A Comparison of Low Versus Standard Dose Pravastatin Therapy for the 
Prevention of Cardiovascular Events in the Elderly: The Pravastatin 
Anti-atherosclerosis Trial in the Elderly (PATE)

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Treatment with low drug doses is generally recommended in the elderly. However, the efficacy of low-dose 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor treatment in elderly hypercholesterolemic patients has never been examined. Therefore, we compared the effect of low-dose with standard-dose pravastatin, an HMG CoA reductase inhibitor, on the incidence of cardiovascular events (CVEs) in elderly patients with hypercholesterolemia in a randomized prospective trial. Subjects aged ≥60 years (73 ± 6 years) with serum total cholesterol (TC) levels of 220-280 mg/dL were randomized to the low-dose (group L, 5 mg/day; n = 334) or standard-dose (group S, 10-20 mg/day; n = 331). Baseline TC levels were similar in the 2 groups (253 ± 15 mg/dL). Patients were followed for 3-5 years (mean 3.9 years). TC levels decreased from baseline by 11-13% in group L and by 15-17% in group S. TC levels at 1 year in S and L group were 209 ± 2 mg/dL (16 ± 1% decrease) and 221 ± 2 mg/dL (12 ± 1% decrease), respectively. Forty-two and 29 CVEs occurred in group L and S, respectively. The incidence of CVEs was significantly lower in group S than in group L (P = 0.046, generalized Wilcoxon test; P = 0.096, log-rank test). The risk ratio for group S compared with group L was 0.674 (95% confidence interval: 0.423-1.074). Subgroup analyses suggested that the difference in the incidence of CVEs between the 2 groups was more clear in subjects without diabetes mellitus, with TC levels of < 253 mg/dL, and with TG levels of ≥133 mg/dL. The incidence of CVEs in group S was significantly lower than that in group L in subjects without both diabetes mellitus and previous cardiovascular disease (P = 0.026, generalized Wilcoxon test; P = 0.032, log-rank test). These findings suggest that standard-dose pravastatin (10-20 mg/day) is more effective in reducing the incidence of CVEs in the elderly than low-dose pravastatin (5 mg/day), especially in nondiabetic elderly patients with mild hypercholesterolemia or previous cardiovascular disease. J Atheroscler Thromb, 2001; 8: 33-44.

Key words: Prospective study, Hypercholesterolemia, Pravastatin, Elderly

Introduction

The impact of elevated serum cholesterol for the development of cardiovascular disease can be reduced by a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor therapy, at least in middle-aged males (1-5). However, the benefit of these drugs in preventing...
cardiovascular events in the elderly have not been established, although meta-analysis of five randomized controlled trials suggested that HMG CoA reductase inhibitor therapy was effective even in the elderly (6). Furthermore, all five trials were undertaken in predominantly Caucasian populations using relatively higher HMG CoA reductase inhibitor doses, and so far no study has examined the effectiveness of HMG CoA reductase inhibitor in an Asian population, whose incidence of cardiovascular disease is lower.

The standard clinical dose of HMG CoA reductase inhibitor in Japan is lower than that in Western countries (7, 8). Although a 15-20% decrease in serum total cholesterol (TC) levels is expected with the standard dose in Japanese hypercholesterolemic patients (9, 10), there is no evidence that the standard dose is effective in reducing the incidence of cardiovascular events (CVEs). In addition, administration of low drug dose is generally recommended for the elderly to avoid the occurrence of adverse drug reactions, although the effectiveness of low-dose HMG CoA reductase inhibitor in reducing the incidence of CVEs has not been previously examined.

We, therefore, conducted a prospective randomized controlled trial to determine the effectiveness of pravastatin, an HMG CoA reductase inhibitor, on the incidence of CVEs by comparing the effect of low-dose pravastatin (5 mg/day) with that of the standard-dose (10-20 mg/day) in elderly Japanese patients with hypercholesterolemia.

Patients and Methods

Patients and Study Design: Patients were recruited from 52 participating institutions. Both males and females, and patients both with and without previous cardiovascular disease were included. All patients were aged ≥60 years with serum cholesterol levels of 220-280 mg/dL. Patients with familial and secondary hypercholesterolemia, and malignancy were excluded.

After informed consent had been obtained, patients were enrolled with the central randomization service at the Department of Biostatistics/Epidemiology, School of Health Science and Nursing, University of Tokyo, Tokyo, Japan, by telephone or facsimile. Patients characteristics (age, gender, fasting TC, high-density lipoprotein cholesterol [HDL-C], and triglyceride [TG] levels, and history of previous myocardial infarction [MI], angina pectoris [AP], cerebrovascular disease [CVD], or atherosclerosis obliterans [ASO]) were obtained at the time of trial registration.

Patients were then randomly allocated to either the low-dose (L) group (pravastatin 5 mg/day) or standard-dose (S) group (pravastatin 10-20 mg/day) by an adaptive balancing method (minimization method with biased coin) using history of disease (MI, AP, CVD, and ASO), TC level, and institution as the balancing factors. Twelve hour fasting serum lipid levels at registration were measured after the cessation of any pharmacological treatment for hyperlipidemia for at least 3 months prior to enrolment in this study. Pravastatin administration started within 2 months after randomization.

Patients were followed for 3-5 years. During this period, reports of endpoints and pravastatin continuation or discontinuation were obtained every 3 months by mail. Fasting serum lipid levels (TC, TG, and HDL-C), blood pressure, and body weight were measured before and one, 3, and 6 months after the initiation of pravastatin treatment and every 6 months thereafter. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using Friedwald's formula (11), unless TG levels were ≥400 mg/dL. When LDL-C levels could not be calculated, LDL-C levels were treated as being absent for the purposes of analysis. Hypertension was defined as systolic blood pressure of ≥160 mmHg and/or diastolic blood pressure of ≥90 mmHg and/or the use of antihypertensive drugs.

Endpoints

The primary endpoint of the trial was the combined incidence of any type of fatal and nonfatal CVEs including CVD, cardiac disease, peripheral vascular disorder (PVD), and sudden death. CVD included cerebral infarction, cerebral hemorrhage, transient ischemic attack (TIA), and subarachnoidal hemorrhage. Cardiovascular diseases included MI, AP, congestive heart failure due to ischemic heart disease, and arrhythmia requiring pharmacological treatment; PVD included ASO, dissecting aortic aneurysm, and peripheral arterial thrombosis. The secondary endpoints were the combined incidence of MI and AP, and death from all causes.

The definition of cardiovascular events were essentially the same as the Lipid Research Clinics Program (12). For the diagnosis of CVD, computed tomography or magnetic resonance imaging findings were also used in this study. Details of definitions of endpoints are described in Appendix 2.

Potential endpoints were reviewed and classified by the Case/Event Evaluation Committee, which was blinded to the identity and group allocation of patients. When the primary report of an event was inadequate, the additional information required for a judgement to be made was requested.

Lipid standardization

Serum lipid levels were determined using enzymatic cholesterol and TG assays. The accuracy and precision of TC, TG, and HDL-C determinations at each institution were assessed by a standardization of lipid determination according to the Lipid Standardization Program of the Centers for Disease Control and Prevention, Atlanta, GA, USA. Accuracy, expressed as the mean %bias for TC, TG, and HDL-C was -1.78±2.24 (mean±SD), 0.57±6.75, and 2.04±6.64%, respectively. Precision, expressed as mean coefficient of variation for TC, TG, and HDL-C...
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C was $0.85 \pm 0.66, 1.39 \pm 2.21,$ and $1.85 \pm 1.42,$ respectively. A detailed analysis of the standardization of lipid determination was reported previously (13).

Assessment of compliance and safety
During the follow-up period, pravastatin continuation and discontinuation were reported every 3 months by mail. Routine medical examinations, including physical examination, peripheral blood cell counts, and blood chemistry (liver and renal function tests, and creatine kinase (CK)), were performed by physicians in charge at least every 6 months.

Adverse events were defined as any new unfavorable symptom or worsening of symptoms existing at the baseline, or any unfavorable change in laboratory findings. The study investigator classified each adverse event into one of 4 categories according to its relationship to pravastatin treatment: definite; possible; definitely not; and unknown. With the exception of the third category, all categories were considered to be an adverse drug reaction (ADR) related to pravastatin therapy. The Case/Event Evaluation Committee also recorded the severity of each ADR as grades 1, 2, or 3 based on World Health Organization criteria (14).

Sample size
Ito and Araki (15) demonstrated that the hazard of ischemic heart disease in Japanese elderly with diabetes mellitus was 0.0307/year. Since the incidence of ischemic heart disease is considered to be higher in patients with hypercholesterolemia than in patients with diabetes mellitus, we postulated the hazard to patients with hypercholesterolemia was 1.5-fold higher than that of patients with diabetes mellitus, i.e. 0.046/year.

It was also suggested that the hazard ratio of group L compared with group S was 1.6 to 1.8. Under these conditions, 400 subjects in each group needed to be included and followed up for four years to have a power of 80% based on the log-rank test with a one-sided significance level of 0.05 (16).

Statistical analysis
Analyses were performed on an intention-to-treat basis unless otherwise indicated. The least-square means calculated using general linear models were used to assess changes in serum lipids before and after pravastatin treatment. Statistical differences between the 2 groups in changes in serum lipids before and after pravastatin were assessed by the analysis of variance [ANOVA] for repeated measurements.

Statistical differences in the incidence of the primary and the secondary endpoints between the 2 groups were assessed using the log rank test, generalized Wilcoxon test, and Cox regression analysis. Two-sided probability values of $ \leq 0.05$ were considered to indicate a statistically significant difference in endpoint analyses. When appropriate, the Wilcoxon or chi-square test was used to analyse the difference between the study groups.

Values are expressed as the mean $\pm \text{SD}$ unless otherwise indicated. All statistical analyses were performed using SAS Release 6.12.

Study organization
Study organization of this study, role and member of each committee were described in Appendix 3 (Fig. 6).

Results
Between January 1, 1991 and March 31, 1993, 703 patients were enrolled in the study and randomly assigned to the 2 study groups. After randomization, 38 patients were excluded from the trial for the following reasons: no attendance at hospital after registration, 19 patients; withdrawal of informed consent, 6 patients; other hypercholesterolemia regimen in use at the start of pravastatin treatment, 4 patients; duplicate entry, 3 patients; active malignancy, 3 patients; familial hypercholesterolemia, 2

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics.</th>
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<td>Body weight (kg)</td>
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<td>Body mass index (kg/m²)</td>
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<td>HDL-C</td>
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<td>LDL-C</td>
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<td>Complications</td>
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<td>Vascular disease</td>
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<td>MI</td>
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<td>Ex-smoker</td>
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<tr>
<td>Current smoker</td>
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<td>Unknown</td>
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</tbody>
</table>

*Calculated using the chi-square test.
**NS, not significant.
patients; and secondary hypercholesterolemia due to hypothyroidism, 1 patient. The remaining 665 patients were followed up.

**Baseline characteristics**

There were no significant differences in the baseline characteristics of the eligible patients between the 2 groups, except the male : female ratio (Table 1). The proportion of women in group L (254/334 ; 76%) was significantly lower than that in group S (273/331 ; 82%).

**Compliance with pravastatin treatment**

The cumulative percentage of patients who discontinued pravastatin treatment during the trial was 23.9%, and the discontinuation rates in 2 groups (26.5% in group S and 21.3% in group L) were similar. The mean pravastatin doses for groups L and S through the study were 4.5±0.1 mg/day and 8.3±0.1 mg/day, respectively.

**Reductions in lipid levels**

Fig. 1 shows changes in TC and LDL-C levels from the baseline during the follow-up period. TC levels decreased 28-32 mg/dL (11-13% reduction) from baseline between 3 months and 3 years after the initiation of treatment in group L and by 38-42 mg/dL (15-17% reduction) in group S (Figs. 1A, 1B). The LDL-C levels decreased 30-34 mg/dL (17-20% reduction) from baseline in group L and by 39-43 mg/dL (23-26% reduction) in group S (Figs. 1C, 1D). The reductions in TC and LDL-C were significantly greater in group S than in group L through all time points (average group effect, $P<0.0001$ by ANOVA). Moreover, although the serum TG levels decreased in both groups, the decrease in group S was significantly greater than that in group L at all time points except at 6 months after the initiation of pravastatin (average group effect, $P=0.001$ by ANOVA) (Fig. 2A). In addition, significantly greater increases in HDL-C were observed in group S than in group L (average group effect, $P=0.003$ by ANOVA) (Fig. 2B).

**Endpoint**

Patients in this trial were followed for 3-5 years (mean follow-up period : 3.9 years in both groups). During the follow-up period, 42 and 29 fatal and nonfatal CVEs were observed in groups L and S, respectively (Table 2). The proportion of patients who did not experience a primary endpoint (fatal and nonfatal CVEs) was higher in group S than in group L ($P=0.046$, generalized Wilcoxon test ; $P=$
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The risk ratio for group S compared with group L, calculated from log-rank scores, was 0.674 (95% confidence interval [CI], 0.423-1.074) (Fig. 4). In addition, a similar risk ratio for group S compared with group L (0.697 [95% CI: 0.433-1.124]) was obtained by Cox regression analysis adjusted for gender, age, diabetes mellitus, previous history of vascular disease (MI, AP, CVD and ASO), cigarette smoking and hypertension.

The differences in the incidence of primary endpoint between groups L and S were further compared in subgroups. When subjects were divided into subgroups according to baseline age, TC, TG or HDL-C, each median value was used as a cut-off point. The existence of an interaction between the subgroups and the treatment groups was also examined using the Cox regression model. No interaction P value between the subgroups was significant. However, taking the low power of the interaction test into account, the low P values and the confidence intervals of the risk ratios suggest that the risk reduction for CVE occurrence in group S was more clear in patients without diabetes mellitus, those with serum cholesterol of <253 mg/dL, and those with TG of ≥133 mg/dL (Table 3).

The secondary endpoints were the combined incidence of MI and AP, and death from any cause. The combined total numbers of patients experiencing MI and AP were 17 in group L and 10 in group S. During the follow-up period, 20 and 14 deaths were observed in groups L and S, respectively. Six of the 20 deaths in group L and 8 of the 14 deaths in group S were due to cardiovascular diseases. Of the remaining 14 and 6 deaths in groups L and S,

![Fig. 2. Changes in serum TG (A) and HDL-C levels (B) due to pravastatin treatment. ---- group S; -----, group L. Each data point shows the least-squares mean ± SE.](image)

<table>
<thead>
<tr>
<th>Classification of events</th>
<th>Group L</th>
<th>Group S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>15 (1)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>TIA</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>7 (3)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>AP</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td></td>
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</tr>
<tr>
<td>disorders</td>
<td></td>
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<tr>
<td>ASO</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dissecting aortic aneurysm</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Left upper limb thrombosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>42 (6)</td>
<td>29 (8)*</td>
</tr>
<tr>
<td>Deaths due to cardiovascular disease</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Deaths due to other causes</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Total no. of deaths</td>
<td>20</td>
<td>14</td>
</tr>
</tbody>
</table>

Figures in parentheses show numbers of deaths.

* : $P=0.046$, Generalized Wilcoxon test; $P=0.096$, log-rank test (95% CI 0.423-1.074)
respectively, 6 in group L and 2 in group S were due to malignant neoplasia.

The secondary endpoint risk ratios for group S compared with group L are shown in Fig. 4. The statistical power of the study to detect differences in this endpoint was not assured because of the small number of patients. However, the tendencies were similar to those observed in the primary endpoint analysis.

Risk ratios for group S compared with group L were clearly lower in patients with diabetes mellitus or previous cardiovascular disease in comparison with each counterpart (Table 3). Therefore, we further compared the incidence of the primary endpoint in groups S and L excluding patients with diabetes mellitus and previous cardiovascular disease. The difference in the proportion of CVE-free patients between groups S and L increased in statistical significance (P=0.026, generalized Wilcoxon test; P=0.032, log-rank test) (Fig. 5).

Fig. 3. Kaplan-Meier curves for the probability of remaining free of the primary endpoint during the follow-up period. Group S, n=331; group L, n=334. The proportion of patients who did not experience a primary endpoint (fatal and nonfatal CVEs) was significantly higher in group S than in group L (p=0.046, generalized Wilcoxon test; p=0.096, log-rank test).

Fig. 4. Risk ratios and 95% CIs for the primary and secondary endpoints in group S compared with group L. Risk ratios were calculated from log-rank scores.

Safety of pravastatin treatment

The prevalence of adverse events other than CVEs and malignant disease was similarly low in groups L (19 events in 18 cases) and S (26 events in 20 cases). The ADRs mainly observed in this study were slight elevations of CK and gastrointestinal symptoms. Furthermore, all adverse events, except 2 grade 2 events in group S (in 1 patient blood urea nitrogen levels increased from 20 mg/dL to 27 mg/dL and in the other from 21 mg/dL to 29 mg/dL) and 1 grade 2 event in group L (peripheral leukocyte counts decreased from 3,900 cells/μL to 2,400 cells/μL), were of grade 1. All grade 2 adverse events were normalized during continuation of drug therapy and no serious adverse events were reported in this trial.

Discussion

This study was the first randomized controlled trial in hypercholesterolemic elderly patients comparing the effects of low and standard doses of pravastatin with the
incidence of CVEs. This study was designed in 1990, and started from January, 1991. At that time, results of prospective interventional studies such as the West of Scotland Coronary Prevention Study (WOSCOPS) (3) and the Scandinavian Simvastatin Survival Study (4S) (4) had not been reported. At that time, the relationships between cholesterol lowering and cardiovascular events in the elderly had not been clarified. Furthermore, it was indicated that there was a possible association between low cholesterol levels and the risk of hemorrhagic stroke. For these reasons, all CVEs including cerebral hemorrhage were employed as primary endpoints. The combined incidences of MI and AP were employed as secondary endpoints. In this study, it was demonstrated that the standard dose of pravastatin for Japanese, 10-20 mg/day, was more effective in reducing the incidence of CVEs in elderly hypercholesterolemic patients than the low dose, 5 mg/day (Figs. 3, 4). Risk reduction for the primary endpoint (the combined incidence of fatal and nonfatal CVEs) for group S compared with group L, was calculated from log-rank scores as 33%. Furthermore, risk reductions in group S were 42% and 29% for the secondary endpoints, the combined incidence of MI and AP, and death from all causes, respectively.

In the subanalysis of the Cholesterol and Recurrent Events (CARE) trial (5, 17), pravastatin treatment was demonstrated to be effective in the secondary prevention of coronary heart disease in elderly patients with normal or slightly elevated cholesterol levels. In addition, subanalysis of WOSCOPS (4) has demonstrated that pravastatin treatment is effective in the primary prevention of coronary heart disease in hypercholesterolemic patients aged ≥55 years as well as in patients aged <55 years. Risk reductions by pravastatin treatment for CVE observed in elderly subgroups in the CARE and WOSCOPS studies were similar to that observed in the present study. However, the doses of pravastatin used in this trial were 5 mg/day and 10-20 mg/day and the difference between these doses was smaller than that in the CARE and WOSCOPS studies in which the difference in dose was 40 mg/day. As a result, the difference in the TC levels between the groups, 10-14 mg/dl, was smaller than that reported in those previous studies.

It is unclear how small differences in TC and LDL-C on pravastatin treatment between the 2 groups in the present study resulted in a substantial risk reduction for CVEs.

### Table 3. Cardiovascular events in subgroups defined by baseline variables.

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of Patients</th>
<th>No. of Patients with events</th>
<th>Risk Ratio (95% C.I.)*</th>
<th>P-Value Generalized Wilcoxon</th>
<th>Log-rank</th>
<th>Interaction P-Value **</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Group L</td>
<td>Group S</td>
<td>Group L</td>
<td>Group S</td>
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<tr>
<td>Age</td>
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<tr>
<td>&lt;72 years</td>
<td>169</td>
<td>166</td>
<td>18</td>
<td>9</td>
<td>0.507(0.238-1.077)</td>
<td>0.048</td>
</tr>
<tr>
<td>≥72 years</td>
<td>165</td>
<td>165</td>
<td>24</td>
<td>20</td>
<td>0.801(0.444-1.447)</td>
<td>0.326</td>
</tr>
<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
<td>80</td>
<td>58</td>
<td>13</td>
<td>5</td>
<td>0.522(0.206-1.327)</td>
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<td>Female</td>
<td>254</td>
<td>273</td>
<td>29</td>
<td>24</td>
<td>0.751(0.438-1.287)</td>
<td>0.204</td>
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<td>Hypertension</td>
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<td>Present</td>
<td>171</td>
<td>167</td>
<td>18</td>
<td>12</td>
<td>0.667(0.326-1.365)</td>
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<tr>
<td>Absent</td>
<td>163</td>
<td>164</td>
<td>24</td>
<td>17</td>
<td>0.677(0.367-1.249)</td>
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<tr>
<td>Present</td>
<td>104</td>
<td>95</td>
<td>17</td>
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<td>0.899(0.449-1.798)</td>
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<td>Absent</td>
<td>230</td>
<td>236</td>
<td>25</td>
<td>14</td>
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<td>8</td>
<td>0.423(0.119-1.495)</td>
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<td>Other</td>
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<td>299</td>
<td>34</td>
<td>27</td>
<td>0.729(0.441-1.205)</td>
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<tr>
<td>Present</td>
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<td>19</td>
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<td>0.737(0.363-1.493)</td>
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<tr>
<td>Absent</td>
<td>239</td>
<td>249</td>
<td>23</td>
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<td>0.680(0.365-1.2649)</td>
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<td>&lt;253 mg/dL</td>
<td>163</td>
<td>167</td>
<td>24</td>
<td>13</td>
<td>0.515(0.270-0.981)</td>
<td>0.022</td>
</tr>
<tr>
<td>≥253 mg/dL</td>
<td>171</td>
<td>164</td>
<td>18</td>
<td>16</td>
<td>0.902(0.460-1.766)</td>
<td>0.629</td>
</tr>
<tr>
<td>Triglyceride</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;133 mg/dL</td>
<td>160</td>
<td>152</td>
<td>11</td>
<td>13</td>
<td>1.231(0.553-2.742)</td>
<td>0.706</td>
</tr>
<tr>
<td>≥133 mg/dL</td>
<td>155</td>
<td>159</td>
<td>25</td>
<td>14</td>
<td>0.526(0.280-0.985)</td>
<td>0.019</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;53 mg/dL</td>
<td>145</td>
<td>142</td>
<td>15</td>
<td>8</td>
<td>0.525(0.232-1.188)</td>
<td>0.084</td>
</tr>
<tr>
<td>≥53 mg/dL</td>
<td>157</td>
<td>159</td>
<td>20</td>
<td>17</td>
<td>0.829(0.453-1.579)</td>
<td>0.427</td>
</tr>
</tbody>
</table>

* : calculated using log-rank scores
** : calculated using Cox regression analysis
Recent publications of the WOSCOPS (18) and CARE (19) studies demonstrated that there was no relationship between the magnitude of cholesterol lowering and the event rate while on pravastatin treatment.

These findings and those of the present study may indicate the importance of some ancillary effects of pravastatin other than its cholesterol-lowering effect in reducing the incidence of CVEs. Anti-platelet thrombus formation activity (20) and an endothelial function protective effect (21) of pravastatin may have a role, since platelet functions increase and endothelium functions deteriorate in the elderly (22, 23).

One other possible explanation for marked difference in the incidence of CVEs between the 2 groups in the present study despite the small difference in on-treatment TC levels is that a threshold TC level for the effect of cholesterol-lowering to reduce the occurrence of CVEs may exist. The subanalysis suggested a clear difference between groups L and S among those with TC levels of < 253 mg/dL, but not in those with TC levels of ≥ 253 mg/dL (Table 3). The insufficient decreases in the TC and LDL-C levels in those with the initial TC levels of ≥ 253 mg/dL on the test dose in this study may explain these findings. The on-treatment TC levels after pravastatin were about 205 mg/dL and 215 mg/dL, respectively, in groups S and L in those who had TC levels of < 253 mg/dL, and 215 mg/dL and 225 mg/dL, in groups S and L in those who had TC levels of ≥ 253 mg/dL, respectively. These findings suggest that the threshold TC level for the effect of cholesterol-lowering to reduce the occurrence of CVEs in elderly Japanese may lie between 205 mg/dL and 215 mg/dL in the on-treatment TC level.

The proportion of males in group L was significantly higher than that in group S (Table 1). The LIPID study (24) and the subanalysis of the CARE study (25) demonstrated that the effect of pravastatin in reducing the incidence of coronary heart disease and stroke, respectively, was more prominent in males than in females. Therefore, the difference in gender distribution in the 2 arms of the present study may have influenced the results. However, Cox regression analysis adjusted for gender, age, diabetes mellitus, PVD, cigarette smoking, and hypertension produced similar risk ratios between groups S and L. Thus, the difference in gender distribution between groups S and L appeared to have no crucial effect on the results.

The risk ratios suggest that the difference between groups L and S in the CVE incidence was more marked in subjects without diabetes mellitus and in those with TG levels of ≥ 133 mg/dL, as well as in subjects with TC levels of < 253 mg/dL (Table 3). We also showed that the significance of the difference in the incidence of CVEs between the 2 groups became greater when patients with both diabetes mellitus and previous cardiovascular disease were excluded (Fig. 5).

Although the reason(s) for these findings remain unclear, the number of patients in the present study was insufficient for further analyses to clarify the reasons for the findings of subgroup analyses.

Compliance with the oral administration of pravastatin in this trial was fairly good, with the cumulative rate of pravastatin discontinuation being 23.9%. This figure is similar to or better than that observed in previous studies: the discontinuation rate was 24.7% at year 4 in WOSCOPS (4) and 31.3% at year 4 in the Helsinki Heart Study (2). In addition, the tolerability of pravastatin was good, and no significant adverse effects were observed in the present study.

From the findings obtained, together with recent studies demonstrating hypercholesterolemia is one of the important risk factors even in the elderly (26-32), it is suggested that hypercholesterolemia in the elderly is a morbid state requiring treatment and that pravastatin at the standard dose (10-20 mg/day) is more useful in the treatment of elderly hypercholesterolemic patients to reduce the incidence of cardiovascular disease than low-dose pravastatin. While the Japanese standard dose of 10-20 mg/dL is lower than that generally used in western countries, the fat intake and the body size of Japanese, especially the elderly, is also smaller. These differences in the fat intake and the body size and the characteristics of patients in this study who had only mild hypercholesterolemia (serum TC of 220-280 mg/dL), may explain why pravastatin 10-20 mg/day was effective in reducing the incidence of CVEs in this study population. Further studies are needed to elucidate whether a higher dose of pravastatin could reduce the CVE incidence in elderly Japanese patients with higher serum TC levels or in younger patients.

References

I. Ischemic cardiac pain: severe substernal pain having a deep or visceral quality and lasting for half an hour or more

II. Electrocardiogram (classified by Minnesota Code)

A. Diagnostic
   Either of the following must be present:
   1. Unequivocal Q or QS pattern (Code 1-1)
   2. Q or QS pattern (Codes 1-2-1 to 1-2-7), plus any T-wave item (Codes 5-1 to 5-3)
   Only the first criterion applies in the presence of ventricular conduction defects.

B. Equivocal
   Any of the following must be present:
   1. Q or QS pattern (Codes 1-2-1 to 1-2-7)
   2. S-T junction and segment depression (Codes 4-1 to 4-3)
   3. T-wave items (Codes 5-1 to 5-2)
   4. Left bundle branch block (Code 7-1)

III. Enzymes

A. Diagnostic enzymes-all of the following conditions:
   1. CK, GOT, or LDH determined coexistent with the event
   2. The upper limit of normal for the local laboratory is recorded
   3. The determined value for one or more enzymes is at least twice the upper limit of the local laboratory but does not exceed fifteen times that value.

B. Equivocal
   1. CK, GOT, or LDH determined coexistent with the event
   2. The upper limit of normal for the local laboratory is recorded
   3. The determined value for one or more enzymes is elevated but does not fulfill criteria for diagnostic enzymes

II. Endpoints

I. Atherosclerotic coronary heart disease death—either or both of the following categories:

A. Death with consistent underlying or immediate cause plus either of the following:
   1. Pre-terminal hospitalization with definite or suspected myocardial infarction (see below)
   2. Previous definite angina or suspected or definite myocardial infarction when no cause other than atherosclerotic coronary heart disease could be ascribed as the cause of death

B. Sudden and unexpected death (requires all three characteristics)
   1. Deaths occurring within 1 hr after the onset of severe symptoms or having last been seen without them
   2. No known non-atherosclerotic acute or chronic process or event that could have been potentially lethal
   3. An unexpected death occurs only in a person who is not confined to their home, hospital, or other institution because of illness within 24 hr prior to death

II. Criteria for non-fatal myocardial infarction—any one or more of the following categories using the stated definitions:

A. Diagnostic ECG at the time of the event
Pravastatin and Cardiovascular Events in the Elderly

B. Ischemic cardiac pain and diagnostic enzymes
C. Ischemic cardiac pain and equivocal enzymes and equivocal ECG
D. A routine ECG is diagnostic for myocardial infarction while the previous one was not

III. Angina Pectoris:
Chest pain or discomfort with all of the following characteristics:
(1) Its site must include the sternum (any level)
(2) It must occur during a form of exertion or stress and must usually last at least 30 sec
(3) It must on most occasions disappear within 10 min or less from the time with rests or decreases the intensity of the exertion
(4) It must usually be relieved in 2-5 min by nitroglycerine (does not apply if nitroglycerine has never been taken)

In the case with angina pectoris at the baseline, chest pain or discomfort should disappeared or be controlled at entry. Reappearance or exacerbation of chest pain or discomfort with characteristics fulfilled by (1)-(4) was considered as an event. Subjects with uncontrolled angina pectoris at entry were not enrolled into this study.

IV. Arterial peripheral vascular disease (ASO: Arteriosclerosis obliterans): One or more of the following are present:
(1) Intermittent claudication
(2) Femoral pulsation is absent or weak unilaterally
(3) Dorsalis pedis and posterior tibial pulses are absent or weak unilaterally
(4) Dorsalis pedis and/or posterior tibial pulses are absent or weak bilaterally
(5) Ankle pressure index < 0.8
(6) Arterial stenosis demonstrated by angiography
(7) Foot gangrene/ulcer

In cases with ASO at the baseline, symptoms should be controlled not to disturb daily life and the gangrene or ulcer should be healed. Reappearance or exacerbation of symptoms was considered as an event.

V. Cerebrovascular disease
A diagnosis requires all of the following:
(1) History of recent onset of unequivocal and objective findings of a localizing neurologic deficit documented by a physician
(2) Findings persist longer than 24 hr
(3) The neurologic findings are not referable to an extracranial lesion
(4) Findings of a computed tomographic (CT) or magnetic resonance image (MRI) taken within 3 weeks after onset, or autopsy record to classify the cerebrovascular disease into cerebral hemorrhage, cerebral infarction or subarachnoidal hemorrhage. Cerebral infarction was defined as a stroke accompanied by CT and/or MRI scan(s) that showed an infarct in the expected area on the basis of the clinical findings or a stroke for which there was evidence of cerebral infarction at autopsy. Cerebral hemorrhage and subarachnoidal hemorrhage were classified on the basis of evidence obtained on CT or MRI scan or at autopsy, excluding hemorrhagic conversion of infarction.

In cases with cerebrovascular disease at the baseline, the appearance of new unequivocal and objective findings of a localizing neurologic deficit documented by a physician which persist longer than 24 hr was considered as an event and classified on the basis of evidence obtained on CT or MRI scanning or at autopsy. Cerebral infarction without obvious neurologic symptoms demonstrated by CT or MRI scan taken incidentally was not considered as an event.

VI. Transient cerebral ischemic attack:
A diagnosis requires all of the following:
(1) History of sudden onset of symptoms of a localizing neurologic deficit
(2) Symptoms lasting less than 24 hr
(3) Objective findings, if any, are noted by a physician but also disappear within 24 hr
(4) No history of any disease process which might potentially cause transient deficits such as atrial fibrillation or flutter, myocardial infarction in the preceding 2 months, mitral stenosis, hypoglycemia, trauma, or arrhythmia

VII. Congestive heart failure
Congestive heart failure required administration or increase in the dosage of diuretics and/or digitalis

VIII. Arrhythmia
Arrhythmia required a new pharmacological treatment

IX. Others
- Dissecting aortic aneurysm:
  A diagnosis requires symptom and definite evidence on a CT or MRI scan
- Peripheral arterial thrombosis:
  A diagnosis requires symptoms and absence of a pulse in the peripheral artery

Appendix 3
The Study organization was constructed by the Executive Committee, the Coordinating Statistician, the Case/Event Evaluation Committee, the Analysis Statistician, Registration Center, Data Center, the LIPID Standardization Committee and the Monitoring Committee as illustrated in Fig. 6.

Roles and Members of Committees:

Executive Committee:
Organization and conduction of the study
Members; Hajime Orimo, Chairman (Tokyo Metropolitan Geriatric Hospital); Haruo Nakamura (National Defense Medical College); Yasushi Saito (University of Chiba); Yasuyoshi Ouchi (University of Tokyo); Hideki Ito
PATE Study Organization

Executive Committee
Coordinating Statistician

Monitoring Committee

Case / Event Evaluation Committee

Lipid Standardization Committee

Analysis Statistician

Registration Center

Data Center

Fig. 6. Study organization of PATE study.

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Ouchi (University of Tokyo); Hideki Ito (Tokyo Metropolitan Geriatric Hospital); Toshitsugu Ishikawa (National Defense Medical College); Kenzo Ohba (Nippon Medical School); Hiroshi Nagura (Tokyo Metropolitan Geriatric Hospital); Setsu Iijima (International University of Health & Welfare).

Monitoring Committee:
Evaluation of the study from the ethical and scientific standpoint
Members: Norio Sasaki (Mitsui Memorial Hospital); Akira Kubo (Saiseikai Central Hospital); Yasuo Ohashi (University of Tokyo).

Registration Center:
Registration and randomization of subjects
Member: Yasuo Ohashi (University of Tokyo)

Data Center:
Input of data with a neutral manner
Member: EPS CO.Ltd.

LIPID Standardization Committee:
Standardization of measurements of serum lipids
Members: Masaichi Nakamura (Osaka Medical Center Cancer and Cardiovascular Disease), Minoru Iida (Osaka Medical Center Cancer and Cardiovascular Disease)

Analysis Statistician:
Data analysis
Members: Yutaka Matsuyama (University of Tokyo), Ikuko Toyoda, Taro Shibata (University of Tokyo)