Safety and Efficacy of Pitavastatin in Patients With Impaired Fasting Glucose and Hyperlipidemia: A Randomized, Open-Labeled, Multicentered, Phase IV Study

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ABSTRACT

Purpose: Although the role of high-intensity lipid-lowering therapy in cardiovascular protection has broadened, concerns still exist about new-onset diabetes mellitus (NODM), especially in vulnerable patients. This study aimed to compare the effect of high-dose (4 mg/d) and usual dose (2 mg/d) pitavastatin on glucose metabolism in patients with hyperlipidemia and impaired fasting glucose (IFG).

Methods: In this 12-month study, glucose tolerance and lipid-lowering efficacy of high-dose pitavastatin (4 mg [study group]) was compared with that of usual dose pitavastatin (2 mg [control group]) in patients with hyperlipidemia and IFG. The primary end point was the change of glycosylated hemoglobin (HbA_{1c}) after 24 weeks of treatment. The secondary end points were as follows: (1) NODM within 1 year after treatment, (2) change of lipid parameters, (3)

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changes of adiponectin, and (4) change of blood glucose and insulin levels.

Findings: Of the total 417 patients screened, 313 patients with hypercholesterolemia and IFG were randomly assigned into groups. The mean (SD) change in HbA_{1c} was 0.06% (0.20%) in the study group and 0.03% (0.22%) in the control group ($P = 0.27$). Within 1 year, 27 patients (12.3%) developed NODM, including 12 (10.6%) of 113 patients in the study group and 15 (14.2%) of 106 in the control group ($P = 0.43$). The study group had a significantly higher reduction of total cholesterol and LDL-C levels and a higher increase in apolipoprotein A1/apolipoprotein B ratio (0.68 [0.40] vs 0.51 [0.35], $P < 0.01$).

Implications: The high-dose pitavastatin therapy did not aggravate glucose metabolism compared with the usual dose therapy. Moreover, it had a better effect on cholesterol-lowering and apolipoprotein distribution in the patients with hyperlipidemia and IFG. (*Clin Ther*. xxxx;xxx:xxx) © 2020 Published by Elsevier Inc.

Key words: hyperlipidemia, impaired fasting glucose, new-onset diabetes mellitus, pitavastatin.

INTRODUCTION

Substantial evidence supports the role of the 3-hydroxymethyl-3-methylglutaryl coenzyme A reductase inhibitors, statins, for the primary and secondary prevention of cardiovascular diseases (CVDs).[1–3] A meta-analysis from the Cholesterol Treatment Trialists' Collaboration suggested that lowering the LDL-C concentration by 1 mmol/L (38.7 mg/dL) would reduce CVD events by 22% in 5 years.[4] In addition, higher doses of statins are associated with further cardiovascular benefits.[5,6]

Although the risk-to-benefit ratio of statins is usually high, concerns exist regarding the risk of new-onset diabetes mellitus (NODM) associated with the use of statins.[7] Statins have been associated with a different incidence of DM, ranging from 28% in the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study to 43% in the UK clinical practice cohort.[8,9] Generally, meta-analyses reported that the use of statins was associated with a modestly increased risk of DM (overall odd ratio = 1.09; 95% CI, 1.02−1.17) and that the OR for individual statins ranged from 0.98 to 1.18.[10] Not all statins have the same effect on inducing DM. For example, atorvastatin, rosuvastatin, and simvastatin have the most substantial effect,[11] whereas lovastatin, pravastatin, and pitavastatin have neutral or beneficial effects.[12,13] Lipophilic statins are said to be more diabetogenic than hydrophilic statins because they can easily diffuse into cells and potently inhibit isoprenoid production. Moreover, those diabetogenic effects are only associated with relatively high statin concentrations.[14] Notwithstanding the diabetogenic effect, the benefit of statin therapy exceeded the risk of NODM.

The next issue is the risk-to-benefit ratio of intensive statin therapy. More intensive statin therapy was associated with a significantly higher risk of NODM (12% increase in pooled risk) than less intensive statin therapy and with a 16% reduction in the incidence risk of CVD in drug comparison studies.[15] Remarkably, in the Randomized Evaluation of Aggressive or Moderate Lipid-Lowering Therapy With Pitavastatin in Coronary Artery Disease (REAL-CAD) study, the adverse event (AE) rates were similar among the lower dose (1 mg) and the higher dose of pitavastatin (4 mg). In contrast, substantially better effects were observed, which suggested that the administration of maximum tolerable doses of statins would be the preferred statin strategy in patients with established coronary artery disease regardless of baseline LDL-C levels,[5]

Previous studies and meta-analyses have suggested that pitavastatin, a moderate-intensity lipophilic statin, has neutral or beneficial effects on glucose metabolism.[13,16] The Livalo Effectiveness and Safety (LIVES) study, an observational study of approximately 20,000 Japanese patients, found that pitavastatin had no adverse effect on glycosylated hemoglobin (HbA_{1c}) during a 2-year follow-up.[17] A retrospective study reported that pitavastatin decreased HbA_{1c} in patients with type 2 DM with a higher baseline HbA_{1c} level, especially in patients who had been previously treated with atorvastatin.[18] In randomized clinical trials, pitavastatin had a lipid-lowering efficacy similar to atorvastatin, but its effect on fasting blood glucose in patients with DM was more neutral,[19] In addition, the Prospective Comparative Clinical Study Evaluating the Efficacy and Safety of Pitavastatin in patients with metabolic syndrome (PROPIT) suggested that pitavastatin treatment combined with lifestyle modifications

improves metabolic risk among patients with central obesity and prediabetes.[20]

In this study, we compared the effects of high-dose (4 mg/d) and usual dose (2 mg/d) pitavastatin on HbA_{1c} in patients with hyperlipidemia and impaired fasting glucose (IFG). It was reported that the high-dose pitavastatin reduced LDL-C levels by 39%−45%, which was equipotent with 20 mg of atorvastatin and 5−10 mg of rosuvastatin and that the usual dose pitavastatin reduced LDL-C levels by 30%−36%, which was equipotent with 10 mg of atorvastatin according to the 2018 Korean guidelines for the management of dyslipidemia.[2]

METHODS

Study Patients

Eligible patients were men and women 20−69 years of age with hypercholesterolemia and IFG. Hypercholesterolemia was defined as a fasting LDL-C level ≥100 mg/dL or treatment with statins, and IFG was defined as a fasting plasma glucose level ≥100 mg/dL but not ≥126 mg/dL twice. Exclusion criteria were as follows: (1) familial hypercholesterolemia, (2) patients diagnosed with DM at the screening (diagnostic criteria for DM were HbA_{1c} ≥ 6.5% or those who received hypoglycemic treatment within 6 weeks before screening), (3) history of malignant tumor within the last 10 years, (4) serum creatinine level ≥2.0 mg/dL and liver transaminase levels ≥2.5 times the upper normal limits, and (5) women who were pregnant or lactating.

Study Design

The Safety and Efficacy of Pitavastatin in Patients With Impaired Fasting Glucose and Hyperlipidemia (SIPHON) study was a 120 month, randomized, open-labeled, multicentered, Phase IV study to evaluate glucose tolerance and lipid-lowering efficacy of high-dose (4 mg [study group]) pitavastatin compared with that of the usual dose (2 mg [control group]) in patients with hyperlipidemia and IFG. The study comprised 3 periods: the screening period (including 2−4 weeks of washout and placebo run-in period with maximal lifestyle modification), the main study period (24 weeks), and the extension study period (24 weeks) (Figure 1). Before entering the washout and placebo run-in period, the research coordinator used printed educational materials to educate the screened patients on the lifestyle modification method, including diet and exercise control. Although this study was designed as an open-labeled test, the primary efficacy end point was an objective value, such as the change of HbA_{1c}, and the allocation was strictly randomized according to a predetermined set of assignments.

The primary end point was the change of HbA_{1c} from the baseline to the end of the week. The secondary end points were as follows: (1) NODM

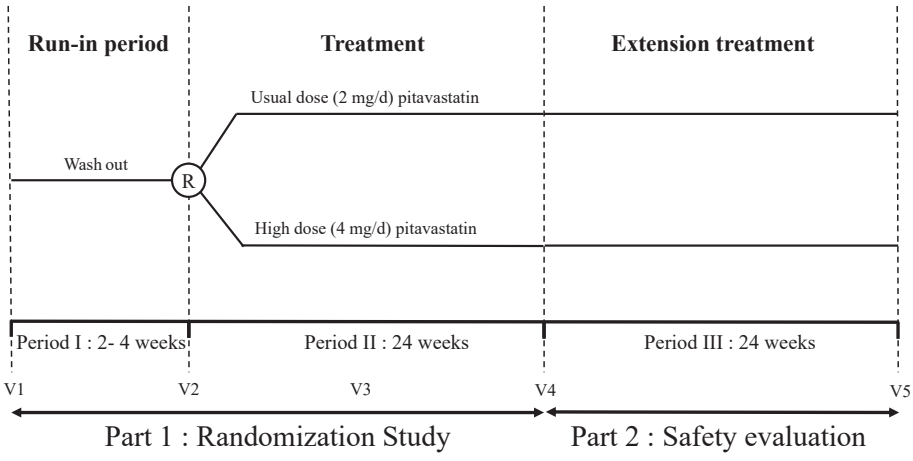

Figure 1. Study design. The study was composed of 3 periods: the screening (2- to 4-week washout and placebo run-in period), main study (24 weeks), and extension study (24 weeks) periods. R = randomization; V = visit.

within 1 year of treatment (with DM defined as fasting plasma glucose level ≥126 mg/dL or the taking of hypoglycemic agents), (2) change of the lipid composition {total cholesterol, triglyceride, LDL-C, HDL-C, and apolipoprotein A1/apolipoprotein B (ApoA1/ApoB) ratio, (3) changes in adiponectin, and (4) change of blood glucose and insulin levels.

Safety assessments included monitoring and recording all laboratory tests, vital signs, ECG, AEs, serious AEs, and possible association of AEs with the study drugs. Self-reported and physician-reported events were recorded and classified according to organ class and severity.

The study protocols were reviewed and approved by the institutional review board of each participating hospital before patient enrollment. In addition, the study was conducted following the current Good Clinical Practices and other applicable laws and regulatory requirements in Korea. This study was registered in ClinicalTrials.gov (NCT02056847).

Statistical Analysis

We calculated the number of patients in the study group to be tested for study noninferiority compared with the control group in the 24-week HbA_{1c} change (the primary end point of this study). For calculation of the number of patients to be tested for noninferiority in this study, the mean (SD) change of pitavastatin 2 mg and pitavastatin 4 mg was −0.11% (1.10%), and the noninferiority threshold was set at 0.4%. We used the difference values observed as ancillary findings in the subanalysis of he LIVES study.[21] For noninferiority, the following hypotheses and assumptions were established: $\mu T - \mu C \geq 0.4$ (hypothesis 0) vs $\mu T - \mu C < 0.4$ (hypothesis 1), where μT is the change of HbA_{1c} in the study drug and μC is the change of HbA_{1c} in the control drug. The 1-sided level of significance (α) is 0.025, the type 2 error (β) is 0.2, and the power of the test is 80%. In addition, the patients were randomized as a 1:1 ratio. With these assumptions, the required number of test patients is 119. Therefore, in this trial, the number of patients to be tested was set at 318, including a dropout rate of 25%.

Data are expressed as mean (SD) for the continuous variables and as number (percentage) of patients for the categorical variables. A Pearson χ^2 test or Fisher exact test was used to analyze categorical variables and an independent 1-sample *t* test for normal distribution, whereas the Wilcoxon rank-sum test was used for nonnormal distribution. In addition, for comparison within groups, the paired *t* test was used for normal distribution, and the Wilcoxon signed-rank test was used for nonnormal distribution. All the AEs and the adverse drug reactions, which manifested more than once, were described as number (percentage). The χ_2 test or Fisher exact test was used for intergroup comparison about the rate of AEs and adverse drug reactions.

RESULTS

Baseline Characteristics

Of the 417 patients screened, 313 were randomly assigned to the study, of whom 299 were included in the safety analysis group and in the intention-to-treat (ITT) analysis group, excluding 14 individuals who withdrew their consent without taking any study drugs. Among the patients included in the ITT analysis group, 80 dropped out during the study. The reasons for dropout were classified as consent withdrawal in 23 individuals; major protocol violation, including DM diagnosis before treatment, in 33 patients; AEs in 9 patients; follow-up loss in 11 patients; and the medication nonadherence in 75% or less. Finally, 219 patients were included in the per-protocol (PP) analysis group, and 188 patients finished the 12-month visit (Figure 2).

Table I presents the baseline characteristics of the 299 patients included in the ITT analysis. The 2 groups were well balanced with regard to age, sex, and medical history. With regard to mean age, the groups did not differ: 57.4 (7.3) years in the pitavastatin 4 mg group and 58.6 (8.0) in the pitavastatin 2 mg group ($P = 0.09$). The distribution, according to the age group, was >80% similar in both the 50s and the 60s (data not shown, $P = 0.14$). No significant differences were found in the previous history of dyslipidemia treatment and in concomitant medication use between the 2 groups. The most frequently identified comorbidities were cardiovascular disorders. The prevalence of hypertension, coronary artery diseases, and heart failure was similar between the 2 groups.

Primary Efficacy End Point

The primary efficacy end point was the change of HbA_{1c} from the baseline to the end of week 24 of the study. The primary evaluation was performed in the PP analysis group but also evaluated in the ITT

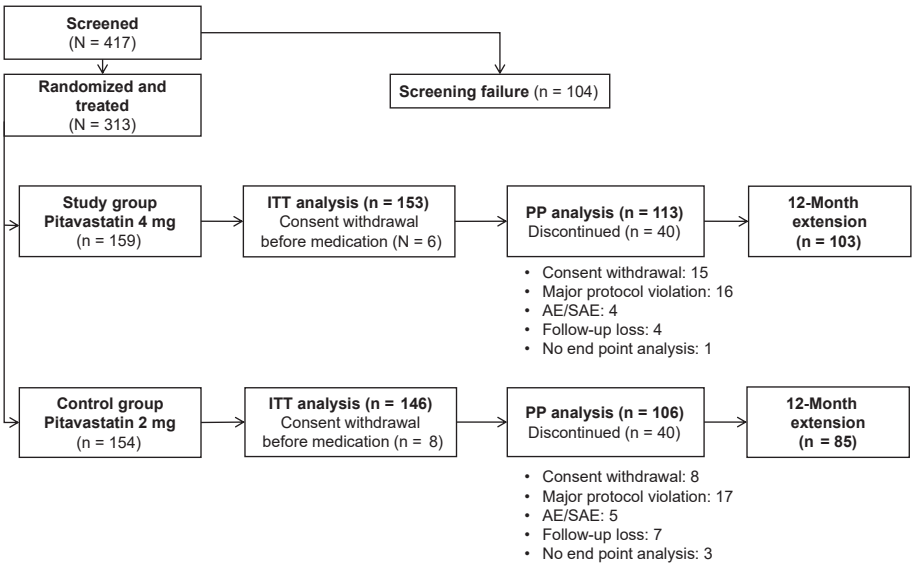

Figure 2. Flow of patients throughout the study. ITT = intention to treat; PP = per protocol.

Table I. Baseline characteristics (intention-to-treat analysis set).*

Characteristic	Study Group (n = 153)	Control Group (n = 146)	Total (N = 299)	*P*
Age, mean (SD), y	57.4 (7.3)	58.6 (8.0)	58.0 (7.7)	0.09†
Male	60.13	58.90	59.53	0.83‡
BMI, mean (SD), kg/m^2	25.93 (3.02)	25.54 (2.90)	25.74 (2.97)	0.36§
Previous history of dyslipidemia treatment	77.8	76.7	77.3	0.83
Cardiovascular disease	70.6	76.0	73.2	0.29‡
Hypertension	68.6	75.3	71.9	0.20‡
Angina pectoris	32.0	24.7	28.4	0.16‡
Myocardial infarction Heart failure	7.8	8.9	8.4	0.74‡
	1.3	1.4	1.3	>0.99‡
Concomitant medication				0.42‡
β-blocking agent	9.8	13.0	11.4	0.38‡
Calcium channel blocker	16.3	14.4	15.4	0.64‡
RAS-acting agent	23.5	23.3	23.4	0.96‡
Diuretic	4.6	2.1	3.3	0.34‖
Aspirin	19.0	17.8	18.4	0.80‡

RAS = renin angiotensin system.
* Data are presented as percentage of patients unless otherwise indicated.
† *t* test.
‡ Pearson χ^2 test.
§ Wilcoxon's rank-sum test.
‖ Fisher exact test.

analysis group. In the PP analysis, baseline HbA_{1c} levels in the study group and the control group were 5.84% (0.25%) (40.33 mmol/mol) and 5.83% (0.27%) (40.22 mmol/mol), respectively (to convert to millimoles per mole, multiple by 10.93, then subtract 23.5). At 24 weeks, the values were 5.90% (0.31%) (40.99 mmol/mol) ($P = 0.82$) and 5.87 (0.31%) (40.66 mmol/mol) ($P = 0.36$), respectively. The change in HbA_{1c} from baseline to 24 weeks was 0.06% (0.20%) (median, 0.00%) in the study group and 0.03% (0.22%) (median, 0.00%) in the control group. The mean difference between groups was 0.03% (95% CI, −0.02 to 0.08; $P = 0.27$). The upper bound (0.08%) of the 2-sided 95% CI was greater than the acceptable noninferiority margin of 0.4%.

The ITT analysis found the same tendency. Baseline HbA_{1c} levels in the study group and the control group were 5.88% (0.31%) (40.77 mmol/mol) and 5.87% (0.35%) (40.66 mmol/mol), respectively. At 24 weeks, the values were 5.94% (0.34%) (41.42 mmol/mol) ($P = 0.7170$) and 5.90% (0.37%) (40.99 mmol/mol) ($P = 0.32$), respectively. The change in HbA_{1c} from baseline to 24 weeks was 0.06% (0.21%) (median, 0.00%) in the study group and 0.03% (0.22%) (median, 0.00%) in the control group. The mean difference between groups was 0.03% (95% CI, −0.02 to 0.08; $P = 0.24$). The upper limit of the CI was 0.08%, which was less than the acceptable noninferiority margin of 0.4% (Table II).

Next, we evaluated the predetermined subgroup analysis according to the baseline body mass index (≥25 or <25 kg/m^2). In patients with a body mass index ≥25 kg/m^2, only the HbA_{1c} levels of those in the study group were elevated by 0.06% (0.35%) ($P = 0.03$), and the change in HbA_{1c} from baseline to 24 weeks was 0.07% (0.19%) (median, 0.10%; $P = 0.02$) in the study group and 0.08% (0.25%) (median, 0.10%; $P = 0.04$) in the control group. The mean difference between the 2 groups was −0.02% (95% CI, −0.11 to 0.07; $P = 0.95$) (Table III).

Secondary Efficacy End Points

Glucose Metabolism

The changes in HbA_{1c} from baseline until the end of week 52 were evaluated. In the PP group, HbA_{1c} levels were elevated in both group after 52 weeks by 0.10% (0.25%) (median, 0.10%; $P < 0.01$) in the study group and by 0.10% (0.30%) (median, 0.10%; $P < 0.01$) in the control group (Figure 3). However, the mean difference between the groups was 0.00 mg/dL (95% CI, −0.07 to 0.08; $P = 0.91$). The ITT analysis found the same tendency (data not shown).

Baseline fasting plasma glucose levels in the study and control groups were 107.62 (6.82) mg/dL and 106.42 (8.74) mg/dL ($P = 0.26$), respectively. With regard to fasting plasma glucose, the test and control levels at 24 weeks were 109.09 (9.70) mg/dL and 109.74 (10.58) mg/dL, respectively, whereas those at 12 months were

Table II. Change in HbA_{1c} from the baseline until the end of week 24.

Time Point	HbA_{1c}, Mean (SD), %			*P*
	Study Group	Control Group	Total	
PP analysis				
Baseline	5.84 (0.25)	5.83 (0.27)	5.84 (0.26)	0.82
24 Weeks	5.90 (0.31)	5.87 (0.31)	5.89 (0.31)	0.36
24 Weeks – baseline	0.06 (0.20)	0.03 (0.22)	0.05 (0.21)	0.27
P (within group)	<0.01	0.26	<0.01	
ITT analysis				
Baseline	5.88 (0.31)	5.87 (0.35)	5.88 (0.33)	0.72
24 Weeks	5.94 (0.34)	5.90 (0.37)	5.92 (0.35)	0.32
24 Weeks – baseline	0.06 (0.21)	0.03 (0.22)	0.05 (0.22)	0.24
P (within group)	<0.01	0.14	<0.01	

HbA_{1c} = glycosylated hemoglobin; ITT = intention to treat; PP = per protocol.

Table III. Predetermined subgroup analysis of the change of in HbA_{1c} according to BMI.

Time Point	HbA_{1c}, Mean (SD), %			*P*
	Study Group	Control Group	Total	
BMI ≥25 kg/m^2				
Baseline	5.81 (0.21)	5.82 (0.26)	5.81 (0.24)	0.78
24 Weeks	5.87 (0.29)	5.82 (0.28)	5.84 (0.28)	0.31
24 Weeks – baseline	0.06 (0.21)	−0.00 (0.18)	0.03 (0.20)	0.09
P (within group)	0.03	0.67	0.18	
BMI <25 kg/m^2				
Baseline	5.89 (0.29)	5.85 (0.28)	5.87 (0.28)	0.48
24 Weeks	5.96 (0.33)	5.94 (0.33)	5.95 (0.33)	0.78
24 Weeks − baseline	0.07 (0.19)	0.08 (0.25)	0.07 (0.22)	0.95
P (within group)	0.02	0.04	<0.01	

BMI = body mass index; HbA_{1c} = glycosylated hemoglobin.

108.65 (11.23) mg/dL and 110.00 (13.62) mg/dL, respectively ($P = 0.32$ at 24 weeks and $P = 0.26$ at 12 months). Baseline fasting serum insulin levels in the study and control groups were 7.18 (4.55) μg/dL and 6.37 (3.36) μg/dL ($P = 0.14$), respectively. With regard to fasting serum insulin, the test and control levels at 24 weeks were 8.68 (13.27) μg/dL and 6.95 (4.35) μg/dL, respectively, whereas those at 12 months were 7.62 (4.50) μg/dL and 7.26 (4.66) μg/dL, respectively ($P = 0.21$ at 24 weeks and $P = 0.57$ at 12 months). Baseline homeostatic model assessment of insulin resistance (HOMA-IR) values of the test and control groups were 1.93 (1.32) μg/dL and 1.69 (0.96) μg/dL ($P = 0.12$), respectively. The HOMA-IR values of the test and control groups at 24 weeks were 2.49 (4.81) and 1.92 (1.36), respectively, whereas those at 12 months were 2.10 (1.39) and 2.06 (1.75) ($P = 0.42$ at 24 weeks and $P = 0.81$ at 12 months), respectively. In addition, the change in HOMA-IR was not significant compared with the baseline or between groups.

During 1 year, 27 patients (12.33%) in the PP group developed NODM, including 12 of the 113 patients in the study group (10.62%) and 15 of the 106 patients in the control group (14.15%) ($P = 0.43$). With regard to the ITT patients, a total of 57 (19.06%) developed NODM, including 31 (20.26%) of the 153 patients in the study group and 26 (17.81%) of the 146 patients in the control group ($P = 0.59$).

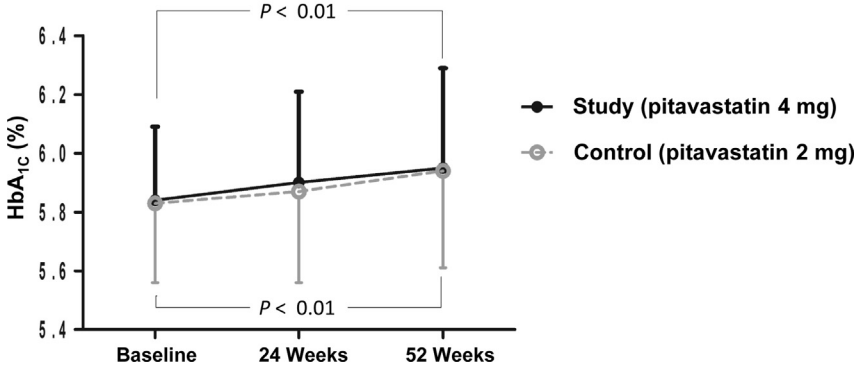

Figure 3. Glycosylated hemoglobin (HbA_{1c}) changes from baseline to study weeks 24 and 52.

Cholesterol and Adiponectin

Baseline total cholesterol levels in the study and control groups were not significantly different. After 24 weeks of treatment, the reduction of total cholesterol in the study group was significantly higher than in the control group ($P < 0.01$). Baseline LDL-C levels in the study and control groups were not significantly different. After 24 weeks of treatment, the reduction in the study group was significantly higher than that in the control group ($P < 0.01$). Baseline triglyceride levels in the study and control groups were not significantly different. No significant difference was found in the change between the 2 groups ($P = 0.80$). Baseline HDL-C levels in the study and control groups were not significantly different. The change at 24 weeks was not significantly different between the groups ($P = 0.88$). The baseline ApoA1/ApoB ratios in the study and control groups were not significantly different. Interestingly, after the 24-week treatment, the ApoA1/ApoB ratio was significantly higher in the study than the control group ($P < 0.01$) (Table IV).

Table IV. Changes in cholesterol, inflammation, and adiponectin after 24 weeks.

Time Point	Study Group	Control Group	Total	*P*
Total cholesterol, mean (SD), mg/dL				
Baseline	220.34 (42.73)	223.32 (37.55)	221.78 (40.24)	0.59
24 Weeks	161.65 (35.00)	173.95 (29.43)	167.60 (32.93)	<0.01
24 Weeks – baseline	−58.69 (31.42)	−49.37 (30.32)	−54.18 (31.17)	<0.01
P (within group)	<0.0001	<0.0001	<0.0001	
LDL-C, mean (SD), mg/dL				
Baseline	144.59 (40.69)	149.62 (33.02)	147.03 (37.18)	0.32
24 Weeks	90.43 (28.90)	101.55 (25.63)	95.81 (27.87)	<0.01
24 Weeks – baseline	−54.16 (30.67)	−48.08 (31.20)	−51.21 (31.01)	<0.01
P (within group)	<0.0001	<0.0001	<0.0001	
Triglyceride, mean (SD), mg/dL				
Baseline	200.94 (191.04)	164.49 (87.23)	183.30 (150.82)	0.08
24 Weeks	146.70 (72.95)	137.81 (66.38)	142.40 (69.83)	0.35
24 Weeks – baseline	−54.24 (181.68)	−26.68 (66.00)	−40.90 (138.73)	0.80
P (within group)	<0.0001	<0.0001	<0.0001	
HDL-C, mean (SD), mg/dL				
Baseline	47.46 (13.62)	50.05 (12.21)	48.71 (12.99)	0.14
24 Weeks	51.71 (13.62)	53.97 (13.02)	52.81 (13.35)	0.21
24 Weeks – baseline	4.25 (8.65)	3.93 (8.47)	4.09 (8.55)	0.88
P (within group)	<0.0001	<0.0001	<0.0001	
ApoA 1/ApoB ratio				
Baseline	1.20 (0.32)	1.21 (0.32)	1.21 (0.32)	0.68
24 Weeks	1.87 (0.57)	1.72 (0.42)	1.80 (0.50)	0.03
24 Weeks – baseline	0.68 (0.40)	0.51 (0.35)	0.60 (0.39)	<0.01
P (within group)	<0.0001	<0.0001	<0.0001	
Adiponectin, mean (SD), µg/dL				
Baseline	8169.73 (4789.26)	8810.43 (5996.45)	8479.84 (5404.27)	0.39
24 Weeks	7641.56 (7906.65)	7675.00 (6993.57)	7657.74 (7461.62)	0.98
24 Weeks – baseline	−528.18 (7946.96)	−1135.43 (7698.47)	−822.10 (7815.65)	0.81
P (within group)	0.02	0.02	<0.01	

ApoA1/ApoB = apolipoprotein A1/apolipoprotein B; BMI = body mass index.

Baseline adiponectin levels in the study and control groups were 8169.7 (4789.3) μg/dL and 8810.4 (5996.5) μg/dL ($P = 0.39$). After the 24-week treatment, adiponectin levels were significantly decreased in both groups (–528.2 [7947.0] μg/dL, $P = 0.02$ in the study group and –1135.4 [7698.5] μg/dL, $P = 0.02$ in the control group), with no significant difference between the groups ($P = 0.81$). The percentage change in secondary efficacy end points from the baseline is illustrated in Figure 4.

Safety

In the ITT analysis group, 85 AEs in 57 patients (37.25%) in the study group and 59 of 47 patients (32.19%) in the control group were reported ($P = 0.36$). Among them, 8 cases in 7 patients (4.58%) in the study group and 7 in 6 patients (4.11%) in the control group were considered to be related to the study medication ($P = 0.84$). According to the World Health Organization Adverse Reactions Terminology System-Organ Class classification, the most frequently expressed abnormalities were central and peripheral nervous system disorders, such as headache, dizziness, and tingling sense, occurring in 17 cases (9.15%) in the study group and 11 cases in the control group (7.53%).

Serious AEs were reported in 7 patients (8.24%) in the study group and 6 (10.17%) in the control group. In the study group, 2 cases of tendon rupture and 1 case each of chest pain, bladder carcinoma, laryngeal neoplasm, skin laceration, and intracranial hemorrhage were reported. In the control group, 1 case each of lower leg fracture, rotated cuff syndrome, spinal stenosis, hyponatremia, angina pectoris, and abscess were reported. Among these cases, the angina pectoris in the control group was considered to be possibly related to the study medication. No significant blood test and vital sign abnormalities were reported during the study. In addition, no severe adverse drug reaction was reported.

DISCUSSION

The results of the present study indicate that high-dose pitavastatin does not aggravate glucose metabolism compared with usual dose pitavastatin in patients with hyperlipidemia and IFG. In patients with hyperlipidemia and IFG, pitavastatin therapy did not improve glucose metabolism. Conversely, in both groups, there was a significant but clinically negligible increase in HbA_{1c} (0.03%−0.05%). Indeed, in this study, very mild but apparent signs of glucose metabolism aggravation, such as increased HbA_{1c} and decreased adiponectin, were found in the high-dose pitavastatin group. In contrast, high-dose pitavastatin had a superior effect on cholesterol lowering and the ApoA1/ApoB ratio.

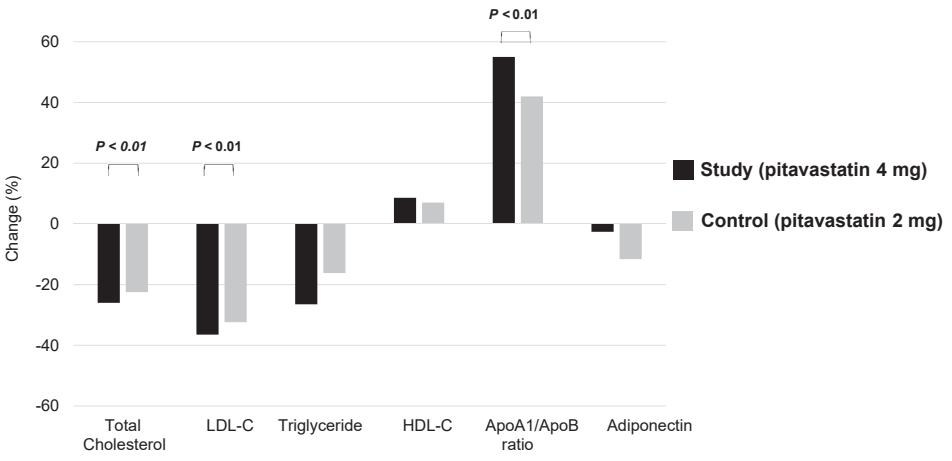

Figure 4. Secondary efficacy end point changes from baseline to week 24. ApoA1/ ApoB = apolipoprotein A1/ apolipoprotein B.

Although recent guidelines recommend high-intensity statin therapy in patients with atherosclerotic CVD, this therapy is not widely implemented in daily clinical practice (particularly in Asia) because of concerns about AEs.[22–24] Under these circumstances, the REAL-CAD study compared the preventive effect of high-dose with low-dose pitavastatin in atherosclerotic CVD, reporting the benefit of the maximum tolerable statin doses.[5] The SIPHON study focused on the possible diabetogenic effect of high-dose pitavastatin compared with the usual dose. Similarly, the Livalo in Acute Myocardial Infarction Study (LAMIS) II found that 4 mg of pitavastatin was superior at LDL-C lowering compared with 2 mg of pitavastatin, without adverse effects on glucose tolerance, in 1101 patients with acute myocardial infarction.[25]

The remarkable finding in the present study is the high incidence of NODM, reaching 12% during the 1-year follow-up period. However, it might be an incidence similar to that of a longitudinal cohort study in Japan, which reported a 38% incidence (for 5 years, and >10% in the first year) of NODM in the prediabetic population.[26] Similarly, the study by Ko et al[27] included 17,080 patients with myocardial infarction >65 years old who were prescribed intensive-dose or moderate-dose statin at hospital discharge and reported a 13% incidence of NODM during the 5-year follow-up period. Among various statins, pitavastatin reportedly has the lowest diabetogenic potential.[28–30] However, it failed to exert a protective effect against the high-risk NODM population. Concerning the effects of pitavastatin on DM, 2 studies have found neutral effects.[13,17] Compared with other statins, pitavastatin was as potent as atorvastatin at equivalent doses but had a less diabetogenic effect in the primary prevention in the obese population[19] and a secondary prevention study in patients with acute coronary syndrome.[31] Notably, a study of 20,000 pitavastatin-treated Japanese patients with hyperlipidemia found a neutral effect in patients without DM and a beneficial effect in patients with DM via HbA_{1c} reduction by 0.28%.[17] Conversely, a retrospective observational study suggested that pitavastatin increased diabetes risk more than other statins.[32] This discrepancy might be confounded by the clinicians' preference for statin use because statins are thought to be less diabetogenic in patients at a higher risk of developing diabetes.

There are several possible mechanisms for the diabetogenic effect of statins, with the simplest being a possible relationship between increases in calorie and fat intake after statin treatment and NODM.[33] However, statin-induced sarcopenia and muscle destruction can be associated with DM development.[34,35] Statins reportedly increase LDL-receptor expression via the activation of sterol regulatory element–binding proteins, which are also causally related to insulin resistance.[36] The disruption of voltage-gated calcium channel function in pancreatic β cells[37] and mitochondrial function in pancreatic β cells,[38] which leads to cellular apoptosis and impaired insulin secretion,[39] might affect serum glucose levels. Statin-induced cholesterol-dependent conformational changes in glucose transporter proteins might impair cellular glucose uptake.[40] The statin-induced decreased biosynthesis of the isoprenoid side chain of coenzyme Q10 has been implicated in the downregulation of glucose transporter 4 synthesis, mitochondrial oxidative stress, delayed adenosine triphosphate production, and β-cell apoptosis, resulting in impaired glucose-stimulated insulin secretion.[41,42] Currently, there are conflicting reports that refute[43] or support[44] the positive effect of coenzyme Q10 on insulin sensitivity, which warrants further evaluation.

The findings of the present study also indicate that high-dose lipid-lowering therapy could exert a more evident beneficial effect on usual dose lipid-lowering therapy, with negligible NODM risk. High-dose pitavastatin had a more potent LDL-C–lowering efficacy (by 5%), consistent with the well-established rule of 6%.[45] Moreover, high-dose lipid-lowering therapy reportedly turns the balance of proatherogenic and antiatherogenic particles to the antiatherogenic direction reflected by the higher ApoA1/ApoB ratio.[46] This findings might have clinical implications, thereby offering a plausible mechanism by which high-dose pitavastatin (4 mg/d) significantly reduces cardiovascular events, compared with low-dose (1 mg/d) pitavastatin therapy, in the REAL-CAD study.[5]

The present study has some notable limitations. First, we estimated the sample size with the predicted difference in HbA_{1c} between 2 groups as 0.11%. However, the observed difference between the 2 groups was 0.03%, which might have led to false-

negative results for the primary end point. Second, >75% of the patients received statin therapy before enrolling in the study. Although we implemented a 2- to 4-week washout and placebo run-in period to minimize the effect of the previous therapy, there could still be selection bias, especially for AE rate, which might leave legacy effects on glucose metabolism and NODM development. However, the institutional review board committee was concerned about having a more extended run-in period for the sake of patient tolerability, especially for secondary prevention cases.

In conclusion, high-dose pitavastatin (4 mg/d) did not aggravate glucose metabolism compared with usual dose pitavastatin (2 mg/d) in patients with hyperlipidemia and IFG. In contrast, high-dose pitavastatin had a better effect on cholesterol-lowering and apolipoprotein distribution.

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DECLARATION OF COMPETING INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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