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Original article

Comparison of pitavastatin with atorvastatin in increasing HDL-cholesterol and adiponectin in patients with dyslipidemia and coronary artery disease: The COMPACT-CAD study

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ABSTRACT

Background: Many large-scale clinical trials have confirmed that statins are effective in reducing low-density lipoprotein cholesterol (LDL-C) level, resulting in reducing cardiovascular events. Recent studies have focused on the effects of statins on high-density lipoprotein cholesterol (HDL-C). Here we compared the effects of two statins on lipid profile and other metabolic parameters.
Methods: The study population included 129 patients with stable coronary artery disease, hypercholesterolemia, and hypo-HDL-cholesterolemia (HDL-C < 50 mg/dl). They were randomly allocated to treatment by pitavastatin 2–4 mg/day or atorvastatin 10–20 mg/day and followed-up for 30 months. The primary endpoint was percent changes in HDL-C and adiponectin during the study. The secondary endpoints were percent and absolute changes in markers of glucose metabolism, serum lipids, and apolipoproteins.
Results: The effects of 30-month treatment with pitavastatin on HDL-C were significantly greater than those of atorvastatin (%change: pitavastatin: 20.1 ± 25.7%, atorvastatin: 6.3 ± 19.8%, $p = 0.01$; absolute change: pitavastatin: 7.3 ± 9.1 mg/dl, atorvastatin: 2.3 ± 8.0 mg/dl, $p = 0.02$). A similar trend was seen with regard to apolipoprotein-AI (ApoAI) (%change: pitavastatin: 20.8 ± 19.3%, atorvastatin: 11.4 ± 17.6%, $p = 0.03$; absolute change: pitavastatin: 23.1 ± 20.2 mg/dl, atorvastatin: 12.1 ± 19.4 mg/dl, $p = 0.02$). Treatment with pitavastatin, but not atorvastatin, significantly increased adiponectin levels. Neither statin had a significant effect on hemoglobin A1c. No severe adverse events were registered during the study.
Conclusion: Long-term treatment with pitavastatin resulted in significantly greater increases in serum HDL-C and ApoAI levels without adverse effects on glucose metabolism, compared with atorvastatin.

Introduction

Several large-scale clinical trials have shown that 3-hydroxy-3-methyl-glutaryl co-enzyme A reductase inhibitors (statins) are effective in reducing low-density lipoprotein cholesterol (LDL-C) levels, resulting in a significant reduction in cardiovascular events [1–3]. Furthermore, aggressive lipid-lowering treatment with atorvastatin resulted in a greater reduction in the progression of coronary atherosclerosis and prevention of cardiovascular events than moderate treatment with pravastatin [4]. In this regard, elevated LDL-C is considered the primary target of lipid-lowering therapy, and the concept of "the lower, the better" in LDL-C is widely recognized in Western countries. In the post hoc analysis of the "Treating to New Targets (TNT)" study, despite strict control of LDL-C (LDL-C < 70 mg/dl) with statins, the risk of cardiovascular events remained high in patients with low levels of high-density lipoprotein cholesterol (HDL-C) [5]. In this regard, HDL-C plays an important role in atherosclerosis based on its anti-atherosclerotic properties, and recent research has strongly focused on improvement in HDL-C level as a residual risk for prevention of cardiovascular events in the era of statin-treatment.

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Pitavastatin is a strong statin and commonly used in Japan. It reduces cholesterol synthesis in the liver through competitive and effective inhibition of 3-hydroxy-3-methyl-glutaryl co-enzyme A reductase. It also induces the expression of LDL-C receptors, resulting in increased hepatic uptake of LDL-C from the circulation [6]. On the other hand, pitavastatin increases serum levels of HDL-C [7,8] although it does not have harmful effects on glucose tolerance [9]. Recent reports have shown that pitavastatin has pleiotropic effects.

The use of pitavastatin is reported to produce significant regression of coronary plaques in patients with acute coronary syndrome [10,11]. In one study of patients with hyper-LDL-cholesterolemia and glucose intolerance, 52-week treatment with pitavastatin was associated with significantly greater increases in HDL-C and apolipoprotein AI (ApoAI) levels than atorvastatin [12]. To our knowledge, however, the precise differences between these two statins with regard to their effects on HDL-C levels, glucose metabolism, and adiponectin levels in very high-risk patients with stable coronary artery disease (CAD) and hypo-HDL-cholesterolemia have not been determined. The present study compared the outcome of 30-month treatment with pitavastatin and atorvastatin on changes in HDL-C, adiponectin, and other metabolic parameters, in patients with stable CAD, hypercholesterolemia, and hypo-HDL-cholesterolemia.

Methods

Patient population

Eligible patients were men and women, aged 20–85 years, with clinically evident stable CAD, which was defined by one or more of the following: previous myocardial infarction, previous or current angina with objective evidence of obstructive atherosclerotic CAD (≥75% stenosis in major coronary arteries), and history of coronary revascularization including coronary artery bypass grafting (CABG). Eligible criteria were serum HDL-C < 50 mg/dl and LDL-C > 100 mg/dl under statin treatment or LDL-C > 140 mg/dl without lipid-lowering medications at randomization. Unstable patients with acute myocardial infarction (AMI) within three months after onset, and coronary intervention including CABG within one month were excluded. The exclusion criteria included allergy to pitavastatin or atorvastatin, familial hypercholesterolemia, severe hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg), renal disorders (serum creatinine > 1.5 mg/dl) or current dialysis, family history of hypothyroidism or muscular dystrophy, history of drug-induced hepatic disorder, drug abuse or dipsomania, cardiogenic shock, and females who were pregnant or who planned to become pregnant during this study.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki established by the World Medical Association and 'Ethical Principles in Clinical Studies' published by the Ministry of Health, Labor and Welfare of Japan, and following the approval of the institutional review board of Kumamoto University and each participating institution. The study protocol was explained to patients who met the criteria for inclusion and written informed consent was obtained from the participants.

Study design

Comparison of pitavastatin with atorvastatin in increasing HDL-cholesterol and adiponectin in patients with dyslipidemia and coronary artery disease (COMPACT-CAD) was a 30-month randomized, non-blinded, multicenter study of patients with stable CAD. Enrollment and randomization were carried out from September 2008 to September 2009. Eligible patients were randomized (1:1) to receive pitavastatin (2–4 mg) or atorvastatin (10–20 mg) once daily for 30 months. Factors used for allocation were LDL-C level, sex, having diabetes mellitus (DM) or not, and prior statin usage. Throughout the study, the attending physician was free to change the dose of statins to achieve lipid control (LDL-C < 70 mg/dl). The effects of the two statins on the primary and secondary endpoints were assessed at baseline, and at 6, 12, and 30 months later.

Primary and secondary endpoints

The primary endpoint was the percent changes in HDL-C and adiponectin levels at 30 months relative to the baseline values. The secondary endpoints included (1) absolute and percent changes in glucose metabolism markers: fasting glucose, and HbA1c; (2) absolute change in adiponectin; (3) absolute and percent changes in serum lipids and apolipoproteins [total cholesterol, LDL-C, triglyceride, HDL-C, non-HDL-C, LDL-C/HDL-C, ApoAI, ApoB, ApoB/ApoAI]; (4) death and any adverse cardiac events; and (5) adverse effects including changes in laboratory data.

Laboratory measurements

Peripheral blood samples were obtained after a 12-h overnight fast at baseline and after 6, 12, and 30 months of treatment. Serum was separated by centrifugation at 3000 rpm at 10 °C for 10 min and stored at −20 °C then transferred to the central laboratory (SRL Inc., Tokyo, Japan). Serum HDL-C concentration was determined by direct method using cholesterol oxidase. Adiponectin levels were measured using latex agglutination-turbidimetric immunoassay. Total cholesterol levels were measured using cholesterol dehydrogenase-UV method. Triglyceride levels were measured using enzymatic method. LDL-C levels were measured using direct method. ApoAI and ApoB were measured using turbidimetric immunoassay. Fasting glucose levels were measured using the hexokinase-ultraviolet method. HbA1c values were determined using latex agglutination-turbidimetric immunoassay.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the distribution of continuous data. Normally distributed data were expressed as mean ± standard deviation, whereas those with skewed distribution were expressed as the median value with interquartile range (IQR). Categorical data were presented as frequencies and percentages. Differences between the two groups were tested with the chi-square test for categorical variables. Differences in continuous variables were analyzed by the unpaired *t*-test or Mann–Whitney *U*-test, as appropriate. The Bonferroni corrected *t*-test was used to analyze differences in the two groups at follow-up of 6, 12, and 30 months of treatment. Significance levels of adjusted *p*-value at each follow-up point were set at <0.05 at 6 months, <0.025 at 12 months, and <0.017 at 30 months.

The primary endpoints, percent changes in HDL-C and adiponectin levels at 30 months, were analyzed by unpaired *t*-test. The mean difference in percent change and the two-sided 95% confidence interval were calculated for the difference in drug effect between the pitavastatin and atorvastatin groups, at baseline, and at 6, 12, and 30 months later. The one-sample *t*-test was used to assess the efficacy of each drug at 6, 12, and 30 months of treatment. The secondary endpoints were analyzed using the same approach. The numbers of cardiovascular events and adverse events were also assessed to determine the safety profile. The total numbers of side effects and adverse events were assessed and categorized according to severity. Differences in treatments were evaluated by

the intention to treat analysis and considered statistically significant at a p-value < 0.05 or under the Bonferroni adjusted p-value as appropriate. All statistical analyses were conducted using IBM SPSS statistics 20 (Chicago, IL, USA).

Results

Patient characteristics

A total of 129 patients were enrolled from September 2008 to September 2009 in 17 hospitals in Japan. Of these, 65 patients were assigned to pitavastatin treatment and 64 patients were assigned to atorvastatin treatment randomly. Before the end of 12 months of treatment, 5 patients discontinued treatment because of adverse events, and 21 patients failed to return to the hospital after registration, and were considered to have withdrawn consent. At the end of the 30-month treatment, 58 patients had finally failed to return to the hospital. Thus, 71 patients were included in the effectiveness analysis. The mean dose of pitavastatin was 2.2 ± 0.6 mg/day while that of atorvastatin was 10.5 ± 2.1 mg/day.

Table 1 summarizes the baseline characteristics of the study participants. There were no significant differences between the two groups in all the tested parameters. The majority of the study patients were men (81.4%), and the prevalence of diabetes mellitus was 40.3%. At the start of the study, 62.0% of the patients were not receiving statin treatment. HDL-C levels at baseline were 39.9 ± 6.5 mg/dl in the pitavastatin group and 40.1 ± 5.5 mg/dl in the atorvastatin group (p = 0.90). At baseline, serum adiponectin level was 9.4 ± 7.1 μg/ml in the pitavastatin group, and 9.5 ± 5.6 μg/ml in the atorvastatin group (p = 0.96).

Efficacy

As stated above, 71 patients completed the 30-month study. They included 32 of the pitavastatin and 39 of the atorvastatin group. Table 2 summarizes the percent and absolute changes in the primary and secondary endpoint parameters (differences in each variable between baseline and after 30 months of treatment) between these two groups. With regard to the primary endpoint, the percent and absolute changes in HDL-C and ApoAI, were significantly greater in the pitavastatin group than in the atorvastatin group. On the other hand, there were no significant differences in the effects of pitavastatin and atorvastatin on LDL-C, total-C, non-HDL, triglyceride, and ApoB at 30 months treatment. During the study, serum HDL-C levels increased progressively over time in the pitavastatin group, with an increase of 9.4% (p = 0.71) at 6 months, 15.8% (p = 0.037) at 12 months, and 20.1% (p = 0.013) at 30 months (Figs. 1 and 2). On the other hand, HDL-C level ceased to increase by 6 months (10.7%) and decreased at 12 months (9.3%) and 30 months (6.3%) in the atorvastatin group (Figs. 1 and 2). ApoAI levels increased over time, with increase of 7.9% (p = 0.63) at 6 months, 13.0% (p = 0.035) at 12 months, and 20.8% (p = 0.034) at 30 months in the pitavastatin group, though there were no inter-group differences, as tested by Bonferroni adjusted p-values at follow-up points (Figs. 3 and 4). We found that LDL-C/HDL-C ratio at 30 months treatment was significantly lower in the pitavastatin group (<1.5) compared to the atorvastatin group and the decreasing percent changes in LDL-C/HDL-C ratio were significantly greater in the pitavastatin group than in the atorvastatin group. ApoB/ApoAI ratio was also significantly decreased after 30 months in both groups and pitavastatin treatment exhibited significantly lower levels of ApoB/ApoAI ratio compared to atorvastatin treatment at 30 months (Table 2).

There were no significant inter-group differences between pitavastatin and atorvastatin groups in terms of total adiponectin, fasting glucose, and HbA1c. Adiponectin levels progressively increased over time in the pitavastatin group, but did not change significantly in the atorvastatin group (Fig. 5). In the pitavastatin group, fasting blood glucose level was higher at 30 months compared with the baseline, but there were no significant changes in the percent and absolute changes between the two groups. HbA1c level was significantly higher at 6 months in the atorvastatin group,

Table 1
Baseline characteristics of study patients.

	All (n = 129)	Pitavastatin (n = 65)	Atorvastatin (n = 64)	p-Value
Age (years)	68.2 ± 10.1	68.4 ± 9.1	68.9 ± 10.2	0.77
Males	105 (81.4%)	53 (81.5%)	52 (81.3%)	0.96
Body mass index (kg/m^2)	24.5 ± 3.24	24.3 ± 3.05	24.8 ± 3.41	0.26
Systolic blood pressure (mmHg)	131 ± 16.7	131 ± 16.7	132 ± 17.6	0.80
Diastolic blood pressure (mmHg)	74 ± 10.8	73 ± 10.7	75 ± 11.1	0.34
Hypertension	107 (82.9%)	54 (83.1%)	53 (82.8%)	0.97
Diabetes mellitus	52 (40.3%)	27 (41.5%)	25 (39.1%)	0.77
Current smoking	39 (30.2%)	20 (30.8%)	19 (29.7%)	0.95
Family history of CAD	25 (19.4%)	12 (18.5%)	13 (20.3%)	0.93
Old myocardial infarction	65 (50.4%)	33 (50.8%)	32 (50.0%)	0.93
Percutaneous coronary intervention	110 (85.3%)	55 (84.6%)	55 (86.0%)	0.86
Total cholesterol	192.1 ± 26.9	191.5 ± 25.3	192.6 ± 28.6	0.83
Low-density lipoprotein cholesterol	122.7 ± 22.5	122.6 ± 21.2	122.9 ± 23.9	0.94
High-density lipoprotein cholesterol	39.8 ± 5.9	39.9 ± 6.5	40.1 ± 5.5	0.90
Triglyceride	124 (33, 165)	114 (83, 164)	133 (98, 165)	0.43
Adiponectin	9.4 ± 6.4	9.4 ± 7.1	9.5 ± 5.6	0.96
Glucose	125.0 ± 50.0	126.6 ± 59.8	120.4 ± 34.4	0.62
Hemoglobin A1c	5.9 (5.5–6.6)	5.9 (5.5–6.6)	5.9 (5.4–6.5)	0.77
Statin	49 (38.0%)	25 (38.5%)	24 (37.5%)	0.76
Calcium-blocker	64 (49.6%)	31 (47.7%)	33 (51.6%)	0.66
β-Blocker	42 (32.6%)	22 (33.8%)	20 (31.3%)	0.75
Angiotensin-converting enzyme inhibitor	44 (34.1%)	22 (33.8%)	22 (34.4%)	0.95
Angiotensin II receptor blocker	46 (35.7%)	23 (35.4%)	23 (35.9%)	0.95
Insulin	25 (19.4%)	20 (30.8%)	5 (7.8%)	0.26
Sulfonylurea	16 (12.4%)	9 (13.8%)	7 (10.9%)	0.62
α-Glucosidase inhibitor	11 (8.5%)	6 (9.2%)	5 (7.8%)	0.77
Antiplatelet agents	128 (99.2%)	65 (100%)	63 (98.4%)	0.31
Nitrate	29 (22.5%)	15 (23.1%)	14 (21.9%)	0.87

Data are mean ± SD or number of patients (percent). Triglyceride is expressed as medians with interquartile range. CAD, coronary artery disease.

Table 2
Changes in laboratory data after 30 months of treatment.

	Pitavastatin ($n=32$)		Atorvastatin ($n=39$)		p-Value
	Baseline	30 months	Baseline	30 months	
HDL-C	40.66 ± 7.16	47.97 ± 9.67**,†	40.18 ± 5.48	42.44 ± 8.76	–
Absolute change	4 (1 to 13)		3 (−2 to 7)		0.015
%Change	11.1 (2.2 to 35.3)		8.1 (−5.3 to 16.3)		0.013
Triglyceride	104 (75–131)	103 (69–128)	149 (124–196)	116 (85–191)†	–
Absolute change	−13 (−48 to 20)		−21 (−49 to 5)		0.62
%Change	−12.8 (−41.6 to 24.1)		−15.8 (−32.1 to 25.5)		0.29
Total cholesterol	189.0 ± 26.5	158.7 ± 21.8**	196.5 ± 30.76	161.9 ± 29.6**	–
Absolute change	−29 (−51 to −17)		−35 (−59 to −8)		0.59
%Change	−14.9 (−24.3 to −9.1)		−12.5 (−26.2 to −3.3)		0.60
LDL-C	121.5 ± 23.6	87.3 ± 21.1**	123.2 ± 25.7	92.3 ± 26.2**	–
Absolute change	−32 (−55 to −19)		−29 (−45 to −7)		0.64
%Change	−28.7 (−40.8 to −16.8)		−25 (−36.4 to −8.4)		0.57
Non-HDL-C	148.4 ± 27.1	71.44 ± 10.1**	156.3 ± 29.7	69.62 ± 12.07**	–
Absolute change	−74 (−92 to −62)		−87 (−106 to −69)		0.16
%Change	−52.4 (−60 to −43.7)		−54.3 (−61.6 to −48.9)		0.12
LDL-C/HDL-C	3.12 ± 1.08	1.20 ± 0.60**,†	3.12 ± 0.74	2.25 ± 0.76**	–
Absolute change	−1 (−1.7 to −0.7)		−0.7 (−1.4 to −0.4)		0.08
%Change	−38 (−49.9 to −29.2)		−30.8 (−39.7 to −14.7)		0.029
ApoAI	115.8 ± 15.82	138.9 ± 23.2**,†	116.7 ± 14.9	128.8 ± 19.2**	–
Absolute change	20 (10–34)		13 (1–24)		0.023
%Change	15.9 (8.3–31.3)		11 (0.8–23.4)		0.034
ApoB	103.2 ± 16.7	82.3 ± 17.0**	107.5 ± 19.1	88.6 ± 21.2**	–
Absolute change	−20 (−33 to −13)		−18 (−30 to 4)		0.67
%Change	−19.8 (−29.2 to −12.7)		−18.1 (−28.7 to −4.6)		0.46
ApoB/ApoAI	0.92 ± 0.25	0.61 ± 0.17**,†	0.93 ± 0.18	0.7 ± 0.2**	–
Absolute change	−0.25 (−0.4 to −0.21)		−0.22 (−0.36 to −0.07)		0.12
%Change	−32.4 (−43.3 to −24.6)		−27.3 (−36.7 to −9.9)		0.053
Adiponectin	10.14 ± 9.82	12.79 ± 10.87*	9.07 ± 5.34	9.74 ± 6.21	–
Absolute change	1 (−0.2 to 3.8)		0.9 (−0.7 to 2.7)		0.10
%Change	13.4 (−3.6 to 42.6)		12.1 (−10 to 25.8)		0.15
Glucose	112.6 ± 34.7	124.6 ± 36.0*	125.8 ± 40.4	126.4 ± 43.6	–
Absolute change	6 (−6 to 22)		−1 (−17 to 11)		0.22
%Change	6 (−6.5 to 20.8)		−0.9 (−12 to 11.6)		0.33
HbA1c	5.8 (5.5–6.7)	5.8 (5.4–6.5)	6.0 (5.6–6.7)	6.1 (5.7–6.8)	–
Absolute change	−0.1 (−0.5 to 0.2)		0 (−0.1 to 0.2)		0.83
%Change	−1.7 (−7.1 to 3.6)		0 (−1.9 to 3.0)		0.62

Data are mean ± SD. Triglyceride is expressed as medians with interquartile range. The percent change and absolute change of each parameter is expressed as medians with interquartile range. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; HbA1c, hemoglobin A1c.

* $p<0.05$ vs. baseline.
** $p<0.01$ vs. baseline.
† $p<0.05$ between 30 months.

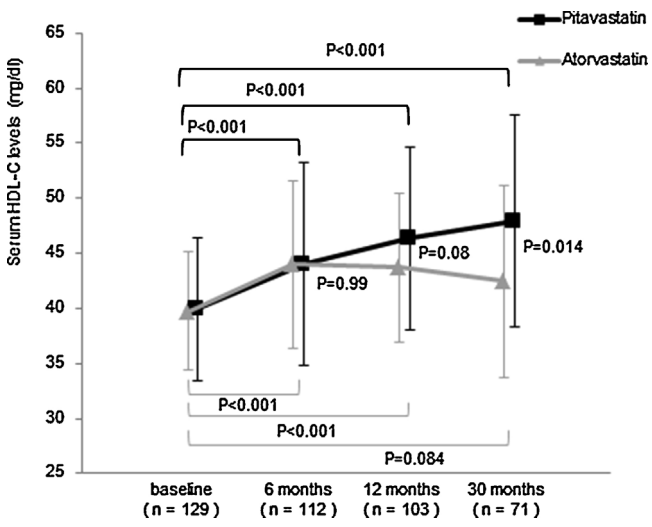

Fig. 1. Serum levels of high-density lipoprotein cholesterol (HDL-C) at baseline, and after 6, 12, and 30 months of treatment with pitavastatin and atorvastatin. Data are mean ± SD of the indicated number of patients.

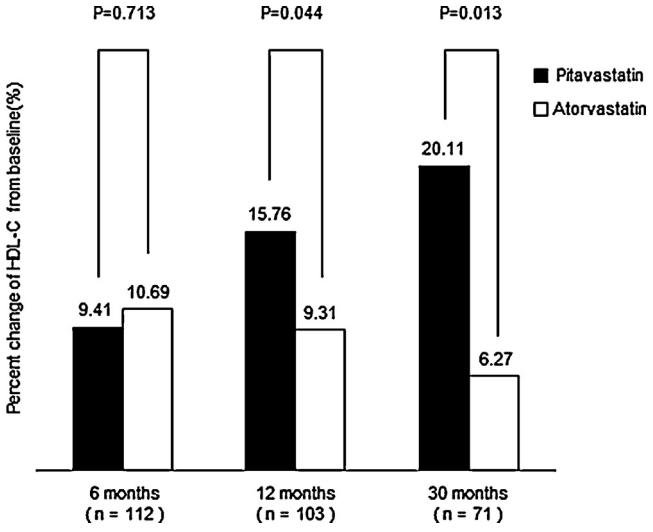

Fig. 2. Percent change in high-density lipoprotein cholesterol (HDL-C) levels during the course of the 30-month study. Data are mean ± SD of the indicated number of patients.

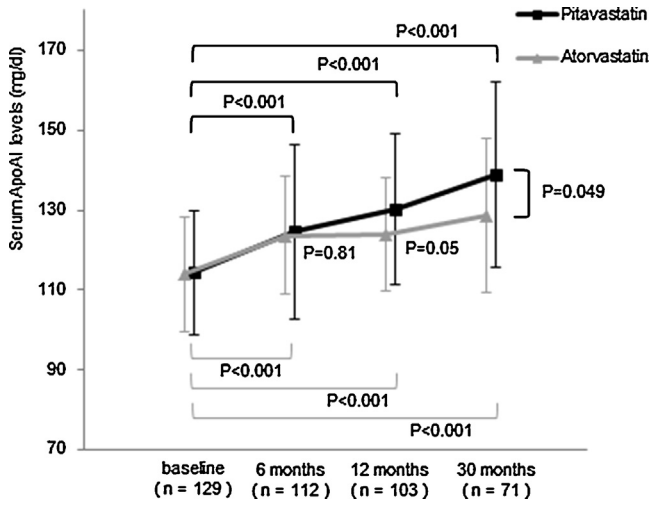

Fig. 3. Serum levels of apolipoproteinAI (ApoAI) at baseline, and after 6, 12, and 30 months of treatment with pitavastatin and atorvastatin. Data are mean ± SD of the indicated number of patients.

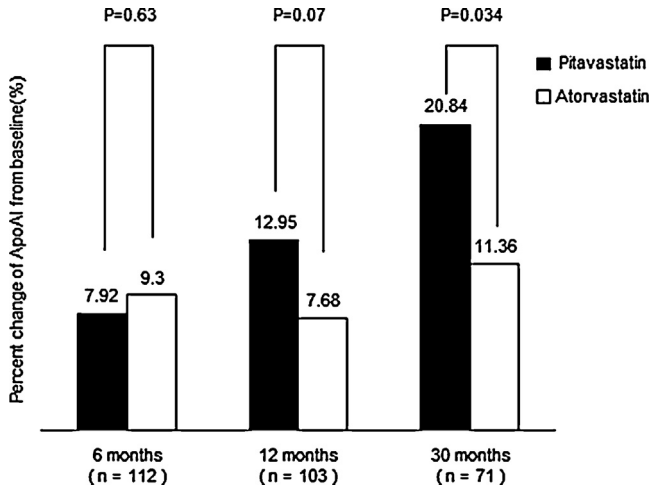

Fig. 4. Percent change in apolipoproteinAI (ApoAI) levels during the course of the 30-month study. Data are mean ± SD of the indicated number of patients.

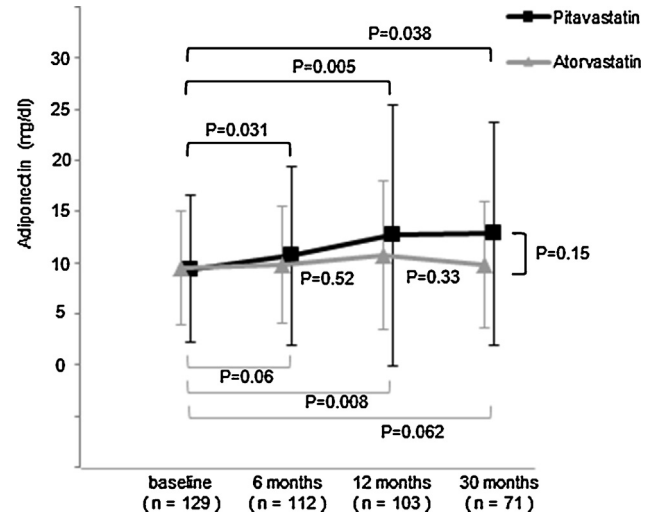

Fig. 5. Serum levels of adiponectin at baseline, and after 6, 12, and 30 months of treatment with pitavastatin and atorvastatin. Data are mean ± SD of the indicated number of patients.

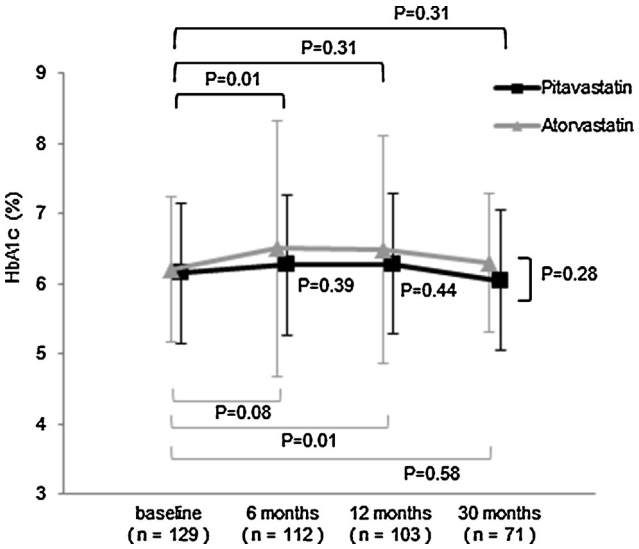

Fig. 6. Serum levels of hemoglobinA1c (HbA1c) at baseline, and after 6, 12, and 30 months of treatment with pitavastatin and atorvastatin. Data are mean ± SD of the indicated number of patients.

but no significant change was noted at 30 months (relative to the baseline), and no significant difference was observed between the two treatment groups (Fig. 6).

Among the sub-population of patients with HDL-C < 40 mg/dl, we found 11 patients in the pitavastatin group and 17 in the atorvastatin group. We analyzed changes in serum HDL-C levels in these patients. The percent and absolute changes in HDL-C were significantly greater in the pitavastatin group compared to the atorvastatin group (% HDL-C change: pitavastatin 35.0 [6.4–62.5]% vs. atorvastatin 11.8 [−5.2 to 18.9]%, $p = 0.013$; absolute HDL-C change: pitavastatin 12 [2–19] mg/dl vs. atorvastatin 4 [−2 to 7] mg/dl, $p = 0.018$).

In the present study, 103 patients (79.8% of All) were followed until 12 months of treatment. Of these 103 patients, we compared the drug effects between patients who completed the 30-month study (effectiveness population; $n = 67$) and those who dropped out before 30 months (dropped out population; $n = 36$). In the pitavastatin group, there were no significant differences between the patients included in the effectiveness population and those in the dropped out population with regard to the primary end point; the percent and absolute changes in HDL-C (percent change: 15.2 ± 15.1% vs. 16.6 ± 14.2%, $p = 0.75$; absolute change: 6.1 ± 6.0 mg/dl vs. 6.3 ± 5.6 mg/dl, $p = 0.93$). Also in the atorvastatin group, there were no significant differences between the effectiveness population and those in the dropped out population with regard to the percent and absolute changes in HDL-C (percent change, 9.1 ± 17.5% vs. 9.9 ± 13.2%, $p = 0.87$; absolute change, 3.2 ± 6.3 mg/dl vs. 3.9 ± 5.4 mg/dl, $p = 0.69$).

Safety and tolerability

Adverse events related to the study drugs occurred in 3 patients (4.6%) of the pitavastatin group and 2 patients (3.1%) of the atorvastatin group. Adverse events considered to be related to pitavastatin were skin eruptions ($n = 2$), and general fatigue ($n = 1$), while those considered to be related to atorvastatin were skin eruptions only ($n = 2$). There was no significant difference in the frequency of adverse events between the two groups ($p = 0.66$). In general, pitavastatin and atorvastatin were well tolerated. No cardiac event was registered during the 30-month study period.

In this study, we were able to follow-up 55% of the participants at 30 months. There were no significant differences in the

baseline characteristics, except for history of old myocardial infarction between the two groups (efficacy group: 63.4%, drop-out group: 34.5%, $p = 0.02$).

Discussion

In patients with stable CAD, pitavastatin significantly increased serum levels of HDL-C and this increase was significantly larger than that produced by atorvastatin after 30 months of treatment. Treatment with pitavastatin, but not atorvastatin, significantly increased serum levels of adiponectin. We found pitavastatin continuously increased HDL-C without adverse effects on glucose metabolism in the long-term follow up compared to atorvastatin.

Hypo-HDL-cholesterolemia is an independent risk factor for atherosclerotic cardiovascular events [13]. HDL-C exerts many biological effects through its anti-atherosclerotic actions. The most accepted property of HDL-C is reverse cholesterol transport (RCT), which involves the transfer of excess cholesterol from the peripheral tissues to the liver [14]. Furthermore, HDL-C exhibits favorable effects on inflammation, LDL-C oxidation, platelet activation and thrombosis, and restoration of endothelial integrity through the promotion of endothelial nitric oxide (NO) release and anti-apoptotic effects [15]. Despite strict control of LDL-C using lipid-lowering agents (statins) for the treatment of dyslipidemia, the risk of cardiovascular events remained high in patients with low serum HDL-C levels in the TNT trial [5]. The present results showed that pitavastatin increased HDL-C during the 30-month study period, although it significantly lowered LDL-C levels similar to atorvastatin. These effects might be beneficial in preventing cardiovascular events in patients with CAD for long-term treatment.

The clinical strategies used to increase HDL-C levels are, in general, lifestyle interventions such as weight loss, exercise, cessation of smoking, and moderate alcohol consumption [16]. Statins are one of the major pharmacotherapeutic options for increasing HDL-C levels. Statins vary in their potency in increasing HDL-C level, and have been reported to increase HDL-C by 5–7% [17], whereas some studies reported reduction in HDL-C level following the prolonged use of statins [12,18]. In LIVALO Effectiveness and Safety (LIVES) study extension, HDL-C levels increased progressively over time, with an increase of about 10 mg/dl (28.9%) after 5 years of treatment in patients with low HDL-C levels (HDL-C < 40 mg/dl) [19]. In the present COMPACT-CAD study, patients with low HDL-C (HDL-C < 50 mg/dl) showed a progressive increase in serum HDL-C level over time, with a percent increase of $20.1 \pm 25.7\%$ after 30 months of continuous treatment. Our results support the results of LIVES study extension. In any treatment that focuses on HDL-C, it is important to consider the effect of the treatment on HDL-C function, in addition to increasing serum levels of HDL-C. Previous studies demonstrated that inhibition of cholesterol ester transfer protein (CETP) using torcetrapib did not prevent the progression of atherosclerosis and conversely elevated overall mortality, despite the significant increase in HDL-C levels (72.1%) [20]. Statins are thought to increase serum HDL-C level through two major mechanisms. One is to produce ApoAI, which is considered to increase functional HDL-C particles that can activate RCT, and the other is to inhibit CETP, which is thought to produce dysfunctional HDL-C with pro-inflammatory and atherogenic properties [21]. The available literature suggests that in comparison to atorvastatin, pitavastatin increases the mRNA levels of ATP-binding cassette transporter A1 (ABCA1), which appears to be involved in the control of ApoAI-mediated cholesterol efflux [22]. In our study, ApoAI levels increased progressively during the 30-month period in patients treated with pitavastatin compared to atorvastatin. Considered together, these results suggest that pitavastatin increases HDL-C levels and could improve HDL-C function by elevating ApoAI levels and activating RCT.

A recent meta-analysis study found that treatment with hydrophilic and lipophilic statins was associated with a slight increase in the risk of diabetes [23]. In the present study, pitavastatin tended to improve HbA1c levels at 30 months, albeit insignificantly, compared with atorvastatin. We also found treatment with pitavastatin, but not atorvastatin, significantly increased adiponectin levels in the present study. The precise mechanisms of the increase in serum adiponectin levels associated with pitavastatin treatment remain uncertain. According to one study, pitavastatin has been reported to activate peroxisome proliferator-activated receptor (PPAR) γ in macrophages [24], suggesting the possibility that pitavastatin could activate PPARγ in the adipose tissue. Pitavastatin also attenuated the development of adipose tissue inflammation [25] and did not impair differentiation/maturation of preadipocytes and prevented adipocyte hypertrophy in obese mice (KKAy mice) [26]. These effects of pitavastatin could contribute to the increase in serum adiponectin levels.

Long-term follow-up of the effects of these medications on glucose metabolism should be determined in future studies.

In the present study, adiponectin levels progressively increased over time in the pitavastatin group, but not in the atorvastatin group, while fasting glucose levels were higher at 30 months compared with the baseline in the pitavastatin group. We have no clear answer to this discrepant result. Fasting glucose levels were higher at 30 months compared with the baseline, while HbA1c levels were slightly lower at 30 months from baseline in the pitavastatin group. These results suggest that mean serum glucose levels were not elevated and the postprandial glucose metabolism could not be impaired in the pitavastatin group. On the other hand, in the atorvastatin group, fasting glucose levels did not change but HbA1c levels were slightly increased from baseline. Thus, this result suggested that atorvastatin treatment might impair the postprandial glucose metabolism compared with the baseline condition. During the treatment period, pitavastatin, but not atorvastatin, significantly increased adiponectin levels. We suppose these changes could partly affect the changes in HbA1c levels. To clarify the precise correlations and mechanisms, further clinical studies using recently recognized new glucose metabolism markers such as postprandial glucose, 1, 5-anhydro-D-glucitol, and continuous glucose-monitoring system, would be required.

In this 30-month COMPACT-CAD study, pitavastatin treatment was associated with significant increase in serum levels of HDL-C and ApoAI, compared with atorvastatin in patients with stable CAD. Pitavastatin increased serum HDL-C levels without adverse effects on glucose metabolism, compared with atorvastatin. Taken together, pitavastatin seems to have well-balanced beneficial effects in patients at high risk for cardiovascular events and these effects are mediated by reducing LDL and increasing HDL-C levels.

The present study has certain limitations. Although the study was prospective in nature, we were able to obtain blood samples to examine the endpoint items after 30 months of continuous treatment from 55% of the participants who registered at study entry. Because subjects of this clinical study were volunteers with no incentives for participation, patient motivation over the long follow-up period proved difficult. In the present study, many patients unfortunately failed to complete the 30-month follow up mainly because of withdrawal of consent. But at 12 months from baseline, both in the pitavastatin and atorvastatin group, we found similar therapeutic effects of these two statins on the primary end point and other parameters between the patients with the

effectiveness population ($n = 67$) and with the dropped out population ($n = 36$). Based on these results, it could be suggested that high drop-out rate after 12 months might not strongly affect the main results of the present study at 30 months. Further clinical studies of long-term follow-up with higher follow-up rate are required to confirm our results.

Regarding the entry criteria, definition of hypo-HDL-cholesterolemia was serum HDL-C concentration < 50 mg/dl in this study. In a post hoc analysis of the TNT trial which was conducted in patients with CAD taking 10 mg of atorvastatin, the risk of cardiovascular events was significantly reduced in those with serum HDL-C ≥ 55 mg/dl [5]. And in the whole study population of the TNT study, serum HDL-C ≥ 43 mg/dl was significantly associated with a decrease in cardiovascular events. Furthermore, in the Japan Lipid Intervention Trial (J-LIT), the incidence of coronary events was significantly lower in patients with serum HDL-C ≥ 50 mg/dl [27]. Based on these facts, we applied the essential entry criteria as serum HDL-C < 50 mg/dl in this study. Although similar results were observed in the subpopulation of patients with HDL-C < 40 mg/dl in the present study, further studies with a large number of patients are needed to confirm our results in CAD patients with hypo-HDL-cholesterolemia defined as HDL-C < 40 mg/dl.

Conclusion

In patients with stable CAD, hyper-LDL-cholesterolemia, and hypo-HDL-cholesterolemia, 30-month treatment with pitavastatin was associated with significantly greater increases in serum HDL-C and ApoAI than atorvastatin.

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