an uncommon but serious and sometimes fatal ADR that is associated with a variety of

drugs. One patient in this study died from thrombocytopenia. This patient received 10 different drugs, 5 of which were continued until the death occurred, and so the causal relationship between this complication and simvastatin therapy is unclear. Medication should have been discontinued when the thrombocytopenia was detected and withheld until the platelet count normalized. There is a possibility that simvastatin impairs heamatopoiesis. One case of aplastic anemia occurred and the incidence of aplastic anemia is higher in Japanese patients than in Western countries;[18] for reasons that are still unclear.

The rate of serious drug-related adverse events was only 57 cases per 1,000,000 patients-year, and the overall frequency of ADRs over the 6 years was 3.3% of subjects.

We have also reported[19,20] that the concentration of serum cholesterol correlated with the incidence of CHD in Japanese hypercholesterolemic patients with or without a history of CHD in the J-LIT study, which strongly suggests that cholesterol-lowering medication prevents CHD in Japanese hypercholesterolemic patients.

In conclusion, cholesterol-lowering therapy using low-dose simvastatin is highly effective in controlling serum lipid concentration and is safe, and well tolerated by Japanese hypercholesterolemic patients. Additionally, a low fat diet may be beneficial to patients, by decreasing the incidence of drug-related adverse events.

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ORIGINAL ARTICLE

Strategy for treating elderly Japanese with hypercholesterolemia*

Hisanori Horiuchi,[1] Yuji Matsuzawa,[2] Hiroshi Mabuchi,[3] Hiroshige Itakura,[4] Jun Sasaki,[5] Mitsuhiro Yokoyama,[6] Yuichi Ishikawa,[7] Shinji Yokoyama,[8] Seijiro Mori,[9] Takashi Ohrui,[10] Masahiro Akishita,[11] Toshio Hayashi,[12] Kiminori Yamane,[13] Genshi Egusa[14] and Toru Kita[15]

[1]Departments of Geriatric Medicine and [15]Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, [2]Department of Internal Medicine, The Sumitomo Hospital, Osaka, [3]The Second Department of Internal Medicine, School of Medicine, Kanazawa University, Kanazawa, [4]Ibaraki Christian University, Ibaraki, [5]International University Graduate School of Health and Welfare, Fukuoka, [6]Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine and [7]Faculty of Health Sciences, Kobe University School of Medicine, Kobe, [8]Department of Biochemistry, Cell Biology and Metabolism, Nagoya City University Graduate School of Medical Sciences, and [12]Department of Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, [9]Department of Internal Medicine, Matsudo Municipal Hospital, Matsudo, [10]Department of Geriatric and Respiratory Medicine, Tohoku University School of Medicine, [11]Department of Geriatric Medicine, Kyorin University School of Medicine, Mitaka, [13]The Second Department of Internal Medicine, Hiroshima University School of Medicine, and [14]The Egusa Genshi Clinic, Hiroshima, Japan

Background: It has been widely accepted that control of serum cholesterol levels is effective for prevention of cardiovascular events. Recent data have suggested that this is also the case in the elderly.

Methods: A research group (chaired by T. Kita) was organized as part of the Comprehensive Research on Aging and Health conducted by the Japanese Ministry for Health, Labour, and Welfare in 1999–2002 to determine the best strategy for control of cholesterol levels in elderly Japanese with hypercholesterolemia. In order to do this a review of the literature was conducted.

Conclusion: The research group concluded: (i) Japanese patients aged 65–74 years with hypercholesterolemia should be treated by following the Guideline for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases by the Japan Atherosclerosis Society (2002), as cholesterol-lowering therapy would bring a similar, or even larger, preventive effect to the elderly, whose absolute risk of cardiovascular events is higher than that in the younger population; (ii) target cholesterol levels in elderly Japanese aged ≥ 75 years with

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Correspondence: Dr Toru Kita, Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, 606–8507, Japan. Email: tkita@kuhp.kyoto-u.ac.jp

*Based on the report of the Research Group for 'Long-term prognosis of elderly Japanese with hypercholesterolemia' in the Comprehensive Research on Aging and Health.

hypercholesterolemia should be determined individually according to their physical activities. It is noted that the elderly are more susceptible to drug-related adverse effects than the younger since renal and liver functions, required for metabolizing drugs, in the elderly are relatively weaker.

Keywords: cardiovascular event, elderly, hypercholesterolemia, Japanese, statin.

Introduction

It is well known that cardiovascular events occur in elderly people more frequently than in the younger population. It is also known that the incidence of these events increases as serum cholesterol levels are elevated. In Japan, populations of elderly people are rapidly increasing and serum cholesterol levels have been clearly rising in all ranges of ages probably due to westernization of our dietary habits.[1] Therefore, a rapid increase in atherosclerotic diseases is anticipated in Japan, especially in the elderly, without appropriate prevention.

Data obtained in many clinical studies performed in Western countries have demonstrated that cholesterol-lowering therapy with HMG-CoA reductase inhibitors, statins, reduces cardiovascular events by 26–37%.[2–4] Therefore, therapeutic intervention to control serum cholesterol levels is widely accepted. So far, guidelines for controlling cholesterol levels have been established in several countries, such as ATPIII (http://www.nhlbi.nih.gov/guidelines/cholesterol/atp_iii.htm) in the USA. Since the incidence of cardiovascular events in the Japanese population is clearly lower than that in Western countries, establishment of the Japanese guideline has been considered necessary. The first Japanese guideline was established by the Japanese Atherosclerosis Society in 1997 and it has been revised in 2002 (http://jas.umin.ac.jp). Since the subjects for the guideline are those aged ≤ 65 years, the guideline for elderly Japanese has been expected to be established.

In 1996–99, the research group for 'Establishing Japanese guidelines for treating atherosclerotic diseases in the elderly' was organized as part of the Comprehensive Research on Aging and Health conducted by the Japanese Ministry for Health, Labour and Welfare and the first guideline was proposed in 1999 (Kita & Hata *et al.* unpublished report to the Japanese Ministry of Health and Welfare 1999). In this guideline, the target cholesterol levels for the elderly were recommended to be 20 mg/dL higher than those for the younger population, based on the comparison of relative risk increase in relation to serum cholesterol levels between younger people and the elderly (Kita & Hata *et al.* unpublished report to the Japanese Ministry of Health and Welfare 1999). Since then, several important clinical datasets in Western countries and results of studies conducted in Japan,[2–4] such as the *KLIS*,[5,6] the *J-LIT* and PATE have been produced.[7–9] Therefore, the research group was again organized in 1999–2002 in order to conduct a research project entitled 'Long-term prognosis of the elderly with hyperlipidemia' (chaired by T. Kita) as a part of the Comprehensive Research on Aging and Health with a view to re-evaluating the proposed guideline (Kita & Hata *et al.* unpublished report to the Japanese Ministry of Health and Welfare 1999). The research group has concluded that serum cholesterol levels in Japanese aged 65–74 years are recommended to be controlled in the same way as for patients aged ≤ 65 years by following the Guideline for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases (2002) by the Japan Atherosclerosis Society (http://jas.umin.ac.jp/), and that for those aged ≥ 75 years the control levels should be determined individually based on their physical activities (Kita & Matsuzawa *et al.* unpublished report to the Japanese Ministry of Health and Welfare 2002).

Clinical data in Western countries

Secondary prevention studies such as 4S and CARE have been analyzed with a focus on the elderly.[10,11] In both studies, treatment with simvastatin and pravastatin in the elderly patients was as safe and effective for reducing serum cholesterol levels as it was in younger patients.[10,11] In the 4S study, 4444 patients with established coronary heart diseases were divided into simvastatin and placebo groups, and followed for 5.4 years.[10] In this study, simvastatin treatment reduced total cholesterol levels by 26% in the elderly aged 65–70 years and by 25% in younger patients,[10] indicating that the cholesterol lowering effect of simvastatin in the elderly is similar to that in the younger. The relative risk reduction of major coronary events, including coronary artery death and non-fatal myocardial infarction, by simvastatin in the elderly patients was 34%, similar to that in younger patients aged < 65 years.[10] In the CARE study, 4159 patients were divided into pravastatin and placebo groups and followed for 5 years.[11] In this study, pravastatin treatment reduced total cholesterol levels by 19% in the elderly aged 65–75 years and by 20% in patients aged < 65 years,[11] indicating that the cholesterol lowering effect of simvastatin in the elderly is similar to that in younger patients. The relative risk reduction in the elderly group was 39% while that in the younger was 13%.[11] Because of the higher absolute risk and greater effect on risk reduction in the elderly group, the number

needed to treat (NNT) in the 5-year follow-up period in the elderly group was 15 while that in the younger group was 67.[11]

Recently, the results of the PROSPER study have been published.[12] In this study, approximately 5800 high-risk patients aged 70–82 (mean 75 years) with normal total cholesterol levels (mean 217 mg/dL) were divided into pravastatin and placebo groups, and followed for 3 years. In this elderly population, the statin reduced coronary events by 19%. Since the preventive effects by statins become obvious in 1–2 years after starting the medication in many studies,[2-4] the risk reduction ratio in the PROSPER study could be relatively smaller during the 3-year follow-up period.[12] In the ASCOT study, approximately 19 000 hypertensive high-risk patients with total cholesterol levels of ≤ 250 mg/dL (213 mg/dL average), aged 40–79 years (mean 63 years), were assigned into placebo and 10 mg/day atorvastatin groups, and followed for 3 years.[13] The results showed that treatment with atorvastatin reduced coronary events by 36%. The risk reduction in the subgroup aged ≥ 60 years was also 36%, which was similar to that in younger patients aged < 60 years. Thus, it has been demonstrated in studies conducted in Western countries that cholesterol-lowering therapy in the elderly brings similar, or even better, effects in the prevention of coronary events, compared with its effects on younger patients.

It has been demonstrated that cholesterol lowering therapy by statins slowed the narrowing of coronary arteries and reduced intima-media thickness in carotid arteries.[14,15] Thus, cholesterol lowering by statins could stabilize atheromatous plaque, thereby inhibiting the event occurrence.

Clinical data in Japan

The Hisayama study was an epidemiological study conducted in the Hisayama community in Japan.[16] In this study, where 2673 people aged ≥ 40 years were followed from 1988 to 1996, the absolute risk for ischemic heart diseases (myocardial infarction and sudden death) was reported to be 2.3/1000/year and that for cerebral infarction to be 3.1/1000/year.[17]

The J-LIT study was a cohort observational study in Japan. In this study, approximately 50 000 hypercholesterolemic patients aged ≤ 70 years undergoing 5–10 mg/day simvastatin treatment were followed for 6 years. A subanalysis focusing on elderly patients without prior coronary events was performed.[18] In both the elderly group, aged 65–70 years (mean 67 years) and consisting of 9860 patients, and the younger group, aged ≤ 64 years (mean 55 years) and consisting of 32 500 patients, total cholesterol levels were approximately 270 mg/dL at enrollment and 210–220 mg/dL during follow-up periods under simvastatin treatment. Changes in low-density lipoprotein (LDL)-cholesterol levels were also similar: levels of approximately 180 mg/dL at the baseline were reduced to approximately 130 mg/dL in the follow-up periods in both groups. No severe drug-related adverse effects occurred in either group. Thus, statin treatment in the elderly is as safe and effective for reducing serum cholesterol levels as it is in younger patients. The doses of the statin were lower than those used in Western countries, where 20–40 mg/day simvastatin was used.[2]

In the J-LIT study, the incidence of coronary events (sudden cardiac death and acute myocardial infarction) in the elderly was 1.30/1000/year and that in the younger 0.8/1000/year. When occurrence of angina was included in coronary events, the incidence in the elderly was 2.25/1000/year and that in the younger 1.35/1000/year. Cox-biohazard analysis revealed that the relative risks of coronary events increased by 1.7% as serum LDL-cholesterol levels increased by 1 mg/dL, which were similar in both groups.[18] Importantly, in any LDL-cholesterol levels, the absolute risk in the elderly was higher than that in the younger. Generally, coronary events occur twice as often in men as in women, which was also observed in the J-LIT study.[7,8] In the J-LIT study, 35% of the study subjects were male in the younger group and 21% were male in the elderly group.[18] Therefore, upon interpretation of this J-LIT data, the male : female ratio should be considered. Indeed, in male patients, the coronary events (sudden cardiac death and acute myocardial infarction) occurred at a rate of 2.45/1000 patients/year in the elderly and 1.41/1000 patients/year in younger patients.

The KLIS study was planned as a primary prevention study for male patients aged 45–74 years with serum cholesterol levels ≥ 220 mg/dL.[5,6] Enrolled patients were assigned into a conventional therapy group and a pravastatin group, and followed for 5 years. However, since the results of several studies revealed superior effects of statin therapy for the event prevention during the study period, the assignment could not be kept completely. As a result, 2219 cases in the pravastatin group and 1634 cases in the conventional therapy group were analyzed. Coronary events (sudden death, myocardial infarction, coronary intervention and bypass surgery) occurred in 5.95/1000 per year in the conventional therapy group and 5.77/1000 per year in the pravastatin group. Cerebral infarction occurred in 5.15/1000 per year in the conventional therapy group and 4.19/1000 per year in the pravastatin group. In the pravastatin group, 1105 cases were of good compliance for the drug-intake. The relative risk of coronary events plus cerebral infarction of the good-compliance group was 0.57 (0.54–0.98) compared with that of the conventional therapy group. A subanalysis examining those aged ≥ 65 years in this study revealed a tendency similar to that observed in the J-LIT study.[18] Namely, coronary events increased as

serum LDL-cholesterol levels increased in both elderly and younger groups, and the absolute risks in the elderly were higher than those in the younger in any given LDL-levels (Sasaki *et al.* in preparation).

In the PATE study, 665 patients (male ratio 21%) aged ≥ 60 years (mean 73 years) with serum total cholesterol levels of 220–280 mg/dL were followed for 3–5 years (mean 3.9 years) under treatment with low-dose (5 mg) or high-dose (10–20 mg) pravastatin.[9] In this study, events were defined as cerebral bleeding, cerebral infarction, transient ischemic attack, subarachnoid hemorrhage, myocardial infarction, angina pectoris, cardiac failure, arrhythmia, arteriosclerosis obliterance, dissecting aortic aneurysm, and peripheral artery thrombosis. During the follow-up period, acute myocardial infarction occurred in 11 cases (4.2/1000/year). In the patient group without diabetes and with serum cholesterol levels of < 253 mg/dL and triglyceride levels of ≥ 133 mg/dL, the event-free ratio in the high-dose group was significantly higher than that in the low-dose group.

Thus, we could expect similar, or even more beneficial, effects of cholesterol-lowering therapy to reduce cardiovascular events in elderly Japanese compared with those in the younger population, although the studies described above appear to be somewhat indirect. Urgently and absolutely required are complete epidemiological and/or interventional large-scale studies, from which we can definitely estimate the absolute risks and the risk reduction rates in the current Japanese population.

Cerebral infarction and hypercholesterolemia

Cerebral infarction is also a disease that occurs more frequently in the elderly. Cerebral infarction is classified into following three: (i) lacunar infarction caused by small artery occlusion which is correlated with hypertension; (ii) cardiogenic cerebral embolism, which is usually associated with atrial fibrillation; and (iii) cerebral infarction caused by atherothrombotic arterial occlusion. Hypercholesterolemia is considered to be linked to atherothrombotic occlusion.

In the 4S secondary prevention study, simvastatin reduced total strokes by 35%.[2] The data obtained in secondary prevention studies with pravastatin, including the LIPID and CARE studies, have been combined and analyzed.[19] The results demonstrated that pravastatin treatment reduced total strokes by 22% and nonhemorrhagic strokes by 23%.[19] In the ASCOT study, atorvastatin reduced fatal and non-fatal strokes by 27%.[13] In the MRC/BHF Heart Protection Study, where approximately 20 000 high-risk patients aged 40–80 years had been randomly assigned into placebo and simvastatin-treated groups and followed for 5 years, simvastatin reduced ischemic strokes by 29%.[20] In the KLIS study conducted in Japan, the incidence of cerebral infarction was 5.15/1000 per year in the conventional therapy group and 4.19/1000 per year in the pravastatin group.[5,6] In the KLIS study, the incidence of cerebral infarction increased as LDL-cholesterol levels increased in elderly aged ≥ 65 years (Sasaki *et al.* in preparation). In the J-LIT study, the incidence of ischemic cerebrovascular events was 1.41/1000 per year in the subgroup without prior coronary or cerebral infarction (Nakaya *et al.* unpublished data). In both studies, the incidence of ischemic cerebral events was clearly higher in the elderly than that in the younger. Thus, evidence is accumulating to support the preventive effects of serum cholesterol-lowering on the occurrence of cerebral infarction. We may expect risk reduction for not only coronary events but also cerebral infarction in cholesterol-lowering therapy. Although the incidence of coronary events in Japan is much lower compared with that in Western countries, the incidence of cerebrovascular events are similar. Since incidence of cerebrovascular events in Japan is similar to that of coronary events, impact of the prevention of cerebrovascular events is as large as that of coronary events in Japan.

Conclusions: Strategy for treating elderly Japanese with hypercholesterolemia

As reviewed above, the control of serum cholesterol levels appears effective in risk reduction of cardiovascular events in elderly Japanese as well as in the younger population. The incidence of such events in the elderly is generally higher than that in younger people. Therefore, the elderly would be even more suitable subjects for preventative intervention. Although it may take long periods to develop atherosclerosis, the preventive effects for cardiovascular events become apparent in 1–2 years after cholesterol-lowering therapy has started, as demonstrated in many studies.[2,3,11,12,20] Therefore, it is not too late for us to start cholesterol-lowering therapy in the elderly. We have concluded after discussion in the research group 'Long-term prognosis of elderly Japanese with hypercholesterolemia' that we could expand the subjects of the Guideline for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases by the Japan Atherosclerosis Society (2002) to include elderly Japanese aged ≤ 74 years (Kita & Matsuzawa *et al.* unpublished report to the Japanese Ministry of Health and Welfare 2002). In the guideline, patients are divided into several categories based on risk factors and the target cholesterol levels for each category is indicated (http://jas.umin.ac.jp/). Aging, ≥ 45 years for men and ≥ 55 years for women, is defined as a risk factor. Therefore, the target total cholesterol level for the elderly aged 65–74 years without additional risk factors is to be less

than 220 mg/dL and the target LDL-cholesterol level, less than 140 mg/dL. The target levels become lower when elderly patients possess additional risk factors. As described in the guideline (http://jas.umin.ac.jp/), the control of cholesterol levels should be started by changing life styles, followed by drug therapy when appropriate cholesterol levels are not obtained.

For the elderly aged ≥ 75 years, few data for Japanese are available at the moment. Furthermore, it was reported that all causes of mortality increased in the group with lower total cholesterol levels due to an increase in death from infections and malignant tumors in an investigation in Holland, where people aged ≥ 85 years were enrolled.[21] Furthermore, in the Honolulu Heart Program, Japanese–Americans aged 75–93 years (mean 78 years) with a mean total cholesterol level of 149 mg/dL have been reported to have higher mortality than the other groups with the levels at 178, 199 and 232 mg/dL.[22] The physical and nutritional conditions of the highly-aged elderly are various and low cholesterol levels may reflect their worsened health conditions. Therefore, we concluded that, for the highly-aged elderly ≥ 75 years, the target cholesterol levels should be determined individually according to physical and nutritional factors, although a higher absolute risk of cardiovascular events would be expected in the elderly aged ≥ 75 years.

Finally, we again emphasize that physicians should be more careful in their use of drugs in elderly patients since physiological functions of the elderly, such as renal and liver functions required for metabolizing drugs, are not as good as those of the younger patients.

The recommended strategy for treatment for elderly Japanese with hypercholesterolemia

Patients aged 65–74 years

Follow the Guideline for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases by the Japan Atherosclerosis Society (2002) (http://jas.umin.ac.jp/).

Patients aged ≥ 75 years

The target values of total and LDL-cholesterol levels should be determined individually.

Points of consideration for treatment of elderly with hypercholesterolemia

1 Cholesterol-lowering therapy reduces relative risk of coronary events in not only the younger but also in the elderly to a similar extent.
2 The elderly would be even more suitable subjects of lipid-lowering therapy, since the absolute risk in the elderly is higher than that in the younger.
3 The elderly might be more susceptive to drug-related adverse effects than the younger since renal and liver functions, required for metabolizing drugs, in the elderly are weaker.

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Primary Cardiovascular Events and Serum Lipid Levels in Elderly Japanese with Hypercholesterolemia Undergoing 6-Year Simvastatin Treatment: A Subanalysis of the Japan Lipid Intervention Trial

Hisanori Horiuchi, MD, Toru Kita, MD,* Hiroshi Mabuchi, MD,† Masunori Matsuzaki, 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*

OBJECTIVES: To determine the relationship between serum lipid levels and the incidence of coronary events in older Japanese hypercholesterolemic patients without prior coronary heart disease (CHD).

DESIGN: Post hoc subanalysis of the results in the Japan Lipid Intervention Trial.

SETTING: A large-scale cohort observational study conducted throughout Japan.

PARTICIPANTS: Men aged 35 to 70 and postmenopausal women younger than 70 with serum total cholesterol (TC) level of 220 mg/dL or greater treated for 6 years with low-dose simvastatin (52,421 total patients). After exclusion of 5,127 patients because of prior CHD and 4,934 patients because of incomplete data, 42,360 patients were divided into an older (9,860 patients, aged 65–70, mean age 67.1) and younger (32,500 patients, younger than 65, mean age 54.9) group and analyzed.

MEASUREMENTS: Fasting serum lipid levels were measured every 6 months. Major coronary events, including fatal or nonfatal myocardial infarction, and sudden cardiac death as the primary endpoint and other cardiovascular diseases, including onset of angina pectoris, cerebrovascular events, and any causes of death, as the secondary endpoints were monitored.

RESULTS: Simvastatin treatment in older patients was as safe and effective as in younger patients. Incident rates of major coronary events were 1.30 per 1,000 patient-years in the older group and 0.80 per 1,000 patient-years in the younger group. The incidence of a major coronary event was correlated to serum TC and low-density lipoprotein cholesterol (LDL-C) levels in both groups. The absolute risk of major coronary events in the older group was higher than in the younger group at any level of LDL-C, whereas the relative risk increased by 1.7% with an elevation of each 1 mg/dL LDL-C level in both groups. In the older group, the risk of major coronary events also increased as triglyceride level increased, whereas the risk decreased as high-density lipoprotein cholesterol level increased above 60 md/dL.

CONCLUSION: The LDL-C level-dependent increase of relative risk of CHD was similar in elderly and younger patients, whereas the absolute risk at any LDL-C level in elderly patients was higher than in younger patients. J Am Geriatr Soc 52:1981–1987, 2004.

Key words: serum cholesterol; coronary event; J-LIT study; elderly Japanese; simvastatin

Controlling serum cholesterol levels is a rational strategy for prevention of coronary heart disease (CHD), as epidemiological and lipid intervention studies conducted in the United States and Europe have shown.[1–3] In those countries, CHD has been the main cause of death, and 21% to 24% of people have died of CHD,[4,5] whereas CHD accounts for merely 7% to 8% of deaths in Japanese living in Japan.[6] Despite this striking difference in CHD mortality between these populations, serum lipid levels have recently

From the *Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan; †Department of Molecular Genetics and Cardiovascular Disorders, Kanazawa University Graduate School of Medicine, Kanazawa, Japan; ‡Department of Cardiovascular Medicine, Yamaguchi University Graduate School of Medicine, Ube, Japan; §Sumitomo Hospital, Osaka, Japan; ‖Nakaya Clinic, Tokyo, Japan; ¶Third Department of Internal Medicine, Nippon Medical School, Tokyo, Japan; #Department of Clinical Cell Biology, Chiba University Graduate School of Medicine, Chiba, Japan; **International University Graduate School of Health and Welfare, Fukuoka, Japan; ††Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan; and ‡‡Ibaraki Christian University, Ibaraki, Japan.

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Address correspondence to Toru Kita, MD, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto 606–8507, Japan. E-mail: tkita@kuhp.kyoto-u.ac.jp

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been similar in both populations.[7] The difference in mortality may be due to genetic backgrounds or environmental conditions, which are yet to be clarified.

The American guidelines for CHD prevention, Adult Treatment Panel III,[8] recommend that cholesterol levels should be controlled according to the individual absolute risk of CHD, estimated by the results of the Framingham study.[1] Nonetheless, the estimate of absolute risk of CHD in Japanese individuals is difficult, because no large-scale cohort studies have not been performed so far, only some small studies.[9–11] Recently, the dietary preferences of Japanese people have become progressively westernized, and their serum lipid profiles have been deteriorating rapidly.[12] It has currently become urgent in Japan to evaluate the relationship between lipid levels and the incidence of coronary events based on large-scale cohort studies, which provide fundamental data for preventive medicine. In addition, the elderly population in Japan has been rapidly increasing. In 2020, more than 30 million of 127 million people will be aged 65 and older.[6] Because cardiovascular events more frequently occur in the aged,[1,4,8] the incidence of CHD is likely to increase remarkably in Japan. Under these circumstances, the Japan Lipid Intervention Trial (J-LIT),[13–16] a large-scale observational cohort study in which many physicians throughout Japan participated, was conducted.

Subanalyses of lipid intervention studies with statins (3-hydroxy-3 methyl glutaryl coenzyme A reductase inhibitors) conducted in Western countries revealed that the treatment in older patients was as effective as that in younger patients for the prevention of CHD.[17–21] Recently, the Prospective Study of Pravastatin in the Elderly at Risk[22] conducted in Europe indicated that lipid-lowering therapy reduced CHD risk 21% in high-risk elderly subjects aged 75 to 82, but it was reported that increased serum cholesterol levels correlated with decreased mortality in patients aged 85 and older.[23] Furthermore, the Honolulu study[24] demonstrated that mortality was highest in the lowest quartile of total cholesterol (TC) level in Japanese Americans aged 72 to 92. Thus, lipid-lowering therapy, especially for elderly patients without prior CHD, should be well tuned to accomplish the goal.

To provide fundamental data about the relationship between serum cholesterol levels and CHD risk in elderly Japanese, the results of the J-LIT study were analyzed, focusing on patients aged 65 to 70 without a history of CHD.

METHODS

Study Design

The design of the J-LIT was described previously.[13] Briefly, men aged 35 to 70 and postmenopausal women younger than 70 with serum TC levels of 220 mg/dL or greater were enrolled. The exclusion criteria included recent myocardial infarction (MI) or stroke occurrence within a month, uncontrolled diabetes mellitus, serious complications of hepatic or renal disease, secondary hypercholesterolemia, malignant tumors, and illness with poor prognosis. More than 6,500 general practitioners throughout Japan treated patients with open-label simvastatin (5–10 mg/d) for 6 years during 1993–99. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula.

Serum lipid levels, drug-related adverse events, and clinical status were monitored every 6 months. The primary endpoint was a major coronary event, defined as fatal and nonfatal MI, and sudden cardiac death. The secondary endpoints were other cardiovascular diseases, including onset of angina pectoris; cerebrovascular accidents; and any other causes of death. The Endpoint Classification Committee of the study verified all coronary events and death. The Adverse Event Evaluation Committee evaluated the adverse drug events. Each patient was informed of the study purpose, drug efficacy, and need for long-term treatment. Of the 52,421 enrolled patients, 5,127 were excluded because of prior CHD (*International Classification of Disease* code I20 to I25 and prior coronary intervention), and 4,934 patients were excluded for the following reasons: violation of the protocol (n = 995), unwillingness to participate (n = 6), and incomplete data for covariates (n = 3,933). The remaining 42,360 patients were divided into two groups (aged 65–70: 9,860 patients, mean age 67.1; aged <65: 32,500 patients, mean age 54.9) and analyzed.

Statistical Analysis

All data were analyzed using the survival analysis method. The baseline lipid profiles and continuous variables were assessed using the paired or unpaired *t* test or chi-square test. For analysis of baseline characteristics determined using categorical outcomes and adverse drug events, the differences between groups were compared using the chi-square test. The incidence of the events was analyzed in relation to average lipid levels during the follow-up period, and the differences between groups were compared using log-rank test. The relative risk and its 95% confidence interval and incidence of the primary endpoint was calculated using the Cox proportional hazards model with adjustment for baseline characteristics such as sex, hypertension, diabetes mellitus, and smoking. For all statistical analysis, $P < .05$ was considered significant. All statistical calculations were performed using SAS software (version 6.12, SAS Institute, Inc., Cary, NC).

RESULTS

Baseline Characteristics

The baseline characteristics of the older and younger groups are shown in Table 1. Fewer men than women were enrolled in both groups. In addition, there was a smaller percentage of male patients in the older group than in the younger group (24.1% vs 35.1%). There were fewer smokers and alcohol consumers in the older group. Other baseline characteristics between the two groups were largely similar (Table 1). Most patients (97%) in both groups took simvastatin 5 mg/d. Other medications were nearly similar in both groups. The most frequently used drugs in both groups were calcium-channel blockers (31.4% in the older group and 21.4% in the younger group), angiotensin-converting enzyme inhibitors (13.0% and 12.4%, respectively), and beta-blockers (7.6% and 9.0%, respectively).

Of enrolled patients without prior CHD, 42,360 (91.5%) were followed, and 4,934 were excluded. No differences were observed in baseline characteristics, including mean age, sex ratio and serum TC level, between the

Table 1. Relative Risk (RR) of Major Coronary Events at Baseline

Risk Factor	Age <65* (n = 32,500) %	Age <65* (n = 32,500) RR (95% CI)	Age 65–70† (n = 9,860) %	Age 65–70† (n = 9,860) RR (95% CI)
Male	35.1	2.25 (1.51–3.34)	21.2	2.03 (1.17–3.52)
Obesity (body mass index >25 kg/m^2)	24.4	0.93 (0.66–1.33)	21.1	1.05 (0.62–1.75)
Hypertension	44.1	2.24 (1.58–3.17)	51.9	2.13 (1.27–3.55)
Diabetes mellitus	15.2	2.11 (1.46–3.06)	15.3	2.36 (1.41–3.95)
Electrocardiogram abnormality	12.0	1.87 (1.25–2.81)	16.4	1.70 (1.00–2.90)
Family history of coronary heart disease	5.1	2.67 (1.63–4.39)	3.5	2.57 (1.11–5.94)
Smoker	18.7	1.64 (1.10–2.45)	9.2	1.46 (0.73–2.89)
Alcohol drinker	32.4	0.63 (0.41–0.98)	17.7	0.63 (0.31–1.29)

Mean ± standard deviation = * 54.9 ± 6.7; † 67.1 ± 1.6 years old.
CI = confidence interval.

followed and excluded patients in the older group. In the younger group, slight differences between the followed and excluded patients were observed in proportion of men (39.2% vs 35.1%) and mean age (53.9 vs 54.9 years), whereas no difference was observed in TC level. It is unlikely that these differences in the younger group affect the results of this subanalysis.

Lipid Profiles

The baseline levels of TC, LDL-C, and high-density lipoprotein cholesterol (HDL-C) were similar between the two age groups, whereas triglyceride (TG) level was lower in the older group (Table 2). The mean baseline TC levels were 267 mg/dL in the older group and 271 mg/dL in the younger group. The mean reduction rates during the follow-up period under low-dose simvastatin treatment in the older and younger groups were 19.5% and 18.1% for TC, 28.2% and 26.2% for LDL-C, and 14.9% and 16.3% for TG, respectively. HDL-C level was 4.9% and 4.4% elevated, respectively (Table 2). The reduction in LDL-C level in both groups was similar at 6 months of treatment and continued throughout the follow-up period (data not shown). Thus, the lipid profiles of the two groups were similar at baseline and during treatment, indicating that simvastatin is as effective in older patients as in younger patients.

Drug-Related Adverse Events

Overall drug-related adverse events were observed in 3.18% of the older and 3.19% of the younger group ($P = .99$). The most frequently observed adverse events in both groups were hepatic dysfunction (0.99% in the older and 1.02% in the younger group, $P = .79$) and musculoskeletal disorders (0.81% and 0.90%, respectively, $P = .40$). No rhabdomyolysis occurred in either group,

Table 2. Patients' Lipid Profiles at Baseline and During Treatment

Lipid Profile (mg/dL)	Age <65 (n = 32,500) Mean ± Standard Deviation (% Change)	Age 65–70 (n = 9,860) Mean ± Standard Deviation (% Change)
Baseline		
TC	271 ± 36	267 ± 29
LDL-C	183 ± 34	181 ± 31
Triglyceride	202 ± 184	175 ± 110
HDL-C	52.8 ± 15.1	53.4 ± 15.1
During treatment		
TC	222 ± 30 (−18.1)*	215 ± 27 (−19.5)*
LDL-C	135 ± 30 (−26.2)*	130 ± 27 (−28.2)*
Triglyceride	169 ± 110 (−16.3)*	149 ± 68 (−14.9)*
HDL-C	55.1 ± 13.7 (+4.4)*	56.0 ± 13.7 (+4.9)*

* $P < .001$ baseline vs during treatment.
TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

although myopathy was reported in one patient in the older group and three patients in the younger group. The incidence of renal dysfunction was slightly higher in the older group (0.32%) than in the younger group (0.14%) ($P<.01$). None of differences in these adverse events were clinically significant. The incidence of other adverse events was not statistically significantly different between the two groups. It was concluded that simvastatin treatment in older patients aged 65 to 70 was as safe as in younger patients.

Coronary and Cerebrovascular Events and Death

Incidence rates during treatment of major coronary events, including fatal or nonfatal MI and sudden cardiac death, were 1.30 per 1,000 patient-years in the older group and 0.80 per 1,000 patient-years in the younger group ($P<.001$) (Table 3). Incidence rates of major coronary events in male patients were 2.45 per 1,000 patient-years in the older group and 1.41 per 1,000 patient-years in the younger group ($P=.003$). In female patients those rates were 1.00 and 0.47 per 1,000 patient-years, respectively ($P<.001$). Incidence rates of total coronary events, including major coronary events and newly developed angina pectoris, were 2.24 per 1,000 patient-years in the older group and 1.35 per 1,000 patient-years in the younger group ($P<.001$) (Table 3).

Incidence rates of ischemic cerebrovascular events, including cerebral thrombosis, cerebral infarction, transient ischemic attack, and reversible ischemic neurological deficit, were 2.61 per 1,000 patient-years in the older group and 1.29 per 1,000 patient-years in the younger group ($P<.001$) (Table 3). Thus, the incidence of major coronary events and ischemic cerebral accidents was higher in the older group.

Overall mortality was 2.4 times higher in the older group than in the younger group (Table 3). The proportions of cardiac deaths, death from malignancy, and death from other causes were similar in both age groups (Table 3).

Effects of Conventional CHD Risk Factors on the Development of Major Coronary Events

The contribution of the conventional risk factors for CHD to the development of major coronary events was analyzed (Table 1). Male sex, hypertension, diabetes mellitus, and family history of CHD were found to be significant risk factors of CHD in both age groups. Electrocardiogram abnormalities and smoking were statistically significant only for the younger group, possibly because of fewer patients enrolled in the older group. Body mass index of 25 kg/m^2 or greater did not increase the risk of CHD in either group in this study. Moderate alcohol consumption seemed to be a negative risk factor for CHD in both groups to a similar extent, although it was statistically significant only for the younger group. These conventional risk factors appear to contribute similarly in both age groups.

Incidence of Major Coronary Events and Lipid Profiles During the Follow-Up Period

The incidence rate of the major coronary events was analyzed in relation to serum lipid levels stratified by the average values during the follow-up period. As shown in Figures 1A and 1B, the incidence rate of major coronary events was higher in the older group than in the younger group at any level of serum TC and LDL-C. In both groups, major

Table 3. Death and Coronary and Cerebrovascular Events During Treatment

Adverse Event	<65 (n = 32,500)		65–70 (n = 9,860)		
	n	Incidence Rate†	n	Incidence Rate†	*P*-value*
Death, total	489	2.79	355	6.70	<.001
Cardiac	45	0.26	38	0.72	<.001
Noncardiac	444	2.53	317	5.98	<.001
Malignancy	185	1.06	132	2.49	<.001
Other	259	1.48	185	3.49	<.001
Coronary endpoint	236	1.35	119	2.24	<.001
Major coronary event	140	0.80	69	1.30	<.001
Myocardial infarction (fatal)	31	0.18	20	0.38	.007
Myocardial infarction (nonfatal)	105	0.60	42	0.79	.12
Sudden cardiac death	4	0.02	7	0.13	.001
Angina pectoris	96	0.55	50	0.94	.002
Cerebrovascular event	397	2.26	211	3.99	<.001
Ischemic cerebrovascular event	226	1.29	138	2.61	<.001
Cerebral thrombosis	120	0.68	66	1.25	<.001
Cerebral infarction	56	0.32	44	0.83	<.001
Transient ischemic attack, reversible ischemic neurological deficit	50	0.29	28	0.53	.008
Cerebral hemorrhage	83	0.47	31	0.59	.30
Subarachnoid hemorrhage	44	0.25	14	0.26	.86
Unclassified stroke	44	0.25	28	0.53	.002

* For log-rank test.
† Per 1,000 patient-years.