Effectiveness and Tolerability of *Simvastatin* Plus *Fenofibrate* for Combined Hyperlipidemia (The SAFARI Trial)

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Patients with combined hyperlipidemia (elevated triglyceride [TG] levels, elevated low-density lipoprotein [LDL] cholesterol, and multiple lipoprotein abnormalities) are at increased risk for coronary heart disease. We conducted a multicenter (in the United States), randomized, double-blind, active-controlled, 18-week study to determine if combination therapy with simvastatin plus fenofibrate is more effective in reducing elevated TG levels, thus improving the lipoprotein pattern in patients with combined hyperlipidemia compared with simvastatin monotherapy, and to evaluate safety and tolerability. Patients (aged 21 to 68 years) with a diagnosis of combined hyperlipidemia (fasting TG levels ≥150 and ≤500 mg/dl, and LDL cholesterol >130 mg/dl) received simvastatin monotherapy (20 mg/day, n = 207) or simvastatin 20 mg plus fenofibrate (160 mg/day) combination therapy (n = 411) for 12 weeks following a 6-week diet and placebo run-in period. From baseline to week 12, median TG levels decreased 43.0% (combination therapy) and 20.1% (simvastatin monotherapy [treatment difference −23.6%, p <0.001]). Mean LDL cholesterol levels decreased 31.2% and 25.8% (treatment difference −5.4%, p <0.001), and high-density lipoprotein cholesterol levels increased 18.6% and 9.7% (treatment difference 8.8%, p <0.001) in the combination therapy versus monotherapy groups, respectively. No drug-related serious adverse experiences were observed. No patient experienced clinical myopathy or severe abnormalities in liver function. Combination therapy with simvastatin 20 mg and fenofibrate 160 mg in patients with combined hyperlipidemia resulted in additional improvement in all lipoprotein parameters measured compared with simvastatin 20 mg monotherapy and was well tolerated. Thus, this combination therapy is a beneficial therapeutic option for managing combined hyperlipidemia. **(Am J Cardiol 2005;95:462–468)**

In patients with combined hyperlipidemia and atherogenic dyslipidemia,[1] increased levels of low-density lipoprotein (LDL) cholesterol can be effectively reduced with competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins). In addition to lowering LDL cholesterol, statins reduce very LDL (VLDL) cholesterol levels, and some can modestly increase high-density lipoprotein (HDL) cholesterol. To achieve further improvement in LDL cholesterol and HDL cholesterol levels, higher doses of statins can be administered. However, even with high doses of statins, atherogenic dyslipidemia is not completely reversed. For this reason, other approaches to treatment of combined hyperlipidemia may be considered. One alternative is to combine fibrates with statin therapy. To examine the efficacy and safety of a statin plus fibrate in a large clinical study, we compared simvastatin monotherapy at a dose of 20 mg/day with a combination therapy with simvastatin 20 mg plus fenofibrate 160 mg/day in the treatment of >600 patients with combined hyperlipidemia. This trial greatly increases the number of subjects compared with a trial of 20 subjects by Vega et al,[2] in which simvastatin 10 mg plus fenofibrate 200 mg/day tested against simvastatin 10 mg/day showed improvement in the overall lipoprotein profile. The present trial provides robust data on the efficacy and safety of combination therapy with a moderate dose of simvastatin and fenofibrate in patients with combined hyperlipidemia.

METHODS

Patient population: Patients between 21 and 68 years of age with a diagnosis of combined hyperlipidemia, defined as a fasting triglyceride (TG) level ≥150 and ≤500 mg/dl and an LDL cholesterol >130 mg/dl were included. Patients with alanine aminotransferase (ALT) or aspartate aminotransferase (ASP) levels >30% the upper limit of normal, a serum creatinine level >1.5 mg/dl, the presence of active liver disease, creatine kinase levels >50% the upper limit of normal, or hemoglobin A_{1C} ≥10% (in those with type 2 diabetes mellitus) were excluded.

Study design: This was a multicenter, randomized, double-blind, active-controlled, 18-week study. The

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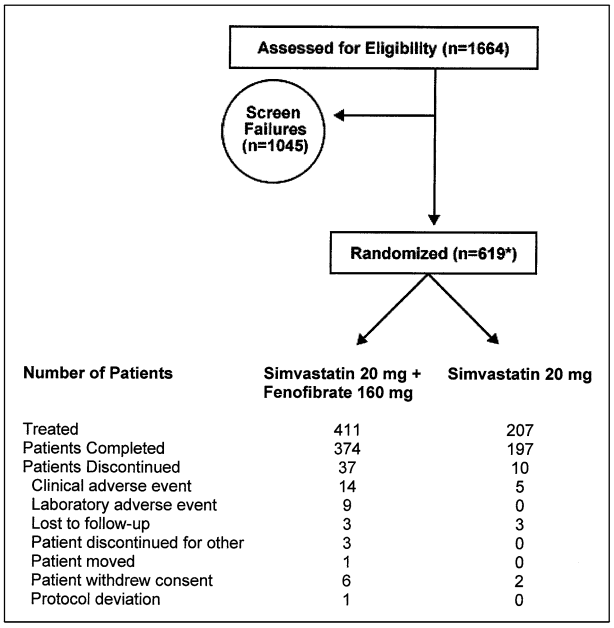

Number of Patients	Simvastatin 20 mg + Fenofibrate 160 mg	Simvastatin 20 mg
Treated	411	207
Patients Completed	374	197
Patients Discontinued	37	10
Clinical adverse event	14	5
Laboratory adverse event	9	0
Lost to follow-up	3	3
Patient discontinued for other	3	0
Patient moved	1	0
Patient withdrew consent	6	2
Protocol deviation	1	0

FIGURE 1. Patient accounting.

study protocol was approved by the institutional review board at each site, and all patients provided written consent. Patients underwent a 6-week diet run-in period that included 2 weeks of placebo run-in. Washout periods were 6 weeks for any previous statin, niacin in doses of >200 mg/day, or bile acid sequestrants, and 8 weeks for any previous fibrates. Eligible patients with combined hyperlipidemia meeting all inclusion criteria and no exclusion criteria were centrally randomized, 2:1 to daily double-blind treatment for 12 weeks, with either simvastatin 20 mg taken in the evening and fenofibrate 160 mg taken in the morning daily, or simvastatin 20 mg taken in the evening and placebo for fenofibrate taken in the morning. Simvastatin 20 mg was chosen as the active comparator because of its well-established safety profile. Randomization was centrally stratified by baseline TG levels (≥150 to <300 mg/dl and ≥300 to ≤500 mg/dl), and HDL cholesterol levels (men, <40 or ≥40 mg/dl; women, <50 or ≥50 mg/dl). After patient randomization, follow-up visits were scheduled on the last days of treatment weeks 6 and 12. All protocol-specified laboratory measurements were obtained at each visit.

Efficacy and safety criteria: The primary efficacy end point was the percent change from baseline in fasting TG levels to the end of the 12-week treatment period. Secondary efficacy measures included the percent change from baseline for total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, VLDL cholesterol, VLDL-TG, apolipoprotein B, and apolipoprotein A-I after 12 weeks of treatment. In addition, changes in LDL subclass patterns from baseline were analyzed.

Key safety variables included the proportion of patients with any clinical or laboratory adverse experiences, including drug-related (investigator determined as possibly, probably, or definitely related to study drug) muscle and liver adverse events, and discontinuation from study drug due to a drug-related clinical or laboratory adverse event. Prespecified statistical tests were performed for the prespecified key laboratory safety variables with respect to the incidence of ≥1 consecutive elevation >3 times the upper limit of normal for ALT, AST, or single elevations in creatine kinase >5 times to ≤10 times the upper limit of normal with muscle symptoms, or any single elevation in creatine kinase >10 times the upper limit of normal with or without muscle symptoms. The protocol required that patients with consecutive elevations in ALT or AST >3 times the upper limit of normal, or single elevations in creatine kinase >10 times the upper limit of normal accompanied by muscle symptoms be discontinued from the study.

Laboratory methods: Fasting plasma samples were analyzed by Medical Research Laboratories International (Highland Heights, Kentucky), a Center for Disease Control certified laboratory. Total cholesterol and TG were quantified by cholesterol oxidase and glycerokinase enzymatic assays on Hitachi 747 analyzers (Roche Diagnostics Corp., Indianapolis, Indiana). HDL cholesterol was quantified by the cholesterol oxidase colorimetric assay of the supernatant from the precipitation of non-HDL lipoproteins with heparin and manganese chloride. LDL cholesterol levels were calculated using the Friedewald equation (LDL cholesterol = total cholesterol − [HDL cholesterol + TG/5]). Plasma levels of apolipoprotein B and apolipoprotein AI were measured using immunonephelometry. The Vertical Auto Profile method (Atherotech, Birmingham, Alabama) was used to analyze the LDL subclass pattern. The units for the LDL subclass are reported in "seconds" to reflect the position of the cholesterol peak in the density gradient. The LDL subclass pattern B (predominance of smaller, more dense LDL particles) is set at <115 seconds, pattern A/B (intermediate in density between A and B) for ≥115 and <118 seconds, and pattern A (predominance of larger, more buoyant particles) for ≥118 seconds.

Statistical analyses: For all efficacy analyses, a modified intention-to-treat model was used that included all randomized and treated patients with a baseline and at least 1 valid on-treatment measurement. The week 6 observation was carried forward to week 12 if week 12 data were missing.

Because the TG distribution was skewed, a nonparametric analysis of variance model was used to compare treatment effect on the percent change from baseline to week 12. Data transformation (using Tukey's normal scores) was performed before executing the analysis of variance model, which included terms for treatment, baseline TG levels, and baseline HDL cholesterol levels. The p value was based on the nonparametric results, whereas the between-treatment differences were estimated on Hodges-Lehmann location shift. The distribution-free 95% confidence intervals (CIs) for the difference were based on the Wilcoxon's rank-sum test statistics.

For the other efficacy parameters, a parametric analysis of variance model, similar to that previously

TABLE 1 Patient Characteristics at Baseline

Variable	Simvastatin 20 mg + Fenofibrate 160 mg/d (n = 411)	Simvastatin 20 mg/d (n = 207)	Total n = 618
Men	203 (49.4%)	112 (54.1%)	315 (51.0%)
Women	208 (50.6%)	95 (45.9%)	303 (49.0%)
Age (yrs)			
Mean ± SD	52.3 ± 8.7	53.5 ± 8.2	52.7 ± 8.6
Range	28–68	26–66	26–68
BMI (kg/m^2)			
Men ≥30	106 (52.2%)	56 (50.0%)	162 (51.4%)
Women ≥30	109 (52.4%)	49 (51.6%)	158 (52.1%)
Waist circumference (cm)			
Men >102	103 (50.7%)	64 (57.1%)	167 (53.0%)
Women >88	158 (76.0%)	72 (75.8%)	230 (75.9%)
Race			
White	90.8%	87.9%	89.8%
Hispanic American	5.6%	8.2%	6.5%
Black	2.9%	2.4%	2.8%
Other	0.7%	1.4%	1.0%
Clinical atherosclerotic disease			
Known CHD	46 (11.2%)	28 (13.5%)	74 (12.0%)
Other*	12 (2.9%)	12 (5.8%)	24 (3.9%)
Hypertension	194 (47.2%)	95 (45.9%)	289 (46.8%)
Diabetes mellitus	64 (15.6%)	38 (18.4%)	102 (16.5%)
Cigarette smoker	53 (12.9%)	29 (14.0%)	82 (13.3%)
HDL <40 mg/dl	166 (40.4%)	84 (40.6%)	250 (40.5%)
None†	129 (31.4%)	62 (30.0%)	191 (30.9%)
Metabolic syndrome (≥3 NCEP ATP III criteria)‡			
Men	136 (67.0%)	76 (67.9%)	212 (67.3%)
Women	159 (76.4%)	66 (69.5%)	225 (74.3%)

*Peripheral arterial disease, abdominal aortic aneurysm, and/or symptomatic carotid artery disease.
†Four patients in combination therapy group had no information on CHD risk factors.
‡≥3 of the following: (1) waist circumference >102 cm in men, >88 cm in women; (2) TG level ≥150 mg/dl, (3) HDL cholesterol level <40 mg/dl (men), and <50 mg/dl (women), (4) diagnosis of hypertension or use of antihypertensive medications or systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg, and (5) diagnosis of type 2 diabetes, use of antidiabetic medication, or fasting glucose ≥110 mg/dl.
BMI = bone mass index; CHD = coronary heart disease; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

described, was used for treatment comparisons. The p values and 95% CIs for within- and between-treatment differences were calculated using the model-based least-squares means and associated SEs.

A supportive analysis of the percent change from baseline to week 6 was analyzed in the same fashion for all parameters: Fisher's exact tests were used for safety hypothesis testing to compare treatments with respect to the proportion of patients with any clinical or laboratory adverse event and clinically significant AST, ALT, or creatine kinase abnormalities. The 95% CIs were calculated using Wilson's score method.[3]

The primary efficacy end point was tested at the 0.025 (2-sided) level at both a planned interim analysis (n = 279) for efficacy and safety data for an abstract submission and at the final analysis to preserve the overall experiment-wise α level at 0.05 (a Bonferroni adjustment). To preserve the overall significance level for hypothesis testing on the key secondary efficacy variables (LDL cholesterol, HDL cholesterol, non-HDL cholesterol, VLDL cholesterol, and VLDL-TG), the Hochberg step-up procedure was used at the final analysis to guide statistical inferences.[4] All other secondary efficacy variables (total C, apolipoprotein A-I, apolipoprotein B, and LDL subclass patterns), as well as the safety comparisons, were tested at the 0.05 level (2-sided).

RESULTS

A total of 72 study sites in the United States screened 1,664 patients, of whom 619 were found eligible and randomized (Figure 1). The modified intent to treat (MITT) population included 600 patients, 399 on simvastatin 20 mg plus fenofibrate 160 mg combination therapy and 201 on simvastatin 20 mg monotherapy; 2.9% of patients (12 of 411) taking combination therapy and 2.9% of patients (6 of 207) taking simvastatin 20 mg were excluded from the analyses due to a lack of valid on-treatment data.

Patient characteristics: Men and women were evenly enrolled, although the percentage of women taking combination therapy was slightly higher than that on simvastatin 20 mg (Table 1). Mean age, racial distribution, TG, HDL cholesterol strata, and baseline LDL subclass pattern were balanced between treatment groups. Approximately 71% of subjects (437 of 618) in this study had the metabolic syndrome with ≥3 of 5 criteria as defined by The National Cholesterol Education Program Adult Treatment Panel III criteria.[5] This included almost half of the patients with categorical obesity (body mass index ≥30 kg/m^2); slightly more than half of the men and approximately 3/4 of the women had abdominal obesity. The distributions of race and age were similar between treat-

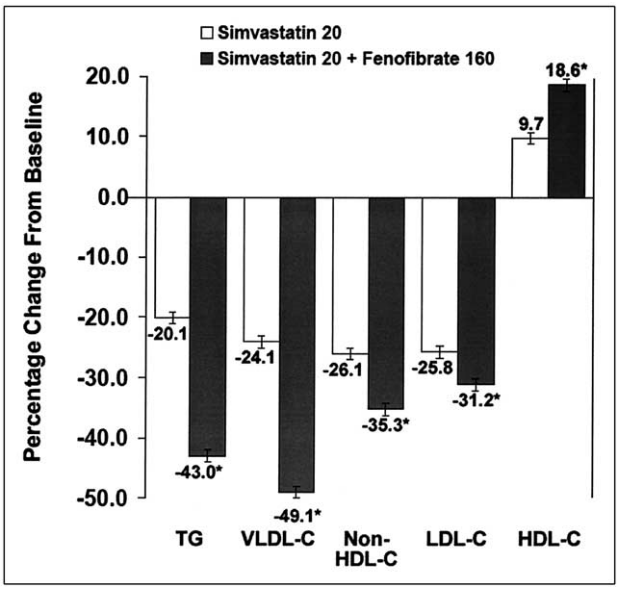

FIGURE 2. Change from baseline in lipid parameters.

ment groups for patients with and without the metabolic syndrome (data not shown). A relatively high percentage of patients had other cardiovascular risk factors, particularly hypertension and low HDL cholesterol (Table 1).

Changes in lipids, lipoproteins, and apolipoproteins: Combination therapy (simvastatin 20 mg plus fenofibrate 160 mg/day) was significantly more effective in reducing TG levels than monotherapy (simvastatin 20 mg) after 12 weeks of treatment (Figure 2). Median TG levels decreased 43.0% from baseline to week 12 in the combination therapy group and 20.1% in the monotherapy group, resulting in a treatment difference of −23.6% (95% CI −27.6% to −19.8%, $p < 0.001$; Table 2). A similar treatment difference was seen at week 6 (−22.6%, 95% CI −26.4% to −18.9%; $p < 0.001$).

Combination drug therapy also significantly improved plasma concentrations of VLDL cholesterol, non-HDL cholesterol, LDL cholesterol, and HDL cholesterol ($p < 0.001$; Figure 2), as well as total cholesterol, VLDL-TG, apolipoprotein A-I, and apolipoprotein B compared with simvastatin monotherapy at week 12 ($p < 0.001$, Table 2). Similar treatment differences were seen for each parameter at week 6 (data not shown).

After 12 weeks of treatment, patients taking combination therapy had a significant shift ($p < 0.001$) in LDL subclass pattern from baseline. The trend to a larger percentage of LDL particles in subclasses A and AB was evident after treatment compared with particles at baseline. In addition, the distribution of LDL subclass patterns was significantly different ($p < 0.001$) between the 2 treatment groups. More patients taking combination therapy tended to have a larger percentage of LDL particles in subclass patterns A and AB than patients taking simvastatin monotherapy at the end of 12 weeks of treatment (Figure 3).

Clinical adverse experiences: Clinical adverse events were similar in both treatment groups. During the study, 43.8% of patients taking combination drug therapy reported ≥1 clinical adverse event than 45.4% of patients taking simvastatin alone. The reporting of clinical serious adverse events was also similar between treatment groups: 2.4% on combination therapy and 2.9% on simvastatin alone. Eighteen patients discontinued the study because of clinical adverse events: 3.2% on combination therapy and 2.4% on simvastatin alone. Drug-related clinical adverse events accounted for 1.5% of patients discontinuing combination therapy (due to myalgia, arthralgia, musculoskeletal pain, gastroesophageal reflux disease, cholecystitis not otherwise specified, and nausea) and 1.4% on monotherapy (due to myalgia, arthralgia, and headache). Two patients (0.5%) on combination therapy discontinued due to serious clinical adverse events, none drug-related. There were no serious drug-related clinical adverse experiences in either treatment group throughout the study.

Muscular adverse experiences: There were no cases of rhabdomyolysis or clinical myopathy, defined as creatine kinase >10 times the upper limit of normal with muscle symptoms, in either treatment group during this study (Table 3). One patient randomized to combination drug therapy had creatine kinase >10 times the upper limit of normal on day 43 of combination therapy. No muscle symptoms were observed in this patient, and subsequent creatine kinase levels were near normal. This patient remained on combination drug therapy and completed the trial. The incidences of drug-related muscular adverse events and muscular adverse events, regardless of relation to study drug, were similar in both treatment groups. The most common of these drug-related muscular adverse event was myalgia (Table 3). None of these muscular adverse event was associated with increases in creatine kinase.

Liver adverse experiences: Results for elevations in ALT and AST are presented in Table 4. Drug-related laboratory liver adverse events, all of which were observed in the combined drug therapy group, occurred in 16 patients (4.0%) and included consecutive elevations in ALT (3.2%) and AST (2.5%) >3 times the upper limit of normal. No patient in either treatment group experienced an increase in total bilirubin. There was no significant difference for consecutive elevations in ALT >3 times the upper limit of normal between treatment groups. There was a significant difference between treatment groups for ≥1 elevation in ALT >3 times the upper limit of normal. Three patients discontinued due to increased ALT, and 1 discontinued due to increased ALT and AST, all in the combination therapy group. No patient in the monotherapy group discontinued because of elevations in ALT or AST.

DISCUSSION

In this study, the addition of fenofibrate to simvastatin therapy improved the lipoprotein profile compared with simvastatin monotherapy in a large cohort

TABLE 2 Serum Lipids, Lipoproteins, and Apolipoproteins (milligrams per deciliter)

Lipid Parameters	Simvastatin 20 mg + Fenofibrate 160 mg			Simvastatin 20 mg			Treatment Difference With Respect to Percent Changes	
	Baseline	Wk 12	Percent Change*	Baseline	Wk 12	Percent Change*	Estimate (95% CI)	p Value
Total triglycerides (median)	234.0	130.0	−43.0	227.0	183.0	−20.1	−23.6 (−27.6, −19.8)	<0.001
Total cholesterol (mean)	257.0	187.7	−26.3	256.1	202.5	−20.3	−6.0 (−8.0, −4.0)	<0.001
VLDL (mean)	49.6	23.0	−49.1	50.3	36.3	−24.1	−25.1 (−30.1, −20.0)	<0.001
VLDL-TG (median)	166.0	79.0	−53.5	163.0	127.0	−20.6	−31.1 (−36.1, −26.1)	<0.001
LDL (mean)	163.4	108.3	−31.2	161.7	115.2	−25.8	−5.4 (−8.4, −2.4)	<0.001
HDL (mean)	43.6	51.1	18.6	43.2	46.9	9.7	8.8 (6.0, 11.7)	<0.001
Non-HDL (mean)	213.4	136.6	−35.3	212.9	155.6	−26.1	−9.2 (−11.6, −6.7)	<0.001
Apolipoprotein A-I (mean)	148.6	161.5	8.8	148.6	155.4	4.8	4.0 (1.8, 6.2)	<0.001
Apolipoprotein B (mean)	165.8	110.4	−32.6	164.6	125.5	−22.8	−9.8 (−12.2, −7.5)	<0.001

*All percent changes from baseline were statistically significant (p <0.001).

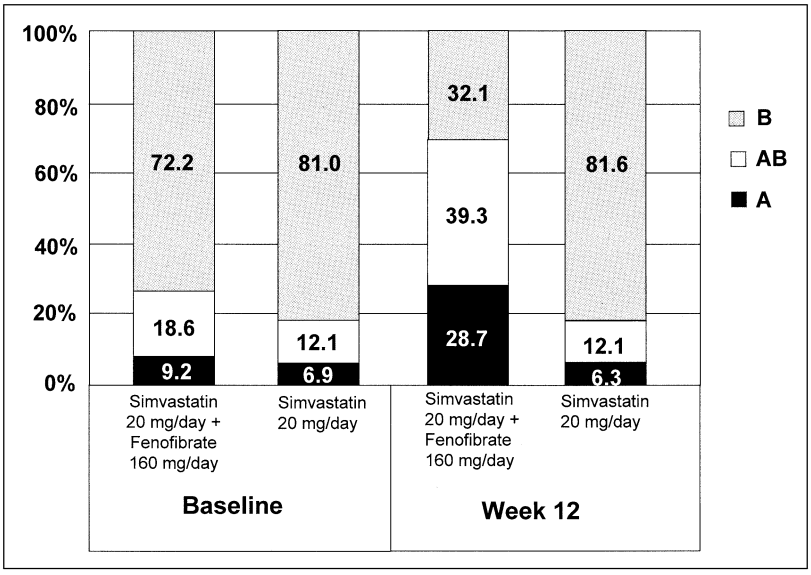

FIGURE 3. Change from baseline in LDL pattern.

of patients with combined hyperlipidemia, most with the metabolic syndrome (≥3 of 5 National Cholesterol Education Program Adult Treatment Panel III criteria). Compared with simvastatin monotherapy, combination drug therapy further reduced TG and VLDL cholesterol by 23.6% and 25.1%, respectively. Combination therapy, moreover, raised HDL cholesterol by 18.6% compared with that at baseline; this increase was twice that observed with simvastatin monotherapy. Significantly greater reductions in LDL cholesterol, non-HDL cholesterol, total cholesterol, and apolipoprotein B were achieved with combination therapy than with simvastatin alone.

In the management of combined hyperlipidemia, a fundamental question is whether combined drug therapy is more efficacious in reducing risk for coronary heart disease than statin therapy alone. Several major, randomized, controlled, and primary and secondary prevention trials demonstrated that statin-induced reductions in normal to high levels of LDL cholesterol significantly reduced the progression of coronary atherosclerosis and cardiovascular death.[6–8] Although most of the risk reduction in such patients has been attributed to a decrease in LDL cholesterol levels, the extent to which a portion of the benefit could be secondary to reduction in atherogenic TG-rich lipoproteins or to increases in HDL cholesterol remains to be clarified.[9] Although lowering LDL cholesterol produces significant risk reduction in a large percentage of patients, abnormalities in other lipoproteins may play an important role in coronary heart disease events. Several clinical trials with drugs that primarily target atherogenic dyslipidemia, such as fibrates or nicotinic acid, support the use of 1 of these agents in patients with combined lipid abnormalities. In the Veteran Affairs High Density Lipoprotein Intervention Trial, the fibrate gemfibrozil provided a significant 22% reduction in relative risk of coronary heart disease events and a 24% reduction in combined outcome of death from coronary heart disease, nonfatal myocardial infarction, or stroke. LDL cholesterol levels, which were considered low in this population (mean 111 mg/dl), did not change, but TG levels were reduced 31% and HDL cholesterol increased 6% from baseline compared with placebos.[10] Likewise, in the Bezafibrate Infarction Prevention study, bezafibrate treatment reduced TG levels 21% and increased HDL cholesterol 18%. Although the coronary heart disease event reduction was small (7%) and not significant in this trial, post hoc analyses suggested a preferential benefit of coronary heart disease risk reduction in the subgroup of patients with TG levels ≥200 mg/dl.[11] There is less clinical trial experience with nicotinic acid, but significant risk reduction was achieved in at least 2 trials.[12,13] In the Stockholm trial, the combination of nicotinic acid and a fibrate was particularly efficacious in risk reduction in patients with hypertriglyceridemia.[14] The question of whether the combi-

TABLE 3 Creatine Kinase and Drug-related Muscular Adverse Experiences

Variable	Simvastatin 20 mg + Fenofibrate 160 mg (n = 403)	Simvastatin 20 mg (n = 202)	Difference in Proportion (95% CI)*
Creatine kinase >5 ≤10 × ULN			
With muscle symptoms	0	0	0.0 (−1.9, 0.9)
With or without muscle symptoms	2 (0.5%)	0	0.5 (−1.4, 1.8)
Creatine kinase >10 × ULN			
With or without muscle symptoms	1 (0.2%)	0	0.2 (−1.6, 1.4)
	(n = 411)	(n = 207)	
Muscular AEs			
Overall	10 (2.4%)	6 (2.9%)	−0.5 (−3.9, 2.1)
Discontinued due to AEs	2 (0.5%)	1 (0.5%)	0.0 (−2.2, 1.3)
By preferred term			
Arthralgia	1 (0.2%)	0	0.2 (−1.6, 1.4)
Muscle cramp	0	1 (0.5%)	−0.5 (−2.7, 0.5)
Musculoskeletal discomfort	1 (0.2%)	0	0.2 (−1.6, 1.4)
Musculoskeletal pain	1 (0.2%)	0	0.2 (−1.6, 1.4)
Musculoskeletal stiffness	1 (0.2%)	0	0.2 (−1.6, 1.4)
Myalgia	8 (1.9%)	5 (2.4%)	−0.5 (−3.7, 1.8)

*The 95% CIs were calculated using Wilson's score method.
AE = adverse event; ULN = upper limit of normal.

TABLE 4 Laboratory Adverse Experiences: Liver Enzymes

	Simvastatin 20 mg + Fenofibrate 160 mg (n = 403)	Simvastatin 20 mg (n = 202)	Difference in Proportion (95% CIs)	Between-treatment p Value
ALT >3 Times Upper Limit of Normal				
Consecutive	8 (2.0%)	0	2.0 (−0.1–3.9)	0.057
≥1	9 (2.2%)	0	2.2 (0.1–4.2)	0.033
AST >3 Times Upper Limit of Normal				
Consecutive	2 (0.5%)	0	0.5 (−1.4–1.8)	0.554
≥1	6 (1.5%)	0	1.5 (−0.5–3.2)	0.186

Values are expressed as number (%) unless otherwise indicated.

nation of simvastatin and fenofibrate provides additional risk reduction compared with statin therapy remains to be answered by a large outcome trial.

Although monotherapy with higher doses of statin can result in greater improvements in TG and HDL cholesterol, as well as LDL cholesterol, such treatment still does not correct all of the lipoprotein abnormalities in patients with combined hyperlipidemia. Among their other benefits, fibrates significantly reduced TG-rich lipoproteins, as well as the LDL cholesterol fraction of small, dense particles.[14] Because fibrates and statins each regulate serum lipids by different mechanisms, combination therapy may offer particularly desirable benefits in patients with combined hyperlipidemia. In the present study, the combination of simvastatin 20 mg plus fenofibrate 160 mg/day compared with simvastatin monotherapy was highly efficacious in reducing TG and VLDL cholesterol levels and significantly improving multiple other lipoprotein abnormalities in patients with combined hyperlipidemia.

The association of LDL subclass patterns with elevated levels of TG and low levels of HDL cholesterol has been described by Austin and colleagues.[15] They showed that the enhanced cardiovascular risk associated with LDL subclass pattern B, characterized by a preponderance of small, dense LDL particles, is associated with a greater risk of myocardial infarction and is highly influenced by the levels of HDL cholesterol. Given the efficacy of fenofibrate therapy on reducing levels of TG-rich lipoproteins (VLDL, intermediate-density lipoprotein, and LDL) and raising levels of HDL cholesterol, it is not surprising that combination therapy with simvastatin 20 mg/day plus fenofibrate 160 mg/day also improved the LDL subclass pattern compared with statin monotherapy. At the end of 12 weeks of treatment, a greater percentage of patients on combination therapy had a distinct shift to higher percentages of LDL subclass patterns A and AB from the baseline profile, representing a shift in LDL particle size from a predominance of smaller and denser to more larger and more buoyant LDL cholesterol particles. Because small, dense LDL cholesterol particles have been shown to be more atherogenic, this

compositional change in the LDL cholesterol particle with combination therapy is likely beneficial.

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