Efficacy and Safety of Fenofibrate-Statin Combination Therapy in Patients With Inadequately Controlled Triglyceride Levels Despite Previous Statin Monotherapy: A Multicenter, Randomized, Double-blind, Phase IV Study

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ABSTRACT

Purpose: Residual cardiovascular risk reduction by fenofibrate in patients with high serum triglyceride (TG) levels despite previous statin monotherapy is not well characterized. The purpose of this study was to evaluate the efficacy and safety of a combination of choline fenofibrate and statin in patients with inadequately controlled TG levels despite previous statin monotherapy.

Methods: This prospective, multicenter, randomized, double-blind study was conducted in Korea. A total of 133 patients with controlled LDL-C but elevated TG levels, already receiving statin monotherapy, were enrolled in the study, which was conducted from July 2018 to December 2019. Patients were randomly assigned to receive combination therapy with choline fenofibrate and statin or statin monotherapy in a 1:1 ratio. After 8 weeks of treatment, the lipid profiles and safety parameters of the patients in the 2 groups were compared.

Findings: The study included 127 patients (64 in the combination group and 63 in the control group) older than 19 years. After 8 weeks of therapy, mean serum TG levels significantly decreased from 269.8 to 145.5 mg/dL ($P < 0.0001$) in the combination therapy group, whereas no significant changes occurred in the statin monotherapy group (from 271.1 to 280.5 mg/dL). Contrarily, the mean serum HDLC levels significantly increased from 45.0 to 50.4 mg/dL ($P = 0.0004$) in the combination therapy group, whereas there were no significant changes in the monotherapy group (from 44.3 to 44.7 mg/dL). There were no additional serious adverse events in the combination therapy group compared with the statin monotherapy group.

Implications: The combination therapy using choline fenofibrate and statin was found to be effective in serum TG control and likely tolerable in patients with high TG levels despite statin monotherapy. A larger study, conducted for a longer duration, is needed

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to evaluate the effectiveness of this combination in reducing cardiovascular risk. ClinicalTrials.gov identifier: NCT03874260. (*Clin Ther.* 2021;43:1735–1745.)

Key words: fenofibrate, hyperlipidemia, Korea, Phase IV, statin, triglyceride.

INTRODUCTION

Fenofibrate is a peroxisome proliferator activated receptor α agonist that is thought to help control triglyceride (TG) levels and reduce residual cardiovascular risk, which cannot be achieved with statin therapy alone.[1] In the Fenofibrate Intervention and Event Lowering of Diabetes (FIELD) study, a major, large-scale randomized controlled trial that evaluated the effects of fenofibrate on cardiovascular risk reduction, cardiovascular death, and nonfatal myocardial infarction, the incidence of coronary events was 11% lower in patients treated with fenofibrate than in the control group. However, this difference was not statistically significant.[2] Another large-scale randomized controlled trial, the Action to Control Cardiovascular Risk in Diabetes–lipid (ACCORD-lipid), found that fenofibrate was unable to reduce cardiovascular mortality.[3] However, in both studies, the incidence of cardiovascular events was significantly reduced in patients with high TG levels and low HDL-C levels. Therefore, the potential clinical implications of fenofibrate continue to be studied.[4]

Fenofibrate is a promising option for the treatment of hypertriglyceridemia and reduces TG levels by 25% to 50% below the baseline.[5] Statins are the drugs of choice for the control of LDL-C levels and are the key to cardiovascular risk reduction. However, statins do not exhibit sufficient potency in the regulation of TG levels in the body.[6] Therefore, combination therapy using fenofibrate along with statins has been evaluated to effectively control the levels of both LDL-C and TG, but safety issues have been raised for this combination.[7]

Elevated TG levels are associated with vascular injuries that result from damage to endothelial and vascular smooth muscle cells, foam cell formation, and increased oxidative stress.[8] Studies conducted in animal models have found that TG-rich lipoproteins promote atherosclerosis by triggering endothelial cells and macrophages to secrete inflammatory markers, including tumor necrosis factor α, interleukin 1β, monocyte chemotactic protein 1, intercellular adhesion molecule 1, and matrix metalloproteinase 3.[9,10]

This study was designed to evaluate the efficacy and safety of a combination of choline fenofibrate and statin compared with statin monotherapy in patients with elevated TG and controlled LDL-C levels. Inflammatory markers and the reactive hyperemia peripheral arterial tonometry (RH-PAT) index were also evaluated.

PARTICIPANTS AND METHODS

Study Design and Patient Population

This prospective, multicenter, double-blind randomized controlled trial was conducted in patients with dyslipidemia who had controlled levels of LDL-C and elevated levels of TG across 15 sites in the Republic of Korea. Patients enrolled for the study were older than 19 years, had LDL-C levels below the treatment goal according to the risk categories (Supplemental Table I[11]), and had TG levels in the range of 200 to 499 mg/dL; moreover, they were receiving statin monotherapy with atorvastatin (10 or 20 mg) or rosuvastatin (10 mg), with no changes to the drug or dose for at least 4 weeks, and planned to continue this dosing regimen during the study. Patients with the following comorbidities were excluded from the study: secondary dyslipidemia caused by Cushing syndrome or nephrotic syndrome, uncontrolled thyroid disease, elevated levels of aspartate transaminase (AST) or alanine aminotransferase (ALT) [$\geq$2.5 $\times$ upper limit of normal (ULN)], estimated glomerular filtration rate <60 mL/min/1.73 m^2, poorly controlled diabetes (glycosylated hemoglobin $\geq$9% or fasting blood glucose $\geq$160 mg/dL), medical history of musculopathy, or elevated levels of serum creatine kinase (CK) ($\geq$2 $\times$ ULN). Additional lipid modulators including ω3 polyunsaturated fatty acid, drugs such as glucocorticoid that may affect lipids, or drugs that may affect the efficacy of statins or choline fenofibrate were limited for use in the study duration.

After at least 4 weeks of statin monotherapy, all eligible patients were randomly assigned to the combination group (treated with fenofibrate plus statin) or the control group (treated with statin alone) in a 1:1 ratio. Patients in both groups continued taking the statin one of atorvastatin 10 mg and 20mg and rosuvastatin 10 mg, which was already in their treatment regimen. In addition, the combination group

was administered 178.8 mg of choline fenofibrate orally, once a day, whereas the control group was given a placebo. The treatment was continued for 8 weeks, and follow-up visits were scheduled 4 and 8 weeks from the start of treatment, during which the patients gave blood samples for testing. The doses of statin and fenofibrate were not altered during the study.

This study protocol adhered to the guidelines of the International Conference on Harmonisation, Korean Good Clinical Practice, and the Helsinki Declaration. The study protocol was approved by the ethics committee or institutional review board at each participating center, and written informed consent was signed by all participants before any study procedure was conducted.

Efficacy and Safety Evaluation

TG, total cholesterol (TC), LDL-C, HDL-C, apolipoprotein A-1 (apoA1), and apolipoprotein B (apoB) levels were measured at the beginning of the study (baseline) as well as at weeks 4 and 8. The primary end point was the change in mean serum TG level from the baseline after 8 weeks of treatment. The secondary end points included the following: change in mean serum TG from baseline at week 4; changes in mean serum levels of TC, LDL-C, HDL-C, apoA1, and apoB from the baseline at weeks 4 and 8; the rates of achievement of treatment goals, measured via TG levels at weeks 4 and 8. Some institutions also evaluated inflammatory markers and RH-PAT index at the beginning of the study as well as after 8 weeks.

Safety profiles were evaluated based on the following: incidence of adverse events (AEs) and serious adverse events (SAEs); changes in laboratory parameters, including serum AST, ALT, CK, and creatinine levels; and incidence of myopathies, such as rhabdomyolysis.

Statistical Analysis

It was calculated that a sample size of 180 patients would be required to compare the effectiveness of the combination therapy and monotherapy, considering a 2-sided α of 0.05, 80% power, 20% dropout rate, and estimated TG reduction effect of choline fenofibrate as 16%. Efficacy data were analyzed in the full analysis set, which included all patients who were randomized and had posttreatment values, and in the per-protocol set, which included all patients who had no major protocol violations. All patients who received treatment were included in the safety analysis set. The primary end point, the mean percent change in TG, was analyzed using a 2-sample t test or Wilcoxon rank sum test. To evaluate tolerability, the number of patients who experienced AEs was recorded. Continuous variables were evaluated using the t test or the Wilcoxon rank-sum test, and the results were presented as means (SDs). Categorical variables were presented as numbers (percentages), and the Pearson χ^2 test or Fisher exact test was used to compare the 2 groups. All tests were 2-tailed and were considered statistically significant when $P < 0.05$.

RESULTS

From July 2018 to December 2019, a total of 133 patients were enrolled across the 15 sites in the Republic of Korea. The study flowchart is shown in Figure 1. All 133 patients who met the inclusion and exclusion criteria were randomly allocated to the combination group (67 patients) or the control group (66 patients). Four patients who did not take the investigational product were excluded from the study, and 129 patients were included in the safety set (65 from the combination group and 64 from the control group). Two more patients were excluded because of insufficient TG level measurements being obtained, so the full analysis set included 127 patients (64 from the combination group and 63 from the control group).

The demographic and baseline characteristics of the study population are given in Table I. Among the overall population, the prevalence of coronary vascular disease was 16.5% and the prevalence of type 2 diabetes mellitus was 39.8%. No statistically significant differences were found with respect to age, sex, body mass index, or underlying disease conditions between the 2 groups.

The changes in mean serum cholesterol level from the baseline to weeks 4 and 8 are summarized in Table II. Coadministration of fenofibrate with statin produced a TG reduction of 32.49% at 4 weeks ($P < 0.0001$) and 44.47% at 8 weeks ($P < 0.0001$) compared with statin alone. The mean TG level in the combination group decreased from 269.8 mg/dL before treatment to 151.7 and 145.5 mg/dL after 4 and 8 weeks of combined medication, respectively. The target TG level of 150 mg/dL was achieved by 51.67% and 65.57% of the patients after 4 and 8 weeks, respectively. Meanwhile, in the control group, the mean TG level changed from a baseline of 271.1 mg/dL to 238.3 and 280.5 mg/dL after 4 and 8 weeks of

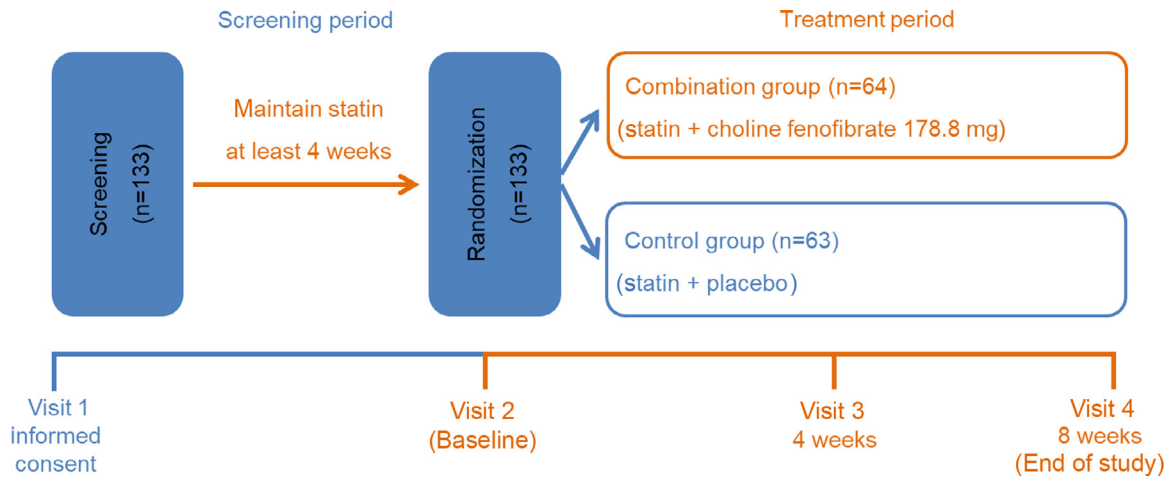


Figure 1. Study flowchart.

Table I. Baseline characteristics.*

Characteristic	Combination Group (n = 67)	Control Group (n = 66)	Total (N = 133)	*P*
Age, mean (SD), y	57.6 (9.8)	59.8 (10.1(	58.7 (10.0)	0.207
Age ≥65 y	14 (20.9)	22 (33.3)	36 (27.1)	0.106
Male	44 (65.7)	41 (62.1)	85 (63.9)	0.670
BMI, mean (SD), kg/m^2	26.5 (3.1)	26.3 (3.2)	26.4 (3.2)	0.773
Smoking	19 (28.4)	16 (24.2)	35 (26.3)	0.635
Alcohol	38 (56.7)	33 (50.0)	71 (53.4)	0.663
CVD	10 (14.9)	12 (18.2)	22 (16.5)	0.613
Stroke	0 (0)	1 (1.52)	1 (0.75)	0.496
Type 2 diabetes mellitus	25 (37.3)	28 (42.4)	53 (39.8)	0.547
Hypertension	57 (85.1)	54 (81.8)	111 (83.5)	0.613

BMI = body mass index; CVD = cardiovascular disease.
* Data are presented as number (percentage) of patients unless otherwise indicated.

treatment with statin, respectively. Furthermore, only 15.52% and 17.24% of patients achieved the target TG level after 4 weeks and 8 weeks of treatment, respectively. Changes in the mean serum TG level percentage in both the combination group and the control group were statistically significant at both weeks 4 and 8 ($P < 0.0001$). The difference in the target achievement rate between the 2 groups was also statistically significant ($P < 0.0001$). HDL-C increased by 11.19% after 4 weeks and 13.75% after 8 weeks in the combination group, whereas it increased by 3.53% after 4 weeks and 3.16% after 8 weeks in the control group. The difference in mean serum HDL-C level percentage between the 2 groups was statistically significant at both weeks 4 and 8 ($P = 0.0021$ and 0.0004, respectively) (Figures 2 and 3). The changes in serum levels of TC, LDL-C, apoA1, and apoB did not differ between the 2 groups. The TG-lowering effect of the combination therapy was consistent across sex and type 2 diabetes mellitus in the low HDL-C subgroup and in the obese subgroup (Figure 4). No statistically significant difference was found in the proportion of statin use in both groups. The proportions of atorvastatin 10 mg and 20 mg and rosuvastatin 10 mg used in the combination group were 39.1%, 34.4%, and 26.6%, respectively. In the

Table II. Changes of mean serum lipid levels.

Component	Mean (SD) Lipid Levels, mg/dL		
	Baseline	4 Weeks	8 Weeks
TG, combination group (n = 64)	269.8 (55.2)	151.7 (52.6)*	145.5 (53.6)*
TG, control group (n = 63)	271.1 (63.3)	238.3 (104.2)*	280.5 (400.6)*
HDL, combination group	45.0 (9.7)	49.6 (10.7)*	50.4 (10.6)*
HDL, control group	44.3 (10.2)	45.1 (9.8)*	44.7 (10.7)*
LDL, combination group	82.0 (20.5)	88.0 (18.9)	90.0 (20.7)
LDL, control group	75.9 (22.5)	81.1 (23.2)	79.5 (23.4)
TC, combination group	154.3 (25.4)	152.1 (19.4)	154.2 (22.2)
TC, control group	147.5 (27.6)	149.8 (29.1)	152.1 (37.8)
APO A1, combination group	145.2 (24.2)	150.2 (25.4)	151.3 (24.6)
APO A1, control group	140.6 (22.0)	140.7 (20.8)	140.5 (21.7)
APO B, combination group	82.6 (18.1)	79.1 (15.5)	80.7 (15.8)
APO B, control group	79.9 (19.7)	81.8 (18.4)	81.1 (17.5)

APO = apolipoprotein; TC = total cholesterol; TG = triglycerides.
Statistically significant difference between the 2 groups ($P < 0.05$).

control group, the proportions were 38.1%, 30.2%, and 31.8%, respectively. No significant difference was found in the TG reduction effect in the subgroup analysis according to the type of statin (Figure 4).

The safety analysis set included 129 patients. No SAEs occurred in the combination group. The incidence of adverse drug reactions was 4.6% in the combination group (3 cases) and 6.3% in control group (4 cases); this difference was statistically insignificant. The 3 cases of adverse drug reactions in the combination group were abdominal distension, positional vertigo, and headache. Moreover, the 4 cases in the control group were diarrhea, urticaria (2 cases), and facial edema (Figure 5). The risk of AEs, particularly nephrotoxicity, hepatotoxicity, and myopathy, in the test group were of special interest. Therefore, changes in serum creatinine, liver function, and CK levels were monitored (Table III). Serum creatinine levels did not change during the 8 weeks in the control group but increased by approximately 0.14 mg/dL in the combination group. However, this increase did not cause any clinical problems or symptoms. The difference in changes of AST, ALT, and total bilirubin levels between the 2 groups was not statistically significant. One case of acute hepatitis was identified in the control group but was attributed to heavy drinking. The CK levels of patients in the 2 groups were not significantly different, and no cases of myopathy or rhabdomyolysis were reported. One case of increased CK level occurred in the control group, but this increase was attributed to muscular exercise and was not thought to be a sign of statin-induced myopathy.

Although it was not a part of the primary objective of this trial, several inflammatory markers and RH-PAT index were assessed at the beginning of the study and after 8 weeks, as part of an exploratory study. With the exception of C-reactive protein (CRP), the levels of all other markers did not differ significantly between the 2 groups. After 8 weeks of treatment, the mean CRP level in the combination group did not change but increased in the control group. This finding appeared to be a result of a large increase in the CRP level of 1 patient in the control group after 8 weeks. These data were available for only a limited number of patients (28 in the test group and 20 in the control group), and the overall results are given in Supplemental Table II.

DISCUSSION

In this prospective, multicenter, randomized controlled trial, conducted in patients with controlled LDL-C levels and elevated TG levels, the effectiveness and tolerability of combination therapy (choline fenofibrate and statin) were compared with statin monotherapy. The test drug was a combined form of choline

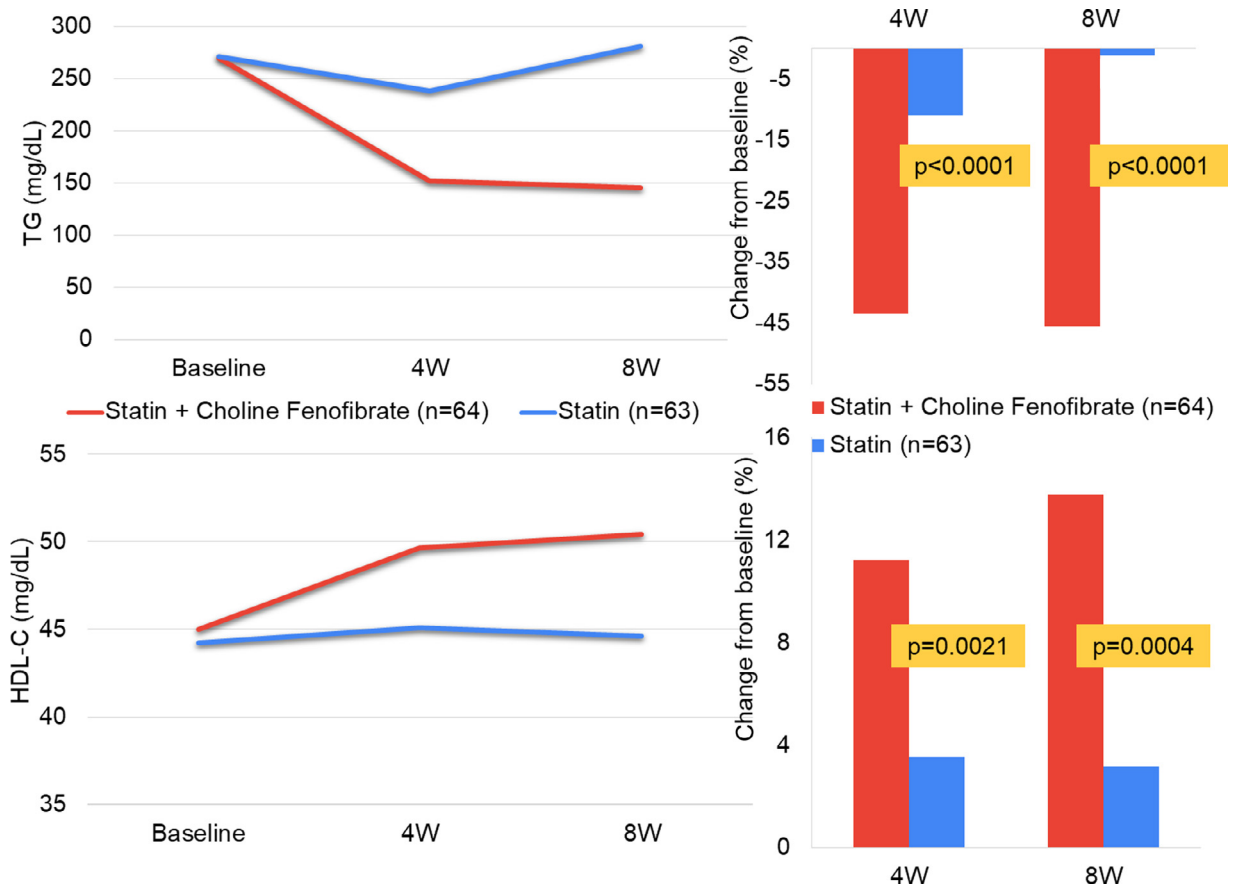


Figure 2. Changes from baseline to 4 weeks (4W) and 8 weeks (8W) in triglycerides (TG) and HDL-C.

Table. III. Changes of serum chemistry level.

Component	Mean (SD) Level		
	Baseline	4 Weeks	8 Weeks
Creatinine, combination group (n = 65), mg/dL	0.81 (0.19)	0.92 (0.22)*	0.95 (0.22)*
Creatinine, control group (n = 64), mg/dL	0.80 (0.17)	0.82 (0.17)*	0.81 (0.18)*
AST, combination group, IU/L	25.6 (7.8)	24.4 (6.5)	25.6 (7.6)
AST, control group, IU/L	27.3 (10.0)	26.1 (9.7)	55.6 (223.8)
ALT, combination group, IU/L	29.0 (11.8)	23.6 (10.0)	25.7 (15.4)
ALT, control group, IU/L	33.1 (18.0)	32.2 (18.4)	49.5 (134.8)
Total bilirubin, combination group, mg/dL	0.73 (0.35)	0.62 (0.26)	0.65 (0.28)
Total bilirubin, control group, mg/dL	0.73 (0.36)	0.69 (0.28)	0.69 (0.28)
CK, combination group, IU/L	117.5 (50.1)	121.0 (57.6)	127.0 (60.6)
CK, control group, IU/L	117.1 (59.2)	162.2 (385.1)	110.8 (53.8)

ALT = alanine aminotransferase; AST = aspartate transaminase; CK = creatine kinase.
* Statistically significant difference between the 2 groups ($P < 0.05$).

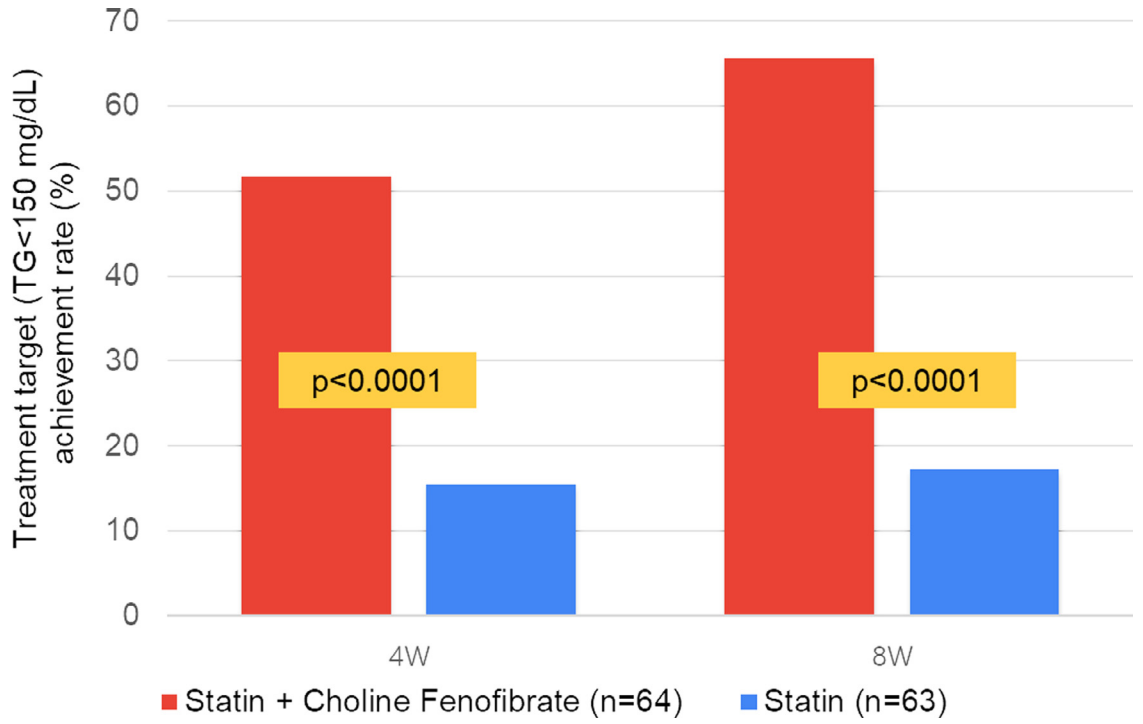


Figure 3. Treatment target achievement rate in the 2 study groups at 4 weeks (4W) and 8 weeks (8W).

salt and fenofibric acid. On ingestion, the choline salt dissociates because of the pH conditions in the gastrointestinal tract and gets converted to the active form, fenofibric acid.[12] Therefore, choline fenofibrate can be taken regardless of food, whereas traditional

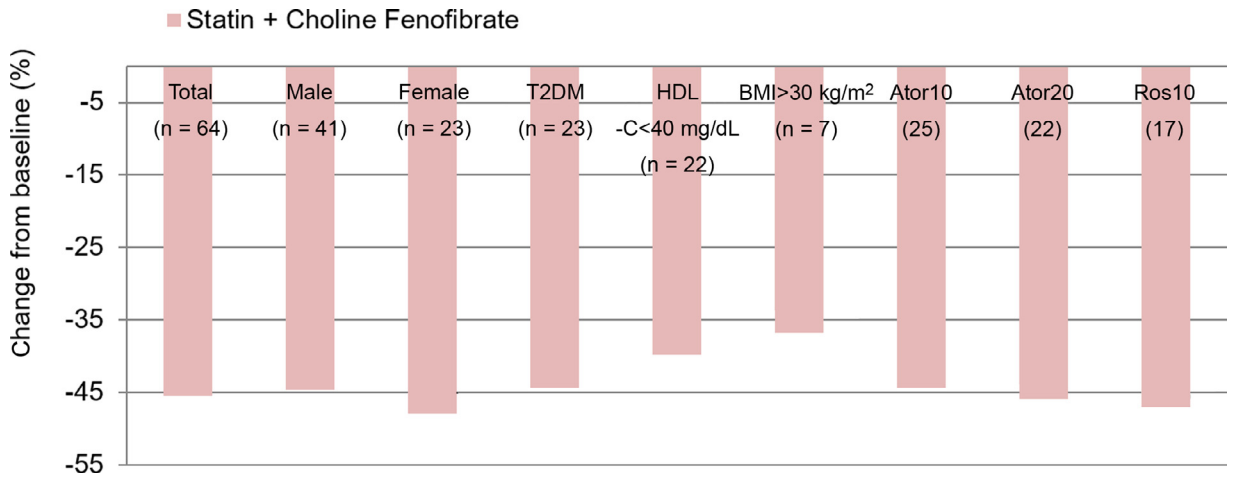
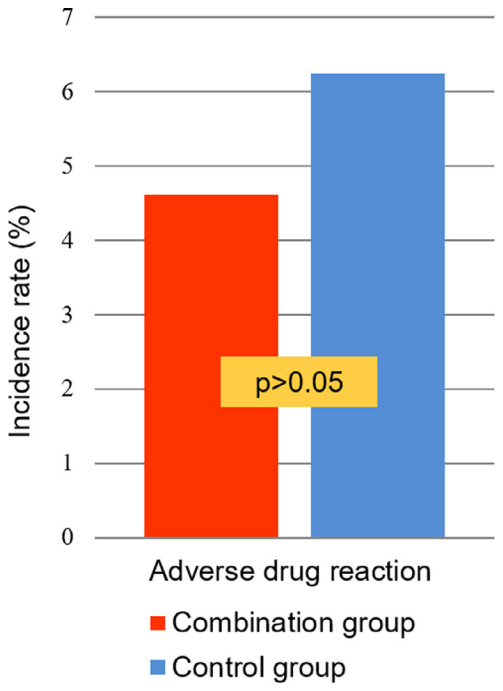


Figure 4. Triglyceride reduction effect of each subgroup after 8 weeks of combination therapy. Ator10 = atorvastatin 10 mg; Ator20 = atorvastatin 20 mg; BMI = body mass index. T2DM = type 2 diabetes mellitus; Ros10 = rosuvastatin 10 mg.



Combination group	Control group
Abdominal distension	Diarrhea
Positional vertigo	Urticaria (x2)
Headache	Face edema

Figure 5. Adverse drug reactions in the 2 study groups.

fenofibrate needs to be taken immediately after meals.[13]

After 8 weeks of combination therapy, there was a 45.57% reduction in TG levels, and 65.57% of the patients achieved the target TG level of 150 mg/dL. The pharmacologic potency of choline fenofibrate in this study is not inferior to that reported in previous studies.[14–17] Other studies have reported a TG-lowering effect of 25% to 50%[14] and a target achievement rate of 49%.[15] Fenofibrate has previously been reported to increase HDL-C levels by approximately 10%.[16] Although the mechanism for this has not been fully understood, it is assumed that the ability of fenofibrate to reduce the expression of cholesteryl ester transfer protein may play a major role.[17] In this study, HDL-C levels increased by 13.75% compared with baseline and by 10.58% compared with the control group, which was similar to the data from previous studies.[16,17]

It is controversial whether elevated TG levels are an independent risk factor for cardiovascular disease.[18–20] Most studies assessing this risk have been conducted in the West. However, several reports have suggested that after adjusting for other risk factors, elevated TG levels are an independent predictor of cardiovascular disease in the Asian population.[21,22] Among studies subsequently conducted in the Asian population, the Effectiveness of Fenofibrate Therapy in Residual Cardiovascular Risk Reduction in the Real World Setting (ECLIPSE-REAL) study published in 2019 is noteworthy. This cohort study of patients with Korean metabolic syndrome compared the cardiovascular events occurring in patients given statin monotherapy and those given combination therapy (fenofibrate and statin). The primary outcome was a 26% reduction in cardiovascular events in the combination therapy group compared with the monotherapy group. The most significant limitation of this study was that it was not a double-blind, randomized study. However, the study included only Asian patients.[23] As a result of ethnic variations, Asians are metabolically more susceptible to hypertriglyceridemia than people of other ethnicites.[24] The cause of these differences may be genetic; for example, the *APOA5* gene linked to hypertriglyceridemia is expressed more commonly in Koreans than in other populations.[25] These differences could be the reason that hypertriglyceridemia is an independent risk factor of cardiovascular disease in the Asian population.[26,27] Therefore, management of lipid levels, including TG, is particularly important in those of Asian ethnicity,[28] and fenofibrate-statin combination therapy could be an effective strategy to achieve this treatment goal.

However, there are several safety concerns about the use of this combination therapy.[29] Similar to what was seen in this study, most other clinical trials using fenofibrate have also found a slight elevation in serum creatinine levels within weeks of starting therapy.[30] This elevation in serum creatinine level could be more severe in those with chronic kidney disease, those taking high doses of fenofibrate, those taking other medications that affect renal function (eg, angiotensin receptor blockers), and in elderly populations.[31] The elevated serum creatinine levels

can be reversed by terminating fenofibrate therapy but are sometimes recovered without having to stop use of medication.[32] Although the exact mechanism for this is not known, the most widely accepted hypothesis is that fenofibrate inhibits the synthesis of a vasodilatory prostaglandin, thereby reducing renal plasma flow.[33,34] No evidence that fenofibrate causes deterioration of kidney function exists.[35] Rather, fenofibrate exhibits a renoprotective effect against the pathologic changes that occur in diabetic nephropathy and against hypertensive glomerulosclerosis in animal models.[36–39]

Both fenofibrate and statin can cause an elevation in serum liver enzyme levels. A meta-analysis found that a higher incidence of ALT elevation is seen in fenofibrate-statin combination therapy than in statin monotherapy (odds ratio = 1.67; $P < 0.05$).[40] The incidence rate of elevated ALT levels (ALT $\geq 3 \times$ ULN) in fenofibrate and simvastatin combination therapy was reported to be 1.9% in the ACCORD trial.[3] Cases of catastrophic hepatotoxicity caused by fenofibrate are rare, but routine liver function tests are recommended.[41,42]

Another concern in the administration of fenofibrate-statin combination therapy is the risk of rhabdomyolysis, which is slightly more common than that with statin monotherapy. The actual risk, however, is very low.[43] Furthermore, data from the ACCORD trial suggest that combination therapy does not increase the risk of rhabdomyolysis.[3] Some cases of serious rhabdomyolysis have been reported when using a combination of statin and gemfibrozil.[44,45] Gemfibrozil is a TG-lowering agent, which is able to increase the plasma concentration of statins by inhibiting their metabolism through the glucuronidation pathway, which may be responsible for the increased risk of rhabdomyolysis.[46] Fenofibrate, on the other hand, does not affect statin metabolism and thus should not significantly increase the risk of rhabdomyolysis.[47] However, fenofibrate-statin combination therapy should be used with caution in patients with chronic kidney disease, considering the high risk of muscle-related toxic effects, including rhabdomyolysis.[48]

This study has some limitations. It The SD of the TG changes of the control group is unusually high. All patients have received therapeutic lifestyle changes education, included diet control, exercise program, and weight reduction. One individual in the control group had a high TG level because of frequent drinking despite education, which resulted in an increase in the SD of the control group.

The treatment period was short (8 weeks), and the sample size is relatively small. Because the incidence of AE was very low, these data may not be sufficient to prove the tolerability of fenofibrate-statin combination therapy. However, the tolerability of this combination has been confirmed in previous large-scale trials and meta-analyses, and this study is meaningful in that it has a double-blind, randomized design and was conducted in the Korean population. A larger study, conducted over a longer duration, is needed to evaluate the effectiveness of this combination in reducing cardiovascular risk.

CONCLUSIONS

A combination strategy using choline fenofibrate and statin was 44% effective in reducing serum TG levels compared with statin monotherapy in Korean patients who had LDL levels well controlled by statin monotherapy but elevated TG levels. In addition, adverse events did not increase in combination therapy compared with monotherapy.

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DISCLOSURES

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

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SUPPLEMENTARY MATERIALS

Supplemental Table I. Target LDL-C goals according to risk category

Risk	Classification criteria	LDL-C goal (mg/dL)
Very high risk group	Coronary artery disease Ischemic stroke and transient ischemic attack Peripheral artery disease	< 70
High risk group	Carotid artery disease[a] Abdominal aneurysm Diabetes	< 100
Moderate risk group	Two or more major risk factors[b]	< 130
Low risk group	One or fewer major risk factors[b]	< 160

[a] In case of significant stenosis (≥50%) of the carotid artery
[b] Smoking, hypertension or taking antihypertensive medication, low HDL-C (<40 mg/dL), age (male ≥ 45 years, female ≥ 55 years), family history of premature coronary artery disease

Supplemental Table II. Changes of RH-PA index and inflammatory markers.

	Combination group (n=28)	Control group (n=20)
RH-PAT index, baseline	1.60 ± 0.38	1.76 ± 0.62
RH-PAT index, 8 weeks	1.67 ± 0.40	1.54 ± 0.36
CRP, baseline	1.01 ± 0.98	0.60 ± 0.36
CRP, 8 weeks*	0.68 ± 0.57	4.84 ± 10.90
TNF-α, baseline	1.39 ± 0.99	1.39 ± 0.76
TNF-α, 8 weeks	1.67 ± 1.81	2.41 ± 3.07
IL-6, baseline	2.14 ± 1.91	2.67 ± 2.13
IL-6, 8 weeks	2.44 ± 2.40	4.05 ± 3.83
Granzyme B, baseline	8.11 ± 4.87	7.65 ± 5.96
Granyme B, 8 weeks	8.26 ± 5.32	7.22 ± 4.50
MCP-1, baseline	369.41 ± 114.29	408.07 ± 78.66
MCP-1, 8 weeks	392.14 ± 91.59	393.20 ± 105.85
MIP-1α, baseline	69.07 ± 102.09	55.66 ± 23.03
MIP-1α, 8 weeks	93.78 ± 145.97	152.78 ± 309.44

(*continued on next page*)

Supplemental Table II. (*continued*)

	Combination group (n=28)	Control group (n=20)
MIP-1β, baseline	177.59 ± 314.18	176.42 ± 108.50
MIP-1β, 8 weeks	203.88 ± 308.23	285.65 ± 376.00
CXCL9, baseline	91.66 ± 52.86	108.50 ± 100.33
CXCL9, 8 weeks	108.45 ± 132.41	136.16 ± 155.00
CXCL10, baseline	134.35 ± 53.60	137.74 ± 76.08
CXCL10, 8 weeks	136.00 ± 64.04	163.44 ± 94.20
CXCL11, baseline	64.38 ± 7.27	64.44 ± 8.69
CXCL11, 8 weeks	80.08 ± 81.89	94.79 ± 133.02
CCL21, baseline	860.40 ± 293.71	945.20 ± 1020.86
CCL21, 8 weeks	952.74 ± 288.50	1015.72 ± 972.20

* marking means statistically significant difference between two group as p-value < 0.05
CRP, C-reactive protein, mg/L
TNF-α, Tumor necrosis factor-α
IL-6, Interleukin-6
MCP-1, Monocyte chemoattractant protein-1
MIP-1α, Macrophage inflammatory protein-1α
MIP-1β, Macrophage inflammatory protein-1β
CXCL, C-X-C motif chemokine ligand
CCL21, C-C motif chemokine ligand 21