Large-scale cohort study on the relationship between serum lipid concentrations and risk of cerebrovascular disease under low-dose simvastatin in Japanese patients with hypercholesterolemia: Sub-analysis of the Japan Lipid Intervention Trial (J-LIT)

Large-Scale Cohort Study on the Relationship Between Serum Lipid Concentrations and Risk of Cerebrovascular Disease Under Low-Dose Simvastatin in Japanese Patients With Hypercholesterolemia
—— Sub-Analysis of the Japan Lipid Intervention Trial (J-LIT) ——

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Background The Japan Lipid Intervention Trial was a nationwide cohort study of 52,421 hypercholesterolemic patients treated with open-labeled simvastatin for 6 years under standard clinical practices. Cerebrovascular disease (CVD) is one of the leading causes of death in Japan, but the effect of hypercholesterolemia on CVD has not been well established in Japanese patients. This study aimed to determine the relationship between the risk of CVD and serum lipid concentrations during treatment in Japan.
Methods and Results Patients were treated with 5–10 mg/day of simvastatin and all, including those who discontinued simvastatin for any reason, had their lipid concentrations and incidence of CVD monitored for 6 years. Data of 41,088 patients were analyzed in this study, excluding those who had a history of coronary heart disease or CVD. The risk of cerebral infarction was higher in patients whose mean total cholesterol concentrations during treatment were ≥240 mg/dl, low-density lipoprotein cholesterol concentrations ≥160 mg/dl, triglycerides ≥150 mg/dl and high-density lipoprotein cholesterol concentrations <40 mg/dl. There was no obvious correlation between cerebral hemorrhage and serum lipid concentrations.
Conclusion Improvement of serum lipid concentrations is important for reducing the incidence of cerebral infarction. (*Circ J* 2005; **69**: 1016–1021)

Key Words: Cerebrovascular disease; Lipids; Primary prevention

Cerebrovascular disease (CVD) is one of the major causes of death in Japan[1] and is a leading cause of disability and increased healthcare costs. A number of studies have already demonstrated that lipid-lowering therapy reduces the risk of coronary heart disease (CHD), but its effect on CVD has not been well established in Japan. The Kyushu Lipid Intervention Study demonstrated a correlation between the serum lipid concentration and the incidence of cerebral infarction, but the number of patients was relatively small[2,3] Several epidemiologic studies have failed to demonstrate an association between cholesterol concentrations and CVD[4–7] although a post hoc finding in the Scandinavian Simvastatin Survival Study

(4S) showed that simvastatin reduced the incidence of CVD by 30%[8] A pooled analysis of 4 trials conducted primarily in CHD patients showed a 62% lower rate of total CVD attributable to pravastatin[9] The Heart Protection Study reported that simvastatin reduced the incidence rate of total and ischemic CVD in UK adults with high risk[10] by 25% and 30%, respectively, and the Anglo-Scandinavian Cardiac Outcomes Trial study reported that atorvastatin reduced the incidence of CVD in hypertensive patients by 27%[11] In Japan, the Oyabe Study reported that the incidence of CVD in Japanese subjects with low concentrations of high-density lipoprotein cholesterol (HDL-C <30 mg/dl) was remarkably higher than that in subjects with high HDL-C (≥60 mg/dl) and the incidence of CVD was higher in the subjects with total cholesterol (TC) concentrations over 220 mg/dl[12] The Eastern Stroke and Coronary Heart Disease Collaborative Research Group reported that there was a trend toward a decrease in the risk of ischemic CVD and an increase in the risk of hemorrhagic CVD with decreasing cholesterol concentrations in populations from eastern Asia[13]

The Japan Lipid Intervention Trial (J-LIT) was a nationwide cohort study of 52,421 hypercholesterolemic patients treated with open-label simvastatin (5–10 mg/day), carried out for 6 years by a large number of physicians under standard clinical practices in order to evaluate the relationship

between cardiovascular disease and lipid concentrations![4-16] The results clearly showed that normalization of the lipid concentration of hypercholesterolemic patients reduced the risk of coronary events. In the present study, we analyzed the relationship between the risk of CVD and lipid concentrations.

Methods

Subjects

The J-LIT study enrolled 52,421 patients with serum TC concentration ≥220 mg/dl: men aged 35–70 years and post-menopausal women under 70 years old. 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 recent acute myocardial infarction or CVD, uncontrolled diabetes mellitus, serious concomitant hepatic or renal disease, secondary hypercholesterolemia, malignancy or any other illness with a poor prognosis. For this study, 41,088 patients without a history of CHD or CVD were selected.

Study Design

The design of the J-LIT study has been described previously![7] Patients were treated with open-label simvastatin according to the approved Japanese labeling of Lipovas®. All patients, including those who discontinued simvastatin for any reason, were monitored for 6 years. Their lipid concentrations, adverse events, and incidence of CHD-related events and CVD were recorded. Cholesterol concentrations were determined locally at the study institutions. Dietary and exercise therapies for hyperlipidemia were recommended to patients by the investigators and additional lipid-lowering agents were allowed at the discretion of the physician. No restrictions were placed on the administration of medical treatment for complications. The low-density lipoprotein cholesterol (LDL-C) concentration in patients with triglyceride (TG) concentration ≤400 mg/dl was calculated using the Friedewald formula![8] 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 type of CVD was determined using clinical symptoms, angiography and/or computed tomography (CT), and classified according to the criteria of the Stroke Committee established by the Japanese Ministry of Education![9] The pre-specified primary endpoints of the sub-analysis were cerebral infarction, including cerebral thrombosis and cerebral embolism, and cerebral hemorrhage pre-specified in the protocol. The first event or death that occurred during the study period were counted once in each patient, and the events were reviewed and determined by the Endpoint Classification Committee. CVD events were counted once. The follow-up data acquired after the onset of disease other than the endpoints were excluded from the analysis. Each patient was informed of the study purpose, as well as drug efficacy and need for long-term treatment. Written informed consent was not obtained from patients, because commercially available simvastatin preparation was used for the open-label study.

Table 1 Baseline Characteristics and Lipid Profiles of the Patients

N	41,088
Males (%)	31.6
Age (years)	57.7±7.9
Body mass index (kg/m²)	24.0±3.2
Hypertension (%)	45.6
Diabetes mellitus (%)	15.1
ECG abnormal (%)	12.8
Coronary heart disease familial history (%)	4.7
Smoking habit (%)	16.5
Alcohol consumption (%)	29
Baseline	
Total cholesterol (mg/dl)	270±34
Low-density lipoprotein cholesterol (mg/dl)	182±33
Triglyceride (mg/dl)	196±171
High-density lipoprotein cholesterol (mg/dl)	53±15
During treatment	
Total cholesterol (mg/dl)	220±30
Low-density lipoprotein cholesterol (mg/dl)	134±30
Triglyceride (mg/dl)	164±103
High-density lipoprotein cholesterol (mg/dl)	55±14

Statistical Analysis

All data, including those obtained after the termination of simvastatin therapy, were analyzed by survival analysis. The mean lipid concentrations were calculated using the data obtained throughout the treatment period, because the mean lipid concentrations were thought to be important for clinical practice. The data for lipid concentrations acquired after the onset of disease were excluded. For analysis of baseline patient age and lipid profile, continuous variables within and between subgroups were assessed using the paired or unpaired t-test. Patients were classified into 3–6 subgroups based on the mean lipid concentrations during the treatment. TC, TG, LDL-C, and HDL-C concentrations and the ratio of LDL-C/HDL-C were classified into discrete intervals of 20, 150, 20 and 10 mg/dl and 0.5, respectively. The reference categories were set on the subgroups with the lowest concentrations.

We calculated the relative risks, with 95% confidence intervals for each endpoint, of each subgroup relative to the reference category, using the Cox proportional-hazards model with adjustment for gender and age at baseline (as a continuous variable), hypertension, diabetes mellitus, and smoking habit. The effects of each baseline characteristic on each endpoint were assessed, except for the effect of age, which was categorized. Data are expressed as the mean±SD. For all statistical analyses, a p-value <0.05 was considered to be significant. All statistical calculations were performed using SAS software (version 6.12, SAS Institute Inc, Cary, NC, USA).

Results

Follow-up

A total of 42,360 of the 52,421 patients enrolled in the J-LIT study were eligible for the primary prevention analysis of CHD and their clinical characteristics have been reported previously![7] In the present study, data were collected from 41,088 patients and 1,272 patients were excluded on the history of CVD. In total, 30,832 patients were followed up by the investigators to the end of the 6th year (mean follow-up, 5.39 years per subject). Baseline characteristics are shown in Table 1. Approximately 46% of patients had hypertension (mean systolic and diastolic

Table 2 Incidence of Cerebrovascular Events During Follow-up Period

	Fatal		Non-fatal		Total	
	No. of events	Incidence	No. of events	Incidence	No. of events	Incidence
Cerebral infarction	22	(0.10)	220	(1.00)	242	(1.09)
Cerebral thrombosis	12	(0.05)	139	(0.63)	151	(0.68)
Cerebral embolism	10	(0.05)	81	(0.37)	91	(0.41)
Cerebral hemorrhage*	22	(0.10)	80	(0.36)	102	(0.46)

*Intracranial. Incidence =/1,000 patients-year.

Table 3 Relative Risk of Cerebrovascular Disease and Serum Lipid Concentrations During Treatment

	Cerebral infarction					Cerebral hemorrhage*			
	Population	Event	Relative risk	95%CI	p value	Event	Relative risk	95%CI	p value
TC (mg/dl)									
<200	9,306	50	1.00			29	1.00		
200-219	12,119	70	1.26	(0.87-1.81)	0.216	34	0.98	(0.60-1.61)	0.940
220-239	10,423	59	1.38	(0.94-2.01)	0.100	17	0.61	(0.34-1.12)	0.112
240-259	5,275	34	1.76	(1.13-2.73)	0.012	11	0.85	(0.42-1.71)	0.638
≥260	3,423	28	2.49	(1.56-3.99)	<0.001	9	1.15	(0.54-2.46)	0.718
LDL-C (mg/dl)									
<120	12,860	74	1.00			32	1.00		
120-139	12,260	76	1.23	(0.89-1.70)	0.200	39	1.41	(0.88-2.26)	0.151
140-159	8,871	36	0.89	(0.60-1.33)	0.575	15	0.82	(0.44-1.51)	0.515
160-179	3,853	30	1.92	(1.25-2.94)	0.003	7	0.95	(0.42-2.16)	0.902
≥180	2,318	24	2.95	(1.85-4.71)	<0.001	6	1.51	(0.62-3.63)	0.363
TG (mg/dl)									
<150	22,413	101	1.00			53	1.00		
150-299	15,577	115	1.54	(1.18-2.02)	0.002	41	0.99	(0.65-1.50)	0.957
≥300	2,532	25	2.31	(1.47-3.63)	<0.001	5	0.73	(0.28-1.86)	0.504
HDL-C (mg/dl)									
<40	4,001	48	1.00			16	1.00		
40-49	11,522	70	0.52	(0.36-0.75)	<0.001	31	0.68	(0.37-1.25)	0.217
50-59	12,162	66	0.49	(0.33-0.71)	<0.001	25	0.54	(0.29-1.03)	0.061
≥60	12,861	57	0.41	(0.28-0.61)	<0.001	28	0.60	(0.32-1.13)	0.117
LDL-C/HDL-C									
<2.0	10,439	55	1.00			25	1.00		
2.0-2.4	9,904	46	0.90	(0.61-1.33)	0.597	24	1.02	(0.58-1.79)	0.943
2.5-2.9	8,682	48	1.11	(0.75-1.63)	0.611	17	0.84	(0.45-1.56)	0.582
3.0-3.4	5,578	37	1.37	(0.91-2.09)	0.136	12	0.95	(0.48-1.89)	0.877
≥3.5	5,559	54	2.13	(1.46-3.11)	<0.001	21	1.75	(0.97-3.14)	0.061
Total	40,546	241				100			

Cerebral infarction, cerebral thrombosis and cerebral embolism; *Intracranial.
CI, confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

blood pressures 150 and 87 mmHg, respectively), and 15% had diabetes mellitus. Hypertension was treated with angiotensin-converting enzyme inhibitors (26%), calcium-channel blockers (53%), β-blockers (18%) and diuretics (6%).

Changes in Serum Lipid Concentrations With Simvastatin Treatment

The mean serum concentrations of TC, LDL-C, and TG at baseline were 270±34, 182±33, and 196±171 mg/dl, respectively, and the mean lipid concentrations during treatment were 220±30 mg/dl, 134±30 mg/dl and 164± 103 mg/dl, respectively. The mean serum HDL-C concentration increased from baseline of 53±15 mg/dl to 55± 14 mg/dl. The mean percent change from baseline in the TC, LDL-C, TG, and HDL-C concentrations was −18%, −27%, −16%, and +4%, respectively, during the treatment period.

Incidence of CVD During the Treatment Period

Cerebral infarction occurred in 242 patients during the course of the study with an incidence of 1.09 events per 1,000 patients-year (Table 2). Cerebral thrombosis occurred in 151 patients, and cerebral embolism in 91 patients. Cerebral hemorrhage occurred in 102 patients with an incidence of 0.46 events per 1,000 patients-year. The incidence of total CVD was 1.55 events per 1,000 patients-year. CT of the head was performed in 77% of the patients with CVD.

Relationship Between the Relative Risk of Cerebral Infarction and Lipid Concentrations

The relative risk of cerebral infarction was higher in patients with TC concentration ≥240 mg/dl compared to those with TC concentration <200 mg/dl (Table 3) and patients with LDL-C concentration ≥160 mg/dl had higher risk than those with a concentration <120 mg/dl. A group of patients with a mean TG concentration ≥150 mg/dl had a higher incidence of cerebral infarction than those with a mean concentration <150 mg/dl. The incidence of cerebral infarction was lower in patients with a mean HDL-C concentration of 40-49 mg/dl compared with a concentration <40 mg/dl. The relative risk of cerebral infarction was

higher in patients with the ratio of LDL-C/HDL-C ≥3.5 compared with a ratio <2.0.

Relationship Between the Relative Risk of Cerebral Infarction and Baseline Characteristics

The risk of cerebral infarction was analyzed using multiple regression (Fig 1). Age correlated with the incidence of cerebral infarction and male patients had higher risk compared with female patients. Hypertension, diabetes mellitus, and ECG abnormalities were also risk factors for cerebral infarction. Alcohol consumption, cigarette smoking and a family history of CHD were not risk factors.

Relationship Between the Relative Risk of Cerebral Hemorrhage and Mean Lipid Concentrations

There was no clear relationship between cerebral hemorrhage and the concentrations of TC, LDL-C, TG and HDL-C or the ratio of LDL-C/HDL-C (Table 3).

Relationship Between the Relative Risk of Cerebral Hemorrhage and Baseline Characteristics

The risk of cerebral hemorrhage was analyzed by multiple regression (Fig 2), which showed that patients aged 60-64 years had a significantly higher risk of cerebral hemorrhage. Hypertension and ECG abnormalities were also risk factors for cerebral hemorrhage.

Relationship Between the Relative Risk of Cerebral Infarction and Hypertension

Hypertension is known to be a dominant risk factor for cerebral infarction, so the effect of lipid concentrations on cerebral infarction was examined in patients stratified by systolic blood pressure (SBP). Table 4 shows the relationship between cerebral infarction and serum lipid concentrations, comparing a SBP at baseline <140 mmHg and SBP ≥140 mmHg. The influence of serum lipid concentrations on cerebral infarction was observed in both the hypertensive and normotensive groups and was also observed in patients stratified by diastolic blood pressure (<90 mmHg and ≥90 mmHg; data not shown). The serum lipid concentrations are thus independent risk factors of cerebral infarction.

Discussion

We analyzed the relationship between the risk of CVD and lipid concentrations using the J-LIT data. During the 6-year treatment period simvastatin reduced the serum concentrations of TC, LDL-C and TG by 18%, 27% and 16%, respectively, from baseline. The concentration of HDL-C continued to increase during the treatment period. The incidence of CVD in Japanese patients without prior CVD or CHD was 1.55 events per 1,000 patients-year in this study, much higher than for primary CHD (0.91 events
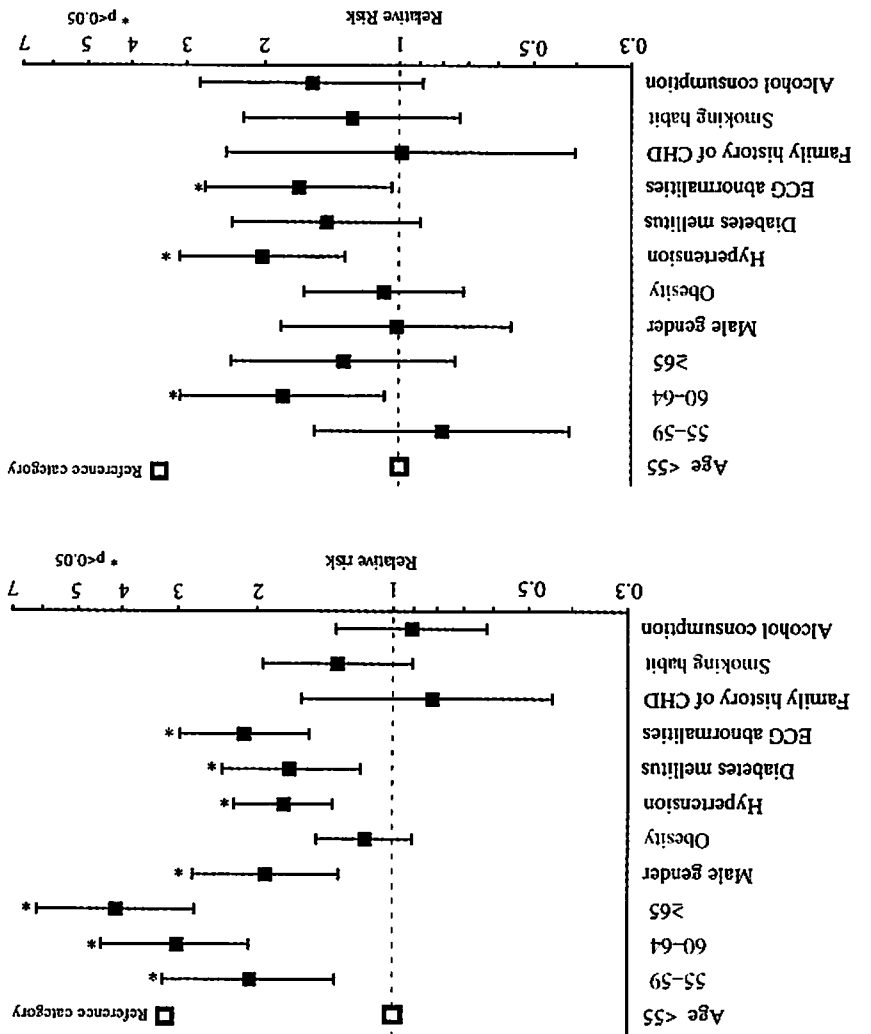
Fig 1. Relationship between the relative risk of cerebral infarction and baseline characteristics of patients maintained on low-dose simvastatin. Data were adjusted for age, sex, hypertension, diabetes mellitus and smoking habit. Bars express the relative risk with a 95% confidence interval. Obesity = body mass index (BMI) ≥25 kg/m², CHD, coronary heart disease.

Fig 2. Relationship between the relative risk of cerebral hemorrhage and baseline characteristics of patients maintained on low-dose simvastatin. Data were adjusted for age, sex, hypertension, diabetes mellitus and smoking habit. Bars express the relative risk with a 95% confidence interval. Obesity = body mass index (BMI) ≥25 kg/m², CHD, coronary heart disease.

Table 4 Relative Risk of Cerebral Infarction and Serum Lipid Concentrations During Treatment

	SBP at baseline <140mmHg					SBP at baseline ≥140mmHg				
	Population	Event	Relative risk	95%CI	p value	Population	Event	Relative risk	95%CI	p value
TC (mg/dl)										
<200	4,246	17	1.00			5,012	33	1.00		
200–219	5,807	32	1.55	(0.86–2.79)	0.148	6,246	38	1.05	(0.66–1.67)	0.844
220–239	5,197	25	1.49	(0.80–2.77)	0.208	5,160	33	1.18	(0.72–1.91)	0.515
240–259	2,710	9	1.18	(0.52–2.66)	0.694	2,538	25	1.96	(1.16–3.32)	0.012
≥260	1,796	12	2.66	(1.26–5.63)	0.010	1,604	16	2.15	(1.18–3.94)	0.013
LDL-C (mg/dl)										
<120	5,888	24	1.00			6,896	50	1.00		
120–139	5,899	36	1.68	(1.00–2.81)	0.051	6,302	40	0.96	(0.63–1.46)	0.840
140–159	4,485	17	1.10	(0.59–2.06)	0.757	4,339	19	0.71	(0.42–1.20)	0.201
160–179	2,041	8	1.29	(0.58–2.88)	0.536	1,789	21	2.03	(1.22–3.40)	0.007
≥180	1,274	10	2.91	(1.38–6.13)	0.005	1,031	14	2.70	(1.48–4.91)	0.001
TG (mg/dl)										
<150	11,548	41	1.00			10,762	59	1.00		
150–299	7,062	44	1.72	(1.12–2.65)	0.014	8,419	71	1.51	(1.07–2.14)	0.021
≥300	1,135	10	3.29	(1.61–6.69)	0.001	1,366	15	1.97	(1.09–3.54)	0.024
HDL-C (mg/dl)										
<40	1,908	19	1.00			2,066	29	1.00		
40–49	5,356	30	0.56	(0.31–0.99)	0.047	6,102	40	0.51	(0.31–0.82)	0.005
50–59	5,851	21	0.36	(0.19–0.68)	0.002	6,249	44	0.57	(0.35–0.92)	0.021
≥60	6,641	25	0.38	(0.21–0.71)	0.002	6,143	32	0.42	(0.25–0.71)	0.001
LDL-C/HDL-C										
<2.0	5,125	22	1.00			5,261	33	1.00		
2.0–2.4	4,710	17	0.85	(0.45–1.59)	0.605	5,125	29	0.93	(0.57–1.54)	0.781
2.5–2.9	4,158	20	1.17	(0.64–2.14)	0.617	4,484	28	1.04	(0.63–1.72)	0.890
3.0–3.4	2,731	16	1.46	(0.77–2.80)	0.248	2,820	20	1.20	(0.69–2.10)	0.517
≥3.5	2,863	20	1.81	(1.98–3.35)	0.057	2,667	34	2.23	(1.38–3.60)	0.001
Total	19,756	95				20,560	145			

Cerebral infarction, cerebral thrombosis and cerebral embolism.
SBP, systolic blood pressure. Other abbreviations see Table 3.

per 1,000 patients-year[14]), and indicates that in Japan the prevention of CVD is as important as that of CHD. The risk of cerebral infarction was higher when the mean TC concentration was ≥240mg/dl and the mean LDL-C concentration ≥160mg/dl, which are the same values for the risk of CHD. The incidence of cerebral infarction increased in the patients with TG concentration ≥150mg/dl, whereas the incidence of CHD increased when TG concentration was ≥300mg/dl, which indicates a closer relationship between cerebral infarction and TG than between CHD and TG. HDL-C inversely correlated with the risk of cerebral infarction. There was no obvious correlation between cerebral hemorrhage and serum lipid concentrations nor could we observe a clear relationship between the incidence of fatal CVD and lipid concentrations. In the preliminary analysis, no different results were obtained when adjusted for SBP. In a meta-analysis of randomized trials[20] lipid-lowering therapy reduced the overall CVD incidence, but not that of fatal CVD incidence and it was concluded that the incidence of hemorrhagic CVD was not influenced by lipid-lowering therapy. Because hemorrhagic CVD is mostly fatal could partly explain the apparent lack of effect of lipid-lowering therapy on fatal CVD in that analysis and might be applicable to our results.

Our findings are generally consistent with the results from the Oyabe Study, a community-based 10-year follow-up study of Japanese men and women[12] although the incidence was much less (crude rates for all CVD incidence per 1,000 person-years were 4.30 in men and 1.98 in women in the Oyabe study). Low HDL-C concentrations (<30mg/dl) led to a significantly and independently increased risk of CVD. The incidence of CVD was higher in the subjects with TC concentrations >220mg/dl and the relationship of TC to the overall incidence of CVD and that of ischemic CVD in particular showed a U-shaped curve with the bottom between TC values of 180 and 220mg/dl. In the present J-LIT study, the incidence of ischemic CVD tended to increase in patients with TC concentrations <180mg/dl, but was not significant (data not shown). The patients who participated in this study were all treated with low-dose of simvastatin, but our results are similar to the result of the Oyabe Study. The Eastern Stroke and Coronary Heart Disease Collaborative Research Group[13] reported that there were trends towards a decrease in the risk of nonhemorrhagic CVD and an increase in the risk of hemorrhagic CVD with decreasing cholesterol concentrations, and in the present study, high TC, LDL-C and TG concentrations and low HDL-C concentrations were risk factors for cerebral infarction. The influence of serum lipid concentrations on cerebral infarction (thrombosis and embolism) was similar in males and females. In the analysis of patients with TC concentrations <180mg/dl, the incidence of cerebral hemorrhage was not increased, compared with those with a TC concentration ≥180mg/dl. A relationship between the effect of lipid concentrations and cerebral infarction, analyzed by hypertension, sex, and types of cerebral infarction, was clearly observed in this study.

The antiatherothrombotic properties of statins[21] apart from their cholesterol-lowering effects, may be the mechanism of the reduction in cardiovascular events. The thrombotic sequelae of plaque disruption may be mitigated by statins through their inhibition of platelet aggregation and maintenance of a favorable balance between prothrombic and fibrinolytic mechanisms[21] These same antiatherothrom-

botic effects may have also affected the present results.

This J-LIT subanalysis is the first report of a correlation between the incidence of cerebral infarction and lipid concentrations in a large number of Japanese hypercholesterolemic patients. Our results show that improving the serum lipid concentrations is also important for reducing the incidence of cerebral infarction.

Study Limitation

Although we refer to this study as J-LIT, in reality it was a cohort and observational study rather than an interventional study.

Acknowledgment

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