apan has one of the lowest incidences of coronary artery disease (CAD) and longest life expectancies among the industrialised nations. Total cholesterol (TC) concentrations in CAD patients in Japan are comparably lower than those in patients from other countries. Several epidemiological studies report that cigarette smoking, hypertension and diabetes mellitus are common risk factors in Japan. However, in recent years, the incidence of cardiovascular disease has been rising as a result of increasingly more sedentary lifestyles and changing dietary patterns. Therefore, it is important for Japanese healthcare decision-makers to verify the effect of cholesterol reduction therapy within Japan.

Cholesterol-lowering clinical trials conducted in many Western countries have shown that treatment with HMG-CoA reductase inhibitors (‘statins’) significantly reduces the incidence of major coronary events in both primary and secondary prevention. Moreover, statins retard the progression of coronary atherosclerosis, as shown by quantitative coronary angiography (QCA) and might even reverse the progression in some patients. Regression can occur in several ways, including depletion of plaque lipid, depletion of connective tissue, lysis of fully occlusive thrombi or mural thrombi, and remodeling of underlying vascular architecture or relaxation of vasomotor tone. The previous studies have suggested a strong link between anatomical changes in coronary atherosclerosis evaluated by QCA and changes in cardiovascular event rates, suggesting that a reduced progression of coronary atherosclerosis is associated with an increased reduction in clinical event rates.

Lower coronary event rates in Asian populations compared with Caucasian populations might be the result of differences in health status, genetic predisposition to atherosclerosis and dietary patterns. It has also been postulated that the reduced coronary event rate observed in Asian populations compared with Caucasian populations might be a result of a difference in the progression of coronary atherosclerosis and the therapeutic response to statins. However, large-scale, randomized clinical trials investigating whether the beneficial effects of statins on coronary plaques seen in Western patients, that also occur in

Background The cardiovascular event rate in Japanese populations is strikingly lower than that in Caucasian populations and it has been postulated that this difference might be because of variations in atherosclerosis progression in patients with coronary artery disease (CAD). However, the rate of angiographically assessed progression and its response to statins has not been well described in Japanese patients.

Methods and Results The angiographic intervention trial using an HMG-CoA reductase inhibitor to evaluate the retardation of obstructive multiple atheroma (ATHEROMA) study was a multicenter, randomized, controlled clinical trial investigating the effects of pravastatin on coronary atherosclerosis in Japanese patients with CAD using quantitative coronary angiography. In total, 361 patients with mild to moderate elevated serum total cholesterol concentrations (195–265 mg/dl) received diet only (n=179) or diet plus pravastatin 10–20 mg/dl (n=182). Over 3 years, low-density lipoprotein-cholesterol in the pravastatin group decreased by 19.5% (p=0.0001). A per-patient analysis showed that minimum lumen diameter increased by 0.034±0.17 mm in the pravastatin group, but decreased by 0.006±0.16 mm in the diet only group (p=0.04). The mean difference between the treatment groups was 0.040 mm (95% confidence interval 0.020, 0.070 mm).

Conclusion The ATHEROMA study indicates that pravastatin 10–20 mg/day for 3 years improves hyperlipidemia, then suppresses progression and induces regression of focal coronary atherosclerosis in Japanese CAD patients with elevated serum cholesterol. (Circ J 2005; 69: 875–883)

Key Words: Cholesterol lowering trial; Pravastatin; Quantitative coronary angiography; Randomized controlled clinical trial; Regression
Japanese, patients have not been conducted in Japan. Retrospective data\textsuperscript{23} indicate that statins have similar treatment effects in Japanese patients, based on the recently published outcome of a Japan Lipid Intervention Trial\textsuperscript{24,25} which is a large-scale but non-randomized open clinical trial. However, the benefit/risk profile concerning statin use in Japanese patients is not yet clear, in either primary or recurrent coronary events. To clarify this situation, a MEGA study\textsuperscript{26} which is a large-scale randomized controlled clinical trial for primary prevention, is currently being undertaken throughout Japan.

The MEGA study was designed to evaluate pravastatin efficacy as an open-label, randomized controlled trial in which 4,000 patients received diet therapy only, and another 4,000 patients received diet plus pravastatin. Both the MEGA study and the current study organized by the Japanese Ministry of Health and Welfare, were started at the same time using a similar supervising system. Only a few angiographic studies\textsuperscript{27–29} have been conducted in Japan, although these studies have tended to be lacking in scientific method and objectivity, eg, non-quantitative data, non-computerized QCA and a small sample size, etc.

The angiographic intervention trial using an HMG-CoA reductase inhibitor to evaluate retardation of obstructive multiple atheroma (ATHEROMA) study was designed as a prospective, multicenter, randomized controlled clinical trial using QCA to assess changes in the lumen diameter of coronary arteries after 3 years of cholesterol-lowering therapy with pravastatin in patients with pre-existing CAD. The present study was started under the supervision of the Japanese Ministry of Health and Welfare, were started at the same time using a similar supervising system. Only a few angiographic studies\textsuperscript{27–29} have been conducted in Japan, although these studies have tended to be lacking in scientific method and objectivity, eg, non-quantitative data, non-computerized QCA and a small sample size, etc.

The angiographic intervention trial using an HMG-CoA reductase inhibitor to evaluate retardation of obstructive multiple atheroma (ATHEROMA) study was designed as a prospective, multicenter, randomized controlled clinical trial using QCA to assess changes in the lumen diameter of coronary arteries after 3 years of cholesterol-lowering therapy with pravastatin in patients with pre-existing CAD. The present study was started under the supervision of the Ministry of Health and Welfare of Japan in 1993, and included 59 cardiovascular medical centers from the western half of Japan. Here, we present the 3-year QCA findings of the ATHEROMA study.

Methods

Protocol

The ATHEROMA study was a multicenter, randomized, prospective clinical trial in patients with CAD, designed to assess the effect on coronary lumen diameter of treatment with a low cholesterol and calorie diet only or diet with pravastatin 10–20\,mg/day for 3 years. The rationale, design and baseline characteristics of patients have been described in detail previously\textsuperscript{26} Briefly, after approval of the protocol by ethical review boards in each participating institution, patients undergoing diagnostic coronary angiography (CAG) were screened for eligibility.

The main eligibility criteria were: age, 40–69 years; serum TC concentration, 195–265 mg/dl; and 1 stenosis of \geq 25\% in major coronary segments on visual assessment, according to the American Heart Association (AHA) reporting system\textsuperscript{31} Written informed consent was obtained from eligible patients.

Patients were given dietary counseling and 4 weeks later initial blood samples were obtained under fasting conditions. Blood samples were sent to a central blood chemistry laboratory (SRL, Tokyo, Japan) directly from participating institutions. If the serum TC concentration was within the limits for eligibility, a second blood sample was taken after an interval of at least 1 week. Patients whose serum TC concentration were 195–265 mg/dl in both samples were randomly allocated into 2 regimens using the minimization methods. Both groups were advised by the institutional dieticians to follow a low-fat and calorie-restricted diet. A step 1 diet was recommended in the case of a TC concentration of <200 mg/dl and a step 2 diet was recommended in the case of a TC concentration of \geq 200 mg/dl, according to the National Cholesterol Education Program\textsuperscript{32} Furthermore, 1 group also received pravastatin at a dose of 10–20\,mg/day. A dose of 20\,mg was recommended for patients in the pravastatin group whose serum TC concentration had risen to 260 mg/dl.

Baseline Measurements

Before randomization, researchers obtained a full medical history and conducted a physical examination of each patient according to the study protocol. Serum lipid parameters were assessed, including TC, triglycerides and high-density lipoprotein (HDL) cholesterol. Low-density lipoprotein (LDL) cholesterol was calculated according to Friedewald’s method\textsuperscript{33} All laboratory and demographic data were sent to the Data Center immediately.

QCA

In order to maintain a strict quality control of the catheterization procedure and photographing cine films, and to ensure the precise reproducibility of the procedures, the Angiography Committee of the ATHEROMA study group produced a standardized catheterization guideline for use by all participating institutions. These guidelines will be reported separately. All films were sent to the Study Coordinating Center for blinding, and all information such as treatment group, date of filming or institution were masked. All baseline and follow-up cine films were then sent to the Core Angiographic Laboratory for QCA analysis. At the Core Angiographic Laboratory, the films were analyzed by 10 experienced QCA analysts using version 2 of the Cardiovascular Angiography Analysis System (CAAS II, PUE Medical, Maastricht, The Netherlands)\textsuperscript{34,35} under the supervision of an expert cardiologist. The QCA data from segments 1, 2, 3, 5, 6, 7, 9, 11, 12 and 13 in the AHA reporting system\textsuperscript{31} were used for the analysis. Segments 4, 8, 10, 14 and 15 were considered unsuitable for QCA analysis because of the small diameters and difficulty identifying lengths of distal site of branches.

QCA parameters evaluated were minimum lumen diameter (MLD), average lumen diameter (ALD) and diameter of stenosis (DS).

In an additional measure to maintain the reproducibility of QCA data, 13 cine films from participating institutions over the course of the study were analyzed for validation according to a standard protocol\textsuperscript{36} These data will be reported separately.

Follow-up Status

Patients were followed-up by the attendant physicians at 3, 6, 12, 18, 24, 30 and 36 months after the commencement of the treatment regimen. At each follow-up visit, clinical events and laboratory measurements were recorded and reported regularly to the Data Center. Blood samples were directly transferred to and tested in the Central Blood Chemistry Laboratory using the same methods as for the baseline measurements. Lipid concentrations were thus recorded 7 times at regular intervals over the course of the study.

When a participant experienced a pre-defined clinical event, details of the event were reported to the Data Center for evaluation by an Event Evaluation Committee. The members of this committee were blinded to the partici-
pant’s treatment allocation. A determination of myocardial infarction (MI) was made on the basis of typical chest pain and several serum enzyme values. A determination of ischemic stroke required both typical symptoms and an ischemic pattern on brain computed tomography (CT) or angiogram. Similarly, a determination of hemorrhagic stroke required both typical symptoms and intracerebral bleeding pattern on brain CT or magnetic resonance imaging. Percutaneous coronary intervention was counted as a clinical event only when it took place as a reasonable necessity for the patient’s clinical condition. When committee members had different opinions over the classification of clinical events, the committee reached a consensus decision, while still blinded to the patient’s treatment allocation.

**Endpoints**

The primary endpoint of the study was the mean change in MLD at 3 years. The MLD per patient was chosen as the primary endpoint because it is the most sensitive QCA marker of atherosclerotic progression. Secondary QCA endpoints were MLD per segment and ALD per patient/segment. Because event numbers were likely to be small, the composite rate of MI, coronary artery bypass graft (CABG), stroke and all-cause mortality was also a secondary endpoint.

**Statistical Analyses**

The difference in the change in MLD between the diet only and the pravastatin treatment groups was expected to be in the range of 0.02–0.03 mm per year with a standard deviation (SD) of 0.13–0.27 mm, based on previous studies.14–16,18 We assumed that the difference in changes in MLD between the groups in the current study would be 0.06 mm with a SD of approximately 0.25 mm. Based on these assumptions a sample size calculation was performed before the study commenced. A sample size of 350 was determined based on a total follow-up rate of 80%, which would give the study a statistical power of 80% using a two-sided 5% level test, according to the normal approximation of binomial distribution.37

Baseline characteristics, including QCA parameters, in the 2 treatment groups were compared and tested for balance with Pearson’s chi-square test, Student’s t-test or Wilcoxon’s rank-sum test where appropriate. For baseline characteristics, a p-value of <0.15 was considered to be statistically significant. The effects of pravastatin on lipid concentrations were assessed with mixed-model ANOVA. The effects of pravastatin on the mean changes with SD in QCA parameters were assessed by the t-test. The continuous variables were presented with means and SD unless otherwise specified. Time to clinical events was analyzed by Cox proportional hazards model and statistical significance was assessed using the log-rank test. Differences between treatment groups were statistically significant when p-values were <0.05. All calculations were performed using SAS package version 6.12.

**Results**

Overall, 936 patients from 59 participating institutions were screened for enrolment between August 1994 and September 1997. Of these, 373 were randomized to treatment; 187 to diet only and 186 to pravastatin (Fig 1). Twelve patients, 8 in the diet only group and 4 in the pravastatin group, withdrew from the study following randomization. Thus, 361 patients, 179 in the diet only group and 182 in the pravastatin group, were followed and analyzed. Furthermore, of these, 146 in the diet only group and 142 in the pravastatin group were analyzed in terms of their quantitative angiographic data. The mean patient age was 59.3 years and 239 patients (83%) were males. The 2 treatment groups were well balanced with respect to baseline demographic characteristics (Table 1). The baseline characteristics of all the followed-up patients were described previously.30

**Lipids**

Patients receiving pravastatin had a significant 12.9% reduction in the concentrations of serum TC (p<0.0001), a significant 19.5% reduction in LDL-cholesterol (p<0.0001), a significant 4.3% increase in HDL-cholesterol (p<0.001) and a significant 13.4% decrease in triglyceride (p<0.001) over the 3-year treatment period. Patients receiving diet only showed no change in any of these parameters except a 3.2% increase in the concentrations of HDL-cholesterol (p<0.01, Table 2).

**QCA**

CAG was performed at baseline and at 3 years’ follow-up in 159 patients (88.8%) receiving diet only and 152 patients (83.5%) receiving pravastatin. Follow-up CAG, scheduled
for 3 years after the date of randomization, was actually performed after a mean ± SD period of 37.2±5.1 months; 36.7±5.3 months in the diet only group and 37.7±5.0 months in the pravastatin group. Of these, 23 cine angiograms (13 in the diet only group and 10 in the pravastatin group) were inappropriate for QCA because they were of poor quality or taken earlier than 3 years after randomization. As a result, cine films from 288 patients had matched baseline and 3-year data, representing 146 patients in the diet only group and 142 in the pravastatin group. Baseline QCA values were similar in the 2 groups (Table 1). MLD was 1.95±0.40 mm in the diet only group vs 1.89±0.35 mm in the pravastatin group, ALD was 2.62±0.47 mm vs 2.55±0.36 mm, and DS was 27.4±6.5% vs 27.1±5.8%.

In the pravastatin treatment group, there was a 0.034±0.17 mm increase in MLD (p=0.02) after 3 years in the per-patient analysis, indicating plaque regression in the most narrow point of the segment. In contrast, there was a slight decrease in MLD of 0.006±0.16 mm in the diet only group (p=0.64, Fig 2). There was a decrease in mean ALD after 3 years in both groups; the change was smaller in the pravastatin treatment group (–0.018±0.14 mm, p=0.12) than in the diet only group (–0.046±0.15 mm, p<0.001).

Per-segment analyses were also undertaken on MLD and ALD. Both parameters showed similar changes to those seen in the per-patient analysis. In the pravastatin treatment group, there was an increase (0.037±0.31 mm, p<0.001) in mean MLD after 3 years, while mean MLD in the diet only

Table 1 Baseline Characteristics of Patients Participating in the ATHEROMA Study

<table>
<thead>
<tr>
<th></th>
<th>Diet only (n=146)</th>
<th>Diet + pravastatin (n=142)</th>
<th>Total (n=288)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean ± SD)</td>
<td>59.4±6.6</td>
<td>59.3±6.4</td>
<td>59.3±6.5</td>
<td>0.90</td>
</tr>
<tr>
<td>Males (n; %)</td>
<td>124 (84.9%)</td>
<td>115 (81.0%)</td>
<td>239 (83.0%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Coronary narrowing (AHA classification; % patients)</td>
<td>25%</td>
<td>42 (28.8%)</td>
<td>39 (27.5%)</td>
<td>81 (28.1%)</td>
</tr>
<tr>
<td>50%</td>
<td>78 (53.4%)</td>
<td>74 (52.1%)</td>
<td>152 (52.8%)</td>
<td></td>
</tr>
<tr>
<td>75%</td>
<td>19 (13.0%)</td>
<td>24 (16.9%)</td>
<td>43 (14.9%)</td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td>7 (4.8%)</td>
<td>5 (3.5%)</td>
<td>12 (4.2%)</td>
<td></td>
</tr>
<tr>
<td>Ischaemia diagnosis (n; %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>22 (15.1%)</td>
<td>19 (13.4%)</td>
<td>41 (14.2%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Old myocardial infarction</td>
<td>44 (31.5%)</td>
<td>44 (31.0%)</td>
<td>88 (31.3%)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>4 (2.8%)</td>
<td>7 (4.9%)</td>
<td>11 (3.9%)</td>
<td></td>
</tr>
<tr>
<td>Stable angina pectoris</td>
<td>22 (15.1%)</td>
<td>12 (8.5%)</td>
<td>34 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>Silent myocardial ischaemia</td>
<td>2 (1.4%)</td>
<td>3 (2.1%)</td>
<td>5 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Pre-existing comorbidities (n; %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>60 (41.1%)</td>
<td>61 (43.0%)</td>
<td>121 (42.0%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23 (15.8%)</td>
<td>31 (21.8%)</td>
<td>54 (18.8%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>11 (7.5%)</td>
<td>15 (10.6%)</td>
<td>26 (9.0%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Lipid profile at baseline (mg/dl; mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>225.6±17.3</td>
<td>227.0±16.9</td>
<td>226.3±17.1</td>
<td>0.46</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>168.3±80.9</td>
<td>182.0±97.0</td>
<td>175.3±89.3</td>
<td>0.23</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>142.6±20.1</td>
<td>143.9±19.7</td>
<td>143.2±19.9</td>
<td>0.66</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>50.2±12.9</td>
<td>49.1±11.2</td>
<td>49.7±12.1</td>
<td>0.63</td>
</tr>
<tr>
<td>Lipoprotein (a)</td>
<td>25.0±24.0</td>
<td>23.2±20.2</td>
<td>24.1±22.2</td>
<td>0.79</td>
</tr>
<tr>
<td>QCA parameters (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum lumen diameter (mm)</td>
<td>1.95±0.40</td>
<td>1.89±0.35</td>
<td>1.92±0.38</td>
<td>0.23</td>
</tr>
<tr>
<td>Average lumen diameter (mm)</td>
<td>2.62±0.47</td>
<td>2.55±0.36</td>
<td>2.58±0.42</td>
<td>0.14</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>27.4±6.5</td>
<td>27.1±5.8</td>
<td>27.3±6.1</td>
<td>0.74</td>
</tr>
</tbody>
</table>

ATHEROMA, HMG-CoA reductase inhibitor to evaluate retardation of obstructive multiple atheroma; SD, standard deviation; AHA, American Heart Association; LDL, low-density lipoprotein; HDL, high-density lipoprotein; QCA, quantitative coronary angiography.

Table 2 Lipid Concentrations at Baseline and After 3 Years of Treatment With Diet or Diet Plus Pravastatin in Patients With Coronary Artery Disease

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 years</th>
<th>Change from baseline (%)</th>
<th>p-value for change from baseline</th>
<th>p-value for between-group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>224.8±17.5</td>
<td>223.2±21.4</td>
<td>–0.7</td>
<td>0.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diet only</td>
<td>226.2±17.2</td>
<td>196.8±23.0</td>
<td>–13.0</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diet + pravastatin</td>
<td>142.0±20.6</td>
<td>140.7±20.1</td>
<td>–0.9</td>
<td>0.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>50.0±12.7</td>
<td>51.6±13.2</td>
<td>3.2</td>
<td>&lt;0.01</td>
<td>0.54</td>
</tr>
<tr>
<td>Diet only</td>
<td>49.1±11.5</td>
<td>51.2±11.0</td>
<td>4.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Diet + pravastatin</td>
<td>167.1±78.5</td>
<td>157.0±68.2</td>
<td>–6.0</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>181.1±96.9</td>
<td>156.8±80.7</td>
<td>–13.4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

All values are mean ± SD. See abbreviations in Table 1.
group did not show a significant change (0.003±0.28 mm, p=0.74). Change in ALD after 3 years in both groups was similar to those of the per-patient analysis, –0.014±0.20 mm, p=0.04 and –0.041±0.19 mm, p<0.001, respectively. Fig 2 also shows the treatment effect of pravastatin on MLD and ALD (ie, the change in the pravastatin group minus the change in the diet only group). For MLD, the per-patient treatment effect was 0.040 mm (p=0.04; 95% confidence interval 0.002, 0.079 mm) and the per-segment effect was 0.034 mm (p<0.01). The corresponding ALD treatment effects were 0.028 mm (p=0.11) and 0.027 mm (p<0.01), respectively.

Clinical Events

There was no significant difference between the 2 treatment groups with regard to the composite rate of clinical events (Table 3). Four patients in the diet only group and 2 patients in the pravastatin group experienced MI (p=0.40). The number of patients who underwent coronary intervention or CABG was similar in both groups. One patient receiving pravastatin and 2 patients receiving diet only died during the course of the study.

Adverse Events

Adverse events (other than those clinical events in the secondary endpoint analysis) were observed in 52 patients (29.1%) in the diet only group and in 46 patients (25.3%) in the pravastatin treatment group over the 3-year follow-up period. There was no significant difference between the groups in the incidence of adverse events. The most common adverse events were exacerbation of diabetes mellitus, occurring in 5 patients in the diet group and 9 in the pravastatin group; gastrointestinal complaints, occurring in 8 and 3 patients, respectively; and neoplasm, occurring in 7 and 4 patients, respectively. Miscellaneous other events were reported by 32 patients in the control group and 30 in the pravastatin group. Of the 46 adverse events occurring in the pravastatin group, 20 were considered to be possibly or probably drug-related. The most common of these were malaise (n=2), hypophagia (n=2) and rash (n=2). No severe
adverse drug reaction was observed.

Discussion

ATHEROMA constitutes the first trial planned and conducted by the Japanese Ministry of Health and Welfare. Very few papers evaluating the effect of statins on coronary atherosclerosis by angiographic assessment in Japanese patients have been published. Although previous epidemiological studies have indicated that the incidence of CAD is much lower in Asians compared with Caucasians, it is unclear whether this difference is a result of variations in the progression of coronary atherosclerosis or because of the good response to statin treatment in Japanese and Western patients. Thus, the purpose of the study was to clarify how statin therapy, specifically pravastatin, benefits CAD patients with slightly to moderately elevated cholesterol concentrations. We found that pravastatin 10–20 mg/day over 3 years reduces serum cholesterol concentrations and results in regression of focal coronary atherosclerosis in Japanese CAD patients with slightly to moderately elevated cholesterol concentrations.

Comparison With Previous Studies

The primary endpoint of this study, MLD, increased in the pravastatin treatment group, but did not change in the diet only group. The majority of previous studies carried out in Europe and USA showed that while statin treatment might retard the progression of coronary atherosclerosis with an actual regression in some segments, marked coronary atherosclerosis progression by QCA did take place, especially in control patients. In the current study, however, we have shown that pravastatin caused actual regression of coronary atherosclerosis in Japanese CAD patients over a 3-year period.

The effect on a single segment or lesion might be obscure if the average values for the entire coronary tree are used. Other studies have shown that the response to statins is heterogeneous along the coronary trees. For example, in the Monitored Atherosclerosis Regression Study trial, lovastatin did not change the mean percent diameter stenosis, and a significant beneficial effect of lovastatin on stenosis was observed only in the stenosis that narrowed >50%. A per-patient and a per-segment analysis in the present study has demonstrated that pravastatin caused regression of coronary atherosclerosis. This is the most important finding of the current study, although the absolute difference between the active treatment group and the control group was small at 0.04 mm.

In the present study, changes in lipid concentrations with pravastatin were within expected ranges: approximately 20% decrease in LDL-cholesterol and 13% in TC, and approximately a 4% increase in HDL-cholesterol. We also found that lipid concentrations, including triglycerides, did not deteriorate with diet only during the 3 years of the study. In a meta-analysis of cholesterol-lowering clinical trials, pravastatin 20 mg was associated with a 26% decrease in LDL-cholesterol, 19% decrease in TC and 6% increase in HDL-cholesterol. We found less marked changes in lipid concentrations than these, possibly reflecting the fact that a number of our patients were receiving a lower dose (10 mg) and that the results were analyzed on an intention-to-treat basis.

The baseline LDL-cholesterol concentration in ATEROMA was similar to that in the Lipoprotein and Coronary Atherosclerosis Study and 7–26 mg/dl lower than that in most of the other angiographic studies. In all these studies, including ATEROMA, there was a similar treatment effect (between-group difference in the change in lumen diameter) of 0.04–0.08 mm increase in MLD with statin therapy across the range of baseline LDL-cholesterol concentrations (143–173 mg/dl).

One of the peculiarities of our results is the small SD of QCA parameters considered as an evidence of precision. Our initial estimate for the SD of changes in MLD per patient was 0.25 mm, although the actual SD in both groups was smaller than this, at 0.17 mm. This is smaller than the SD reported in the Multicentre Anti-Atheroma Study (0.26 mm) and the Regression Growth Evaluation Statin Study (REGRESS, 0.20 mm). Because of the small SD, we were able to show a treatment effect of pravastatin on QCA parameters, even in patients with a slow atherosclerotic progression. The MLD treatment effect in our study of 0.04 mm is lower than that reported in some angiographic studies but is similar to that seen in MARS and Canadian Coronary Atherosclerosis Intervention Trial, despite the smaller extent of LDL reduction with pravastatin. This suggests that the response to statin treatment seems an almost equivalent beneficial effect in Japanese compared with Caucasian patients.

It is important to know whether a similar treatment effect is also observed in CAD patients with higher TC concentrations or in higher-risk patients such as those who have undergone CABG or with acute coronary syndromes.
However, because of ethical reasons, it is not possible to treat hyperlipidemic patients with diet only even for an extended period of time and we are therefore not able to validate whether the treatment effect seen in the current study will be seen in higher-risk Japanese patients.

Over the follow-up period in the present study, the annual treatment effect in MLD was 0.013 mm/year. Higher annual treatment effects of 0.03–0.04 mm/year obtained in previous angiographic studies (Fig 3) were probably related to the much more marked progression in focal atheroma seen in the control groups of those studies. It is important to note that despite such a small progression in the non-drug group, significant suppression of ATHEROMA progression was observed in the current study in patients treated with pravastatin. Interestingly, the relationship between the percent reduction of LDL-cholesterol and the annual change in MLD per year in the current study was very similar to that reported in previous angiographic trials (Fig 3).

**Study Limitations**

The slower atherosclerosis progression in our control group is probably related to the lower incidence of cardiovascular events seen in the Japanese population. The rate of clinical events seen in the present study was much lower than reported previously. MI occurred in 2.2% of patients in the non-drug group in ATHEROMA, compared with 8.4% after a comparable follow-up duration in Pravastatin Limitation of Atherosclerosis in the Coronary arteries-1 and 2.8% after 2 years in REGRESS. Because we excluded subjects with acute coronary syndromes or previous CABG, our study population seems relatively low risk and this is likely to be the major reason for the low event rates observed. We focused on angiographical atherosclerosis progression and regression in order to exclude the confounding effects of mechanical intervention on plaque morphology. We also aimed to provide angiographic data in a Japanese population that was independent of the effects of catheter interventions.

Because of the small sample size as well as the relatively low-risk population, we cannot show the beneficial effects of pravastatin on clinical events in the current study. It is a major limitation of the current study that the sample size was too small to detect differences in clinical outcomes in a population with such a low incidence of cardiovascular events.

**Clinical Implications**

The 10–20 mg/day dosage of pravastatin was chosen for this trial because it has been reported as appropriate for Japanese patients and is recommended by the Ministry of Health and Welfare of Japan. The currently approved dosage of pravastatin in Japan is one-quarter to one-half of the standard approved dose in Europe and USA. The results of the ATHEROMA study suggest that Japanese patients derive almost the same treatment benefit in terms of atherosclerosis regression from this smaller dosage of pravastatin as patients in the USA and Europe do from a higher dose. Indeed, these results are in line with similar changes in lipid profiles observed with 3 years’ pravastatin therapy that have previously been reported in Japan.

The aim of the present study was to clarify the treatment effect of pravastatin in Japanese patients. QCA was chosen as the primary endpoint because of the large sample size that would have been required for a clinical endpoint study in a population at low risk of cardiovascular events. Although QCA is not a ‘hard’ endpoint, it is a scientifically valid method of assessing progression of coronary sclerosis. Indeed, 2 studies published in the early 1990s, FATS and St Thomas’ Atherosclerosis Regression Study, established the foundations for the use of angiography to assess cholesterol reduction therapy. Both studies pioneered the clarification that cholesterol reduction therapy retards progression and promotes regression of coronary atherosclerosis. The clinical event rates reported in the current study might not reflect the true benefit of pravastatin in this population, and the key finding is the fact that pravastatin therapy not only halts progression of atherosclerosis, but also induces regression.

**Conclusions**

The results of this trial show that pravastatin 10–20 mg/day over a 3-year period improves hyperlipidemia, then suppresses progression and induces regression of focal coronary atherosclerosis in Japanese CAD patients with mild to moderately elevated cholesterol concentrations.

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**References**

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Appendix 1

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Appendix 2

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