Efficacy and Tolerability of Pitavastatin Versus Pitavastatin/Fenofibrate in High-risk Korean Patients with Mixed Dyslipidemia: A Multicenter, Randomized, Double-blinded, Parallel, Therapeutic Confirmatory Clinical Trial

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ABSTRACT

Purpose: Dyslipidemia is an important risk factor for cardiovascular disease (CVD). Statins are known to effectively reduce not only low-density lipoprotein cholesterol (LDL-C) level but also death and nonfatal myocardial infarction due to coronary heart disease. The risk for CVD from atherogenic dyslipidemia persists when elevated triglyceride (TG) and reduced high-density lipoprotein cholesterol (HDL-C) levels are not controlled with statin therapy. Therefore, statin/fenofibrate combination therapy is more effective in reducing CVD risk. Here, we assessed the efficacy and tolerability of pitavastatin/fenofibrate combination therapy in patients with mixed dyslipidemia and a high risk for CVD.

Methods: This multicenter, randomized, double-blind, parallel-group, therapeutic-confirmatory clinical trial evaluated the efficacy and tolerability of fixed-dose combination therapy with pitavastatin/fenofibrate 2/160 mg in Korean patients with a high risk for CVD and a controlled LDL-C level (<100 mg/dL) and a TG level of 150−500 mg/dL after a run-in period with pitavastatin 2 mg alone. In the 8-week main study, 347 eligible patients were randomly assigned to receive pitavastatin 2 mg with or without fenofibrate 160 mg after a run-in period. In the extension study, patients with controlled LDL-C and non−HDL-C (<130 mg/dL) levels were included after the completion of the main study. All participants in the extension study received the pitavastatin/fenofibrate combination therapy for 16 weeks for the assessment of the tolerability of long-term treatment.

Findings: The difference in the mean percentage change in non−HDL-C from baseline to week 8 between the combination therapy and monotherapy groups was −12.45% (95% CI, −17.18 to −7.72), and the combination therapy was associated with a greater reduction in non-HDL-C. The changes in lipid profile, including apolipoproteins, fibrinogen, and high-sensitivity C-reactive protein from baseline to weeks 4 and 8 were statistically significant with combination therapy compared to monotherapy at all time points. Furthermore, the rates of achievement of non−HDL-C and apolipoprotein B targets at week 8 in the combination therapy and monotherapy groups were 88.30% versus 77.98% ($P = 0.0110$) and 78.94% versus 68.45% ($P = 0.0021$), respectively. The combination therapy was well tolerated, with a safety profile similar to that of statin monotherapy.

Implications: In these Korean patients with mixed dyslipidemia and a high risk for CVD, combination therapy with pitavastatin/fenofibrate was associated with a greater reduction in non−HDL-C compared with that with pitavastatin monotherapy, and a significantly improvement in other lipid levels. Moreover, the combination therapy was well tolerated, with a safety profile similar to that of statin monotherapy. Therefore, pitavastatin/fenofibrate combination therapy could be effective and well tolerated in patients with mixed dyslipidemia. ClinicalTrials.gov identifier: NCT03618797. (*Clin Ther*. 2020;42:2021−2035)

Key words: cardiovascular disease, dyslipidemia, fenofibrate, non−high-density lipoprotein cholesterol, pitavastatin.

INTRODUCTION

Dyslipidemia is an elevation in plasma cholesterol, triglyceride (TG), or both, or a low high-density lipoprotein cholesterol (HDL-C) level, that contributes to the development of atherosclerosis. Notably, dyslipidemia is an important risk factor for cardiovascular disease (CVD). Low-density lipoprotein cholesterol (LDL-C) transports cholesterol from the liver to the cells. Particularly, if more cholesterol is present than is required by the body, it is retained in the vessel walls, causing atherosclerosis. Studies have reported that a reduced LDL-C level reduces CVD-related morbidity and mortality, and that lowering the LDL-C level is a strategy for reducing the risk for CVD.[1–3] Statin therapy, which effectively lowers the LDL-C level, has been recommended in the 2018 American College of Cardiology/American Heart Association guideline on the management of blood cholesterol over various ranges and for multiple purposes. Furthermore, it has been reported that statin therapy reduces LDL-C level, as well as coronary heart disease (CHD)-induced death and nonfatal myocardial infarction.[4–6]

Pitavastatin demonstrates potent 3-hydroxymethyl-glutaryl coenzyme A reductase inhibition. However, high-dose statin therapy, prescribed in patients with poorly controlled lipid levels, has been associated with an increased prevalence of complications, such as diabetes,[7] as well as severe myopathy, rhabdomyolysis, and elevated liver enzymes.[8,9] The use of statins has been limited due to the risk for CVD from atherogenic dyslipidemia, when an elevated TG and a reduced HDL-C level due to statin therapy cannot be controlled properly. However, combination therapy with fenofibrate can increase the success rate of dyslipidemia treatment when statin monotherapy fails to achieve the desired treatment goals. Fenofibrate, a fibric acid derivative, is known to reduce TG, apolipoprotein (Apo)-B, HDL-C, and Apo A1 levels in patients with mixed dyslipidemia.[10,11] Studies have reported that statin/fenofibrate combination therapy doubled the cholesterol-controlling effects without increasing the risk for adverse events.[12,13] Moreover, in the ACCORD (Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus)[14] study, the risk for CVD was reduced in patients with atherogenic dyslipidemia treated with a combination of a statin and fenofibrate, from 17.3% to 12.4% over 4.7 years, compared with statin monotherapy.

Therefore, this study compared the efficacy and tolerability of pitavastatin/fenofibrate combination therapy versus pitavastatin monotherapy in high-risk patients with CHD and mixed dyslipidemia, with LDL-C levels controlled on statin monotherapy, but with poorly controlled levels of other lipids (eg, TG and HDL-C).

PATIENTS AND METHODS

Study Design

This multicenter, randomized, double-blind, parallel-group, therapeutic-confirmatory clinical trial evaluated the efficacy and tolerability of pitavastatin with or without fenofibrate in high-risk patients with mixed dyslipidemia. The study was composed of a main treatment period and an extension period. The main treatment period included a run-in period of pitavastatin monotherapy, followed by an 8-week treatment period, and the extension study included 16 weeks of combination therapy in participants enrolled in the main study, for the assessment of the tolerability of long-term treatment.

This study was conducted at 25 Korean institutions (The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, and 24 others), and the protocol was approved by the institutional review boards at each participating center. All study participants provided written informed consent. This study was conducted according to the principles set forth in the Declaration of Helsinki and the Good Clinical Practice guidelines (ClinicalTrials.gov identifier: NCT03618797).

Patients were required to discontinue lipid-lowering therapy before entering the run-in period. The run-in period was conducted in participants prescribed pitavastatin 2 mg and in whom the dose was consistent for the 4-week run-in period in those receiving statins or a ≥6-week run-in period in those receiving a fibrate before screening. After the run-in period with pitavastatin 2 mg, patients whose LDL-C was <100 mg/dL and whose TG was between 150 and 500 mg/dL were randomly assigned to receive pitavastatin 2 mg with or without fenofibrate 160 mg for 8 weeks in the main study. In the extension study, patients with an LDL-C of <100 mg/dL and a non−HDL-C of <130 mg/dL (measured at a central

laboratory) were included after the completion of the main study. All participants in the extension study received the pitavastatin/fenofibrate 2/160 mg combination therapy for 16 weeks, regardless of their treatment arm assignment in the main study, for the assessment of the tolerability of long-term treatment. From the start of screening, therapeutic lifestyle changes were conducted throughout the study periods according to the protocol (see Appendix in the online version at https://doi.org/10.1016/j.clinthera.2020.08.002).

Study Population

The baseline characteristics, such as sex, age, weight, body mass index, medical history, and risk factors for CHD were collected (Table I). This study enrolled men and women aged between 19 and 80 years with documented mixed dyslipidemia and high CVD risk according to Adult Treatment Panel III definitions. Patients were required to meet ≥1 of the following criteria: (1) history of CHD, (2) history of other clinical forms of atherosclerotic disease, (3) diabetes, or (4) CHD risk of ≥20% over 10 years as determined by the Framingham risk calculation. The present study excluded patients who had acute coronary syndrome within 3 months or heart failure (New York Heart Association class III/IV) within 6 months before screening; secondary or iatrogenic dyslipidemia caused by hypothyroidism or nephrotic syndrome; >2-fold the upper limit of normal level of aspartate aminotransferase, alanine aminotransferase, or creatine phosphokinase; disease of the gallbladder or pancreatitis; elevated serum creatinine level (≥2.5 mg/dL); creatinine phosphokinase level >2-fold the upper limit of normal; hypersensitivity to hydroxymethylglutaryl coenzyme A reductase inhibitors, fibrate, and/or ketoprofen; uncontrolled hypertension (systolic blood pressure of ≥180 mm Hg or diastolic blood pressure of ≥110 mm Hg); uncontrolled diabetes mellitus (hemoglobin A_{1c} of ≥9.0%); a history of myopathy; a history of muscle toxicity with the use of statins or fibrates; in women (including those of childbearing potential), current or planned pregnancy and/or breastfeeding or inadequate method of contraception; contraindications for participation; inability to participate based on legal reasons or the investigator's decision; and/or concurrent drug therapy that could have interacted with the study drug. Patients who underwent a baseline evaluation and met the eligibility criteria were enrolled.

Eligible patients were randomly assigned to receive treatment with a fixed-dose combination of pitavastatin/fenofibrate 2/160 mg (1 capsule) plus a pitavastatin-matched placebo (1 tablet) (combination therapy group), or a pitavastatin/fenofibrate-matched placebo (1 capsule) plus pitavastatin 2 mg (1 tablet) (monotherapy group), and were followed up as per routine clinical practice.

Efficacy and Tolerability Assessments

The primary efficacy end point of this study was the mean percentage change in non−HDL-C from baseline to the end of the efficacy period (week 8 of treatment). The secondary efficacy end points included the mean percentage change in non−HDL-C from baseline to week 4, as well as the mean percentage changes in LDL-C, HDL-C, remnant cholesterol (remnant C), non−HDL-C/HDL-C, LDL-C/HDL-C, total cholesterol (TC), TG, very low-density lipoprotein (VLDL)-C, TC/HDL-C, Apo A1, Apo B, Apo B/Apo A1, fibrinogen, and hs-CRP from baseline to weeks 4 and 8. According to the National Cholesterol Education Program Adult Treatment Panel III guideline,[15] the *target goal−achievement rate* was defined as the percentage of patients who achieved an LDL-C of <100 mg/dL and a non−HDL-C of <130 mg/dL; target goal−achievement rates were calculated at weeks 4 and 8.

All adverse events from the initiation of the run-in period to the end of extension study were collected for tolerability assessment. Adverse events, serious adverse events, and other adverse events resulting in the termination of treatment were analyzed and are described as the prevalence (%) and number of occurrences in each treatment arm. Tolerability in the main treatment and extension periods were analyzed separately.

Adherence to treatment was assessed using pill counts and was calculated as the percentage of the number of prescribed pills, corrected for the number of returned pills, divided by the period (in days), multiplied by 100%.

Statistical Analysis

Continuous data, such as demographics (age, weight, height, and body mass index), were collected at baseline and analyzed using the *t* test or Wilcoxon

rank-sum test. Categorical data, such as sex and CHD risk factors, were assessed using the χ^2 test or the Fisher exact test. Efficacy variables were compared between treatment groups using the *t* test, and the paired *t* test was used for comparing the variables between treatment groups at each time

Table I. Baseline characteristics of randomized patients in this study of pitavastatin calcium 2 mg with or without fenofibrate 160 mg. Data are given as mean (SD) unless otherwise noted.

Characteristic	Combination Therapy (n = 174)	Monotherapy (n = 173)	All Patients (N = 347)	*P*
Sex, no. (%)				0.2473
Male	116 (66.67)	105 (60.69)	221 (63.69)	
Female	58 (33.33)	68 (39.31)	126 (36.31)	
Age, y	61.68 (10.26)	61.91 (9.26)	61.79 (9.76)	0.9816
Weight, kg	69.07 (11.39)	69.68 (11.82)	69.37 (11.59)	0.7816
BMI, kg/m^2	26.06 (2.85)	26.25 (3.46)	26.16 (3.17)	0.9812
Duration of hyperlipidemia, y	7.58 (5.38)	6.71 (4.94)	713 (5.18)	0.1257
Risk factors, no. (%)				
Smoking habit				0.3763
Nonsmoker	133 (76.44)	139 (80.35)	272 (78.39)	
Smoker	41 (23.56)	34 (19.65)	75 (21.61)	
Diabetes mellitus				0.3172
Yes	146 (83.91)	138 (79.77)	284 (81.84)	
No	28 (16.09)	35 (20.23)	63 (18.16)	
Treatment for hypertension				0.8792
Yes	113 (64.94)	111 (64.16)	224 (64.55)	
No	61 (35.06)	62 (35.84)	123 (35.45)	
MI				0.0703
Yes	26 (14.94)	15 (8.67)	41 (11.82)	
No	148 (85.06)	158 (91.33)	306 (88.18)	
Angina pectoris				0.3508
Yes	35 (20.11)	42 (24.28)	77 (22.19)	
No	139 (79.89)	131 (75.72)	270 (77.81)	
PCI				0.7309
Yes	44 (25.29)	41 (23.70)	85 (24.50)	
No	130 (74.71)	132 (76.30)	262 (75.50)	
Other clinical atherosclerosis				0.3893
Yes	10 (5.75)	14 (8.09)	24 (6.92)	
No	164 (94.25)	159 (91.91)	323 (93.08)	
10-y CHD risk ≥20% by FRS				0.8589
Yes	15 (8.62)	14 (8.09)	29 (8.36)	
No	159 (91.38)	159 (91.91)	318 (91.64)	

BMI = body mass index; CHD = coronary heart disease; FRS = Framingham risk score; MI = myocardial infarction; PCI = percutaneous coronary intervention.

point. Differences in the prevalences of adverse events and serious adverse events observed in the main treatment and extension periods were evaluated using the χ^2 test or the Fisher exact test. All statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Demographic Characteristics

In this study, 347 of the 867 registered participants were randomized. The tolerability analysis was performed in 343 participants (172 in the combination therapy group, 171 in the monotherapy group) who received study medication and were included in the tolerability analysis at least once, and 339 participants (171 in the combination therapy group, 168 in the monotherapy group) were included in the full analysis set. Among participants included in the full analysis set, 296 (145 in the combination therapy group, 151 in monotherapy group) who had completed the clinical study were included in the per-protocol set. For the long-term tolerability analysis during the extension period, 216 participants (113 in the combination therapy group, 103 in the monotherapy group) were included. The main participants for the analysis of the study were included in the full analysis set (Figure 1).

Patients' demographic characteristics are described in Table I. The mean (SD) ages were 61.68 (10.26) and 61.91 (9.26) years in the combination and monotherapy groups, respectively; mean weight, 69.07 (11.39) and 69.68 (11.82) kg. The mean body mass index values were 26.06 (2.85) and 26.25 (3.46) kg/m^2 in the combination and monotherapy groups, respectively. There were no statistically

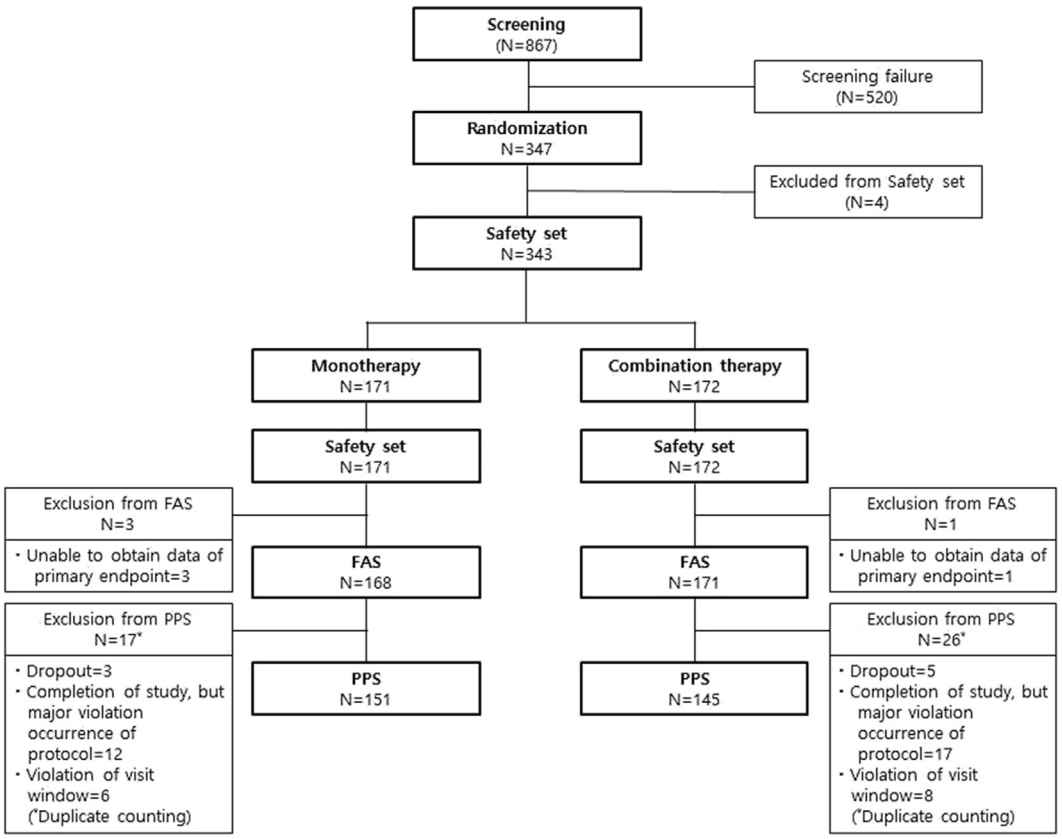

Figure 1. Participant flow chart. FAS = full analysis set; PPS = per-protocol set.

significant differences observed between the 2 groups. There were also no statistically significant differences in sex or risk factors.

Primary Efficacy Evaluation

The primary efficacy end point, the mean (SEM) percentage change in non−HDL-C from baseline to week 8, was −7.38% (1.72%) in the combination therapy group and +5.07% (1.68%) in the monotherapy group. This change was statistically significant in the 2 groups ($P < 0.001$ and $P < 0.01$ vs baseline, respectively). The difference in mean percentage changes in non−HDL-C from baseline to week 8 between the combination and monotherapy groups was −12.45%, which was statistically significant (95% CI, −17.18 to −7.72; $P < 0.001$), with the combination therapy demonstrating a greater reduction in non−HDL-C compared to the monotherapy (Figure 2).

Secondary Efficacy Evaluation

The percentage changes in blood concentrations of non−HDL-C, LDL-C, HDL-C, remnant C, non-HDL-C/HDL-C, and LDL-C/HDL-C from baseline to weeks 4 and 8 of study treatment are shown in Table II. The mean (SEM) percentage changes in non−HDL-C level from baseline to week 4 were −8.11% (1.45%) and +2.00% (1.34%) in the combination and monotherapy groups, respectively ($P < 0.001$ between groups). This change was statistically significant in the combination therapy group ($P < 0.001$ vs baseline).

In both the combination and monotherapy groups, the percentage changes in LDL-C level from baseline to weeks 4 and 8 were statistically significant (all, $P < 0.01$). The differences in the mean percentage changes between the 2 groups were not statistically significant at either time point. However, the mean (SEM) percentage changes in remnant C level from baseline to week 8 were −38.36% (2.60%) and +1.22% (5.68%) in the combination and monotherapy groups, respectively ($P < 0.001$ between groups).

The mean percentage changes in HDL-C level from baseline to week 4 were +16.54% (1.61%) and +3.72% (1.30%) in the combination and the monotherapy groups, respectively (both, $P < 0.01$ vs baseline); at week 8, +20.65% (1.80%) and +2.25% (1.26%) ($P < 0.001$ and P = NS vs baseline). These changes were significantly different between the 2 groups at both time points (both, $P < 0.001$).

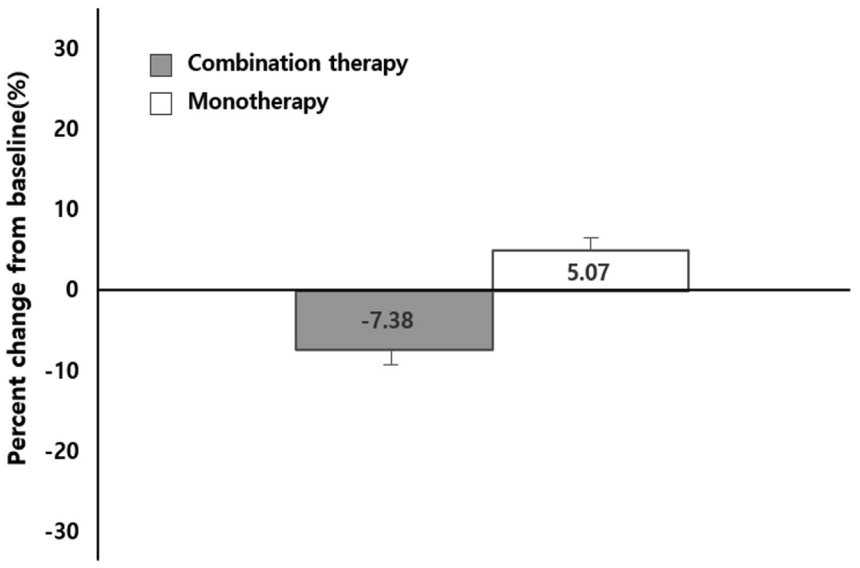

Figure 2. Primary efficacy end point: mean (SEM) percentage changes from baseline in non−HDL-C at week 8 with pitavastatin calcium 2 mg with or without fenofibrate 160 mg. $P < 0.001$ between groups.

Table II. Lipid measurements with pitavastatin calcium 2 mg with or without fenofibrate 160 mg

Lipid	Combination Therapy (n = 174)		Monotherapy (n = 173)	
	Mean (SEM), mg/dL	%Change	Mean (SEM), mg/dL	%Change
Non-HDL-C				
Baseline	107.94 (1.29)		108.57 (1.46)	
Week 4	99.02 (1.80)	−8.11 (1.45)***†††	109.33 (1.57)	2.00 (1.34)
Week 8	99.05 (1.90)	−7.38 (1.72)***†††	112.86 (1.92)	5.07 (1.68)**
LDL-C				
Baseline	77.96 (1.12)	—	78.01 (1.10)	—
Week 4	81.51 (1.62)	6.42 (2.28)***	81.03 (1.42)	5.51 (1.87)**
Week 8	82.25 (1.66)	7.73 (2.22)***	82.57 (1.74)	6.93 (2.18)**
HDL-C				
Baseline	42.06 (0.78)	—	41.38 (0.80)	—
Week 4	48.07 (0.84)	16.54 (1.61)***†††	42.49 (0.87)	3.72 (1.30)**
Week 8	49.79 (0.91)	20.65 (1.80)***†††	42.07 (1.80)	2.25 (1.26)
Remnant C‡				
Baseline	29.98 (0.84)	—	30.65 (1.02)	—
Week 4	17.51 (0.70)	−37.51 (2.51)***†††	28.30 (1.15)	−2.12 (4.99)
Week 8	16.80 (0.64)	−38.36 (2.60)***†††	30.29 (1.32)	1.22 (5.68)
Non−HDL-C/HDL-C				
Baseline	2.72 (0.06)	—	2.84 (0.08)	—
Week 4	2.20 (0.06)	−18.30 (1.77)***†††	2.78 (0.07)	1.01 (1.98)
Week 8	2.13 (0.06)	−19.33 (2.26)***†††	2.93 (0.09)	6.17 (2.43)*
LDL-C/HDL-C				
Baseline	1.95 (0.04)	—	2.01 (0.05)	—
Week 4	1.80 (0.05)	−6.88 (2.12)**†††	2.03 (0.05)	3.06 (1.75)
Week 8	1.76 (0.05)	−7.51 (2.41)**†††	2.09 (0.05)	6.06 (2.20)**

HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.
*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ versus baseline.
†††$P < 0.001$ versus monotherapy.
‡Remnant C = total cholesterol − (HDL-C) − (LDL-C).

The mean percentage changes in non−HDL-C/HDL-C from baseline to week 4 were −18.30% (1.77%) and +1.01% (1.98%) in the combination and monotherapy groups, respectively ($P < 0.001$ and P = NS vs baseline); at week 8, −19.33% (2.26%) and +6.17% (2.43%) ($P < 0.001$ and $P < 0.05$ vs baseline). These changes were significantly different between the 2 groups at both time points (both, $P < 0.001$).

The mean percentage changes in LDL-C/HDL-C from baseline to weeks 4 and 8 were significantly different between the 2 groups at both time points (both, $P < 0.001$).

Changes in Blood Concentrations of TC, TG, VLDL-C, and Other CVD Risk Factors

Comparisons of the changes in TC, TG, VLDL-C, TC/HDL-C, Apo A1, Apo B, Apo B/Apo A1, and fibrinogen from baseline to weeks 4 and 8 of treatment in the combination and monotherapy groups are shown in Table III.

The mean (SEM) percentage changes in TC from baseline to week 4 were −1.42% (1.08%) and +1.71% (0.99%) in the combination and monotherapy groups, respectively; at week 8, −0.18% (1.21%) and +3.60% (1.15%). The difference in these changes between the 2 groups was

statistically significant at both time points (week 4, $P = 0.0330$; week 8, $P = 0.0244$). The mean percentage changes in TG, VLDL-C, and TC/HDL-C from baseline to weeks 4 and 8 were significantly greater in the combination therapy group compared to the monotherapy group (all, $P < 0.001$).

The mean (SEM) percentage changes in Apo A1 from baseline to week 4 were +4.40% (1.12%) and +0.20% (0.82%) in the combination and monotherapy groups, respectively ($P < 0.001$ and P = NS); at week 8, +6.91% (1.28%) and +1.03% (0.89%) ($P < 0.001$ and P = NS). The between-group differences in these changes were statistically significant at both time points (week 4, $P < 0.01$; week 8, $P < 0.001$). The mean percentage changes in Apo B from baseline to week 4 were −3.58% (1.53%) and +3.79% (1.53%) in the combination and monotherapy groups, respectively (both, $P < 0.05$ vs baseline); at week 8, −2.44% (1.66%) and +5.86% (1.82%) (P = NS and $P < 0.01$ vs baseline). The differences in changes were statistically significant between the 2 groups (both, $P < 0.001$). The mean percentage changes in Apo B/Apo A1 from baseline to week 4 were −6.48% (1.70%) and +4.51% (1.85%) in the combination and monotherapy groups, respectively ($P < 0.001$ and $P < 0.05$ vs baseline); at week 8, −6.50% (2.06%) and +6.13 (2.06%). The differences in these changes were statistically significant between the 2 groups (both, $P < 0.001$).

The mean (SEM) percentage changes in fibrinogen level at week 4 were −8.52% (1.49%) and +3.83% (1.80%) in the combination and monotherapy groups, respectively ($P < 0.001$ and $P < 0.05$ vs baseline); at week 8, −10.23% (1.49%) and +4.43% (1.61%) ($P < 0.001$ and $P < 0.01$ vs baseline). These changes were significantly different between the 2 groups (both, $P < 0.001$). The median percentage changes in hs-CRP at week 4 were −20.00% and 0 in the combination and monotherapy groups, respectively; at week 8, −16.67 and 0. These changes were significantly different between the 2 groups (week 4, $P = 0.0042$; week 8, $P = 0.0071$).

Achievement Rates of Target Goals

Patients who achieved an LDL-C of <100 mg/dL and/or a non−HDL-C of <130 mg/dL and an Apo B of <90 mg/dL at week 8 of treatment were included in the calculation of the target goal−achievement rate (Figure 3). A total of 80.12% (137/171) patients in the combination therapy group and 77.98% (131/168) patients in the monotherapy group achieved an LDL-C of <100 mg/dL; this difference was not significant.

With regard to non−HDL-C level, the target-achievement rate at week 8 was greater in the combination therapy group than in the monotherapy group (88.30% [151/171] vs 77.98% [131/168]; $P = 0.0110$). The rates of achievement of both the LDL-C and non−HDL-C targets at week 8 were 79.53% (136/171) in the combination therapy group and 69.64% (117/168) in the monotherapy group. The achievement rate of both the LDL-C and non-HDL-C targets was significantly greater in the combination therapy group than in the monotherapy group ($P = 0.0364$).

The rate of achievement of the Apo B target goal (<90 mg/dL) at week 8 was greater with combination therapy versus monotherapy (78.94% vs 68.45%; $P = 0.0021$).

Tolerability Evaluation

Adverse drug reactions were reported in 3.49% (6/172) and 1.75% (3/171) of patients in the combination and monotherapy groups, respectively, during the 8-week treatment period (Table IV).

The rates of adverse drug reactions reported during the 16-week, long-term tolerability extension study were 3.54% (4/113) and 8.74% (9/103) in the combination and monotherapy groups, respectively (see the Supplemental Table in the online version at doi:10.1016/j.clinthera.2020.08.002).

There was no difference in drug adherence between the 2 groups. Drug-adherence rates were 96.50% (5.53%) in the combination therapy group and 96.77% (6.07%) in the monotherapy group in the main study (data not shown).

DISCUSSION

In this study, the use of pitavastatin (statin)/fenofibrate combination therapy was associated with a decrease in non−HDL-C (primary efficacy end point) that was significantly greater than that with pitavastatin monotherapy in these high-risk patients with mixed dyslipidemia. The LDL-C level was controlled similarly in the pitavastatin/fenofibrate combination and pitavastatin monotherapy groups. However, TG, HDL-C, TC, and other lipids that are difficult to

Table III. Lipid, apolipoprotein, fibrinogen, and hs-CRP measurements with pitavastatin calcium 2 mg with or without fenofibrate 160 mg

Parameter	Combination Therapy (n = 174)		Monotherapy (n = 173)	
	Mean (SEM), mg/dL	%Change	Mean (SEM), mg/dL	%Change
TC				
Baseline	150.00 (1.40)	—	150.04 (1.34)	—
Week 4	147.09 (1.70)	−1.42 (1.08)†	151.82 (1.63)	1.71 (0.99)
Week 8	148.84 (1.90)	−0.18 (1.21)†	154.93 (1.95)	3.60 (1.15)**
TG				
Baseline	244.92 (5.72)	—	255.71 (6.64)	—
Week 4	143.40 (4.65)	−40.09 (1.57)***†††	238.10 (7.97)	−2.84 (2.97)
Week 8	141.95 (4.80)	−39.66 (2.05)***†††	252.83 (9.48)	2.09 (3.13)
VLDL-C				
Baseline	48.98 (1.14)	—	51.15 (1.33)	—
Week 4	28.68 (0.93)	−40.09 (1.57)***†††	47.62 (1.59)	−2.85 (2.97)
Week 8	28.39 (0.96)	−39.66 (2.05)***†††	50.57 (1.90)	2.07 (3.13)
TC/HDL-C				
Baseline	3.72 (0.06)	—	3.84 (0.08)	—
Week 4	3.20 (0.06)	−13.31 (1.26)***†††	3.78 (0.07)	0.04 (1.37)
Week 8	3.13 (0.06)	−14.48 (1.57)***†††	3.93 (0.09)	3.55 (1.63)*
Apo A1				
Baseline	135.87 (1.94)	—	134.72 (1.84)	—
Week 4	139.83 (1.80)	4.40 (1.12)***††	134.42 (1.90)	0.20 (0.82)
Week 8	143.49 (1.96)	6.91 (1.28)***†††	135.30 (1.85)	1.03 (0.89)
Apo B				
Baseline	79.62 (1.09)	—	79.45 (11.10)	—
Week 4	76.34 (1.44)	−3.58 (1.53)*†††	80.99 (1.16)	3.79 (1.53)*
Week 8	76.71 (1.43)	−2.44 (1.66)†††	82.76 (1.29)	5.86 (1.82)**
Apo B/Apo A1				
Baseline	0.61 (0.01)	—	0.61 (0.01)	—
Week 4	0.56 (0.01)	−6.48 (1.70)***†††	0.62 (0.01)	4.51 (1.85)*
Week 8	0.55 (0.01)	−6.50 (2.06)**†††	0.63 (0.01)	6.13 (2.06)**
Fibrinogen				
Baseline	281.78 (4.88)	—	288.39 (4.66)	—
Week 4	252.42 (4.72)	−8.52 (1.49)***†††	294.60 (5.55)	3.83 (1.80)*
Week 8	246.78 (4.14)	−10.23 (1.49)***†††	295.17 (4.69)	4.43 (1.61)**

Table III. (*Continued*)

Parameter	Combination Therapy (n = 174)		Monotherapy (n = 173)	
	Mean (SEM), mg/dL	%Change	Mean (SEM), mg/dL	%Change
hs-CRP‡				
Baseline	0.70 (0.10–28.70)	–	0.75 (0.10, 10.90)	–
Week 4	0.60 (0.10–26.90)	−20.00 (−95.18 to 1683.33)§	0.80 (0.20–115.20)	0.00 (−94.4 to 28700.0)
Week 8	0.60 (0.10–26.70)	−16.67 (−97.56 to 2800.00)§	0.80 (0.20–85.80)	0.00 (−95.00 to 2751.72)

Apo = apolipoprotein; hs-CRP = high-sensitive C-reactive protein; TC = total cholesterol; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol.
*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ versus baseline.
†$P < 0.05$.
††$P < 0.01$, and †††$P < 0.001$ versus monotherapy.
‡Median (range).
§$P < 0.01$ (Wilcoxon rank sum test).

control with pitavastatin monotherapy were well controlled with combination therapy. Combination therapy was more efficacious in reducing levels of inflammatory markers such as fibrinogen and hs-CRP than was monotherapy and had a significant effect on remnant C, which is one of the parameters of atherogenic lipoprotein.

Statins are a standard lipid-lowering medication used for reducing CVD-related morbidity, including atherosclerosis, in patients with dyslipidemia. According to the US AHA/ACC guideline on the management of blood cholesterol (2018),[4] various statin therapy regimens of varying potency are recommended based on the patient's age, sex, weight, demographics, and blood cholesterol levels. However, recent studies have reported that while potent statin therapy reduces the risk for CVD, it could increase the risk for diabetes.[7,16] Some patients receiving statin therapy experience muscle pain.[9] Dyslipidemia is known as the main cause of CVD, and the first-line goal in reducing CVD-related morbidity is to lower LDL-C.[15] However, several studies have indicated that elevated levels of not only LDL-C but also other blood lipids (TC, TG, and VLDL) are risk factors for CVD, and that controlling these lipid levels will further reduce CVD-related morbidity.[4,17,18] In the present study, reductions from baseline in TC, TG, and VLDL-C levels at weeks 4 and 8 were significantly greater with the pitavastatin/fenofibrate combination therapy compared to those with pitavastatin monotherapy. In particular, TG and VLDL-C levels at weeks 4 and 8 were significantly reduced compared to the baseline levels. The findings from the present study suggest that pitavastatin/fenofibrate combination therapy controls levels of blood lipids in addition to LDL-C, with a possibility of lowering the risks for CVD-related morbidity and the adverse events associated with statin administration.

Fenofibrate is known to reduce the blood concentrations of TG and VLDL, increasing the HDL-C level.[19] Previous studies have reported controlled lipid levels with fibrate + statin combination therapy.[12,20,21] In one study, 248 patients with mixed dyslipidemia were treated for 12 weeks with fenofibrate 160 mg with or without pravastatin 40 mg. That study reported that the reduction in non–HDL-C was significantly greater in the combination therapy group compared to that in

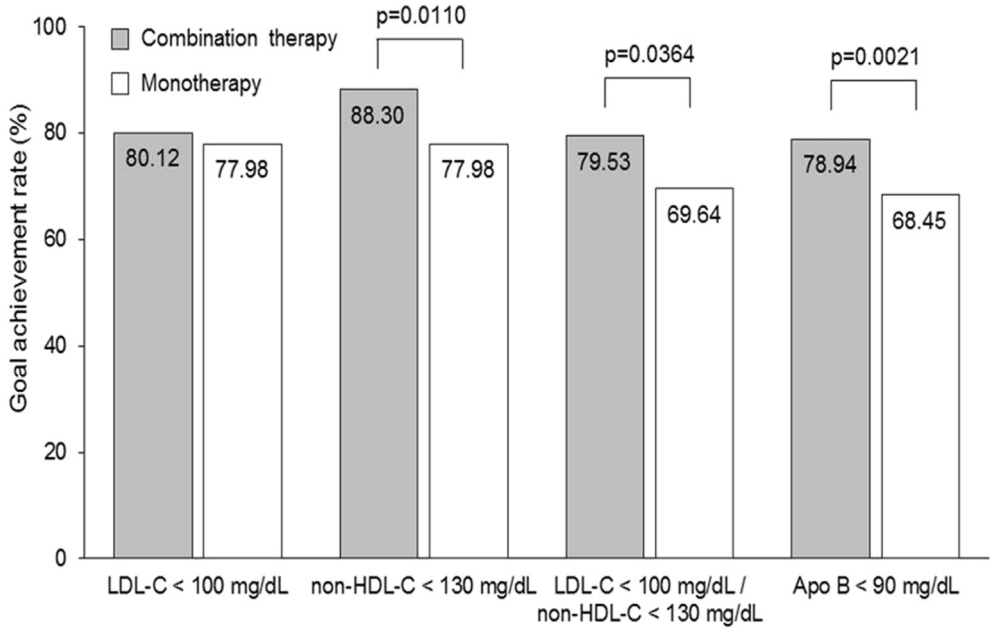

Figure 3. Rates of achievement of LDL-C, non−HDL-C, LDL-C/non−HDL-C, and apolipoprotein (Apo) B goals at week 8 with pitavastatin calcium 2 mg with or without fenofibrate 160 mg.

the monotherapy group (−14.1% vs −6.1%; $P = 0.002$).[19] The patients treated with pravastatin 40 mg for 8 or more weeks achieved an LDL of ≥100 mg/dL and a TG of 150−400 mg/dL and were further treated with pravastatin/fenofibrate 160/40 mg for 12 weeks. It was shown that TG was reduced by ~23% and HDL-C was increased by 6% with the combination therapy. In another study, patients with mixed dyslipidemia and a high or very high CVD risk, characterized by a TG level of ≥150 mg/dL and an LDL-C of 70−130 mg/dL measured after at least 3 months of monotherapy with any statin (excluding simvastatin 80 mg, atorvastatin 40 and 80 mg, and rosuvastatin 20 and 40 mg), were treated with a fixed-dose combination of fenofibrate/simvastatin 145/20 mg or 145/40 mg, simvastatin 20 or 40 mg, or fenofibrate 145 mg for 12 weeks.[12] TG level was significantly reduced and HDL-C level was significantly increased with both fenofibrate/simvastatin fixed-dose combination doses compared with simvastatin alone (treatment differences, −32% and +7.5%; both, $P < 0.001$).

The present study had some novelty and strength. The present study and previous studies predominantly differ in their inclusion criteria. Unlike previous studies, the present study included Korean patients at high risk for CVD who took statin monotherapy and had a target goal of LDL-C but in whom other lipid levels (eg, TG, HDL-C) were uncontrolled. Therefore, the present study included patients with a high risk for CVD and whose residual lipid profiles were not improved even with statin therapy. In addition, 2 mg of pitavastatin, a moderate dose of a moderate-intensity statin, was used as the primary statin. Pitavastatin is a moderate-intensity statin, but its efficacy and tolerability have been proved in Asian populations, and studies have reported a lower prevalence of diabetes in Asian populations, including the Korean population, using pitavastatin when compared to other statins.[4,21] The last is the efficacy. In these patients, pitavastatin/fenofibrate 2/160 mg combination therapy for 8 weeks was associated with reduced TG (by ~40%) and increased HDL-C (by ~21%), suggesting excellent TG and HDL-C results compared to those in previous studies, despite the short treatment duration. Considering the results from previous studies, pitavastatin/fenofibrate combination therapy

Table IV. Adverse drug reactions with pitavastatin calcium 2 mg with or without fenofibrate 160 mg. Data are given as number (%) of patients, number of events.

Adverse drug reaction	Combination Therapy (n = 172)	Monotherapy (n = 171)	All Patients (N = 343)
Investigations	4 (2.33), 6	1 (0.58), 2	5 (1.46), 8
ALT elevated	2 (1.16), 2	1 (0.58), 1	3 (0.87), 3
AST elevated	2 (1.16), 2	0	2 (0.58), 2
GGT elevated	1 (0.58), 1	1 (0.58), 1	2 (0.58), 2
LFT abnormal	1 (0.58), 1	0	1 (0.29), 1
GI disorder	2 (1.16), 2	1 (0.58), 1	3 (0.87), 3
Gastritis	0	1 (0.58), 1	1 (0.29), 1
GERD	1 (0.58), 1	0	1 (0.29), 1
Nausea	1 (0.58), 1	0	1 (0.29), 1
CNS disorders	1 (0.58), 1	0	1 (0.29), 1
Headache	1 (0.58), 1	0	1 (0.29), 1
Musculoskeletal and connective tissue disorders	0	1 (0.58), 1	1 (0.29), 1
Muscle spasms	0	1 (0.58), 1	1 (0.29), 1
Total	6 (3.49), 9	3 (1.75), 4	9 (2.62), 13

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GERD = gastroesophageal reflux disease; GGT = γ-Glutamyl transferase; GI = gastrointestinal; LFT = liver function test.

was associated with not only a reduced TG level and an increased HDL-C level, but further control of elevated blood lipid levels and inflammatory markers known as CVD risk factors, thereby reducing CVD-related morbidity in patients with mixed dyslipidemia.

Elevated levels of Apo A1 and B, which are components of LDL-C and HDL-C that play a role in metabolism, as well as fibrinogen and hs-CRP, are known risk factors for CVD.[22] In the present study, the use of the pitavastatin/fenofibrate combination therapy was associated with a statistically significant increase in the level of Apo A1 compared to that with pitavastatin monotherapy. A decreased Apo B level is considered an important treatment goal in addition to lowered LDL-C and non−HDL-C. In the current study, the Apo B level was significantly decreased. The mean percentage changes in this level at weeks 4 and 8 were statistically different compared to the baseline level. Fibrinogen and hs-CRP are the most well-studied inflammatory markers of atherothrombosis and CVD risk. In the present study, the use of the pitavastatin/fenofibrate combination therapy was associated with statistically significant reductions in fibrinogen and hs-CRP compared with those with monotherapy. It is considered that pitavastatin/fenofibrate combination therapy reduces CVD risk factors, in addition to controlling blood lipid levels, effectively decreasing CVD-related morbidity in patients with dyslipidemia.

The main tolerability concern with statin/fenofibrate combination therapy is myopathy.[23] However, there were no reports of myopathy during the main treatment period in the pitavastatin/fenofibrate group, with 1 case each reported in the pitavastatin/fenofibrate combination and pitavastatin monotherapy groups (0.88% vs 0.97%) during the extension period, suggesting that the combination therapy was well tolerated.

The limitations of the present study included a short treatment period and a lack of study-population diversity. Furthermore, the present study did not assess the efficacy or tolerability of the treatment in elderly patients or in patients with liver or renal dysfunction, owing to the low recruitment in these special patient populations. Additionally, the number of patients with a history of CVD was low and with

significant bias, leading to a limitation in the accurate analysis of the tolerability data. Additional studies are crucial for subgroup analysis. LDL-C was increased in both treatment groups. However, the mean increase in LDL-C was around 5 mg/dL in both groups. The mean LDL-C level was increased until 8 weeks and then fell to near-baseline by 24 weeks (extension period) in both groups. This phenomenon may have been the result of the relatively short administration period (8 weeks). Another possibility is that the participants did not strictly maintain their therapeutic lifestyle changes. This was another limitation of this study. However, the target LDL-C level in the high-risk group was <100 mg/dL, and the LDL-C levels in most of the participants were within the recommended range at baseline and at 4, 8, and 24 weeks of drug administration.

Despite these limitations, in patients with LDL-C controlled on pitavastatin, the addition of fenofibrate therapy further regulated the level of LDL-C and other blood lipids known to be CVD risk factors. In regard to the tolerability of the combination therapy, the current study did not report any adverse reactions additional to those already associated with fenofibrate therapy, suggesting that the pitavastatin/fenofibrate combination is well tolerated.

CONCLUSIONS

In these Korean patients with mixed dyslipidemia and at high risk for CVD, the combination of pitavastatin/fenofibrate was associated with a greater reduction in non−HDL-C than was pitavastatin monotherapy, with significant improvements in other lipid levels. Moreover, the combination therapy was well tolerated, with a safety profile similar to that of monotherapy. Therefore, pitavastatin/fenofibrate combination therapy could be effective and well tolerated in patients with mixed dyslipidemia.

DISCLOSURES

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APPENDIX

Supplemental Table 1. Adverse drug reactions during the extension period

	Extension period		
	Combination therapy group	Monotherapy group	Total
Investigations	1 (0.88) 1	5 (4.85) 5	6 (2.78) 6
Blood creatinine phosphokinase increased	1 (0.88) 1	3 (2.91) 3	4 (1.85) 4
Blood creatinine increased	0 (0.00) 0	1 (0.97) 1	1 (0.46) 1
Gamma-glutamyltransferase increased	0 (0.00) 0	1 (0.97) 1	1 (0.46) 1
Gastrointestinal disorders	0 (0.00) 0	2 (1.94) 2	2 (0.93) 2
Abdominal pain	0 (0.00) 0	1 (0.97) 1	1 (0.46) 1
Gastritis	0 (0.00) 0	1 (0.97) 1	1 (0.46) 1
Infections and infestations	1 (0.88) 1	0 (0.00) 0	1 (0.46) 1
Cystitis	1 (0.88) 1	0 (0.00) 0	1 (0.46) 1
Musculoskeletal and connective tissue disorders	1 (0.88) 1	1 (0.97) 1	1 (0.46) 1
Muscle spasms	1 (0.88) 1	1 (0.97) 1	1 (0.46) 1
Nervous system disorders	0 (0.00) 0	1 (0.97) 1	1 (0.46) 1
Dizziness	0 (0.00) 0	1 (0.97) 1	1 (0.46) 1
Psychiatric disorders	0 (0.00) 0	1 (0.97) 1	1 (0.46) 1
Insomnia	0 (0.00) 0	1 (0.97) 1	1 (0.46) 1
Vascular disorders	1 (0.88) 1	0 (0.00) 0	1 (0.46) 1
Hypertension	1 (0.88) 1	0 (0.00) 0	1 (0.46) 1
Total	4 (3.54) 4	9 (8.74) 9	13 (6.02) 13

Data are presented as number of patients (%) number of events.

APPENDIX — PROTOCOL FOR THERAPEUTIC LIFESTYLE CHANGES: GUIDELINE ON DIET AND EXERCISE FOR THERAPEUTIC LIFESTYLE CHANGES (TLC)

Patients with dyslipidemia should make the lifestyle changes recommended by the Guideline on Diet and Exercise for Therapeutic Lifestyle Changes (TLC). The basic recommendations are as follows:

- Lose weight if obese;
- Reduce total fat consumption;
- Replace saturated fat (e.g., animal oil) with unsaturated fat (e.g., vegetable oil, fish, etc.);
- Eat grains rich in fiber and eat a sufficient amount of vegetables;
- Avoid foods rich in cholesterol as much as possible;
- Avoid overeating;
- Do not eat too much sugar;
- Drink less — Limit alcohol consumption to 1–2 times per week, and drink only 1 or 2 glasses on each occasion (regardless of the type of alcohol).

1. Diet guidelines

1) Body weight and energy

When you intake more energy than required, the unused energy promotes the synthesis of triglycerides and cholesterol in the liver, thereby increasing the blood concentrations of cholesterol and triglycerides. Therefore, a patient with hypercholesterolemia with a higher-than-normal body weight must first try to return to a normal weight by managing his diet.

2) Cholesterol

Serum cholesterol levels are affected by the amount of cholesterol ingested from food and the amount of endogenous cholesterol synthesized in the liver and other organs. Thus, the guideline recommends a daily cholesterol intake of 200 mg or less to lower the serum level of LDL cholesterol.

3) Fat
   (1) Saturated fatDairy products, meat, palm oil, and coconut oil, which are high in saturated fat, should be avoided. Saturated fat intake should be no more than 7% of the total energy intake.
   (2) Trans fatExcessive trans-fat intake increases the serum level of LDL cholesterol and lowers that of HDL cholesterol. Trans fat intake should be no more than 1% of the total energy intake.
   (3) Polyunsaturated fatty acidsPolyunsaturated fatty acids include omega-3 and omega-6 fatty acids. Omega-6 fatty acids are known to lower the serum levels of LDL cholesterol, HDL cholesterol, and triglycerides. Since increasing omega-6 fatty acid intake increases the total fat intake, omega-6 fatty acid intake should not be more than 10% of the total energy intake.Omega-3 fatty acids are known to lower the serum level of triglycerides and prevents cardiovascular diseases. The American Heart Association recommends a daily omega-3 fatty acid intake of 2~4 g/day to lower the serum triglyceride level and 1 g/day to prevent cardiovascular diseases.
4) Dietary fiberWhile insoluble fiber (e.g., wheat husk) does not significantly affect serum cholesterol, soluble fiber (e.g., pectin, alginic acid, etc.) lowers serum cholesterol levels. A daily insoluble fiber intake of 5~10 g/day can lower the serum level of LDL cholesterol by 5%.
5) CarbohydratesCarbohydrates rich in soluble fiber, such as grains, marine algae, vegetables, and fruits, are recommended. Daily carbohydrate intake should be no more than 60% of the total energy intake.
6) AlcoholSince excessive drinking can promote triglyceride synthesis in the liver, it is recommended to drink no more than two glasses per day.

Food type	Recommend daily intake	Examples
Foods rich in cholesterol whose intake must be limited	≤200 mg/day	Egg yolk, squid, animal organ meat, poultry skin, etc.
Foods rich in saturated fat	≤7% of the total energy intake	Greasy meat (pork belly, bacon, rib, ham, sausage, beef bone soup, tripe, etc.), dairy products (butter, cheese, whipped cream, etc.), greasy confectioneries (cake, doughnut, pie, pastries, cookies, etc.), palm oil (coffee creamer, instant noodles, snacks, etc.), etc.
Foods rich in trans fat	≤1% of the total energy intake	Margarine, snacks containing shortening, muffin, confectioneries, fried food, etc.
Foods rich in poly-unsaturated fatty acids	≤10% of the total energy intake	*Omega-6 fatty acid: corn oil, soybean oil, cottonseed oil, perilla oil, etc. *Omega-3 fatty acid: Tuna, mackerel pikes, salmon, mackerel, sardine, herring, etc.

(*continued on next page*)

. (*Continued*)

Food type	Recommend daily intake	Examples
Dietary fiber	Soluble fiber: 10~25 g/day	Fruits, vegetables, grains, marine algae, etc. *Eat one medium-sized apple per day. Drink sugar-free juice.
Carbohydrates rich in soluble dietary fiber	≤60% of the total energy intake	Unrefined whole grains, beans, vegetables, and fruits low in sugar. *Avoid grain products such as bread, noodles, rice cake, potatoes, sweet potatoes, muk, and corn. Replace white rice and flour with mixed grains, brown rice, and whole wheat rich in fiber.
Others		Reduce the amount of sugar, starch syrup, and honey used in cooking. Avoid sugary snacks (drinks, bread, candies, and chocolates, etc.).

2. Exercise guideline

It is advisable to determine the amount of exercise needed to effectively lower serum lipid levels based on daily calorie expenditure.

A patient with hypercholesterolemia must burn at least 2000 calories per week by exercising (approximately 300 kcal/day assuming the patient works out every day) to achieve the desired outcomes.

The goal of exercise therapy for patients with hypercholesterolemia is to increase energy expenditure through aerobic exercise. Aerobic endurance training, which involves rhythmic movements of large muscle groups, includes fast walking, cycling, swimming, and light jogging. All these activities can improve the cardiopulmonary function and significantly increase energy expenditure and are thus appropriate for patients with hypercholesterolemia.

A patient with hypercholesterolemia must also try to increase physical activity in daily life. Walking frequently and when going somewhere near, using the stairs instead of the elevator, watching less TV, and avoiding sitting for a long time (for instance, before the computer) are examples of lifestyle changes that can increase one's level of physical activity during the day.

The exercise intensity needed to improve serum lipid levels is lower than that needed to maximally improve one's strength. Hence, serum lipid levels can be sufficiently improved by mild-to-moderate-intensity exercises.

Patients must exercise at least five times per week at a moderate intensity (walking approximately 100 steps/minute and getting out of breath), which is 40−70% of the maximum intensity. They may work out one to two times per day and should focus on increasing the duration rather than the intensity of the exercise.

Other considerations: different recommendations may apply for patients with other risk factors such as obesity and hypertension.

References

1) 'Guideline on Hyperlipidemia Treatment', Second revised edition, 2009, Korean Society of Lipid and Atherosclerosis.

2) "Health/diet information" on the Korean Society of Lipid and Atherosclerosis website.