目 次

1. なぜこれらの研究が行われるのでしょうか？ …… 1
2. これらの研究はどのように行われますか？ …… 1
3. これらの研究に参加することでどのような恩恵がありますか？ …… 2
4. これらの研究に参加することでどのような危険がありますか？ …… 2
5. ほかの治療法にはどのようなものがありますか？ …… 2
6. プライバシーは守られますか？ …… 2
7. この研究に参加する義務はありますか？ …… 2
8. 詳しい研究内容を知ることは出来ますか？ …… 2
9. 医療費はどのようになりますか？ …… 3
10. 健康被害が発生した場合の補償はありますか？ …… 3
11. この研究の資金源は何ですか？ …… 3
12. この研究で特許等が生み出されることはありますか？ …… 3
13. 質問や問題が生じた場合にはどこに連絡すればいいですか？ …… 3

同意書（担当医用）

同意書（患者さま用）

同意撤回書

1. なぜこれらの研究が行われるのでしょうか？

脳血管疾患（脳卒中）は血圧との関係が強く、コレステロールとの関係は比較的弱いとこれまで考えられていましたが、コレステロールを下げることで脳卒中をある程度予防できる可能性が最近になって示されました。ただし、予防のためにどの程度のコレステロール値が適切かは未だにはっきりしておりません。一方、海外での研究では、体内の炎症活動の程度や動脈硬化の程度が脳卒中の危険性を反映することが報告されていますが、それが日本人にもあてはまるかどうか明らかではありません。そこで今回、コレステロールを下げる薬であるHMG-CoA還元酵素阻害薬（スタチン）が脳卒中の再発予防に役立つかどうか、同時に、炎症活動や動脈硬化の進展を抑える効果があるかを調べるためにこれらの研究が行われます。

2. これらの研究はどのように行われますか？

これらの研究には、脳卒中を経験された方のなかでコレステロールがやや高めの患者さん約3000人が参加する予定です。参加される場合、あなたはHMG-CoA還元酵素阻害薬であるプラバスタチン（メバロチンなど）による治療を受ける群（以下：スタチン群）、または、HMG-CoA還元酵素阻害薬以外の治療を受ける群（以下：非スタチン群）のいずれかに振り分けられます。どちらの群になるかはコンピューターで決められ、担当医やあなたが選ぶことはできません。スタチン群に振り分けられた場合にはプラバスタチンを1日に1回飲んでいただくことになり、非スタチン群に振り分けられた場合には担当医の判断でそれ以外の治療を受けていただくことになります。

スタチン群、非スタチン群のどちらの群になったとしても、今後5年間は月に1度程度来院していただき、脳卒中などの新たな病気の発生の有無や薬の安全性を調べさせていただきます。その為に、半年～1年に1度の血液検査や心電図、胸のレントゲン、2年後と終了時は頭部MRIまたはCT、物忘れや日常生活の状態などについての検査を受けていただくことになります。また、炎症活動の程度と動脈硬化を調べるために、高感度CRP濃度を定期的な採血項目に追加させていただき、年に一度頸動脈エコー検査を受けていただきます。非スタチン群の患者様につきましても検査の時期は同様です。

（詳しい検査日程については次の表をご覧下さい）

	開始時	2週後	2,6ヶ月後	1,3,4,5年後	2年後終了時
血液検査、血圧・脈拍	○	☆	○	○	○
頭部MRI/CT	○				○
物忘れ、日常生活の状態	○				○
胸部レントゲン、心電図	○			○	○
尿検査	○				○
高感度CRP	○		○		○
頸動脈エコー	○			○	○

☆：プラバスタチンを服用する群（スタチン群）の方のみ

3. これらの研究に参加することでどのような恩恵がありますか？

脳卒中の再発を防ぐうえで、プラバスタチンを飲むことがよいかどうかははっきりしていません。かえって他の薬と同様に副作用の心配もあります。私たちは研究期間を通じてスタチン群、非スタチン群、両群全ての方の健康状態を注意深く見守り、新たな病気の発生や薬の安全性を監視します。同時に、この研究や他の研究を通して得られた、健康に関する新たな情報を提供致します。高感度 CRP 検査および頸動脈エコー検査は、その結果をあなた自身にお知らせすることができます。また、私たちは研究期間中、この研究や他の研究を通して得られたあなたの健康に関する新たな情報を提供します。そのため、スタチン群、非スタチン群のどちらになった場合でも、この研究に参加しない場合と少なくとも同等の恩恵を受けられると私たちは考えています。また、この研究から得られた結果は、将来あなたと同じ病気で苦しんでおられる多くの方々の治療にも活かされます。私たちは、この研究が脳卒中の再発予防に新たな治療指針をもたらすことを期待しています。

4. これらの研究に参加することでどのような危険がありますか？

プラバスタチンはわが国でも大変多くの患者さんが服用している薬であり、重大な副作用が少ない薬です。ただし、これまでの経験により約 3%の方に発疹や下痢、胃不快感などの副作用が報告されています。また、横紋筋融解症、肝障害、黄疸、血小板減少などの重大な副作用の報告がまれにありますが、その頻度は明らかではありません。ちなみに、海外の研究では、この薬による横紋筋融解症は 9895 例中 1 例もありませんでした。万一、副作用が生じた際には適切に処置し、重度のものが生じた場合には薬を中止して適切な処置を講じます。高感度 CRP 濃度の測定は、定期的な血液検査項目に追加するだけですので、採血回数が増えることも無く、危険性はありません。また、頸動脈エコーの超音波検査は非侵襲的検査であり、危険性はありません。

5. 他の治療法にはどんなものがありますか？

脳梗塞の再発予防に有効な手段として、高血圧や糖尿病の治療、抗血小板薬の服用、頸動脈内膜剥離術などがあげられます。担当医が必要と判断したときは、研究中であっても、スタチン群、非スタチン群ともにそれらの治療を受けることができます。

6. プライバシーは守られますか？

この研究に関する情報はカルテに記録され、その一部は臨床研究情報センターのコンピューターに記録されます。また、あなたであることを特定できないようにした上で、研究成果を学会や医学雑誌などに報告する場合があります。しかし、いずれの場合にもあなたのプライバシーは厳重に保護され、個人的な情報が外部に漏れる心配はありません。

7. この研究に参加する義務はありますか？

この研究へ参加するかどうかはあなたの自由であり、参加しない場合にも不利益を受けることはありません。また、参加に同意された場合でも、不利益を受けることなくそれを取り消すことができます。しかし、研究の途中で参加を取り消す場合にはそれを担当医に伝えて下さい。

8. 詳しい研究内容を知ることができますか？

ご希望があれば、他の患者さんのプライバシーやこの研究の独創性に支障がない範囲で研究の実施計画書などをお見せします。

9. 医療費はどのようになりますか？

この研究は製薬会社が費用を負担する「治験」ではなく、脳卒中の制圧を心より願う私たち医師が、健康保険の範囲内で行うものです。また、頸動脈超音波検査を含め、行われる全ての検査は通常の脳卒中診療に必要なものと考えられます。従って、この研究に参加していただいた場合にも特別な謝礼は無く、医療費は通常どおり保険診療によるご負担になります。ただし、高感度 CRP 濃度の測定に必要な費用は研究費から支出されますので、患者様のご負担はありません。

10. 健康被害が発生した場合の補償はありますか？

この研究で使われる薬は既に市販され、通常の診療で広く使われているものです。従って、定められた量を指示どおり服用したにもかかわらず、重篤な健康被害が発生した場合には「医薬品副作用被害救済制度」による補償があります。ただし、その補償内容は必ずしも十分とは言えないのが実情です。

11. この研究の資金源は何ですか？

この研究は厚生労働省の助成金で行われ、一部に先端医療振興財団の支援を受けて行われます。研究の結果に関わらず、それが厚生労働省や先端医療振興財団に何ら利益や損害を与えることはありません。

12. この研究で特許等が生み出されることはありますか？

この研究は薬剤の適応拡大を目的とするものではなく、従って、研究成果によって特許等が生み出されることはありません。

13. 質問や問題が生じた場合にはどこに連絡すればいいですか？

下記の担当医または主任研究者までご連絡下さい。

病院名：＿＿＿＿＿＿＿＿＿＿　診療科：＿＿＿＿＿＿＿＿＿＿

担当医：＿＿＿＿＿＿＿＿＿＿　電話番号（内線）：＿＿＿＿＿＿＿＿＿＿

主任研究者：広島大学大学院脳神経内科教授　松本昌泰

〒734-8551　広島市南区霞 1-2-3　電話番号：082-257-5201

同意書（担当医用）

病院　病院長殿

平成　　年　　月　　日

（説明者）
所属
氏名 _____

□ 1）脳血管疾患の再発に対する高脂血症治療薬 HMG-CoA 還元酵素阻害薬の予防効果に関する研究

□ 2）高脂血症治療薬 HMG-CoA 還元酵素阻害薬の総頸動脈内中膜複合体厚へ及ぼす効果に関する研究

□ 3）高脂血症治療薬 HMG-CoA 還元酵素阻害薬の高感度 CRP 濃度へ及ぼす効果に関する研究

同意される研究のチェックボックスすべてにチェックをつけてください。

私は上記の研究において下記の項目について担当医より説明を受け、理解いたしました。
そこで、今回、これらの研究に参加することに同意します。

記

1. 研究の目的と方法
2. 研究に参加することの恩恵と危険性
3. 私が同意しない場合であっても、不利益は受けないこと
4. 私が同意した場合でも、不利益なくそれを撤回できること
5. その他、人権の保護に関する事項
6. 医療費等について

同意年月日　平成　　年　　月　　日
本人：住所

_____

氏名 _____ 印（又は自署名）

生年月日 _____ 年　月　日

同意書（患者さま用）

病院　病院長殿

平成　　年　　月　　日

（説明者）
所属
氏名 _____

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6. 医療費等について

同意年月日　平成　　年　　月　　日
本人：住所

_____

氏名 _____ 印（又は自署名）

生年月日 _____ 年　　月　　日

同意撤回書

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿病院　病院長殿

□ 1）脳血管疾患の再発に対する高脂血症治療薬 HMG-CoA 還元酵素阻害薬の予防効果に関する研究

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該当する研究のチェックボックスすべてにチェックをしてください。

私は上記の研究への参加に同意しましたが、同意を撤回します。

同意撤回年月日　平成　　年　　月　　日

本人：　住所

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

氏名＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿　印（又は自署名）

生年月日　　年　　月　　日生

（資料．3）　文献

Circ J 2002; **66:** 1087–1095

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

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

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

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

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

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

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

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

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

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

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

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

Methods

Subjects

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

Study Design

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

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

Statistical Analysis

All data, including those obtained after the termination of

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

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

Results

Follow-up

A total of 47,294 of the 52,421 patients enrolled in the J-LIT study, were eligible for the primary prevention cohort, and the remaining 5,127 patients who had a history of CHD were enrolled in the secondary prevention cohort, and the clinical characteristics of which are reported elsewhere[16] In the present study, data collected from 42,360 patients were analyzed and data from 4,934 patients were excluded for the following reasons: lack of follow-up data (932 patients), violation of inclusion/exclusion criteria (63 patients), unwillingness to participate (6 patients), and incomplete covariance (3,933 patients). Of the study patients, 31,766 were followed up by the investigators through to the end of the 6th year (average length of follow up, 5.39 years per subject). For the analysis of the baseline characteristics, patients were stratified according to their serum TC concentrations during treatment with every 20 mg/dl. In the analysis with the trend test, a trend in the relationship between average serum total cholesterol concentration during treatment and the baseline characteristics of patients was observed. The percentage of male patients, age, incidence of hypertension, diabetes mellitus, cerebrovascular disease, hepatic disease and abnormal ECG, percentage of patients with a family history of CHD, smoking and drinking increased as average serum total cholesterol concentration during treatment decreased (Table 1). The incidence of obesity and renal disease was similar in all groups. The decrease in average serum TC concentration during treatment was proportional to the patients' baseline concentrations of TC, LDL-C and HDL-C.

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

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

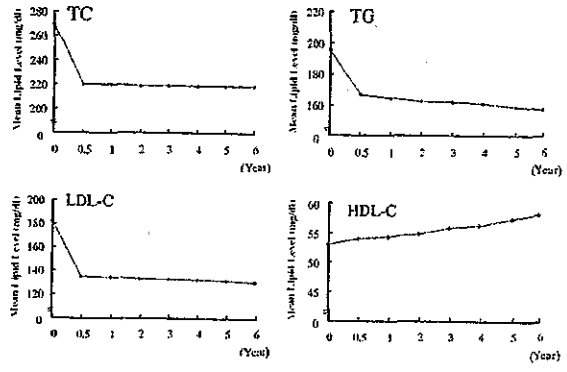

Fig 1. Sequential changes in serum lipid concentrations in patients maintained on low-dose simvastatin.

Safety

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

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

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

MI, myocardial infarction.

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

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

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

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

Changes in Serum Lipid Concentrations With Simvastatin

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

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

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

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

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

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

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

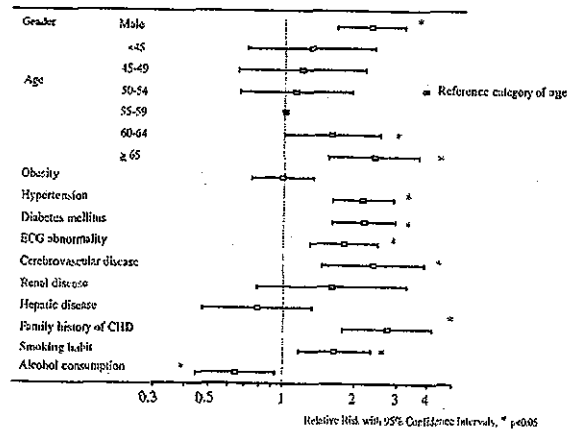

Fig 2. Relationship between the relative risk of coronary events and baseline characteristics of patients maintained on low-dose simvastatin. Bars express the relative risk with a 95% confidence interval. Obesity, body mass index ≥25 kg/m².

Relationship Between the Relative Risk of Overall Mortality and Lipid Concentrations

During the study period, 844 patients died (3.69 deaths

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

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

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

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

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

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

Relationship Between the Relative Risk of Death and Baseline Patient Characteristics

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

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

Discussion

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

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

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

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

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

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

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

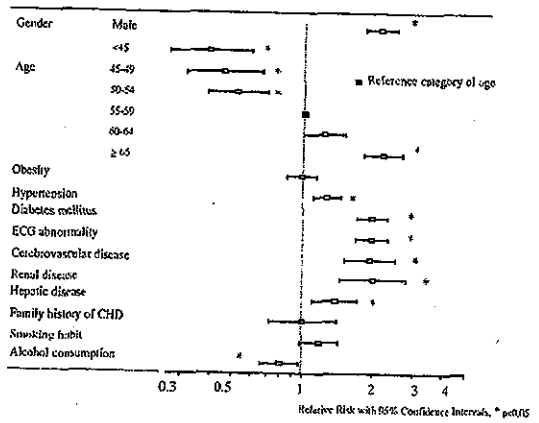

Fig 3. Relationship between the relative risk of death and baseline characteristics of patients maintained on low-dose simvastatin. Bars express the relative risk with a 95% confidence interval. Obesity, body mass index ≥25 kg/m².

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

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

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

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

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

Study Limitation

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

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

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

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

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

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

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

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

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lipid concentrations and the incidence of CHD under low-dose simvastatin treatment in subjects with a history of CHD. We adopted a surveillance model for the study because patients already had a history of coronary disease and thus placebo control was not possible for ethical and feasibility reasons.

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

Methods

Study Design

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

Statistical Analysis

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

Results

Follow-up

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

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

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

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

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

Changes in Serum Lipid Levels With Simvastatin

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

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

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

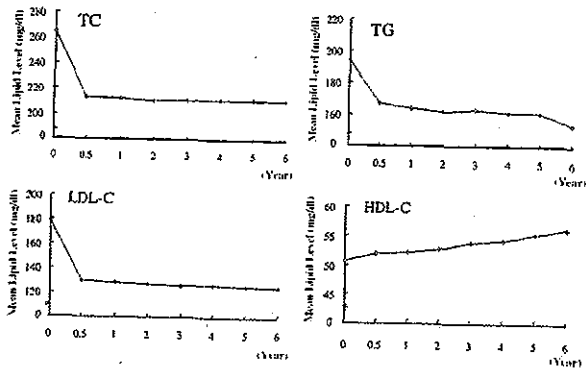

Fig 1. Sequential changes in serum lipid levels in hypercholesterolemic patients with a history of CHD who were maintained on low-dose simvastatin.

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

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

Relationship Between the Risk of Coronary Events and Baseline Patient Characteristics

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

Discussion

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

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

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

MI, myocardial infarction.