Effects of Simvastatin 20 mg/d on Serum Lipid Profiles in Japanese Hyperlipidemic Patients: A Prospective, Open-Label Pilot Study

Hiroshi Yoshida, MD, PhD1,2; Hidekatsu Yanai, MD, PhD1; Toru Shoda, MD, PhD2; Nobuyuki Furutani, MD, PhD1; Noriko Sato1; and Norio Tada, MD, PhD1

1Division of General Medicine, Department of Internal Medicine, Kashiwa Hospital, Jikei University School of Medicine, Kashiwa, Japan; and 2Department of Laboratory Medicine, Kashiwa Hospital, Jikei University School of Medicine, Kashiwa, Japan

ABSTRACT

Background: Hyperlipidemia is a major risk factor for ischemic heart disease. Hydroxymethylglutaryl coenzyme A reductase inhibitors ("statins") (eg, simvastatin) are considered first-line cholesterol-lowering therapy because they are effective and well tolerated, even at high doses. Based on a literature search, no studies have been published concerning the effects of simvastatin 20 mg/d in Japanese patients who had not previously received lipid-lowering treatment.

Objective: The aim of this study was to assess the clinical tolerability and effectiveness of simvastatin 20 mg/d in achieving the target lipid concentrations recommended in the 2002 Japan Atherosclerosis Society (JAS) guidelines in Japanese patients with hyperlipidemia.

Methods: This prospective, open-label pilot study was conducted at Kashiwa Hospital, Jikei University School of Medicine, Kashiwa, Japan. Male and postmenopausal female patients aged ≥18 to 70 years with hyperlipidemia (total cholesterol [TC], ≥220 mg/dL; triglycerides [TG], 150–400 mg/dL) who had not received lipid-lowering medications for at least 6 months before the study were enrolled. Patients received simvastatin 20 mg PO QD for 4 weeks. Effectiveness was assessed using serum concentrations of TC, low-density lipoprotein cholesterol (LDL-C), TG, and lipid peroxide, measured at 0 (baseline) and 4 weeks. Target serum TC and LDL-C concentrations as outlined by the JAS were as follows: category A, TC <240 mg/dL and LDL-C <160 mg/dL; category B1 and B2, TC <220 mg/dL and LDL-C <140 mg/dL; and category C, TC <200 mg/dL and LDL-C <120 mg/dL. A subanalysis of the correlation between baseline high-density lipoprotein cholesterol (HDL-C) and target achievement rates was conducted by baseline HDL-C concentration (<50 or ≥50 mg/dL). Tolerability was assessed using spontaneous reporting of adverse events and laboratory analysis, including liver function tests.

Accepted for publication October 7, 2005. 
Reproduction in whole or part is not permitted.
0011-393X/05/$19.00
**Results:** Twenty-two patients participated in the study (16 women, 6 men; mean [SD] age, 56.0 [8.0] years; mean [SD] body mass index, 23.6 [3.4] kg/m²). Mean serum TC, LDL-C, TG, and lipid peroxide concentrations significantly decreased from baseline (changes, −28.6%, −40.4%, −24.0%, and −14.5%, respectively; \( P < 0.001, <0.001, <0.001, \) and \(<0.01, \) respectively). The mean HDL-C concentration significantly increased from baseline (change, 7.2%; \( P < 0.001 \)); the mean increase was significantly greater in patients with baseline HDL-C <50 mg/dL compared with those with baseline HDL-C ≥50 mg/dL (changes, 11.3% vs 4.4%; \( P < 0.05 \)). Target TC and LDL-C concentrations were achieved in 90.9% of patients. No serious adverse events were observed, and liver enzyme and creatine kinase concentrations did not increase to above-normal values.

**Conclusions:** The results of this study suggest that simvastatin 20 mg/d might be useful in the clinical treatment of hyperlipidemia in Japanese patients. The study drug was well tolerated. (Curr Ther Res Clin Exp. 2005;66:613–629) Copyright © 2005 Excerpta Medica, Inc.

**Key words:** simvastatin 20 mg, low high-density lipoprotein cholesterol, 2002 Japanese Atherosclerosis Society guideline, lipid goal, Japanese hyperlipidemic patients.

---

**INTRODUCTION**

Hyperlipidemia is a major risk factor for coronary heart disease (CHD).\(^1\) Evidence suggests that reducing the serum concentration of low-density lipoprotein cholesterol (LDL-C) decreases the risk for CHD.\(^4\)\(^5\) Many large-scale clinical studies have found that hydroxymethylglutaryl coenzyme A reductase inhibitors ("statins") are effective in improving serum cholesterol levels (total cholesterol [TC] and LDL-C) and preventing CHD.\(^3\)\(^-\)\(^13\)

The advent of statins ~20 years ago has made cholesterol lowering relatively easy. Statins are the first line in cholesterol-lowering therapy because they are effective and well tolerated, even at high doses.\(^3\)\(^,\)\(^14\)\(^-\)\(^17\) However, the doses of statins administered to Japanese patients with hyperlipidemia have typically been lower compared with those administered to hyperlipidemic patients in Western countries, making it difficult to achieve the TC and LDL-C goals (category A, TC <240 mg/dL and LDL-C <160 mg/dL; category B1 and B2, TC <220 mg/dL and LDL-C <140 mg/dL; and category C, TC <200 mg/dL and LDL-C <120 mg/dL) established in the 2002 Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and treatment of atherosclerotic cardiovascular disease.\(^18\)\(^,\)\(^19\)

In the 2002 JAS guidelines, hyperlipidemic patients without CHD or CHD risk factors other than an elevated LDL-C concentration are classified as category A. Patients with CHD risk factors but without CHD are classified as category B,\(^18\)\(^,\)\(^19\) which is divided into 4 subcategories based on the severity of the following CHD risk factors other than elevated LDL-C: age (men, ≥45 years; women, ≥55 years), hypertension, diabetes mellitus, smoking habit, family history of CHD, history of cerebral infarction, and arteriosclerosis obliterans. Patients in category B1 or B2
have 1 and 2 risk factors, respectively, in addition to elevated LDL-C. Patients who have diabetes and a history of cerebral infarction, even with no other risk factors, are classified as category B3 and B4, respectively. Patients with CHD are classified as category C. Target serum TC and LDL-C become increasingly stringent progressing from category A to C. Because of a high CHD risk, more aggressive therapeutic intervention has been recommended for patients with diabetes, hypertension, multiple coronary risk factors, and/or the metabolic syndrome. More potent statins have been developed to aid high-risk patients in achieving the stringent cholesterol goals in the latest treatment guideline. After ~10 years of low-dose (5 mg/d) simvastatin use in clinical practice in Japan, the study of a higher dose (20 mg/d) in Japanese patients is timely. A search of the literature using MEDLINE (key terms: simvastatin, high dose, 20 mg, and Japanese patients; years: 1995–2005) found no such studies.

The aim of this study was to assess the clinical tolerability and effectiveness of simvastatin 20 mg/d in achieving the target lipid levels recommended in the JAS guidelines in Japanese patients with hyperlipidemia.

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

In this prospective, open-label pilot study, male and postmenopausal female patients who met the following criteria were consecutively enrolled from outpatient clinics at Kashiwa Hospital, Jikei University School of Medicine, Kashiwa, Japan: age ≥18 to 70 years, fasting serum concentration of TC ≥220 mg/dL, and fasting triglyceride (TG) concentration 150 to 400 mg/dL. Patients were excluded from the study if they were severely obese (body mass index [BMI], >30 kg/m²), or had clinically evident CHD, endocrine disease, or renal or hepatic dysfunction. Patients with diabetes mellitus were excluded because, although they commonly have high TG and low high-density lipoprotein cholesterol (HDL-C) levels, they rarely have high LDL-C levels. Furthermore, drugs to control glycemia often affect lipid metabolism, and patients with poorly controlled diabetes commonly have dyslipidemia. Patients receiving lipid-lowering drugs within the 6 months before the beginning of the study were also excluded.

During the 6 months before the study, patients were advised to modify lifestyle habits (Step-1 diet [energy, (25–30) × 22 × height (m)² kcal; fat, 20%–25%; fiber, >25 g] and exercise 20 minutes 3 times a week). Elevated serum TC was confirmed on several occasions during that time. Patients were asked not to change their dietary and exercise habits for the duration of the study (4 weeks).

All patients provided written informed consent before participation in the study. The study protocol was approved by the ethics committee at Jikei University. Patients were not compensated for participation.
**Study Design**

Patients were administered one 20-mg tablet of simvastatin QD in the evening (after a meal) for 4 weeks. After an overnight fast at baseline (week 0) and study end (week 4), each patient's height, weight, and blood pressure were recorded, and blood samples were drawn for laboratory analysis.

**Efficacy Assessments**

Serum concentrations of TC; TG; HDL-C; and apolipoprotein (apo) A-I, B, and E were measured using conventional methods. LDL-C concentration was estimated using the Friedewald formula. Non–HDL-C (calculated as the difference between the TC and HDL-C concentrations), non–HDL-C/HDL-C ratio, and apo B/apo A-I ratio were also determined. Lipid peroxide concentrations were measured using a fluorometric thiobarbituric acid reactive substance assay (TestWako LPO kit, Wako Pure Chemical Industries Co., Osaka, Japan).

The percentages of patients achieving TC and LDL-C targets based on the 2002 JAS guidelines was assessed by JAS category.

For subanalysis of the correlation between baseline HDL-C and target achievement rates in patients were divided into 2 groups based on baseline HDL-C level (<50 [lower] or ≥50 mg/dL [higher]), and changes in serum lipid concentrations, non–HDL-C concentration; non–HDL-C/HDL-C ratio (atherogenic index); apo A-I and B concentrations; and apo B/apo A-I ratio were compared between these 2 HDL-C subgroups.

**Tolerability Assessment**

The clinical tolerability of simvastatin was assessed using vital sign measurements and laboratory analyses, including liver function tests (serum concentrations of aspartate aminotransferase [AST], alanine aminotransferase [ALT], creatine kinase [CK], and creatinine [SCr]). Abnormal concentrations were defined as follows: AST or ALT, >3-fold the upper limit of normal (ULN) (normal ranges, 10–35 and 6–35 IU/L, respectively); SCr, ≥1.2; and CK, >3 × ULN (normal range, ≥220 IU/L). Other adverse events obtained by spontaneous reporting by the patients or asked about by the investigators were recorded at the week-4 clinic visit, and the causal relationship to simvastatin was assessed by the investigators as being definite, probable, or possible.

Treatment compliance was assessed using a pill count at the clinic visit.

**Statistical Analysis**

The comparisons of continuous variables between baseline and study end were performed using a 2-tailed, paired t test. The rates of change in serum lipid concentrations between the lower and higher baseline HDL-C groups were compared using a 2-tailed, unpaired t test. StatView version 4.54 (SAS Institute Inc., Cary, North Carolina) was used in the statistical analysis. Differences were considered statistically significant if \( P \) was <0.05. Data are expressed as mean (SD).
RESULTS

Patient Population

Twenty-two patients participated in the study (16 women, 6 men; mean [SD] age, 56.0 [8.0] years; mean [SD] BMI, 23.6 [3.4] kg/m²) (Table I). The mean (SD) baseline concentrations of serum TC, LDL-C, HDL-C, and TG were 283 (22), 187 (27), 61 (17), and 177 (76) mg/dL, respectively. The study included 3 patients who smoked and 7 patients with hypertension, all of whom had good blood pressure control (systolic/diastolic blood pressure [SBP/DBP], <140/<90 mm Hg). Five patients were receiving treatment with antihypertensive drugs (angiotensin II-receptor blockers [3 patients] and calcium-antagonists [2]). None of the patients were receiving supplemental vitamins or other medications. Based on the JAS guidelines, 3 patients were classified as category A; 18, category B1 or B2; and 1, category B3. All of the patients completed the study and were compliant with the treatment regimen, and none of them required a change in medications.

Changes in Serum Lipid Profile

Changes in serum lipid concentrations after 4 weeks of treatment with simvastatin 20 mg/d are shown in Table II. Mean serum concentrations of TC, LDL-C, and TG decreased significantly (by 28.6%, 40.4%, and 24.0%, respectively; all, P < 0.001 vs baseline) (Figure 1). The mean serum HDL-C concentration in-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>56.0 (8.0)</td>
</tr>
<tr>
<td>Sex, no.</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>23.6 (3.4)</td>
</tr>
<tr>
<td>JAS risk category, no.</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>B1/B2</td>
<td>18</td>
</tr>
<tr>
<td>B3</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension, no.</td>
<td>7</td>
</tr>
<tr>
<td>Smoking habit, no.</td>
<td>3</td>
</tr>
</tbody>
</table>

BMI = body mass index; JAS = Japan Atherosclerosis Society. *No significant between-group differences were found.
†Patients assigned to risk categories A, B1, B2, and B3 have 0, 1, 2, and 3 major risk factors, respectively (major risk factors include aging [men, ≥45 years; women, ≥55 years], hypertension, diabetes mellitus, smoking habit, family history of coronary heart disease, and/or high-density lipoprotein cholesterol level <40 mg/dL), in addition to an elevated low-density lipoprotein cholesterol (LDL-C) concentration (categories A, B1/B2, and B3, LDL-C ≥160, ≥140, and ≥120 mg/dL, respectively) without coronary heart disease. Patients with diabetes mellitus were classified as category B3 even if their only other major risk factor was an elevated LDL-C concentration.
Table II. Serum lipid concentrations before (week 0; baseline) and after 4 weeks of treatment with simvastatin 20 mg/d in Japanese patients with hyperlipidemia (N = 22). Values are mean (SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 0</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mg/dL</td>
<td>283 (22)</td>
<td>202 (20)*</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>187 (27)</td>
<td>112 (23)*</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>61 (17)</td>
<td>65 (16)*</td>
</tr>
<tr>
<td>Non–HDL-C, mg/dL</td>
<td>222 (30)</td>
<td>137 (24)*</td>
</tr>
<tr>
<td>Non–HDL-C/HDL-C ratio †</td>
<td>4.0 (1.7)</td>
<td>2.3 (0.8)*</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>177 (76)</td>
<td>126 (46)*</td>
</tr>
</tbody>
</table>

TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

*P < 0.001 versus baseline (paired t test).
†Atherogenic index.

Figure 1. Percentage changes from baseline in serum lipid concentrations after 4 weeks of treatment with simvastatin 20 mg/d in Japanese patients with hyperlipidemia. TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.
creased significantly from baseline (by 7.2%; \( P < 0.001 \) vs baseline). The mean serum non-HDL-C concentration and atherogenic index (non-HDL-C/HDL-C ratio) improved significantly (by 38.3% and 42.1%, respectively; both, \( P < 0.001 \) vs baseline) (Table II).

A significant increase in mean apo A-1 concentration (by 6.9%) and significant decreases in mean apo B and E concentrations (by 34.0% and 28.5%, respectively) were observed (all, \( P < 0.001 \) vs baseline) (Table III). The mean apo B/apo A-1 ratio also decreased significantly (by 38.5%; \( P < 0.001 \) vs baseline), as did the mean serum lipid peroxide concentration (by 14.5%; \( P < 0.01 \) vs baseline).

**Achievement of TC and LDL-C Targets**

Table IV shows the percentages of patients who achieved serum TC and LDL-C targets, by JAS category. Overall, targets were achieved by 20 (90.9%) of 22 patients. In the patients in categories B1 and B2, who accounted for 81.8% (18 patients) of the study population, 16 (88.9%) achieved goals.

Table V shows the changes in mean serum lipid and apo concentrations at baseline and study end. The lower HDL-C group had a higher mean (SD) baseline serum TG concentration compared with that in the higher HDL-C group (222 [82] vs 145 [53]; \( P < 0.05 \)). The percentage changes from baseline in mean serum HDL-C (Figure 2A) and TG (Figure 2B) concentrations were significantly greater in the lower baseline HDL-C group compared with those in the higher baseline HDL-C group (HDL-C, 11.3% vs 4.4%; TG, 34.7% vs 16.5%; both, \( P < 0.05 \)). However, the percentage changes in mean serum concentrations of TC, LDL-C, apo A-1, and apo B were not significantly different between the 2 subgroups.

**Tolerability**

No serious adverse events were observed, and none of the patients required hospitalization or died during the study.

---

**Table III.** Apolipoprotein (apo) and lipid peroxide concentrations before (week 0; baseline) and after 4 weeks of treatment with simvastatin 20 mg/d in Japanese patients with hyperlipidemia (N = 22). Values are mean (SD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Week 0</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo A-1, mg/dL</td>
<td>161 (46)</td>
<td>172 (49)*</td>
</tr>
<tr>
<td>Apo B, mg/dL</td>
<td>140 (18)</td>
<td>92 (17)*</td>
</tr>
<tr>
<td>Apo E, mg/dL</td>
<td>6.1 (2.2)</td>
<td>4.4 (1.4)*</td>
</tr>
<tr>
<td>Apo B/apo A-1 ratio</td>
<td>0.9 (0.3)</td>
<td>0.6 (90.2)*</td>
</tr>
<tr>
<td>Lipid peroxide, nmol/mL</td>
<td>2.9 (0.7)</td>
<td>2.5 (0.5)*</td>
</tr>
</tbody>
</table>

*\( P < 0.001 \) versus baseline (paired t test).
†\( P < 0.01 \) versus baseline (paired t test).
<table>
<thead>
<tr>
<th>Risk Category‡</th>
<th>TC</th>
<th>LDL-C</th>
<th>Abundance Ratio, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Target, mg/dL</td>
<td>Responders, no. (%)</td>
<td>Target, mg/dL</td>
</tr>
<tr>
<td>A (n = 3)</td>
<td>&lt;240</td>
<td>3 (100)</td>
<td>&lt;160</td>
</tr>
<tr>
<td>B1/B2 (n = 18)</td>
<td>&lt;220</td>
<td>16 (88.9)</td>
<td>&lt;140</td>
</tr>
<tr>
<td>B3 (n = 1)</td>
<td>&lt;200</td>
<td>1 (100)</td>
<td>&lt;120</td>
</tr>
</tbody>
</table>

*Patients who achieved the Japan Atherosclerosis Society18 serum total cholesterol (TC) and low-density cholesterol (LDL-C) targets.

‡Patients assigned to risk categories A, B1, B2, and B3 have 0, 1, 2, and 3 major risk factors, respectively (major risk factors include aging [men, ≥45 years; women, ≥55 years], hypertension, diabetes mellitus, smoking habit, family history of coronary heart disease, and/or high-density lipoprotein cholesterol level <40 mg/dL), in addition to an elevated LDL-C concentration (categories A, B1/B2, and B3 LDL-C ≥160, ≥140, and ≥120 mg/dL, respectively) without coronary heart disease. Patients with diabetes mellitus were classified as category B3 even if their only other major risk factor was an elevated LDL-C concentration.18
Table V. Lipid and apolipoprotein (apo) concentrations before (week 0; baseline) and after 4 weeks of treatment with simvastatin 20 mg/d in Japanese patients with hyperlipidemia, by baseline high-density lipoprotein cholesterol (HDL-C) concentration. Values are mean (SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HDL-C &lt;50 mg/dL (n=9)</th>
<th>HDL-C ≥50 mg/dL (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 4</td>
</tr>
<tr>
<td>TC, mg/dL</td>
<td>285 (27)</td>
<td>198 (24)*</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>196 (32)</td>
<td>121 (26)*</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>44 (5)</td>
<td>49 (5)*</td>
</tr>
<tr>
<td>Non-HDL-C, mg/dL</td>
<td>241 (29)</td>
<td>150 (26)*</td>
</tr>
<tr>
<td>Non-HDL-C/HDL-C ratio</td>
<td>5.6 (1.4)</td>
<td>3.1 (0.7)*</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>222 (82)</td>
<td>142 (52)*</td>
</tr>
<tr>
<td>Apo A1, mg/dL</td>
<td>122 (16)</td>
<td>132 (13)*</td>
</tr>
<tr>
<td>Apo B, mg/dL</td>
<td>149 (16)</td>
<td>100 (18)*</td>
</tr>
<tr>
<td>Apo B/apo A1 ratio</td>
<td>1.3 (0.3)</td>
<td>0.8 (0.2)*</td>
</tr>
</tbody>
</table>

TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.
*P < 0.001 versus baseline (paired t test).
†P < 0.05 versus baseline (paired t test).
‡P < 0.01 versus baseline (paired t test).

No clinically significant concentrations of serum hepatic enzymes were found (Table VI). SCr concentrations were below the ULN in all patients. Serum CK concentration was <220 IU/L in all patients, and none exhibited clinically significant levels.

DISCUSSION

Statins have been the most potent agents used for reducing serum LDL-C concentration since they became commercially available ~20 years ago. The effects of statins as primary and secondary prevention of CHD have been established.2-13,18 The major independent CHD risk factors originally identified in the Framingham Heart Study (10-year risk assessment for CHD)23 include elevated serum concentrations of TC and LDL-C, a depressed serum HDL-C concentration, hypertension (SBP/DBP ≥140/≥90 mm Hg), smoking habit, and older age (≥65 years).24-26 Guidelines for the management of individual CHD risk factors have been published by the National High Blood Pressure Education Program,27 the American Diabetes Association,28 and the National Cholesterol Education Program Third Adult Treatment Panel (ATP III).15 In the ATP III guideline,15 reducing the severity of the metabolic syndrome was considered a secondary goal in CHD risk reduction, following the primary goal of decreasing the serum
Figure 2. Percentage changes from baseline in serum concentrations of (A) high-density lipoprotein cholesterol (HDL-C) and (B) triglycerides, by baseline HDL-C concentration, after 4 weeks of treatment with simvastatin 20 mg/d in Japanese patients with hyperlipidemia. *P < 0.05 versus subgroup with baseline HDL-C ≥50 mg/dL (unpaired t test).
Table VI. Serum concentrations before (week 0; baseline) and after 4 weeks of treatment with simvastatin 20 mg/d in Japanese patients with hyperlipidemia (N = 22). Values are mean (SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NV</th>
<th>Week 0</th>
<th>Week 4</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST, IU/L</td>
<td>10–35</td>
<td>23.6 (7.4)</td>
<td>24.3 (7.5)</td>
<td>0.483</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>6–35</td>
<td>27.0 (22.8)</td>
<td>28.3 (22.3)</td>
<td>0.256</td>
</tr>
<tr>
<td>CK, IU/L</td>
<td>&lt;200</td>
<td>112 (45)</td>
<td>119 (51)</td>
<td>0.104</td>
</tr>
<tr>
<td>SCr, mg/dL</td>
<td>&lt;1.2</td>
<td>0.64 (0.21)</td>
<td>0.65 (0.19)</td>
<td>0.718</td>
</tr>
</tbody>
</table>

NV = normal value; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CK = creatine kinase; SCr = serum creatinine.

LDL-C concentration. These goals are in contrast to the Framingham CHD risk reduction, determined using age, sex, TC, HDL-C, smoking status, and SBP. Before the statins became available, the LDL-C target was not achieved in the majority of patients who received lipid-lowering treatment. The Lipid Treatment Assessment Project, a multicenter survey for a community-based assessment of lipid-lowering pharmacotherapy conducted in clinical practice settings in the United States and based on the ATP II guideline, found a high frequency (82%) of prescribing of lipid-lowering agents. LDL-C goals were achieved in 38.4% of 5601 patients overall, 68% of whom were low risk (LDL-C goal, <160 mg/dL); 37% of whom were high risk (LDL-C goal, <130 mg/dL); and 18% of whom had clinically evident CHD (LDL-C goal, <100 mg/dL).

In Japan, the prescription of simvastatin at a dose of >10 mg/d to hyperlipidemic patients was not approved until 2002. A reduction of 28.9% in serum LDL-C concentration was observed with simvastatin 5 mg/d in the Japan Lipid Intervention Trial (J-LIT), which studied primary CHD prevention with simvastatin use and in which 90.7% of 47,294 patients had completed 6 years of treatment. Reductions in serum concentrations of LDL-C and apo B of 27.6% and 21.8%, respectively, were observed in a separate 4-week clinical study of simvastatin 5 mg/d in 24 Japanese patients with hyperlipidemia conducted by the present authors. In the current study, greater reductions in serum LDL-C and apo B concentrations (40.4% and 34.0%, respectively) were achieved with simvastatin 20 mg/d compared with those found in our previous study. The reduction of ~40% in serum LDL-C concentration seems comparable to that achieved with simvastatin 40 mg/d or atorvastatin 10 to 20 mg/d in patients with hyperlipidemia in Western countries and by rosuvastatin 2.5 mg/d in Japanese patients with hyperlipidemia. Stein et al reported that simvastatin 20 mg/d was associated with a 29% reduction in serum LDL-C concentration in 22 US patients with hyperlipidemia, a reduction was similar to that achieved with simvastatin 5 mg/d in Japanese patients with hyperlipidemia. The results of the current study are consistent with those of the landmark studies of atorvastatin.
10 mg/d and simvastatin 40 mg/d conducted in Western countries, in which significant reductions in CHD risk and LDL-C concentrations were achieved in patients with hyperlipidemia.\textsuperscript{8,11-13}

These studies\textsuperscript{8,11} might predict the reduction in CHD risk achieved with simvastatin 20 mg/d in Japanese hyperlipidemic patients. However, the ability of simvastatin to reduce CHD morbidity and mortality in Japanese patients needs to be studied further because the present study investigated only lipid profile changes, a surrogate marker for reduced CHD risk. In the current study, 88.9\% of patients in risk categories B1 and B2 achieved JAS\textsuperscript{18} LDL-C targets with simvastatin 20 mg/d use, whereas in a meta-analysis of Western comparative trials,\textsuperscript{19} 81\% of 249 patients in categories B1 and B2 achieved JAS\textsuperscript{18} LDL-C targets with the use of simvastatin 20 mg/d. The present small-scale pilot study suggests that the lipid profiles of Japanese hyperlipidemic patients might be more responsive to treatment compared with those in hyperlipidemic patients in Western countries: 90.9\% of the study patients achieved the JAS\textsuperscript{18} TC and LDL-C goals. All of the patients reported compliance with the 4-week regimen of simvastatin 20 mg/d, which might explain the greater response to cholesterol-lowering treatment in this study compared with that in previous studies of simvastatin.\textsuperscript{20,31}

In the 2 previous studies of simvastatin in Japanese patients,\textsuperscript{20,31} the increase in serum HDL-C concentration with the use of simvastatin 20 mg/d was nearly 2-fold that with the use of a 5-mg/d dose. A low serum HDL-C concentration is considered a primary CHD risk factor, as indicated in the Framingham Heart Study.\textsuperscript{23,35,36} In several studies,\textsuperscript{37-39} including the Prospective Cardiovascular Munster (PROCAM) study,\textsuperscript{38} a serum HDL-C concentration <39 mg/dL was found to be a significant risk factor for myocardial infarction regardless of LDL-C category. The PROCAM study also found that a high serum HDL-C concentration (≥48 mg/dL) was more protective than a low serum LDL-C concentration (≤132 mg/dL). Namely, this protective effect against myocardial infarction remained after adjustment of other risk factors, including elevated LDL-C and TG concentrations. In J-LIT,\textsuperscript{31} patients with HDL-C >50 mg/dL had a lower CHD risk (as measured by elevated HDL-C) compared with those with HDL-C ≤50 mg/dL. Similarly, in the present study, simvastatin 20 mg/d was associated with a significantly greater increase in serum HDL-C concentration in the subgroup with the lower baseline HDL-C level compared with that in the subgroup with the higher baseline HDL-C level. In contrast, in a US study comparing the efficacy and tolerability of simvastatin 80 mg/d versus atorvastatin 80 mg/d administered for 24 weeks,\textsuperscript{40} 6 to 12 weeks of treatment with simvastatin 80 mg/d was associated with statistically similar HDL-C increases between the lower (11.6\%) and higher (6.9\%) baseline HDL-C subgroups.\textsuperscript{40} As great an increase in HDL-C might be achieved with the use of simvastatin 20 mg/d in Japanese patients as was seen with simvastatin 80 mg/d in patients in the US study,\textsuperscript{40} thereby resulting in a decreased CHD risk in patients with low baseline serum HDL-C concentrations. Our findings suggest that the HDL-C increase and LDL-C decrease might be greater in Japanese dyslipidemic patients compared with those in dys-
lipidemic patients in Western countries. However, comparative clinical trials are needed to support these findings.

HDL-C and apo A-1 concentrations increased significantly with simvastatin 20 mg/d in this study. In contrast, apo A-1 did not change significantly with the use of simvastatin 5 mg/d in our previous study. Apo A-1, a major apolipoprotein of HDL-C, helps protect hyperlipidemic patients against CHD. Although a reduced concentration of apo B is effective in preventing atherosclerosis, the increased apo A-1 concentration achieved with simvastatin therapy is preferable in hyperlipidemic patients because apo A-1 reduces the risk for atherosclerosis through reverse cholesterol transport mechanisms and inhibition of lipoprotein oxidation. The statin-induced increase in apo A-1 concentration has been attributed to the increase in apo A-1 mRNA production resulting from the activation of peroxisome proliferator-activated receptor α (PPAR-α). This PPAR-α-dependent increase in apo A-1 might occur with simvastatin 20 mg/d but not with 5 mg/d, which might in turn lead to the increased HDL-C found with the use of simvastatin 20 mg.

A significant decrease in serum TG concentration was also found with the use of simvastatin 20 mg. However, in J-LIT, no significant changes in TG concentration were observed. In the present study, the subgroup with lower baseline HDL-C had a higher baseline TG concentration compared with that in the subgroup with higher baseline HDL-C, suggesting that fasting serum TG concentration might be inversely correlated with baseline HDL-C concentration. The decrease in serum TG concentration was significantly greater in the subgroup with the lower baseline HDL-C compared with that in the subgroup with higher baseline HDL-C. The impairment of TG-rich lipoprotein catabolism resulting from reduced activity of lipoprotein lipase can create atherogenic lipoprotein characteristics (ie, depressed HDL-C concentration and elevated small, dense [SD] LDL concentration). These abnormalities in lipid profile occur frequently in patients with the metabolic syndrome and/or diabetes and might lead to increased CHD risk. Although the mechanisms of statin-induced amelioration of these atherogenic characteristics have not been fully elucidated, the use of simvastatin 20 mg/d is likely to be associated with an improved lipid profile beyond a decreased LDL-C concentration.

In our previous study of simvastatin 5 mg, the oxidative susceptibility of LDL (as measured using lag time before propagation of lipid peroxidation) was not reduced, and serum concentrations of TG and HDL-C did not change significantly from baseline. In the present study, serum lipid peroxide and TG levels decreased and HDL-C increased significantly with the use of simvastatin 20 mg. The reduction in lipid peroxide level might be related to the changes in TG and HDL-C concentrations: increased HDL-C concentration has been found to enhance protection against LDL oxidation, and reduced TG concentration has been found to decrease SD-LDL, which is susceptible to oxidation. However, further studies are needed to determine whether all statins have a beneficial effect on the oxidative susceptibility of LDL.
This study had several limitations. First, there was no control group with which to compare the simvastatin group. A randomized, double-arm study in which the results from a placebo group or a simvastatin 5-mg/d group could be compared with those from a group receiving simvastatin 20 mg/d is needed. Second, the duration of treatment was relatively short (4 weeks), and the short-term effects found in this study might differ from the long-term effects. Third, the study population was small (22 patients); large-scale, comparative studies are needed.

CONCLUSIONS
The results of this study suggest that simvastatin 20 mg/d might be useful in the clinical treatment of hyperlipidemia in Japanese patients in the initial dose setting. JAS TC and LDL-C targets were achieved in 90.9% of all participants. The study drug was well tolerated.

ACKNOWLEDGMENTS
This study was partly sponsored by a research grant for the Coronary Artery Disease and Remnant Lipoproteinemia Comparative Trial with Statin versus Fibrate, from the Ministry of Health, Labor and Welfare, Tokyo, Japan, and by a research grant from Banyu Pharmaceutical Company, Ltd., Tokyo, Japan.

REFERENCES


40. Ballantyne CM, Blazing MA, Hunninghake DB, et al. Effect of high-density lipoprotein cholesterol of maximum dose simvastatin and atorvastatin in patients with hyper-


*Address correspondence to:* Hiroshi Yoshida, MD, PhD, Division of General Medicine, Department of Internal Medicine, Kashiwa Hospital, Jikei University School of Medicine, 163-1 Kashiwashita, Kashiwa, Chiba 277-8567, Japan. E-mail: hyoshida@jikei.ac.jp