A 52-Week, Randomized, Open-Label, Parallel-Group Comparison of the Tolerability and Effects of Pitavastatin and Atorvastatin on High-Density Lipoprotein Cholesterol Levels and Glucose Metabolism in Japanese Patients with Elevated Levels of Low-Density Lipoprotein Cholesterol and Glucose Intolerance

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ABSTRACT

Background: Statin therapy has been found to produce substantial reductions in low-density lipoprotein cholesterol (LDL-C) levels, resulting in a reduced risk for cardiovascular events. Recently, research interest has focused on modification of high-density lipoprotein cholesterol (HDL-C) levels for the potential prevention of cardiovascular events. The effects of pitavastatin and atorvastatin on HDL-C have not been directly compared.

Objectives: This study compared the effects of pitavastatin and atorvastatin on HDL-C and other lipids and glucose metabolism in Japanese patients with elevated LDL-C levels and glucose intolerance. The tolerability of the 2 treatments was also compared.

Methods: This was a multicenter, open-label, parallel-group trial. Patients with LDL-C levels ≥140 mg/dL and glucose intolerance (defined according to Japanese criteria for borderline diabetes and World Health Organization criteria for impaired fasting glucose and impaired glucose tolerance) were randomly assigned to receive either pitavastatin 2 mg/d or atorvastatin 10 mg/d for 52 weeks. Levels of serum lipids and lipoproteins and measures of glucose metabolism (fasting insulin, fasting glucose, glycosylated hemoglobin, and homeostasis model assessment for insulin resistance) were obtained at baseline and at 8, 26, and 52 weeks of treatment. The effect of study drug on glucose metabolism was evaluated as a tolerability outcome. Tolerability was further assessed based on adverse events, either spontaneously reported or elicited by questioning; physical examination findings; and clinical laboratory test results. Study physicians rated the relationship of adverse events to study medication as unrelated, suspected, or probable.

Results: Two hundred seven patients were enrolled in the study, and efficacy was evaluated in 173 patients (88 pitavastatin, 85 atorvastatin). Thirty-four patients were excluded for reasons including failure to start medication or lack of ≥6 months of follow-up. Women accounted for 62% (108/173) of the evaluable population, which had a mean age of 63.3 years and a mean weight of 63.0 kg; 89% (154/173) had diabetes mellitus. The percent change in HDL-C levels

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was significantly greater in the pitavastatin group compared with the atorvastatin group (8.2 vs 2.9, respectively; $P = 0.031$), as was the percent change in apolipoprotein (Apo) A-I (5.1 vs 0.6; $P = 0.019$). The percent change in LDL-C levels was significantly lower with atorvastatin compared with pitavastatin (–40.1 vs –33.0, respectively; $P = 0.002$), as were the percent changes in non–HDL-C (–37.4 vs –31.1; $P = 0.004$), Apo B (–35.1 vs –28.2; $P < 0.001$), and Apo E (–28.1 vs –17.8; $P < 0.001$). The significant results for these parameters were unchanged when all 189 subjects who received ≥1 dose of study medication were included in the analysis, using last-value-carried-forward methodology. There were no significant differences between treatments with respect to the measures of glucose metabolism. Both statins appeared to be well tolerated. Adverse events occurred in 9% (9/96) of the pitavastatin group and 14% (13/93) of the atorvastatin group (P = NS). Two patients in the pitavastatin group and none in the atorvastatin group had an alanine aminotransferase value >3 times the upper limit of normal (P = NS).

Conclusions: In these patients with elevated LDL-C levels and glucose intolerance, 52 weeks of treatment with pitavastatin 2 mg/d was associated with significantly greater increases in HDL-C and Apo A-I levels than atorvastatin 10 mg/d. Both treatments were well tolerated. (*Clin Ther*. 2008;30:1089–1101) © 2008 Excerpta Medica Inc.

Key words: pitavastatin, atorvastatin, HDL-C, apolipoprotein A-I, statins.

INTRODUCTION

There is a large body of evidence indicating that elevated levels of low-density lipoprotein cholesterol (LDL-C) play a pivotal role in the pathogenesis of atherosclerosis and that lowering LDL-C levels reduces cardiovascular risk.[1–3] Hydroxymethylglutaryl coenzyme A–reductase inhibitors (statins) have been found to be effective in reducing LDL-C levels, resulting in a reduction in cardiovascular events.[4–9] Thus, statins are currently the first choice for the pharmacologic treatment of elevated LDL-C levels; aggressive lipid lowering with a potent statin is currently recommended, particularly for high-risk patients such as those with diabetes mellitus.[10–15] In the Collaborative Atorvastatin Diabetes Study,[14] use of atorvastatin 10 mg/d was associated with a 37% decrease in major cardiovascular events compared with placebo in patients with type 2 diabetes who had an LDL-C level ≤160 mg/dL at baseline.

Another focus of therapeutic interest in the prevention and treatment of cardiovascular events is modification of levels of high-density lipoprotein cholesterol (HDL-C).[16,17] Some primary and secondary prevention trials have reported that statins increased HDL-C levels by 5% to 15%.[5–8] Although the underlying mechanism remains to be determined, observational studies have consistently found a protective association between serum levels of HDL-C and atherosclerotic disease.[18,19] The effect of statins on HDL-C is of particular relevance in patients with diabetes, as these patients often have abnormally low levels of HDL-C and high levels of triglycerides (TG) in the presence of normal levels of LDL-C.[20,21] In the United Kingdom Prospective Diabetes Study,[22] HDL-C was the second most important predictor of the risk for coronary heart disease after LDL-C.

Pitavastatin is a potent statin that has been reported to be well tolerated and effective in reducing LDL-C levels.[23–27] In a 12-week, open-label trial,[28] reductions in LDL-C were similar with pitavastatin and atorvastatin (38% and 41%, respectively). Both pitavastatin and atorvastatin would be expected to be useful for lowering LDL-C in patients with diabetes, but their effects on HDL-C have not been directly compared. In addition, the possibility of adverse effects on glucose metabolism may be a concern with atorvastatin.[29] The present study was undertaken to compare the effects of pitavastatin and atorvastatin on HDL-C and other lipids and glucose metabolism in patients with elevated LDL-C levels and glucose intolerance. The tolerability of the treatments was also compared.

PATIENTS AND METHODS

Patients

Patients were recruited from 34 clinics and hospitals across Kyushu Island, Japan, between October 2004 and March 2007. Eligible patients were men or postmenopausal women aged ≥20 years; had LDL-C levels ≥140 mg/dL, HDL-C levels <80 mg/dL, and TG levels <500 mg/dL; and had glucose intolerance. *Glucose intolerance* was defined as receipt of pharmacologic treatment for diabetes (excluding insulin therapy) or a glucose measurement in the past 3 months indicative of glucose intolerance (ie, fasting blood glucose ≥110 mg/dL, 1-hour blood glucose ≥180 mg/dL,

or 2-hour blood glucose ≥140 mg/dL after a 75-g oral glucose challenge, or a casual blood glucose level ≥140 mg/dL). This definition was based on the criteria for borderline diabetes used in Japan[30] and on World Health Organization criteria for impaired fasting glucose and impaired glucose tolerance.[31]

The exclusion criteria included contraindications to statin use (ie, hepatic impairment or biliary tract obstruction, cyclosporine use, and use of fibrates with an abnormal renal function test result); severe renal impairment or dysfunction (serum creatinine ≥2 mg/dL); secondary hyperlipidemia associated with conditions such as hypothyroidism or Cushing's syndrome; use of steroid hormones, including topical and nasal forms; severe hypertension; cerebrovascular disease in the past 3 months; myocardial infarction or coronary artery reconstruction in the past 3 months; heart failure (New York Heart Association class 3 or higher); history of allergy or serious adverse reactions to the study drugs; poorly controlled diabetes, based on the study physician's judgment; and type 1 diabetes. Patients could also be excluded if their participation was considered inappropriate by the study physician.

Study Design

This was a multicenter, open-label, parallel-group study (**Figure 1**). After written informed consent was obtained, eligible patients were enrolled at the central registration center and were randomly allocated to receive either pitavastatin 2 mg/d or atorvastatin 10 mg/d for 52 weeks. These are the initial doses approved for use in Japan.[32,33] The treatment period was preceded by a run-in period without lipid-lowering medication of 2 to 4 weeks, an interval chosen to correspond to the typical time between clinic visits. For patients who had been taking lipid-lowering drugs before enrollment, a 4-week washout period preceded the run-in period. The study protocol was reviewed and approved by the ethics committee of each participating institution.

A computer-generated list of 220 random assignments was prepared by a statistician at the registration center, using the block method with equal assignments to the 2 treatment groups. The first 200 assignments were created in 2 blocks of 100 random assignments each, and the last 20 assignments were generated in 2 blocks of 10 random assignments each for supplemental registration. Allocation to study treatment was made according to the sequence of the randomization list, which was kept confidential throughout the study. After obtaining informed consent, study physicians reported eligible patients to the registration center by fax and were subsequently notified of the assigned drug during the run-in period. All participating physicians followed the procedures correctly.

Concomitant use of the following drugs was prohibited during the study: lipid-lowering agents other than the study drugs, immunosuppressants, azole antifungals, erythromycin, insulin preparations, and steroids. Oral antidiabetic agents were permitted as long as the dose was not changed during the study.

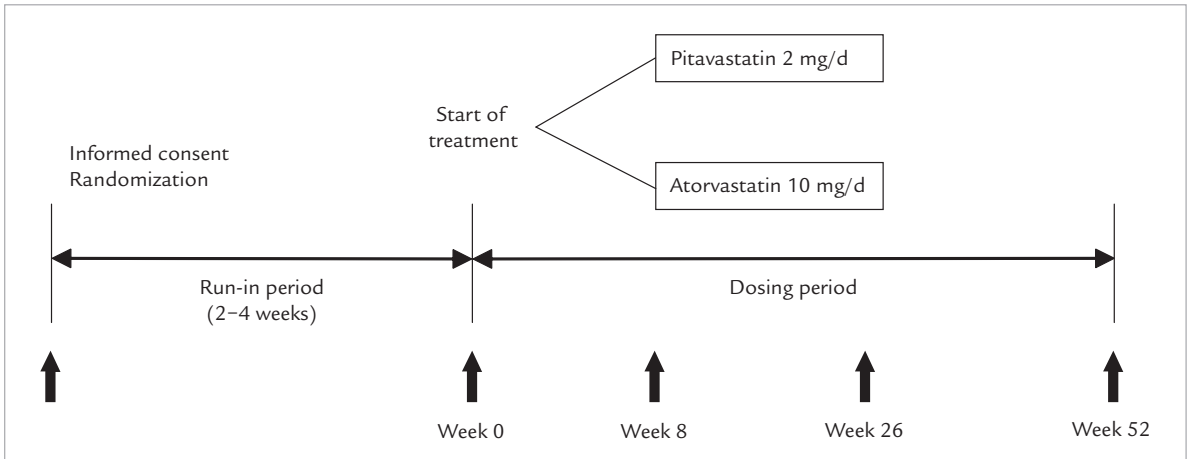

Figure 1. Study design. Large arrows signify times of blood sampling.

Adherence was assessed by asking patients to report their use of the assigned study drug at weeks 8, 26, and 52. They were given 4 options for describing their frequency of drug use in the interval between study visits: daily, 5 or 6 days per week, 3 or 4 days per week, and 1 or 2 days per week. Daily use or use on 5 or 6 days per week was considered good adherence.

Laboratory Measurements

Blood samples were collected after an overnight fast at baseline and at weeks 8, 26, and 52. A 10-mL sample of venous blood was drawn for determination of serum lipids and lipoproteins and measures of glucose metabolism. In addition, 2 mL was drawn into a tube containing sodium fluoride, sodium heparin, and disodium ethylenediaminetetraacetic acid (EDTA-2Na) for the measurement of plasma glucose levels; 2 mL into a tube containing EDTA-2Na for the measurement of plasma insulin levels; and 2 mL into a tube containing dipotassium EDTA for the determination of glycosylated hemoglobin (HbA_{1c}). Serum and plasma were separated by centrifugation at an external laboratory (SRL, Hachiohji, Tokyo, Japan), frozen on dry ice, sent to the central laboratory on the day of collection, and stored frozen at –20°C until analyzed. Blood samples for the determination of HbA_{1c} were stored at 4°C until analyzed.

Serum total cholesterol and TG levels were determined using enzymatic methods.[34,35] Serum concentrations of HDL-C were determined by the detergent selective-inhibition method (Daiichi, Tokyo, Japan),[36] and LDL-C was determined by the N-geneous assay (Daiichi Pure Chemical, Tokyo, Japan).[37] Levels of apolipoprotein (Apo) A-I, Apo B, and Apo E were determined by turbidimetric immunoassays (Daiichi Pure Chemical).[38] Serum glucose concentrations were determined by the glucose oxidase method.[39] Immunoreactive insulin was determined by an enzyme-linked immunosorbent assay, and HbA_{1c} was determined by high-performance liquid chromatography. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using the following formula: fasting blood glucose (mg/dL) × fasting insulin (μU/mL)/405.[40] HOMA-IR was not calculated when the fasting glucose level was >140 mg/dL.

All determinations were performed at a central laboratory, where they were routinely subjected to quality-control procedures. All results were forwarded to the study physicians within 3 working days.

Effectiveness Outcomes

The primary effectiveness measure was the difference in percent change in serum HDL-C concentrations between pitavastatin and atorvastatin. Secondary effectiveness measures included the percent change in other lipid parameters (LDL-C, non–HDL-C, LDL-C/HDL-C ratio, TG, Apo A-I, Apo B, Apo B/A-I ratio, and Apo E).

Tolerability Outcomes

Tolerability was assessed at each study visit and included adverse events, either spontaneously reported or elicited by questioning; physical examination findings; and clinical laboratory test results. Study physicians rated the relationship of adverse events to study medication as unrelated, suspected, or probable. These ratings were finalized by the Safety Monitoring Committee in a blinded fashion. Serious adverse events were defined as any untoward medical occurrences that resulted in death, inpatient hospitalization, a life-threatening situation, or a birth defect.

The effect of study drug on glucose metabolism was evaluated as a tolerability outcome. *Deterioration in glucose metabolism* was defined as the need to start pharmacologic treatment for diabetes, an increase in the existing drug dose for diabetes, or an elevation in HbA_{1c} (a ≥0.5% increase in the absolute value or a change in value from <6.0% to ≥6.0%). Although patients who were not receiving stable doses of oral antidiabetic medications at screening were ineligible for study participation, enrolled patients who had a change in existing antidiabetic therapy in the course of the study remained in the analytic population.

Abnormal laboratory test results were defined as values >3 times the upper limit of normal for alanine aminotranferase (ALT) or aspartate aminotranferase (AST), 10 times the upper limit of normal for creatine kinase (CK), or 1.5 times the upper limit of normal for creatinine.

Statistical Analysis

In previously published studies in Japanese subjects, pitavastatin (1–2 mg/d)[41] and atorvastatin (5–10 mg/d)[42] administered for 52 weeks were associated with increases in HDL-C of 10.7% and 2.4%, respectively. We assumed that HDL-C levels would increase by 10% with pitavastatin treatment and by 0% with atorvastatin treatment. Although a null change in HDL-C with atorvastatin was not clinically unlikely, a

null increase was assumed only for the purpose of simplicity. Because the SD for the percent change in HDL-C after treatment was not reported in the previous studies, we estimated the number of patients that was required to result in mean (SD) HDL-C values after treatment of 55 (10) mg/dL for pitavastatin and 50 (10) mg/dL for atorvastatin. This number was calculated to be 63 per group, with a 2-sided significance level of 0.05 and 80% power. Because this assumption was fairly crude and because some dropouts were anticipated, the number of patients was set at 100 per treatment group.

The primary study end point was the percent change from baseline in HDL-C at 52 weeks, which was compared between groups using a 2-sample *t* test.[43] The mean difference in percent change and 95% CI were calculated. The same method was applied to the secondary efficacy end points of percent change from baseline in LDL-C, non–HDL-C, LDL-C/HDL-C ratio, TG, Apo A-I, Apo B, Apo B/Apo A-I ratio, and Apo E. The effectiveness population included all patients for whom measurements were available at either 6 or 12 months. In the case of missing values at 12 months, 6-month values were substituted when available, as they were considered to represent long-term treatment. The time course of the percent changes from baseline was also examined at 2, 6, and 12 months.

Measures of glucose metabolism (fasting insulin, fasting glucose, HbA_{1c}, and HOMA-IR) were examined in terms of the difference in percent change at 12 months between groups. Deterioration in glucose metabolism; increases in serum AST, ALT, CK, and creatinine; and physician-reported adverse events were expressed as proportions. The Fisher exact test was used to evaluate differences between groups.[43] All statistical computations were performed using Stata release 8.0 (Stata Corporation, College Station, Texas).

RESULTS

Study Population

Two hundred seven patients were enrolled. Of these, 18 failed to return to the clinic after registration, withdrew consent, or were otherwise ineligible. One hundred eighty-nine patients (96 pitavastatin, 93 atorvastatin) were included in the safety analysis. Twelve patients discontinued treatment before 6 months because of adverse events, and 4 patients were not followed for ≥6 months. These 16 patients were excluded from the effectiveness analysis, which thus included 173 patients (88 pitavastatin, 85 atorvastatin) (**Figure 2**). Women accounted for 62% (108/173) of the effectiveness population, and 89% (154/173) had diabetes mellitus. The mean age of the population was 63.3 years, and the mean body weight was 63.0 kg.

Table I summarizes the baseline demographic and clinical characteristics of the effectiveness population. There were no significant differences between the 2 groups in terms of any parameter. Women accounted for 64% (56/88) of the pitavastatin group and 61% (52/85) of the atorvastatin group. The prevalence of diabetes mellitus in the 2 groups was 92% (81/88) and 86% (73/85), respectively. There were no significant differences between groups in terms of smoking or alcohol consumption.

The proportions of patients with good adherence in the pitavastatin group were 98% (86/88) at 8 weeks, 94% (83/88) at 28 weeks, and 93% (79/85) at 56 weeks; the corresponding values in the atorvastatin group were 100% (84/84), 96% (81/84), and 98% (80/82). There was no significant difference between groups in the proportion with good adherence at any time point.

Effectiveness

Table II summarizes the percent changes from baseline in the primary and secondary effectiveness end points after 52 weeks of treatment with pitavastatin or atorvastatin. The percent increase in HDL-C levels (the primary end point) was significantly greater in the pitavastatin group than in the atorvastatin group (8.2 vs 2.9, respectively; $P = 0.031$). The percent change in Apo A-I was also significantly greater in the pitavastatin group compared with the atorvastatin group (5.1 vs 0.6; $P = 0.019$). The atorvastatin group had significantly greater reductions compared with the pitavastatin group in terms of the percent change in LDL-C (–40.1 vs –33.0, respectively; $P = 0.002$), non–HDL-C (–37.4 vs –31.1; $P = 0.004$), Apo B (–35.1 vs –28.2; $P < 0.001$), and Apo E (–28.1 vs –17.8; $P < 0.001$). The percent changes in the LDL-C/HDL-C and Apo B/Apo A-I ratios did not differ significantly between groups, nor was there a significant difference in TG levels.

When the analysis was repeated in the 189 patients who had received ≥1 dose of study medication, carrying forward the last available values (including baseline values, if they were the last values available), the

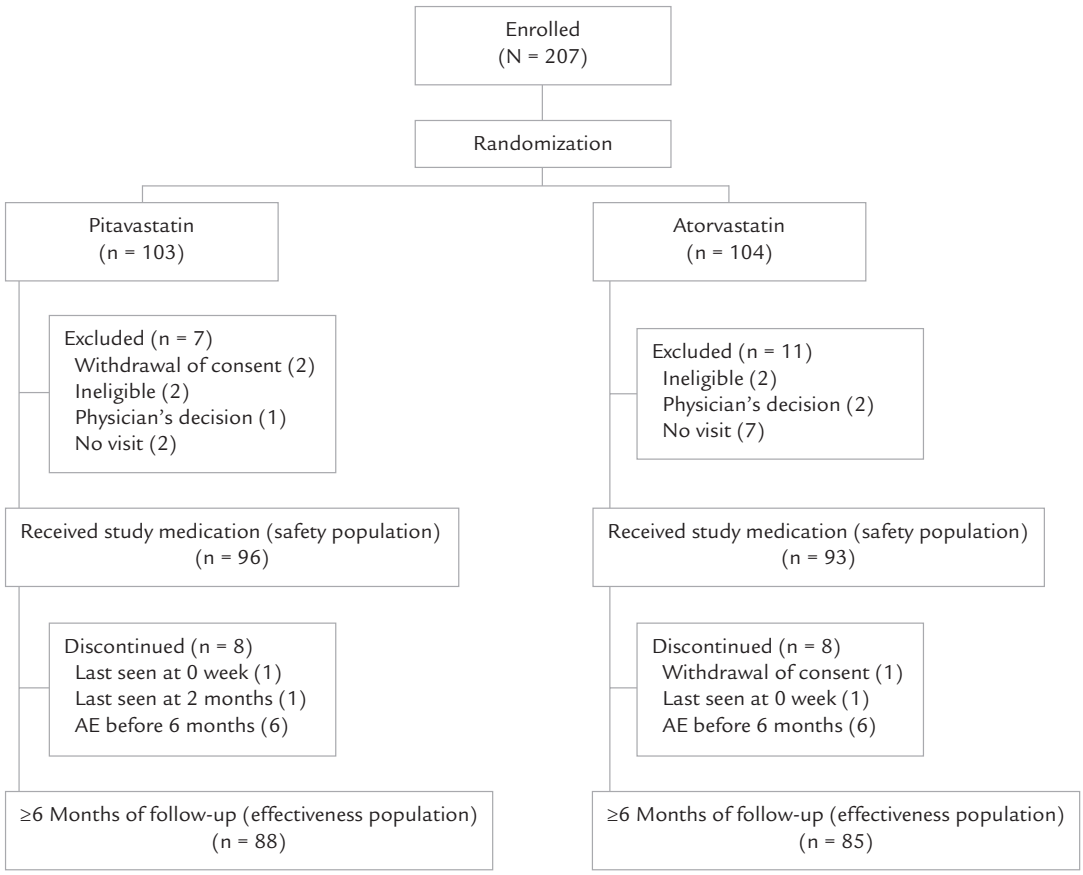

Figure 2. Disposition of study subjects. AE = adverse event.

results were similar to those in the effectiveness population, with no changes in statistical significance. For instance, the increase in HDL-C was 5.4% greater in the pitavastatin group than in the atorvastatin group (95% CI, 0.9–9.9; $P = 0.02$), and the decrease in LDL-C was 6.1% greater in the atorvastatin group compared with the pitavastatin group (95% CI, 1.4–10.8; $P = 0.01$).

HDL-C levels were significantly higher in the pitavastatin group compared with the atorvastatin group at 8 weeks ($P = 0.013$) and 52 weeks ($P = 0.034$) (**Figure 3**). Pitavastatin was associated with consistently higher levels of Apo A-I compared with the atorvastatin group at each time point evaluated (8 weeks: $P = 0.026$; 26 weeks: $P = 0.013$; 52 weeks: $P = 0.031$) (**Figure 4**).

Tolerability

There was no significant difference between pitavastatin and atorvastatin in the percent changes in fasting plasma insulin, fasting plasma glucose, HbA_{1c}, or HOMA-IR (**Table III**). The results were similar when analyzed using last-value-carried-forward methodology in the 189 patients who had received ≥1 dose of study medication.

Deterioration in glucose metabolism was evaluated in 96 patients receiving pitavastatin and 93 patients receiving atorvastatin. Initiation of drug use for diabetes or an increase in the dose of medication for diabetes occurred in 11% (11/96) of the pitavastatin group and 11% (10/93) of the atorvastatin group. Elevations in HbA_{1c} occurred in 63% (60/96) and 52% (48/93)

Table I. Demographic and clinical characteristics of study participants at baseline.

	Pitavastatin		Atorvastatin		
Variable	No. of Patients	Mean (SD)	No. of Patients	Mean (SD)	*P*
Age, y	88	62.9 (8.8)	85	63.7 (9.5)	0.55
Height, cm	87	157.4 (9.4)	84	156.4 (9.0)	0.50
Body weight, kg	88	63.3 (11.1)	83	62.8 (9.8)	0.73
Lipids, mg/dL*					
HDL-C	88	51.9 (12.4)	85	51.6 (11.1)	0.90
LDL-C	88	163.7 (23.7)	85	161.9 (27.6)	0.64
Non–HDL-C	88	195.0 (28.6)	85	195.1 (31.6)	0.97
LDL-C/HDL-C ratio	88	3.32 (0.91)	85	3.26 (0.82)	0.66
TG	88	155.1 (81.8)	85	171.9 (86.0)	0.19
Apo A-I	88	138.7 (21.8)	85	138.9 (21.4)	0.95
Apo B	88	132.8 (18.2)	85	131.4 (19.6)	0.65
Apo B/Apo A-I ratio	88	0.99 (0.23)	85	0.97 (0.20)	0.58
Apo E	88	5.3 (1.3)	85	5.6 (1.7)	0.14
Fasting insulin, μU/mL	86	9.7 (9.9)	80	12.0 (17.0)	0.29
Fasting glucose, mg/dL	86	134.8 (34.2)	79	131.7 (39.4)	0.59
HbA_{1c}, %	88	6.5 (1.2)	85	6.4 (1.0)	0.45
HOMA-IR	86	3.3 (4.3)	79	4.2 (6.9)	0.34

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; Apo = apolipoprotein; HbA_{1c} = glycosylated hemoglobin; HOMA-IR = homeostasis model assessment for insulin resistance.
*Unless otherwise specified.

of the respective groups. Overall, 65% (62/96) and 58% (54/93) of the 2 groups had a deterioration in glucose metabolism (*P* = NS).

Adverse events for which a relationship to study drug was suspected or probable occurred in 9 patients (9%) in the pitavastatin group and 13 patients (14%) in the atorvastatin group (*P* = NS). Adverse events considered related to the use of pitavastatin were double or blurred vision (n = 2), gastrointestinal symptoms (n = 2: abdominal fullness and nausea), general fatigue (n = 2), headache (n = 1), myalgia (n = 1), and pruritus (n = 1). For atorvastatin, drug-related adverse events were gastrointestinal symptoms (n = 5: appetite loss, diarrhea, abdominal pain, gastritis, and stomatitis), myalgia (n = 2), angina pectoris (n = 1), general fatigue (n = 1), headache (n = 1), shoulder stiffness (n = 1), sleep disturbance (n = 1), and thinning of the nails (n = 1). Adverse effects were responsible for 6 discontinuations of study medication in each group.

No patients had serum AST values >3 times the upper limit of normal, CK values >10 times the upper limit of normal, or creatinine values >1.5 times the upper limit of normal. Two patients in the pitavastatin group and none in the atorvastatin group had an ALT value >3 times the upper limit of normal (*P* = NS).

DISCUSSION

This study compared the effects of 52 weeks of treatment with pitavastatin 2 mg/d and atorvastatin 10 mg/d in increasing HDL-C levels in patients with elevated

Table II. Percent change in lipid measures after 12 months of treatment.*

Lipid Variable, mg/dL	% Change from Baseline, Mean (SD)		Difference in % Change, Pitavastatin Versus Atorvastatin (95% CI)	*P*
	Pitavastatin (n = 88)	Atorvastatin (n = 85)		
HDL-C	8.2 (17.1)	2.9 (14.6)	5.3 (0.5 to 10.0)	0.031
LDL-C	–33.0 (16.1)	–40.1 (13.5)	7.0 (2.5 to 11.4)	0.002
Non–HDL-C	–31.1 (16.1)	–37.4 (12.4)	6.4 (2.0 to 10.7)	0.004
LDL-C/HDL-C ratio	–37.0 (17.5)	–40.5 (16.9)	3.6 (–1.6 to 8.7)	0.176
TG	–7.1 (40.4)	–14.6 (49.2)	7.6 (–5.9 to 21.1)	0.269
Apo A-I	5.1 (13.2)	0.6 (11.4)	4.5 (0.7 to 8.8)	0.019
Apo B	–28.2 (13.9)	–35.1 (12.1)	6.8 (2.9 to 10.7)	<0.001
Apo B/Apo A-I ratio	–30.8 (15.7)	–34.5 (16.1)	3.6 (–1.1 to 8.4)	0.135
Apo E	–17.8 (21.6)	–28.1 (16.5)	10.4 (4.6 to 16.2)	<0.001

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; Apo = apolipoprotein.
*Five patients in each group had missing values at 12 months, and 6-month values were used.

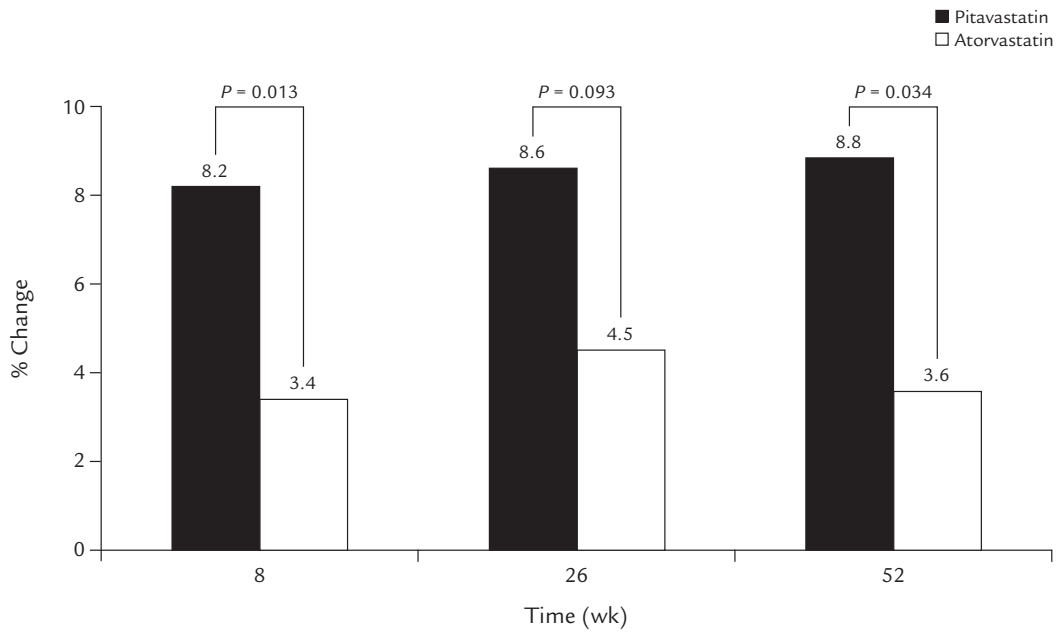

Figure 3. Percent change in high-density lipoprotein cholesterol levels over the course of the study.

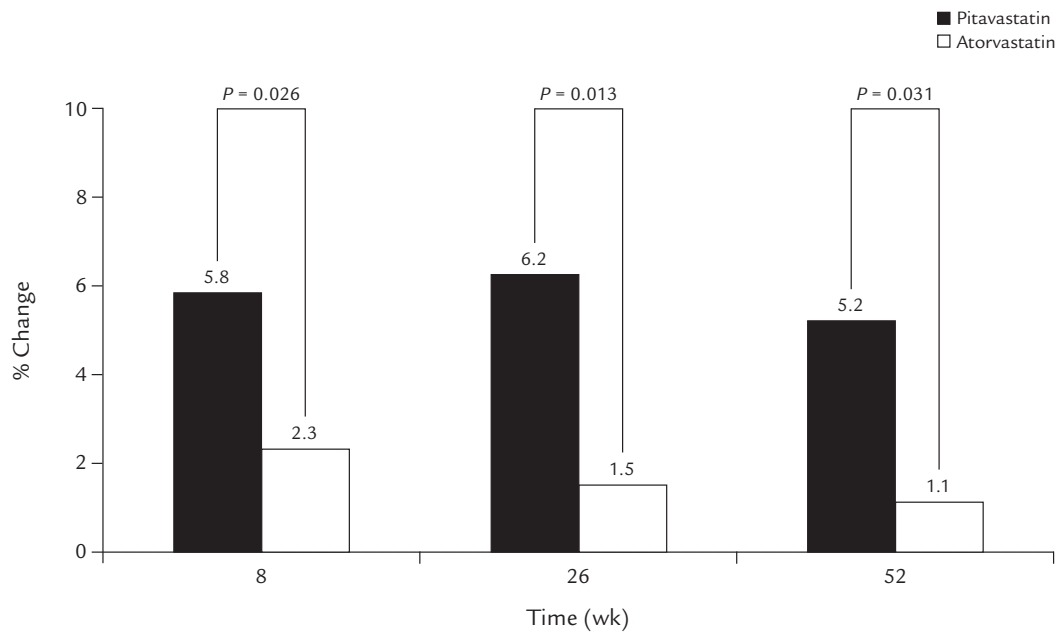

Figure 4. Percent change in apolipoprotein A-I levels over the course of the study.

Table III. Percent change in measures of glucose metabolism after 12 months of treatment.*

Variable	% Change from Baseline, Mean (SD)		Difference in % Change, Pitavastatin Versus Atorvastatin (95% CI)	*P*
	Pitavastatin	Atorvastatin		
Fasting insulin, μU/mL	5.1 (56.8)	12.2 (76.6)	–7.0 (–27.7 to 13.6)	0.50
Fasting glucose, mg/dL	3.8 (29.4)	9.8 (39.2)	–6.0 (–16.7 to 0.5)	0.27
HbA_{1c}, %	5.5 (10.8)	3.9 (9.2)	1.7 (–1.4 to 4.7)	0.28
HOMA-IR	27.0 (132.5)	36.1 (154.5)	–9.1 (–63.0 to 44.7)	0.74

HbA_{1c} = glycosylated hemoglobin; HOMA-IR = homeostasis model assessment for insulin resistance.
*Numbers of patients in the pitavastatin and atorvastatin groups differed slightly for each parameter because of missing values at 6 or 12 months: 85 and 79, respectively, for fasting insulin; 85 and 78 for fasting glucose; 88 and 85 for HbA_{1c}; and 56 and 56 for HOMA-IR. Values at 6 months were substituted for missing values at 12 months.

levels of LDL-C and glucose intolerance. Pitavastatin treatment was associated with a significantly greater increase in HDL-C levels compared with atorvastatin treatment ($P = 0.031$). Pitavastatin also was associated with a significant increase compared with atorvastatin in levels of Apo A-I ($P = 0.019$), a major constituent of HDL-C.

The effects of statins on levels of HDL-C have become a focus of research interest. In a pooled analysis of 4 trials of statins, individuals with a ≥7.5% increase

in HDL-C levels had a statistically significant regression in coronary atherosclerosis ($P < 0.001$), independent of LDL-C levels.[44] In a post hoc analysis of the Treating to New Targets study,[45] HDL-C levels during statin treatment were inversely related to the risk of cardiovascular events, even among patients with LDL-C levels <70 mg/dL.

Individual statins seem to increase HDL-C levels to different degrees. In a comparative study, simvastatin 20 mg/d was associated with a significantly greater elevation in HDL-C after 12 months compared with atorvastatin 10 mg/d ($P < 0.05$).[46] In a 6-week trial, rosuvastatin was more effective in elevating HDL-C levels than atorvastatin, simvastatin, and pravastatin (all comparisons, $P < 0.001$).[47] A multicenter, open-label study of pitavastatin reported an increase in HDL-C of ~10% after 52 weeks of treatment with the initial dose of 2 mg/d,[41] but a comparative trial found no significant difference in the increase in HDL-C between pitavastatin 2 mg/d and simvastatin 20 mg/d,[23] and another found no significant difference between pitavastatin 1 mg/d and atorvastatin 10 mg/d.[28]

During the present study, 3 patients in the atorvastatin group started insulin therapy. Insulin treatment may have increased HDL-C levels and ameliorated glucose metabolism in these patients, but the results of the analysis from which these patients were excluded did not differ from those in the full population; the percent increase in HDL-C was 5.6% greater with pitavastatin treatment compared with atorvastatin treatment (95% CI, 0.8 to 10.4), and the difference in the percent increase in HbA_{1c} between pitavastatin and atorvastatin was 1.3% (95% CI, –1.8 to 4.3).

Decreases in LDL-C ($P = 0.002$), non–HDL-C ($P = 0.004$), Apo B ($P < 0.001$), and Apo E ($P < 0.001$) were significantly greater with atorvastatin than with pitavastatin. The extent of decrease in LDL-C with pitavastatin was less than has been reported elsewhere. In a study in Japanese patients with hypercholesterolemia,[41] LDL-C decreased by 39% after 52 weeks of treatment with pitavastatin (initial dose, 2 mg/d, which could be doubled or halved). A similar reduction was reported in a study in Korean patients after 8 weeks of treatment with pitavastatin 2 mg/d.[23] Twelve weeks of treatment with pitavastatin 1 mg/d was associated with a 38% decrease in LDL-C in another trial in Japanese patients.[28] The discrepancy in LDL-C–lowering effect between the present study and previous studies may be attributable to differences in the characteristics of study subjects, adherence, or other unknown methodologic factors.

Deterioration in glucose metabolism occurred in >50% of patients in the 2 groups, and adverse effects in which a role of study drug was suspected or probable occurred in ≥10%. Because there was no placebo group, the relationship between the adverse effects and study drugs is unclear. However, considering the number of patients who discontinued study drug because of an adverse event (6 in each group), both statins appeared to be well tolerated.

This study had several limitations. The open-label design may have biased the comparison of lipid profiles and may also have affected physicians' assessment of adverse effects. Physicians' judgment was also involved in evaluation of some of the exclusion criteria; therefore, selection bias may have occurred in the recruitment of patients. Other limitations included the use of a definition of renal failure that depended on creatinine values alone, the inclusion of subjects with HDL-C levels as high as 80 mg/dL (in whom increases would not be required), and the use of 6-month data when 12-month data were unavailable.

Although pitavastatin 2 mg/d and atorvastatin 10 mg/d are the initial doses approved in Japan, these doses may not be equipotent. Pitavastatin 2 mg/d is a typical dose in Western countries as well as in Japan, but atorvastatin 10 mg/d is at the low end of the normal prescribing range in Western countries. However, higher doses of atorvastatin are unlikely to result in an increase in HDL-C beyond that observed in the present trial. In a 6-week trial conducted in the United States,[47] daily doses of atorvastatin 10, 20, 40, and 80 mg were associated with respective increases in HDL-C of 5.7%, 4.8%, 4.4%, and 2.1%.

CONCLUSIONS

In this open-label study in which patients with elevations in LDL-C levels and glucose intolerance received 52 weeks of treatment with pitavastatin 2 mg/d or atorvastatin 10 mg/d, levels of HDL-C and Apo A-I were significantly increased in the pitavastatin group compared with the atorvastatin group. Both treatments were well tolerated.

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