Original Article

Effects of Pravastatin and Atorvastatin on HDL Cholesterol and Glucose Metabolism in Patients with Dyslipidemia and Glucose Intolerance: The PRAT Study

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***Aims*: While statins have the property of increasing high-density lipoprotein cholesterol (HDL-C) in addition to lowering low-density lipoprotein cholesterol (LDL-C), a potential adverse effect on glucose metabolism has raised a concern over statin therapy. In a comparative trial, we investigated the effects of low-dose pravastatin and atorvastatin on HDL-C and glucose metabolism in patients with elevated LDL-C levels and glucose intolerance.**

***Methods*: Eligible patients were men aged ≥20 years or postmenopausal women who had LDL-C ≥140 mg/dL, HDL-C <80 mg/dL, and triglycerides <500 mg/dL and who had glucose intolerance. The patients were randomly allocated to either pravastatin (10 mg/day) or atorvastatin (10 mg/day) treatment for 12 months in an unblinded fashion. The percent changes from the baseline were compared between the treatments.**

***Results*: Of 202 patients who were randomized to either of the two treatments, 195 patients started the study medication, and 187 patients underwent the follow-up measurements at 6 or 12 months (pravastatin, $n=93$; atorvastatin, $n=94$). HDL-C increased by 4.3% ($p=0.03$) in the pravastatin group and by 5.8% ($p=0.0005$) in the atorvastatin group and showed no between-group difference ($p=0.38$). LDL-C decreased substantially in both groups (pravastatin, 21.5%; atorvastatin, 35.5%), and the decrease was much greater in the atorvastain group ($p<0.0001$). HbA1c slightly increased in both groups, but showed no measurable difference in the increase between the two treatments ($p=0.30$).**

***Conclusion*: Pravastatin and atorvastatin of 10 mg per day each increased HDL-C by almost the same extent. These two statins did not show a differential effect on glucose metabolism.**

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Key words; Pravastatin, Atorvastatin, HDL-C, Statins, Glucose

Introduction

Statins, HMG-CoA reductase inhibitors, produce a substantial decrease in low-density lipoprotein cholesterol (LDL-C) and are highly effective in reducing the risk of cardiovascular diseases[1, 2]. In addition to the LDL-C lowering effect, some statins have the property of increasing high-density lipoprotein cholesterol (HDL-C), which may be protective against atherosclerosis[3]. For instance, earlier prevention trials have consistently shown that simvastatin or pravastatin treatment results in a moderate increase in HDL-C[4-8]. The effect of statins on HDL-C has an impor-

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tant implication in the treatment of hypercholesterolemia among patients with diabetes mellitus, because abnormally low levels of HDL-C as well as high levels of triglycerides (TG) are often observed in diabetic patients[9]. Low levels of HDL-C have been shown to be an important predictor of coronary events in diabetic patients[10, 11].

While stains decrease the risk of cardiovascular diseases in both diabetic and nondiabetic patients[12-14], a potential adverse effect on glucose metabolism has been a matter of concern regarding statin therapy[15]. In a comparative trial, we investigated the effects of low-dose pravastatin and atorvastatin (10 mg/day each) on HDL-C levels, glucose metabolism, and tolerability in patients with elevated LDL-C levels and glucose intolerance. The trial was named PRAT, a combination of the first two letters of each drug.

Patients and Methods

Patients

The patients were recruited at 33 clinics and hospitals across the Kyushu Region, Japan between October 2005 and September 2006. Eligible patients were men aged ≥20 years or postmenopausal women who had LDL-C ≥140 mg/dL, HDL-C <80 mg/dL, and TG <500 mg/dL and who had glucose intolerance. Glucose intolerance was defined as diabetes under pharmacological treatment other than insulin; fasting plasma glucose ≥110 mg/dL in the past 3 months; 1-hour plasma glucose ≥180 mg/dL or 2-hour plasma glucose ≥140 mg/dL in a 75 g oral glucose tolerance test performed in the past 3 months; or a casual plasma glucose ≥140 mg/dL. This definition was based on the criteria for borderline diabetes in Japan[16] and for impaired fasting glucose and impaired glucose tolerance of the World Health Organization criteria[17].

Patients with the following conditions were not eligible: poorly controlled diabetes mellitus (hemoglobin A1c ≥9.0%); contraindications specified for statin use (i.e., severe hepatic impairment, biliary tract obstruction, and cyclosporine use); severe renal impairment (serum creatinine ≥2 mg/dL); secondary hyperlipidemia associated with conditions such as hypothyroidism or Cushing's syndrome; use of steroid hormones; severe hypertension; cerebrovascular disease in the past 3 months; myocardial infarction or coronary artery reconstruction in the past 3 months; heart failure of New York Heart Association class ≥3 or higher; and a history of allergy or serious adverse reactions to the study drugs. Patients were also excluded if their participation was considered inappropriate by the study physician.

Study Design and Procedures

The PRAT study was a multicenter, open-label parallel-group study. After written informed consent was obtained, eligible patients were enrolled at the central registration center and were randomly allocated to either pravastatin 10 mg/day or atorvastatin 10 mg/day for 12 months. The medication with the study drug was preceded by a run-in-period of 2 to 4 weeks without lipid-lowering drugs. A 4-week washout period was performed if the patients had taken lipid-lowering drugs before enrollment. The study protocol was approved by the institutional review board 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 4 blocks of 50 random assignments each, and the last 20 assignments were generated in one block for supplemental registration. Allocation to a study treatment was performed according to the sequence of the randomization list, which was kept confidential throughout the study. Study physicians reported eligible patients to the registration by fax and were notified of an assigned treatment during the run-in-period. All study physicians followed the procedures correctly.

Use of oral antidiabetic drugs was allowed, but it was requested that the dose be kept unchanged during the study period. The following drugs were not allowed to be used: lipid-lowering drugs other than pravastatin and atorvastatin, insulin, steroids, erythormycine, immunosuppressive agents, and antifungal agents.

Compliance with the study drug was assessed at each study visit (1, 6, and 12 months) on the basis of the patients' report. They were given 4 options for describing their frequency of drug use in the interval between the 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 5-6 days per week was considered good adherence.

Laboratory Measurements

Peripheral blood samples were obtained after an overnight fast at baseline and 1 month, 6 months, and 12 months of treatment. A 10-mL sample of venous blood was drawn for determination of serum lipids, lipoproteins, and insulin. In addition, two samples of 2 mL were obtained for the measurements of plasma glucose levels and glycosylated hemoglobin (HbA1c). Serum and plasma were separated by centrifugation at an external laboratory (SRL Fukuoka Branch, Fukuoka), frozen on dry ice, sent to the central laboratory

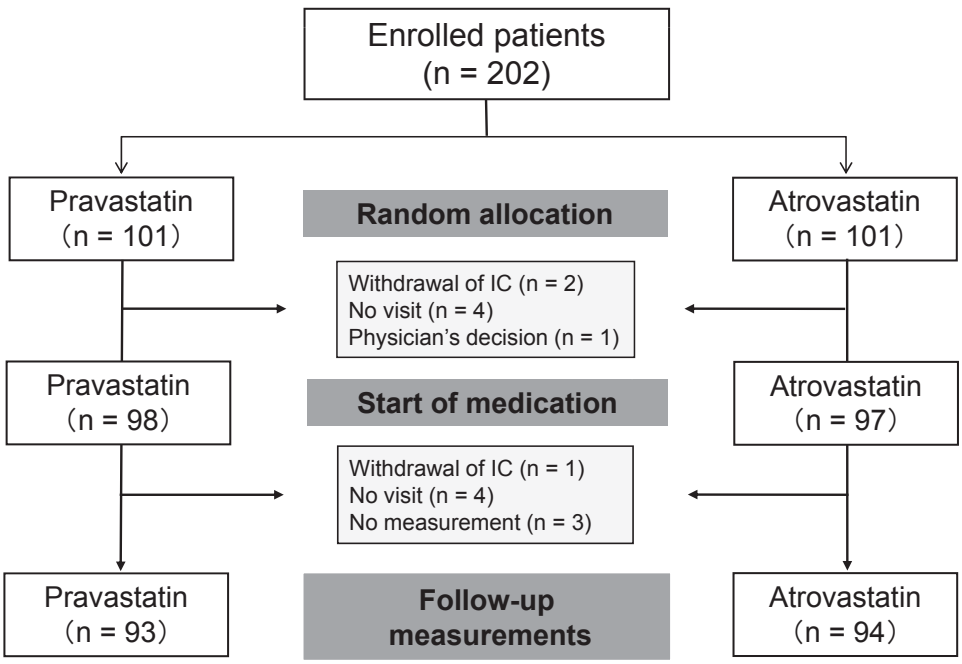

Fig. 1. Enrollment of the patients and outcomes.

(SRL, Tokyo) on the day of collection, and stored frozen at −20℃ until analysis. Blood samples for the determination of HbA1c were stored at 4℃ until analyzed. Sera for high-sensitivity C-reactive protein (hs-CRP) and high-molecular-weight (HMW) adiponectin were stored at −80℃ until completion of the trial.

Serum total cholesterol and TG levels were determined using enzymatic methods. Serum concentrations of HDL-C were determined by the detergent selective-inhibition method and LDL-C was determined by the N-geneous assay, each using commercial reagents (Daiichi Pure Chemical, Tokyo). Levels of apolipoprotein (Apo) A-I, Apo B, and Apo E were determined by turbidimetric immunoassays (Daiichi Pure Chemical, Tokyo)[18]. Serum glucose concentrations were determined by the glucose oxidase method. Immunoreactive insulin was determined by an enzyme-linked immunosorbent assay. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated by dividing the product of fasting plasma glucose (mg/dL) and fasting insulin (μU/mL) by 405[19]. When serum insulin was >30 μU/mL, measurements of glucose, insulin, and TG were discarded because the non-fasting status was dubious. HbA1c was assayed using latex agglutination turbidimetry on an autoanalyzer (JEOL, Tokyo, Japan)[20]. Serum concentrations of hs-CRP were measured using the latex enhanced immunonephelometric assay on a Dade Behring BN II nephelometer (Siemens Healthcare Diagnostics, Marburg, Germany)[21]. Measurements of hs-CRP ≥10 mg /L were not used in the statistical analysis because such values are indicative of acute inflammatory illness[22]. HMW adiponectin concentrations were assayed by the two-step sandwich ELISA method[23], using a commercial kit (Fuji Rebio Inc., Tokyo). All determinations were performed at a central laboratory (SRL, Tokyo), where they were routinely subjected to quality-control procedures. All results except for hs-CRP and HMW adiponectin were forwarded to the study physicians within 3 working days.

Statistical Analysis

The sample size was determined to detect a mean difference of at least 5% in the percent change of HDL-C at 12 months between pravastatin and atorvastatin groups under the assumption of standard deviation of 10%. With allowance for a 5% dropout rate, we estimated that a sample size of 100 patients in each group would provide a statistical power of 80% with a 2-tailed significance level of 0.05.

The primary effectiveness measure was the change in serum HDL-C concentrations at 12 months after the treatment. Secondary effectiveness measures included changes in other lipid parameters (LDL-C, non-HDL-C, TG, Apo A-I, Apo B, and Apo E) and glucose metabolism parameters (fasting plasma insulin, fasting plasma glucose, HOMA-IR, and HbA1c).

Table 1. Characteristics of the study subjects

Variable	Pravastatin ($n=93$)	Atorvastatin ($n=94$)	p^*
Male, n (%)	39 (41.9)	31 (33.0)	0.23
Age (year), mean ± SD	64.7 ± 9.6	64.6 ± 9.5	0.76
Weight (kg), mean ± SD†	62.1 ± 11.7	59.3 ± 11.6	0.10
Smoking, n (%)	17 (18.3)	16 (17.0)	0.85
Alcohol use, n (%)	28 (30.1)	30 (31.9)	0.88
Comorbid condition, n (%)			
Heart disease	14 (15.1)	18 (19.1)	0.56
Diabetes mellitus	67 (72.0)	69 (73.4)	0.87
Use of antidiabetic drug	48 (51.6)	59 (62.8)	0.14
Hypertension	52 (55.9)	48 (51.1)	0.56
Prior history, n (%)			
Myocardial infarction	5 (5.4)	6 (6.4)	1.00
Coronary angioplasty	3 (3.2)	6 (6.4)	0.50
Cerebral infarction	5 (5.4)	6 (6.4)	1.00

IGT: impaired glucose tolerance.
*Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.
†Data were missing for 2 patients in the pravastatin group and one patient in the atorvastatin group.

When the measurements at 12 months were not available, the measurements at 6 months were used for substitution, in accordance with the last observation carried forward (LOCF) method. Thus, the effectiveness population included all patients for whom measurements were available at either 6 or 12 months.

Tolerability was assessed by means of adverse events reported by study physicians and clinical laboratory tests at the study visits. Study physicians rated the relationship of adverse events with the study medication as unrelated, suspected, or probable. Serious adverse events were defined as any untoward medical occurrences that resulted in death, hospitalization, or a life-threatening condition. The effect of the study drugs on glucose metabolism was also evaluated as a tolerability outcome. Deterioration in glucose metabolism was defined as an enhanced pharmacological treatment for diabetes mellitus (start of pharmacological treatment, increase in the dose, addition of a different drug, or change to a more potent drug) or an elevation in HbA1c (an increase of ≥0.5% in the absolute value or a change in value from <6.0% to >6.0%). Abnormal laboratory test results were defined as values >3 times the upper limit of normal for alanine aminotransferase (ALT) or aspartate aminotransferase (AST), 10 times the upper limit of normal for creatine kinase (CK), or 1.5 times the upper limit of normal for creatinine.

Baseline characteristics were examined by using the mean (SD) or proportion, and the between-group comparison was tested by the Wilcoxon rank-sum test or Fisher's exact test. The outcome variables were evaluated by the percent change at 12 months from the baseline. The mean (SD) percent change within each group is presented. The within-group difference and between-group difference in the percent change were tested by the Wilcoxon signed rank test and Wilcoxon rank-sum test, respectively. All statistical computations were performed using Stata release 10.0 (Stata Corporation, College Station, Texas).

Results

Two hundred two patients were randomized to either of the two treatments, and 195 patients started the study medication (**Fig. 1**). Of these, 187 patients underwent the follow-up measurement at 6 or 12 months and were included in the effectiveness population (pravastatin, $n=93$; atorvastatin, $n=94$). Among the 187 patients, one patient was taking fenofibrate (pravastatin group) and 6 patients had HbA1c ≥9.0% at the baseline (1 in the pravastatin group and 5 in the atorvastatin group).

Table 1 summarizes the demographic and clinical characteristics of the effectiveness population. The two groups were very similar with respect to the background characteristics. Patients under medication for diabetes mellitus accounted for 52% in the pravastatin group and 62% in the atorvastatin group. There was no measurable difference in any of the lipid profiles and glucose metabolism parameters at baseline between the two groups (**Table 2**).

Table 2. Serum lipid profiles and glucose metabolism parameters at baseline in pravastatin and atorvastatin treatments

Variable	Mean (SD)		p^*
	Pravastatin ($n=93$)	Atorvastatin ($n=94$)	
HDL-C (mg/dL)	50.5 (11.9)	51.4 (11.6)	0.42
LDL-C (mg/dL)	161.6 (26.7)	160.9 (32.9)	0.95
Non-HDL-C (mg/dL)	196.2 (32.6)	195.1 (37.7)	0.78
LDL-C/HDL-C	3.35 (0.87)	3.27 (1.00)	0.44
TG (mg/dL)†	179.5 (90.0)	165.4 (84.5)	0.27
ApoA-I (mg/dL)	136.7 (22.6)	138.7 (23.5)	0.55
ApoB (mg/dL)	129.1 (18.8)	131.3 (22.3)	0.36
ApoB/ApoA-I	0.97 (0.23)	0.98 (0.27)	0.99
ApoE (mg/dL)	5.40 (1.30)	5.37 (1.43)	0.57
Fasting plasma glucose (mg/dL)†	125.1 (31.4)	134.6 (58.4)	0.88
Fasting serum insulin (μU/mL)†	8.62 (5.67)	9.03 (6.08)	0.68
HOMA-IR†	2.65 (1.75)	3.30 (3.97)	0.59
HbA1c (%)	6.21 (0.92)	6.52 (1.29)	0.09

HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol; TG: triglycerides, Apo: apolipoprotein, HOMA-IR: homeostasis model assessment insulin resistance.
*Based on Wilcoxon rank-sum test.
†Data were missing for 13 patients in the pravastatin group and 11 patients in the atorvastatin group.

The proportions of patients with good adherence (daily or 5-6 days per week) were 98% (91/93) at 1 month, 95% (88/93) at 6 months, and 93% (83/89) at 12 months in the pravastatin group; the corresponding values in the atorvastatin group were 97% (91/94), 96% (88/92), and 95% (82/86), respectively. There was no significant difference between the groups in the proportion with good adherence at any time point. Overall, the average number of days of using the study drug was 6.7 days per week in each group.

Primary Outcome

The percent changes of serum HDL-C levels at 12 months are shown in **Table 3**. HDL-C increased slightly, but statistically significantly, in both groups, and there was no between-group difference in the increase in HDL-C. The increase in HDL-C was observed at 1 month in both groups and was slightly attenuated at 6 and 12 months (**Fig. 2**). Although the between-group difference in HDL-C concentrations was not statistically significant at each point of time, HDL-C concentrations were consistently higher during treatment with atorvastatin.

Secondary Outcomes

Serum Lipids and Apoproteins

Both pravastatin and atorvastatin treatments resulted in substantial decreases in LDL-C, non-HDL-C, and the LDL-C/HDL-C ratio, and the decreases were much greater in the latter than in the former (**Table 3**). A nearly 20% decrease was observed for TG in the atorvastatin group while the decrease was 6% in the pravastatin group, but the difference between the two group was not statistically significant. Apo A-I showed a change similar to that of HDL-C. Apo B, the ratio of Apo B to A-I, and Apo E also showed greater decreases in atorvastatin treatment, while the decreases in pravastatin treatment were also marked.

The mean concentrations of LDL-C decreased markedly at 1 month in both groups and were almost constant during the treatment period (**Fig. 2**). LDL-C concentrations during the treatment were highly significantly lower in the atorvastatin group.

Changes in Glucose Metabolism Parameters

Fasting glucose, fasting insulin, and HOMA-IR showed no measurable change from the baseline with either pravastatin or atorvastatin treatment. HbA1c increased relatively by 2% in the pravastatin group and approximately 4% in the atorvastatin group, the increases being statistically significant. Although the increase in HbA1c was slightly greater in the atorvastatin group, the between-group difference was far from statistically significant.

There was little change in HbA1c concentrations at 1 month in either treatment group, but it had increased at 6 months in both groups (**Fig. 3**). HbA1c concentrations tended to decrease during the latter 6 months in the pravastatin group, but not in the atorv-

Table 3. Percent change of serum lipids and glucose metabolism parameters from baseline after 12-month treatment

Variable	Pravastatin			Atorvastatin			Between-group
	n*	Mean (SD)	p†	n*	Mean (SD)	p†	p‡
HDL-C	93	4.3 (20.8)	0.03	94	5.8 (15.3)	0.0005	0.38
LDL-C	93	−21.5 (17.3)	<0.0001	94	−35.5 (19.0)	<0.0001	<0.0001
Non-HDL-C	93	−17.6 (15.3)	<0.0001	94	−32.3 (18.4)	<0.0001	<0.0001
LDL-C/HDL-C	93	−22.6 (19.5)	<0.0001	94	−37.9 (20.4)	<0.0001	<0.0001
TG	80	−4.4 (45.4)	0.15	83	−20.2 (30.1)	<0.0001	0.11
ApoA-I	93	2.8 (15.1)	0.02	94	2.7 (11.9)	0.02	0.86
ApoB	93	−15.5 (15.0)	<0.0001	94	−30.9 (16.9)	<0.0001	<0.0001
ApoB/ApoA-I	93	−16.0 (20.0)	<0.0001	94	−32.0 (17.4)	<0.0001	<0.0001
ApoE	93	−9.9 (22.7)	<0.0001	94	−23.9 (19.6)	<0.0001	0.0001
Fasting glucose	80	3.5 (19.8)	0.30	83	6.1 (27.6)	0.41	0.84
Fasting insulin	80	29.3 (189)	0.93	83	32.5 (150)	0.51	0.58
HOMA-IR	80	44.5 (280)	0.71	83	55.5 (231)	0.26	0.58
HbA1c	93	1.8 (7.4)	0.002	94	4.2 (13.4)	0.002	0.30

HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglycerides, Apo: apolipoprotein, HOMA-IR: homeostasis model assessment insulin resistance.
*6-month measurements were used for missing values at 12 months: n=6 in the pravastatin group and n=9 in the atorvastatin group for lipids except TG and HbA1c; n=7 in the pravastatin group and n=10 patients in the atorvastatin group for TG, fasting glucose and insulin, and HOMA-IR.
†Within-group comparison based on Wilcoxon sign-rank test.
‡Between-group comparison based on Wilcoxon rank sum test.

astatin group. The mean percent changes were −0.3% at 1 month, 3.7% at 6 months, and 1.1% at 12 months in the pravastatin group while the respective values were −0.3%, 3.6%, and 4.5% in the atorvastatin group. The between-group difference in the percent change of HbA1c was not statistically significant at either 1 month (p=0.87) or 6 months (p=0.71), and nearly significant at 12 months (p=0.07). The change in body weight also showed a small difference between the groups at 12 months (p=0.06), but not at 1 month (p=0.81) or 6 months (p=0.78). At 12 months, body weight had decreased by 0.7 kg on average in the pravastatin group (p=0.07) and increased by 0.4 kg in the atorvastatin group (p=0.36). With adjustment for the change in body weight, the between-group difference in the percent change of HbA1c at 12 months was slightly attenuated; the adjusted mean percent changes were 1.3% in the pravastatin group and 4.4% in the atorvastatin group (p=0.08).

CRP and Adiponectin

Neither hs-CRP nor HMW adiponectin showed a clear change after treatment with pravastatin or atorvastatin., and there was no between-group difference in the change of hs-CRP or HMW adiponectin after treatment (**Table 4**).

Tolerability

Tolerability was evaluated in patients who started the study drug (98 in the pravastatin group and 97 in the atorvastatin group). Adverse effects reported by the study physicians are summarized in **Table 5**. Serious adverse effects were one suicide and hospitalization of 3 patients (spine fracture, gastric cancer, and cerebral infarction). The latter 3 patients continued medication with the study drug for 12 months, however. One patient taking pravastatin discontinued the medication for diarrhea, and 3 in the atorvastatin treatment did so for constipation, myalgia, and lowered LDL-C.

Deteriorated glucose metabolism was observed in 30 (30.6%) in the pravastatin group and in 41 (42.3%) in the atorvastatin group (p=0.10). Of these patients, 7 in the pravastatin group and 14 in the atorvastatin enhanced the regimen of antidiabetic medication (p=0.11). None showed elevated ALT or AST (>3 times the upper limit of normal range) or elevated CK (>10 times the upper limit of normal range) at the follow-up study visits. Elevated creatinine (>1.5 times the upper limit of normal range) was observed among 2 patients in the atorvastatin group and none in the pravastatin group.

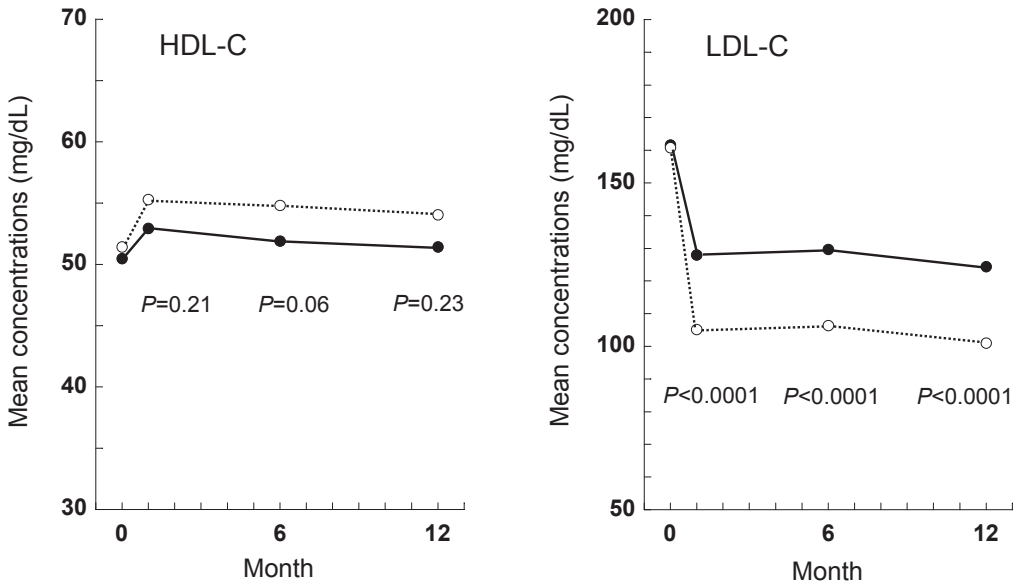

Fig. 2. Mean concentrations of serum high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) by month of treatment with pravastatin (closed circle and solid line) and atorvastatin (open circle and dotted line). The numbers of patients (pravastatin/atorvastatin) were 92/93 at 1 month, 93/93 at 6 months, and 87/85 at 12 months. *P* values represent the between-group comparison during the treatment.

Discussion

In a comparative trial of low doses of pravastatin (10 mg) and atorvastatin (10 mg), both statins increased HDL-C by almost the same extent while the reductions of LDL-C and non-HDL-C were substantially greater in the treatment with atorvastatin. The present study also showed that pravastatin and atorvastatin had a similar effect on Apo A-I while their effects on Apo B and Apo E were substantially different. Fasting glucose and insulin showed no measurable change after either of the treatments, but HbA1c increased in both of the treatments without a statistically significant between-group difference.

The 4.3% increase in HDL-C observed with pravastatin treatment is in agreement with the previous observation. Pravastatin 10 mg per day resulted in a 5% increase in HDL-C after one-year treatment in the MEGA Study in Japan[24]. An increase in HDL-C by pravastatin 40 mg per day was also 5% during long-term treatment in Western populations[6-8]. On the other hand, the effect of atorvastatin on HDL-C varied with studies. Atorvastatin 10 mg per day did not change HDL-C after 6 months or 12 months of treatment or during longer treatment[25]. Even 80 mg per day of atorvastatin did not result in a measurable increase in HDL-C in either long-term or short-term treatment[26, 27]. In contrast, a 4-week cross-over trial of

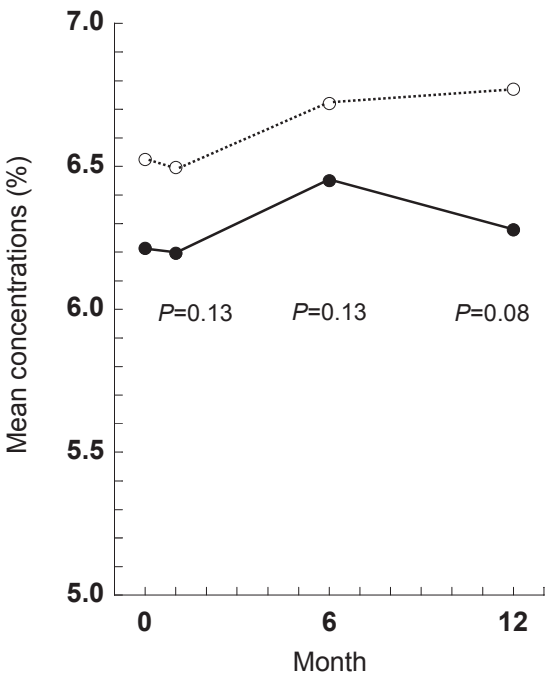

Fig. 3. Mean concentrations of HbA1c by month of treatment with pravastatin (closed circle and solid line) and atorvastatin (open circle and dotted line). The numbers of patients (pravastatin/atorvastatin) were 92/93 at 1 month, 93/93 at 6 months, and 87/85 at 12 months. *P* values represent the between-group comparison during the treatment.

Table 4. Baseline concentrations of high-sensitivity C-reactive protein (hs-CRP) and high-molecular weight (HMW) adiponectin and their percent changes after 6-month or 12-month treatment

Variable	Pravastatin	Atorvastatin	Between-group comparison*
hs-CRP			
Number of patients†	84	87	
Baseline (mg/L), mean (SD)	1.55 (1.91)	1.06 (1.21)	$p=0.09$
Percent change, mean (SD)	84.1 (410)	7.5 (110)	$p=0.15$
Percent change, median (IQR)	−11.4 (−44, 40)	−29.8 (−54, 21)	$p=0.15$
Within-group comparison	$p=0.89$	$p=0.09$	
HMW adiponectin			
Number of patients‡	90	91	
Baseline (μ/mL), mean (SD)	6.34 (5.47)	6.33 (4.66)	$p=0.62$
Percent change, mean (SD)	15.9 (69.1)	22.0 (108)	$p=0.78$
Percent change, median (IQR)	2.5 (−13, 26)	1.4 (−13, 25)	$p=0.78$
Within-group comparison	$p=0.09$	$p=0.24$	

*Based on Wilcoxon rank sum test.
†Measurements at 6 months: $n=21$ in pravastatin group and $n=22$ in atorvastatin group.
‡Measurements at 6 months: $n=23$ in each group.

20 patients with coronary heart disease showed statistically significant increases of 8-11% in HDL-C for both pravastatin and atorvastatin treatments at two doses (20 mg and 40 mg each)[28]. In that study, the baseline HDL-C concentrations were as low as 39 mg/dL[28]. In a 6-week, parallel-group trial[29], a 6% increase in HDL-C was observed for atorvastatin 10 mg per day, but the increase in HDL-C was attenuated gradually with increasing doses. In a comparative trial of atorvastatin and pitavastatin[30], a 2.9% increase in HDL-C was observed among 85 patients after 12-month treatment with atorvastatin.

It may be argued that the eligibility criterion for HDL-C (<80 mg/dL) was too high in the present study. The effect of statins on HDL-C may be more relevant to patients with low HDL-C concentrations. When the patients were stratified into low HDL-C (<50 mg/dL) and high HDL-C (≥50 mg/dL) groups at the median of the baseline concentrations, the increases in HDL-C were almost confined to the low HDL-C group; the mean percent increases at 12 months (LOCF method) were 8.8% (SD 24.7%, $p=0.002$) in the pravastatin treatment and 9.3% (SD 15.7%, $p=0.0002$) in the atorvastatin treatment, while the corresponding values in the high HDL-C group were −1.1% (SD 13.1, $p=0.79$) and 2.8% (SD 14.5%, $p=0.19$), respectively. There was no between-group difference in the percent change in either low ($p=0.65$) or high ($p=0.27$) HDL-C group, however.

Possible beneficial or adverse effects of statin use on glucose metabolism have attracted considerable interest in the past years. While pravastatin was shown to be associated with a lower risk of incident diabetes mellitus in the WOSCOP study[31], a sub-analysis in the PROVE-IT study showed a greater deterioration of HbA1c with atorvastatin 80 mg per day as compared with pravastatin 40 mg per day[32]. According to recent meta-analyses, statin therapy may confer a small increase in the risk of diabetes mellitus[33, 34], and an increased risk, if any, may be associated with high-dose statin therapy[35].

Dose-dependent detrimental effects of atorvastatin on insulin and HbA1c were documented in a trial of 2-month treatment[27]. A high dose of atorvastatin (80 mg/day) resulted in increases in insulin levels and glycated albumin after 6-week treatment[36]. A lower dose of atorvastatin (20 mg per day) did not alter insulin concentrations, HOMA-IR, or HbA1c after 12-week treatment[37]. In another trial of an 8-week treatment[38], however, atorvastatin (20 mg per day) resulted in a 3.0% increase in HbA1c, while no such increase was noted with rosuvastatin (10 mg/day). Insulin and HOMA-IR did not change at all in either group[38]. In a meta-analysis of insulin sensitivity, pravastatin (10-40 mg/day) improved insulin sensitivity while atorvastatin (10-40 mg/day) showed no alteration in insulin sensitivity[39].

It is hypothesized that the Japanese may be more susceptible to the risk of diabetes mellitus than Caucasians because of lower insulin secretion[40, 41]. It is thus an important issue whether statins have any adverse effects on glucose metabolism in the Japanese. Observational studies in Japan showed that atorvastatin 5-10 mg per day, but not pravastatin 5-10 mg per day, was

Table 5. Adverse effects (AE) reported by study physicians

Classification	Individual adverse effects (no. of episodes)	
	Pravastatin	Atorvastatin
Death		Suicide (1)
Hospitalization	Gastric cancer (1)	Cerebral thrombosis (1), spine fracture (1)
Glucose metabolism	Enhanced medication (7)*	Enhanced medication (14)*
Cardiovascular diseases	Atrial fibrillation (1)	Elevated BP (2)
Gastrointestinal diseases/symptoms	Gastritis (1), constipation (1), diarrhea (1), gastric discomfort (1)	Gastritis (1), peptic ulcer (2), esophagitis (2), stomatitis (1), infectious gastroenteritis (1), constipation (1), enema (1)
Musculo-skeletal diseases	Spondylosis (1), osteoarthritis (1), temporomandibular joint (1), trigger finger (1)	Myositis of upper arm (2), myalgia (1), lumbago (1), cervico-omo-brachial syndrome (1), stiff shoulder (1)
Urological/dermatological diseases	Cystitis (1), neurogenic bladder (1), tenea unguim (1), eczema (1)	Cystitis (1), neurogenic bladder (1), tenea unguim (1)
Laboratory changes	Elevated CPK (2), hyperuricemina (1), elevated TG (1)†	Elevated CPK (1), elevated AST/ALT (1), lowered LDL-C (7)
Others	Insomnia (1), URT infection (3), incised wound (1)	Insomnia (2), migraine (1), URT infection (2), fever (1), edema (1)

AST: asparatae aminotransferase, ALT: alanine aminotransferase, CPK creatine phosphokinase, LDL-C: low-density lipoprotein cholesterol, TG: triglycerides,
UTR: urinary tract infection.
*See the text for elevation in HbA1c without enhanced medication.
†Reported for a patient under medication with fenofibrate at enrollment.

associated with deterioration of HbA1c and other parameters in patients with and without glucose intolerence[42-44]. In a randomized control trial of patients with impaired glucose tolerance as determined by a 75-g oral glucose tolerance test[45], 6-month treatment with pravastatin (10 mg per day) was associated with improvement of HbA1c, HOMA-IR, and post-load plasma glucose as compared with dietary counseling (control). In a cross-over trial comparing pravastatin and atorvastatin (each 10 mg per day) among patients with early-stage type 2 diabetes[46], HbA1c and 2-hour post-load plasma glucose, but not fasting glucose, fasting insulin, and HOMA-IR, were lowered after 12-week treatment with pravastatin as compared with atorvastatin. The present study failed to corroborate the previous observation that pravastatin was more favorable for glucose metabolism than atorvastatin.

More than half of the patients were under medication for diabetes in the present study. It may be difficult to find any difference in the effect on glucose metabolism between the two statins in such patients. Thus, we performed a stratified analysis for patients taking medication for diabetes ($n=80$) and those not ($n=107$). HbA1c increased more markedly in the latter group, but the changes did not measurably differ by treatment in either group. In the patients without antidiabetic drugs, the mean percent change in HbA1c at 12 months (LOCF method) was 2.3% (SD 6.8%, $p=0.005$) in the pravastatin treatment and 5.9% (SD 13.3, $p=0.002$) in the atorvastatin treatment (between-group $p=0.31$); the corresponding values in those on antidiabetic drugs were 1.3% (SD 8.0%, $p=0.13$) in the pravastatin treatment and 3.1% (SD 13.4%, $p=0.07$) in the atorvastatin treatment (between-group $p=0.48$). The significant increases in HbA1c observed in the patients without antidiabeteic medication may have reflected the natural course in the absence of a specific intervention.

We explored the effects of pravastatin and atorvastatin on CRP and adiponectin. Statin therapy has been shown to decrease CRP[47, 48], largely dependent on the decrease in LDL-C[49]. Even a short period of treatment with a low dose of pravastatin or atorvastatin resulted in an appreciable decrease in hs-CRP[27, 45]. There was no decrease in hs-CRP in either pravastatin or atorvastatin treatment in the present study; however, it should be noted that the change in hs-CRP was highly variable in the present study. Likewise, the findings for adiponectin were inconsistent with the

previous observation with respect to pravastatin[45] and atorvastatin[27].

Conclusion

In a randomized comparative trial of low-dose pravastatin and atorvastatin (10 mg per day) among patients with elevated LDL-C and glucose intolerance, there was no difference in the changes of HDL-C and glucose metabolism parameters after 12-month treatment. Pravastatin and atorvastatin treatments increased HDL-C by almost the same extent, while the decrease in LDL-C was much greater for atorvastatin than for pravastatin. Both pravastatin and atorvastatin 10 mg per day were well tolerated.

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Conflicts of Interest

J. Sasaki; MSD K.K., Daiichi-Sankyo Co. Ltd., Bayer Yakuhin Ltd..T. Otonari, Y. Uchida, Y. Ikeda, S. Biro and S. Kono declared no conflicts of interest.

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