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Efficacy of Cholesterol-Lowering Treatment in Japanese Elderly Patients With Coronary Artery Disease and Normal Cholesterol Level Using 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitor

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Abstract

The clinical benefit of cholesterol-lowering treatment is unknown in the Japanese elderly in whom the prevalence of morbidity and mortality related to coronary artery disease are known to be low. To evaluate the efficacy of cholesterol-lowering treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor in Japanese elderly patients with documented coronary artery disease, 121 patients with serum cholesterol $\geq$ 150 mg/d*l* prospectively received HMG-CoA reductase inhibitor, and 271 patients undergoing cholesterol-lowering treatment based on dietary therapy alone served as historical controls. The 143 elderly patients age $\geq$ 65 years in the 2 groups had similar baseline serum total cholesterol level (201 ± 30 vs 202 ± 31 mg/d*l*), age (71 ± 4 vs 70 ± 4 years), proportion of men (37/53 vs 64/90), number of diseased vessels (1.7 ± 0.9 vs 1.5 ± 1.0), and incidences of other classical coronary risk factors, including hypertension, diabetes mellitus, smoking, obesity and family history of coronary artery disease. In all 392 patients, similar trends were observed, including serum total cholesterol level (208 ± 33 vs 201 ± 34 mg/d*l*). With HMG-CoA reductase inhibitors, serum total cholesterol level was reduced by 14% in the elderly subjects and by 13% in all patients. During the follow-up of approximately 3 years, cardiac events occurred in 5 patients (one elderly) in the treatment group and 38 patients (12 elderly) in the control group. Kaplan-Meier survival estimates revealed a higher event-free survival rate with HMG-CoA reductase inhibitors in the elderly subjects (98% vs 85%, $p < 0.05$) and in all patients (94% vs 86%, $p < 0.05$). Cox proportional hazard modeling also demonstrated a significant reduction in risk for cardiac events with drug therapy (relative risk 0.32, $p < 0.05$), in addition to the number of diseased vessels (relative risk 1.8, $p < 0.01$). In contrast, no additional risk was observed with advancing age.

Cholesterol-lowering treatment with HMG-CoA reductase inhibitors is effective to improve the prognosis of Japanese elderly patients, including those with normal serum cholesterol level.

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Key Words

■ Cholesterol (hypercholesterolemia) ■ Cholesterol-lowering drugs
■ Coronary artery disease ■ Prognosis

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INTRODUCTION

The prevalence of coronary artery disease (CAD) and CAD-related mortality are known to be low in Japan[1,2]. This is particularly true in the elderly compared with the younger generation, in whom the influence of Western life style is more evident[3]. Although the beneficial effect of cholesterol-lowering medication with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors was recently reported in Western countries[4-6], it is unclear whether this cholesterol-lowering treatment is effective for Japanese elderly patients. Our previous study with Japanese CAD patients found that the serum total cholesterol level should be reduced to < 200 mg/d*l* for secondary prevention even in Japan[7]. We conducted a prospective study to elucidate the effect of cholesterol-lowering treatment with HMG-CoA reductase inhibitors on the prognosis of Japanese elderly patients with CAD.

METHODS

Study design and patients

This study included patients with CAD who were treated medically after an initial evaluation, excluding those with serum total cholesterol < 150 mg/d*l* or left ventricular ejection fraction $< 50\%$. Patients with right heart failure were also excluded. A total of 1,369 patients suspected of having CAD, excluding those who had had coronary artery bypass grafting, coronary angioplasty and previous catheterization, underwent diagnostic coronary catheterization in our department from January 1983 to March 1997. Four hundred eighty-one patients were prospectively evaluated from January 1991 to March 1997, and 204 underwent coronary artery bypass grafting or coronary angioplasty. Of the remaining 277 patients, 121 patients fulfilled the inclusion criteria and gave informed consent to receive 5 mg of simvastatin or 10 mg of pravastatin. Among 888 patients who were evaluated from 1983 to 1990, when HMG-CoA reductase inhibitors were not widely used, 271 patients with CAD fulfilled the inclusion criteria mentioned above, whose cholesterol-lowering treatment consisted of dietary therapy alone, served as historical controls. Thus the final group consisted of 392 patients with CAD treated medically including 143 elderly patients aged ≥ 65 years. The treatment group consisted of 121 patients who received 5 mg of simvastatin or 10 mg of pravastatin once a day to reduce serum total cholesterol to < 200 mg/d*l*. The patients visited the clinics 1, 3 and 6 months after hospital discharge, and every 6 months thereafter for the determination of serum lipids. The study protocol, including its ethical aspects, was approved by the Institutional Review Board in our hospital.

Assessment of coronary risk factors

The fasting serum total cholesterol level was measured in the morning after admission, before diagnostic coronary angiography. Serum total cholesterol was measured by enzymatic methods using an automatic analyzer (Hitachi 7350). The normal range of serum total cholesterol level was 130–230 mg/d*l* in our hospital. In patients previously treated with cholesterol-lowering medication before referral to our institution, the initial value of serum cholesterol data before the initiation of drug therapy was used. Risk factors included in the assessment were hypertension, diabetes mellitus, cigarette smoking (current, past or never), family history of CAD which was documented clinically, obesity defined as body mass index > 26, and hyperuricemia. Hypertension was defined by a history of hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg) or by documented hypertension on at least 2 occasions during the study. Hyperuricemia was defined as a serum uric acid level > 8.0 mg/d*l* in men or > 6.0 mg/d*l* in women according to the criteria of our hospital.

Cardiac catheterization

Coronary angiography was performed in all of the patients by the Judkins or the Sones technique and was interpreted by 2 experienced angiographers based on the criteria proposed by the American Heart Association[8]. A significant stenosis in the 3 major coronary arteries was defined as $\geq 75\%$ diameter narrowing. Using the standard area-length method, ejection fraction was calculated on a Philips DCI System (Best) from traced silhouettes of the biplane left ventriculogram[9].

End-point determination

The primary endpoint of this study was a cardiac event, including cardiac death, nonfatal myocardial infarction, unstable angina, and coronary intervention such as coronary angioplasty or coronary artery bypass grafting. A nonfatal myocardial infarction was defined as typical electrocardio-

Table 1 Baseline characteristics of all patients in the treatment and control groups

	Treatment group (n=121)	Control group (n=271)	p value
Age (yr)	62±10	60±10	<0.05
Male/female	93/28	200/71	NS
Total cholesterol (mg/dl)	208±33	201±34	NS
Hypertension	51(42)	132(49)	NS
Current smoker	61(50)	173(64)	<0.05
Diabetes mellitus	27(22)	67(25)	NS
Obesity	19(16)	42(16)	NS
Family history	23(20)	62(23)	NS
Hyperuricemia	10(8)	27(10)	NS
Number of diseased vessels	1.4±0.9	1.3±1.0	NS
Ejection fraction (%)	64±12	67±11	0.05

( ): %

graphic changes associated with significant cardiac enzyme elevations, excluding silent myocardial infarction[10]. Cardiovascular death was defined as either sudden cardiac death (death within 1 hr after the onset of severe cardiac symptoms), rapid cardiac death (death from 1 to 24 hr since the onset of severe cardiac symptoms) or fatal myocardial infarction.

Statistical analysis

Results are expressed as mean ± standard deviation. Student's t-test or Scheffe's multiple comparison was used to compare the means of the continuous variables, and contingency tables were analyzed using a chi-square test. Kaplan-Meier survival analysis was performed to compare the time to cardiac events according to the treatment. Survival curves were compared by the log-rank test. To adjust for differences in the baseline characteristics, the relative risk of cardiac events with each factor was analyzed by Cox proportional hazard modeling. Statistical significance was considered as a p value of < 0.05. Statistical analysis was performed using the SAS software program.

RESULTS

Patient characteristics at the baseline

All 392 patients had a mean level of serum cholesterol of 208 ± 33 mg/dl (150−292 mg/dl) in the treatment group and 201 ± 34 mg/dl (151−413 mg/dl) in the control group. Other baseline characteristics were similar between the treatment and control groups including the number of diseased vessels, proportion of males, and prevalence of hypertension, diabetes mellitus, obesity, family history of CAD, and hyperuricemia. Patients in the treatment group were older and had a lower incidence of smoking and lower ejection fraction than those in the control group (**Table 1**). Routine laboratory tests showed normal liver function in all patients. In 143 elderly subjects, the mean level of serum total cholesterol was 201 ± 30 mg/dl (150−292 mg/dl) in the treatment group and 202 ± 31 mg/dl (151−312 mg/dl) in the control group. Demographic data including age (71 ± 4 vs 70 ± 4 years), proportion of men (37/53 vs 54/90), prevalence of hypertension (22/53 vs 53/90), current smoker (24/53 vs 49/90), diabetes mellitus (12/53 vs 26/90), obesity (6/53 vs 17/90), family history (9/53 vs 20/90), hyperuricemia (3/53 vs 10/90), number of diseased vessels (1.7 ± 0.9 vs 1.5 ± 1.0), and ejection fraction (62 ± 11% vs 67 ± 11%) were similar in the treatment and control groups (NS).

Serum total cholesterol measurements during follow-up

In all patients, the mean level of serum total cholesterol decreased from 208 to 180 mg/dl, 36 months after the initiation of treatment with HMG-CoA reductase inhibitors, but no significant decline in the level was observed in the control group. In the elderly subjects, the level of total cholesterol decreased from 201 to 172 mg/dl, whereas the level of total cholesterol did not change again in the control group (**Fig. 1**). In the treatment group, the mean level of serum total cholesterol was 176 ± 30 mg/dl with simvastatin in comparison to 190 ± 35 mg/dl with pravastatin (NS), 36 months after the initiation of cholesterol-lowering treatment.

Outcome after follow-up

Follow-up periods were similar between the treatment and control groups (28 ± 11 vs 31 ± 9 months, NS) with a total follow-up rate of 99% (388/392). During this period, 43 patients (12 elderly patients in the control group and one elderly in the treatment group) had the following cardiac events: cardiac death in 6, myocardial infarction in 10, unstable angina in 8, congestive heart failure in 3, coronary angioplasty in 5 and coronary artery bypass grafting in 11. Additional 3 patients (one in the treatment group and 2 in the control group, NS)

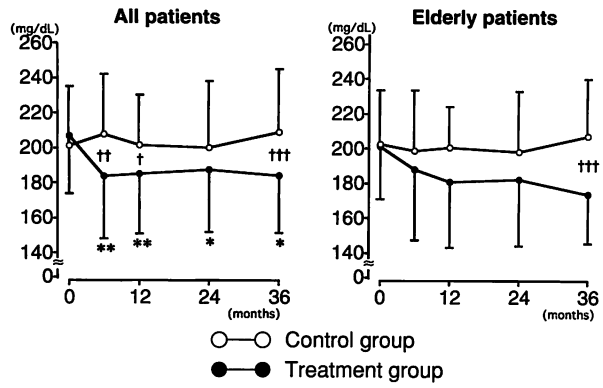

Fig. 1 Mean changes in plasma total cholesterol levels after the initiation of cholesterol-lowering therapy
$^{*}p < 0.01$, $^{**}p < 0.001$ vs baseline level; $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$ vs control group.

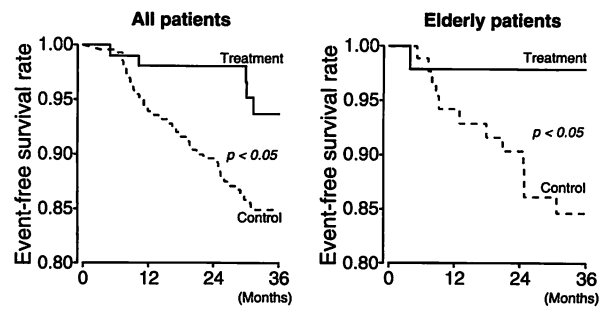

Fig. 2 Kaplan-Meier survival estimates of the incidence of cardiac events in the treatment and control groups
All patients are presented in the left panel and elderly patients in the right panel.

died from non-cardiac causes: malignancy in one, and car accidents in 2. In patients with or without cardiac events, the percentages of users of β-blockers (3/43 vs 22/349, NS), nitrates (34/43 vs 288/349, NS), calcium channel blockers (36/43 vs 283/349, NS), angiotensin converting-enzyme inhibitors (2/43 vs 31/349, NS) and diuretics (7/43 vs 54/349, NS) were similar. No adverse effect was observed that was considered related to HMG-CoA reductase inhibitors such as an abnormal increase in the serum level of creatinine phosphokinase or liver enzymes. In all 392 patients, Kaplan-Meier survival estimates revealed a significantly higher event-free survival rate in the treatment group than in the control group (94% vs 86%, $p < 0.05$; **Fig. 2**). The survival analysis in 143 elderly subjects with similar survival curves also revealed a significantly higher event-free survival rate in the treatment group than in the control group (98% vs 85%, $p < 0.05$; **Fig. 2**). Thus, reductions in the 3-year cardiac event rate were 8% in all patients and 13% in the elderly patients. To adjust for differences in the baseline characteristics, a multivariate analysis was performed. Cox proportional hazard modeling revealed that the only 2 factors associated with prognosis were drug therapy with HMG-CoA reductase inhibitors (relative risk 0.32, $p < 0.05$) and the number of diseased vessels (relative risk 1.8, $p < 0.01$). In contrast, no additional risk was observed with advancing age (**Fig. 3**).

DISCUSSION

The morbidity and mortality related to CAD are low in Japan[1,2]. This trend is observed more frequently in the elderly compared with the younger generation, in whom the influence of Western life style is more evident[3]. Although serum lipoprotein levels decrease with advancing age[11], few studies have addressed the effect of cholesterol-lowering treatment in elderly subjects[12,13]. The question arises whether such cholesterol-lowering treatment is beneficial in this potentially low-risk patient subset. The present study suggested that cholesterol-lowering treatment with HMG-CoA reductase inhibitors is feasible and effectively improves the prognosis of Japanese elderly patients with established CAD. These results may imply that the mechanisms underlying the relationship between serum cholesterol level and the development of coronary atherosclerosis may differ from the mechanisms contributing to therapeutic benefit from cholesterol-lowering treatment in the setting of established CAD[13]. With 5 − 10 mg of simvastatin or 10 − 20 mg of pravastatin, a smaller dose compared with the previous studies[4-6], serum total cholesterol decreased by 14% with a mean level of 172 mg/dl in the elderly patients, which resulted in a significantly better event-free survival rate. Excess non-cardiac mortality such as suicides and car accidents which may be related to medication was not observed[14]. A reduction in the 3-year cardiac event rate of 13% in the elderly was modest compared with the previous secondary prevention trials[4,5]. This may be due either to a smaller dose of HMG-CoA reductase inhibitors administered in comparison to previous studies[4-6], or to our patient population of Japanese elderly. To increase the dose of HMG-CoA reductase inhibitors to achieve further reduction in serum total cholesterol level is theoret-

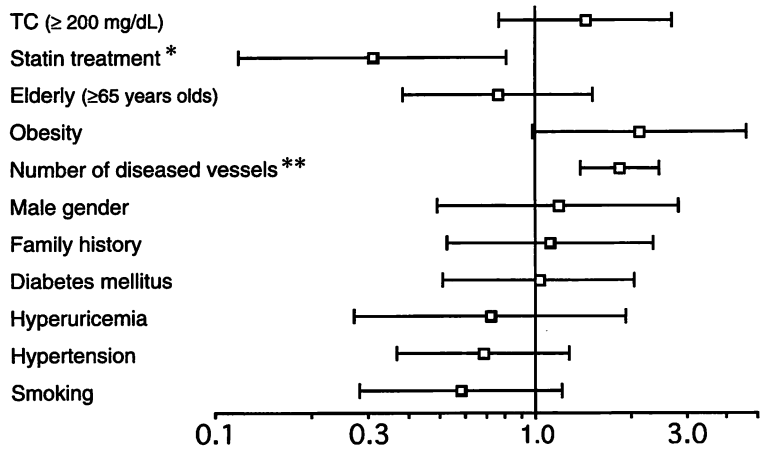

Fig. 3 Relative risk of cardiac events by Cox proportional hazard modeling
Odds ratios and 95% confidence intervals for individual risk factors are shown.
$^{*}p < 0.05$, $^{**}p < 0.01$.
Statin = 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor; TC = total cholesterol.

ically sound. This approach, however, will not be practical in clinical medicine in Japan, since the Department of Health and Welfare in the Japanese Government regulates the maximum dose of simvastatin as 10 mg and that of pravastatin as 20 mg. Moreover, the smaller dose of simvastatin and pravastatin applied in this study significantly reduced serum total cholesterol level to < 200 mg/dl with the result of better survival. Although the mechanisms related to basic science regarding the dose of HMG-CoA reductase inhibitors and prognosis of Japanese patients remain to be clarified, the results of this study emphasize the importance of the medical control of serum cholesterol level to be < 200 mg/dl to improve the prognosis of CAD patients even in Japanese elderly patients.

Large clinical trials in Western countries have demonstrated the beneficial effect of cholesterol-lowering therapy with HMG-CoA reductase inhibitors on the prognosis of patients with CAD[4,5,15]. However, patient population varied among these studies since the highest mean serum total cholesterol of 261 mg/dl was reported in the Scandinavian Simvastatin Survival Study (4S) compared with that of 218 mg/dl in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial and 209 mg/dl in the Cholesterol And Recurrent Events (CARE) study. In the present study, the mean level of serum total cholesterol at the baseline was 208 mg/dl in the treatment group and 201 mg/dl in the control group. Furthermore, the majority of patients had a cholesterol level of ≤ 220 mg/dl, which was previously recognized as within the normal range in Japan[7]. The results of our study, therefore, are similar to those of the CARE study or LIPID trial[5,15], rather than the 4S study[4]. In our preliminary study, the separation of the prognostic curve between the treatment and control groups (**Fig. 2**) occurred earlier than in the large clinical trials, in which the separation was usually observed 1−2 yr after randomization[4,5,15]. With the accumulation of patients, it is possible that the prognostic curve with HMG-CoA reductase inhibitors in Japanese patients will become similar to the curves observed in large clinical trials of Western countries.

The patient population in this study included only those with left ventricular ejection fraction ≥ 50% and serum total cholesterol level ≥ 150 mg/dl. These criteria were chosen to avoid excess cardiac mortality from congestive heart failure, which is not usually related to the progression of coronary atherosclerosis[4]. Patients with right heart failure and/or severe liver dysfunction were also excluded since the effect of HMG-CoA reductase inhibitors may depend upon liver function. In addition, a historical control group rather than a placebo group was compared with the treatment group in the present study, since it is difficult to conduct double-blind controlled trials in Japan at the present time[16], and it might not be considered ethical to recruit control subjects for a cholesterol-lowering study whose cholesterol level is ≤ 150 mg/dl. While baseline characteristics including classical coronary risk factors and angiographic findings were similar in the elderly between the treatment and control groups, minor differences existed in all the patient groups. To adjust for these differences in baseline parameters, multivariate analysis with Cox proportional hazard modeling was performed. Cholesterol-lowering treatment with HMG-CoA reductase inhibitors and the number of diseased

vessels were the only 2 factors that were related to prognosis regardless of age, suggesting that cholesterol-lowering treatment had a significant impact on the prognosis of patients with CAD. The fact that advancing age is not selected as a prognostic factor in this multivariate analysis indicates that cholesterol-lowering treatment is effective for the prognosis independent of age.

Secular trends in the therapeutic strategy for CAD may also have confounded the influence on the prognosis of patients in this study. In fact, the choice of coronary intervention in the early 1980s was coronary bypass grafting, and since then, the number of patients undergoing coronary angioplasty has increased in our institution[7]. The criteria for which patients receive medical treatment may also be changing. In the present study, however, minor differences in baseline characteristics as adjusted by multivariate analysis did not have a significant effect on the prognosis of these patients. Since the management of these characteristics, including coronary risk factors and coronary artery stenosis, is reported to have the greatest prognostic influence on patients with CAD[17], the 2 groups were considered comparable with respect to important prognostic factors. Moreover, the fact that patients with or without cardiac events did not differ in the use of cardioactive medications such as β-blockers and angiotensin-converting-enzyme inhibitors, which are known to improve the prognosis of patients with CAD, suggests that confounding effect of secular trends in the medical therapy was probably minimal[18,19].

In conclusion, this preliminary study with cholesterol-lowering treatment using HMG-CoA reductase inhibitors suggests significant improvement in the prognosis of Japanese elderly patients with established CAD and normal serum total cholesterol levels. A double-blind investigation of the effects of HMG-CoA reductase inhibitors in this patient population is warranted.

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要　約

日本人の高齢者虚血性心疾患に対するヒドロキシメチルグリタリル補酵素A還元酵素阻害薬を用いたコレステロール低下療法の効果

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近年，薬剤によるコレステロール低下療法の予後改善効果が報告されているが，我が国の高齢者に対する有効性は明らかではない．このため，高齢者虚血性心疾患患者にヒドロキシメチルグリタリル補酵素A(HMG-CoA)還元酵素阻害薬を用いてコレステロール低下療法を行い，心事故発生の予防に寄与するか否かを検討した．

対象は虚血性心疾患患者392例で，HMG-CoA還元酵素阻害薬の投与を受けた121例，および同剤が使用可能となる前の271例をそれぞれ治療群・対照群とし，高齢群と中年群で予後を比較した．高齢群(65歳以上)143例においては治療群と対照群間で総コレステロール値(201±30 vs 202±31 mg/dl)，年齢(71±4 vs 70±7歳)，男性の頻度(37/53 vs 64/90)，病変指数(1.7±0.9 vs 1.5±1.0)および高血圧，糖尿病，喫煙，肥満，家族歴などの他の危険因子に有意差を認めなかった．また，全症例においても2群間で総コレステロール値(208±33 vs 201±34 mg/dl)を含め同等の傾向を認めた．薬物療法により総コレステロール値は高齢群で14%，全症例で13%低下した．約3年間の経過観察期に治療群の5例(高齢者1例)，対照群の38例(高齢者12例)の計43例に心事故を認めた．Kaplan-Meier法による心事故回避生存率は，高齢群において対照群に比べ治療群で良好で(98 % vs 85%，$p<0.05$)同様な結果が全症例においても認められた(94% vs 86%，$p<0.05$)．Cox比例ハザード法による検定では，HMG-CoA還元酵素阻害薬により心事故の有意な低下を認め(相対危険度0.32，$p<0.05$)，他に病変指数により危険度は増加するが(相対危険度1.8，$p<0.01$)，加齢による危険度の変化は認められなかった．

我が国の高齢者虚血性心疾患患者に対しても，総コレステロール値正常例を含めて，HMG-CoA還元酵素阻害薬によるコレステロール低下療法を行うことで，その予後が改善されることが示唆された．

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