VAP II analysis of lipoprotein subclasses in mixed hyperlipidemic patients on treatment with ezetimibe/simvastatin and fenofibrate

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Abstract **This analysis evaluates the effects on lipoprotein subfractions and LDL particle size of ezetimibe/simvastatin with or without coadministration of fenofibrate in patients with mixed hyperlipidemia. This multicenter, double-blind, placebo-controlled, parallel-group study included 611 patients aged 18–79 years randomized in 1:3:3:3 ratios to one of four 12 week treatment groups: placebo; ezetimibe/simvastatin 10/20 mg/day; fenofibrate 160 mg/day; or ezetimibe/simvastatin 10/20 mg/day + fenofibrate 160 mg/day. At baseline and study endpoint, cholesterol associated with VLDL, intermediate density lipoprotein (IDL), LDL, and HDL subfractions was quantified using the Vertical Auto Profile II method. LDL particle size was determined using segmented gradient gel electrophoresis. Whereas fenofibrate reduced cholesterol mass within VLDL and IDL, and shifted cholesterol from dense LDL subfractions into the more buoyant subfractions and HDL, ezetimibe/simvastatin reduced cholesterol mass within all apolipoprotein B-containing particles without significantly shifting the LDL particle distribution profile. When administered in combination, the effects of the drugs were complementary, with more-pronounced reductions in VLDL, IDL, and LDL, preferential loss of more-dense LDL subfractions, and increased HDL, although the effects on most lipoprotein subfractions were not additive. Thus, ezetimibe/simvastatin + fenofibrate produced favorable effects on atherogenic lipoprotein subclasses in patients with mixed hyperlipidemia.**—Farnier, M., I. Perevozskaya, W. V. Taggart, D. Kush, and Y. B. Mitchel. **VAP II analysis of lipoprotein subclasses in mixed hyperlipidemic patients on treatment with ezetimibe/simvastatin and fenofibrate.** ***J. Lipid Res.*** **2008.** 49: **2641–2647.**

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Elevated triglycerides (TGs) along with elevated LDL-cholesterol (LDL-C) and reduced HDL-cholesterol (HDL-C) are consistent with the lipoprotein phenotype observed in mixed (or combined) hyperlipidemia. As more data accrue in this area, it is becoming apparent that individuals displaying these lipid characteristics also generally exhibit a preponderance of smaller, more-dense LDL particles, which correlates with the high-risk LDL subclass pattern B phenotype. These lipoprotein changes and the associated particle size distribution have been shown to be altered to a greater degree in patients with established cardiovascular disease or in patients at high risk for a coronary event (1–6).

Large clinical trials focusing on serum lipid changes and their relationship to risk reduction have observed treatment effects on coronary heart disease (CHD) risk that were greater than expected from the changes in traditional lipid parameters such as total plasma cholesterol and TGs. Patients with the lipid triad (elevated LDL-C and TG and low HDL-C levels) are at greater risk for CHD than the general population, and they benefit from treatment with simvastatin (7) or fibrate (8, 9). Therefore, changes in lipoprotein subclasses and particle size may contribute to these beneficial outcomes. Unfortunately, to date, there are limited data specifically comparing on-treatment changes in lipoprotein subclasses with reduction in risk for CHD events (5).

Recognizing the complex nature of mixed hyperlipidemia, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines recommend treating patients with mixed hyperlipemia with a combination of lipid-lowering agents (10). Fibrates are often employed in the treatment of mixed hyperlipidemia and have been shown to lower TG by 20–50% and LDL-C by 5–20%, and to raise HDL-C by 10–20% (11). The reductions in LDL-C with fibrate monotherapy are relatively modest and often insufficient, based on current guidelines (10). Further, paradoxical increases in LDL-C with fibrate therapy have been reported in patients with moderate to severe hypertriglyceridemia (11–13). Therefore, additional

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agents are needed to treat the cholesterol component of mixed hyperlipidemia.

The use of simvastatin, a statin, and more recently the cholesterol absorption inhibitor ezetimibe with fenofibrate have been reported to provide improved lipoprotein profiles (14, 15). The use of both cholesterol-lowering agents, simvastatin and ezetimibe, together with fenofibrate has also been reported (16). The effects of the combination of ezetimibe/simvastatin + fenofibrate were demonstrated to result in significantly greater reduction in LDL-C than for fenofibrate alone. This could be attributed mainly to the effect of ezetimibe/simvastatin, inasmuch as there was little or no incremental LDL-C reduction from baseline observed for the addition of fenofibrate (16). Similarly, the change in HDL-C could be attributed mainly to fenofibrate, inasmuch as there was little or no incremental change in the combination treatment compared with those observed for fenofibrate alone.

The effect of ezetimibe/simvastatin + fenofibrate on non-HDL, apolipoprotein B (apoB), and TG were significantly greater for the combination than for either treatment alone, raising the possibility that their effects may be complementary or overlap in pathways affecting these parameters, resulting in an effect that was less than additive when compared with the sum of the results for the separate treatments.

In addition, and consistent with the well-known effects of fenofibrate on plasma TG, VLDL-C, and LDL-C subclass distributions, nearly 66% of the patients on either ezetimibe/simvastatin + fenofibrate or fenofibrate alone had a larger, more-buoyant LDL-C subclass pattern compared with fewer than 20% at baseline (16). The purpose of the analysis presented here was to evaluate the effects of ezetimibe/simvastatin and fenofibrate, both as monotherapy and in coadministration, in more detail by examining their effects on individual lipoprotein subclasses using the Vertical Auto Profile II (VAP II) and segmented gradient gel electrophoresis (S_3GGE™) methods in patients with mixed hyperlipidemia.

DESIGN AND METHODS

The complete details of study design and patient entry criteria are published elsewhere (16). In brief, this was a multicenter, international, randomized, double-blind, placebo-controlled, parallel-group study. The study was approved by local investigation review boards, and all patients provided written informed consent. Eligible patients were men and women aged 18 to 79 years with mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2 diabetes), or CHD risk score >20% as defined by NCEP ATP III. After drug washout and a run-in period with a lipid-altering diet and placebo study drug, lipid criteria for randomization were LDL-C 130 to 220 mg/dl inclusive and TG 150 to 500 mg/dl inclusive. Patients with type 2 diabetes were limited to those with LDL-C of 100 to 180 mg/dl inclusive. Patients were randomized in a 1:3:3:3 ratio to one of four treatment groups: placebo; ezetimibe/simvastatin 10/20 mg/day; fenofibrate 160 mg/day; or ezetimibe/simvastatin 10/20 mg/day + fenofibrate 160 mg/day for 12 weeks. Patients were also stratified for statistical analysis by TG less than 250 mg/dl and TG equal to or greater than 250 mg/dl. The primary efficacy endpoint of the trial was percent change in LDL-C from baseline to study endpoint after treatment with ezetimibe/simvastatin + fenofibrate versus fenofibrate alone (16). The current predefined analysis evaluates effects of the drug combinations on lipoprotein subfractions and LDL particle size by use of well-defined methods using molecular density, size, and/or charge as means of separation and subsequent measurement of the lipid content of the particles (17–19).

Blood collection and lipid analyses

Lipid and lipoprotein measurements were performed using fasting (12 h) EDTA plasma collected at baseline and study endpoint (week 12). Cholesterol associated with individual lipoprotein subfractions was quantified using the VAP II method, a validated ultracentrifugation method that involves direct cholesterol measurements in eluting fractions including two VLDL subfractions (VLDL-C 1+2 and VLDL-C 3), intermediate density lipoprotein-C (IDL-C), four LDL subfractions (LDL-C 1 to 4), lipoprotein [a] (Lp[a]), and HDL subfractions (HDL-C_2 and HDL-C_3) (17–19). A value for LDL-C, designated "real LDL-C" (LDL-CR), was calculated from all fractions containing true LDL-C particles and excludes the contributions of IDL-C and Lp[a] included in the standard LDL-C measurements. All VAP II lipid measurements were performed by Atherotech, Inc. (Birmingham, AL) with technicians blinded to study drug treatment.

LDL particle size was assessed based on S_3GGE™ performed by Berkeley HeartLab, Inc. (Burlingame, CA). Particle size (in angstroms) was determined for the predominant LDL peak on densitometric scans of the gels based on standards of known size. All measurements were performed by technicians blinded to study drug treatment.

Statistical analysis

Endpoints in this exploratory analysis included percent change from baseline to study endpoint in cholesterol associated with individual lipoprotein subfractions including VLDL-C 1+2 and VLDL-C 3, IDL-C, LDL-C 1 to 4, Lp[a], HDL-C_2 and HDL-C_3, and changes in LDL particle size. A modified intention-to-treat approach was used with all randomized patients who had baseline values, had taken at least one dose of study medication, and had at least one postbaseline measurement. An analysis-of-covariance (ANCOVA) model with terms for treatment (placebo, ezetimibe/simvastatin, fenofibrate, ezetimibe/simvastatin + fenofibrate) and baseline TG was used to compare each efficacy parameter. For data not normally distributed, e.g., TG, a nonparametric test (ANCOVA model based on Tukey's normalized ranks) was used for inferential testing of between-treatment differences. Change data were expressed as mean or median percent change [95% confidence interval (CI)]. Hodges-Lehmann estimates of the median difference between treatments with a corresponding distribution-free CI based on Wilcoxon's rank sum test were used to determine the CI for median data.

RESULTS

Baseline characteristics

The treatment groups were generally well-matched with respect to baseline demographics and traditional lipid parameters (16). Overall, patients had a mean LDL-C of 160 mg/dl and a mean HDL-C of 45 mg/dl, and median TG was 229 mg/dl at baseline (16). There did not appear to be any clinically meaningful differences among the treatment groups at baseline in terms of cholesterol

associated with individual lipoprotein subfractions determined using the VAP II method (**Table 1**). Among the LDL-C subfractions, LDL-C 4 exhibited the lowest mass and LDL-C 3 exhibited the greatest mass (accounting for about 12% and 63%, respectively, of the total LDL-C subfraction mass) in all four treatment groups. The baseline values for LDL-CR were approximately 30 mg/dl lower than the LDL-C value determined following preparative ultracentrifugation owing to the lack of inclusion of cholesterol associated with IDL and Lp[a]. Importantly, although LDL-CR values were lower, they were highly correlated with standard LDL-C values.

Treatment-induced changes in lipoprotein subfractions

Median percent changes from baseline to study endpoint for VLDL-C, IDL-C, and LDL-CR are shown in **Fig. 1**. Relative to placebo, ezetimibe/simvastatin, fenofibrate, and ezetimibe/simvastatin + fenofibrate significantly reduced cholesterol mass in all of these lipoprotein classes. With both ezetimibe/simvastatin and ezetimibe/simvastatin + fenofibrate, the most pronounced (percent) changes were observed for IDL-C. The effects of ezetimibe/simvastatin, fenofibrate, and ezetimibe/simvastatin + fenofibrate on VLDL subclasses (**Fig. 2**) were similar in pattern to those for VLDL-C overall (Fig. 1); effects for all treatments appeared to be slightly more pronounced for VLDL-C 1+2 than for VLDL-C 3. Although the changes in VLDL-C are approximately the same for either ezetimibe/simvastatin or for fenofibrate alone, coadministration demonstrates an increased effect that is less than expected from the sum of each of the treatments. The changes in IDL-C are essentially maximized by ezetimibe/simvastatin with little additional effect of fenofibrate.

The modest 10% reduction in LDL-CR with fenofibrate treatment (Fig. 1) was accounted for by reductions in LDL-C 1, LDL-C 3, and LDL-C 4, which are, respectively, the most buoyant, the second most dense, and the most dense subfractions (**Fig. 3**) offset by the highly significant 66% increase in LDL-C 2, the second most buoyant of the LDL fractions. Significant reductions were observed for all LDL-C subfractions, LDL-C 1, C 2, C 3, and C 4, following ezetimibe/simvastatin treatment.

When coadministered, the distinctive effects of both fenofibrate and ezetimibe/simvastatin were evident. Ezetimibe/simvastatin + fenofibrate produced a pattern of changes similar in direction to those of fenofibrate alone, suggesting that the change in LDL-C pattern was primarily a function of fenofibrate. Coadministration led to greater but not additive cholesterol lowering in LDL-C 3, the most abundant LDL-C fraction, whereas treatment with fenofibrate alone gave a greater effect for LDL-C 4. With the exception of LDL-C4, the relative quantitative changes were greatest for either ezetimibe/simvastatin alone or the combination, suggesting that this effect is attributable mainly to ezetimibe/simvastatin. Thus, the separate beneficial effects of each therapy were captured in the combination therapy.

Cholesterol associated with Lp[a] was not significantly different from placebo for any of the groups (data not shown). Fenofibrate and ezetimibe/simvastatin + fenofibrate similarly increased median HDL-C_2 and HDL-C_3 compared with ezetimibe/simvastatin or placebo (**Fig. 4**), suggesting that this effect is attributable mainly to fenofibrate.

The effects of treatment are further illustrated in overlaid baseline and endpoint VAP II scans from patients representative of the median values for each treatment group (**Fig. 5**). The ezetimibe/simvastatin-treated patient exhibited marked reductions within the VLDL-C, IDL-C, and LDL-C density ranges without a shift in LDL-C density distributions and an increase in the HDL-C range. In the fenofibrate-treated patient, VLDL-C and IDL-C were reduced, HDL-C was increased, and there was a pronounced shift in the distribution of LDL-C toward larger, more-buoyant LDL-C particles without a large effect on LDL-C values overall. Coadministration substantially reduced VLDL-C, IDL-C, and LDL-C, elevated HDL-C, and promoted a shift from smaller, more-dense to larger, more-buoyant LDL-C subfractions.

Treatment-induced changes in LDL particle size

The size of the predominant LDL peak was similar among the treatment groups at baseline. Ezetimibe/simvastatin did not significantly affect LDL particle size, whereas both fenofibrate and ezetimibe/simvastatin + fenofibrate increased LDL particle size (**Table 2**). As previously published,

TABLE 1. Cholesterol associated with lipoprotein subclasses at baseline as measured by VAP II Method

Variables	Placebo	Ezetimibe/simvastatin	Fenofibrate	Ezetimibe/simvastatin + fenofibrate
			mg/dl	
VLDL-C	33.0 ± 10.2	33.0 ± 10.7	34.0 ± 9.8	33.0 ± 11.2
VLDL-C 1+2	15.2 ± 5.1	15.3 ± 5.5	15.3 ± 6.2	14.7 ± 6.1
VLDL-C 3	18.0 ± 4.7	18.0 ± 5.6	18.0 ± 5.6	18.0 ± 4.7
IDL-C	24.0 ± 8.8	24.0 ± 14.0	23.0 ± 13.5	23.0 ± 12.1
LDL-CR	126.5 ± 33.5	133.0 ± 27.9	131.0 ± 29.3	125.0 ± 32.6
LDL-C 1	24.9 ± 9.3	26.1 ± 9.2	25.6 ± 8.2	23.8 ± 7.5
LDL-C 2	24.5 ± 19.3	21.0 ± 21.8	23.2 ± 18.8	19.4 ± 19.2
LDL-C 3	63.3 ± 16.2	63.7 ± 18.2	64.0 ± 20.1	63.0 ± 18.9
LDL-C 4	13.4 ± 10.3	17.0 ± 16.2	16.1 ± 17.9	16.2 ± 18.8
Lp[a] cholesterol	11.0 ± 23.7	9.5 ± 22.3	9.0 ± 11.6	8.0 ± 17.6
HDL-C_2	9.0 ± 3.3	9.0 ± 3.7	9.0 ± 3.7	8.5 ± 3.7
HDL-C_3	33.0 ± 8.4	35.5 ± 8.4	35.0 ± 7.9	33.0 ± 7.4

Data are presented as median ± a robust standard deviation (SD). Placebo, n = 56; ezetimibe/simvastatin, 10 mg, n = 168; fenofibrate, 160 mg, n = 176; ezetimibe/simvastatin, 10/20 mg + fenofibrate, 160 mg, n = 170. VAP II, Vertical Auto Profile II; IDL, intermediate density lipoprotein; LDL-CR, "real LDL-C."

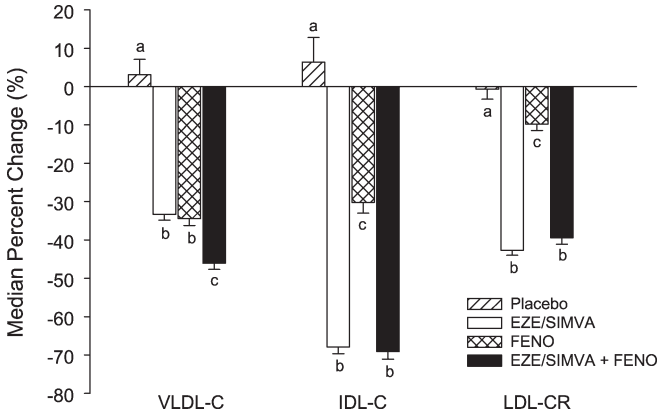

Fig. 1. Median (± SE) percent change from baseline to study endpoint for cholesterol associated with VLDL-cholesterol (VLDL-C), intermediate density lipoprotein-C (IDL-C), and "real LDL-C" (LDL-CR). For any pair-wise comparison, a significant between-treatment difference is denoted by the presence of a different letter above the bar (e.g., VLDL-C). Different letters above/below each bar indicate that the percent changes for the groups were significantly different from each other [placebo < ezetimibe (EZE)/simvastatin (SIMVA) = fenofibrate (FENO) < EZE/SIMVA + FENO].

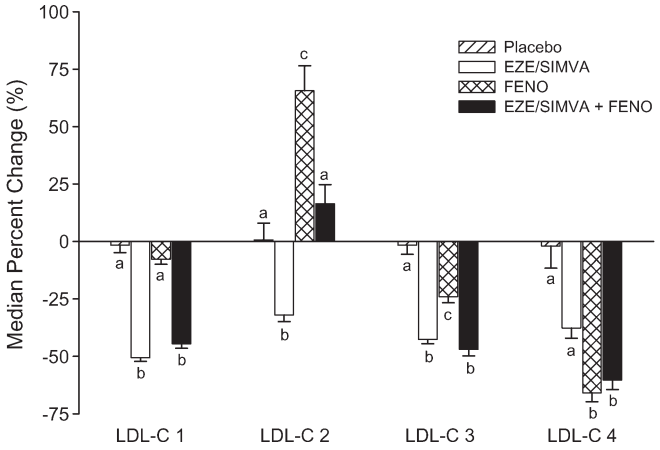

Fig. 3. Median (± SE) percent change from baseline to study endpoint for cholesterol associated with LDL-C subclasses. For any pair-wise comparison, a significant between-treatment difference is denoted by the presence of a different letter above/below the bar (e.g., for LDL-C 1). Different letters above/below each bar indicate that the changes were significantly different from each other [placebo = fenofibrate (FENO) < ezetimibe (EZE)/simvastatin (SIMVA) = EZE/SIMVA + FENO].

the proportions of patients exhibiting LDL size pattern B at baseline were 64%, 55%, 59%, and 63% in the placebo, ezetimibe/simvastatin, fenofibrate, and ezetimibe/simvastatin + fenofibrate groups, respectively (16). At study endpoint, the percentages of patients exhibiting LDL size pattern B changed to 64%, 49%, 14%, and 17% in the placebo, ezetimibe/simvastatin, fenofibrate, and ezetimibe/simvastatin + fenofibrate groups, respectively.

DISCUSSION

The interesting finding is that for this combination of therapeutic agents, it appears that the forte of each of the separate therapies was preserved in the case of LDL-C-lowering effects for ezetimibe/simvastatin and HDL-raising, triglyceride-lowering, and buoyancy-raising effects for fenofibrate. In this set of patients with mixed hyperlipidemia, fenofibrate had only modest effects on overall LDL-C mass, but led to a marked redistribution within LDL subclasses characterized by a loss of mass in the physically smaller, more-dense LDL-C 3 and LDL-C 4 subclasses and an increase of mass in the larger, more-buoyant LDL-C 2. These results are consistent with previous observations and are attributed to the marked effects of fenofibrate on TG metabolism. On the other hand, ezetimibe/simva-

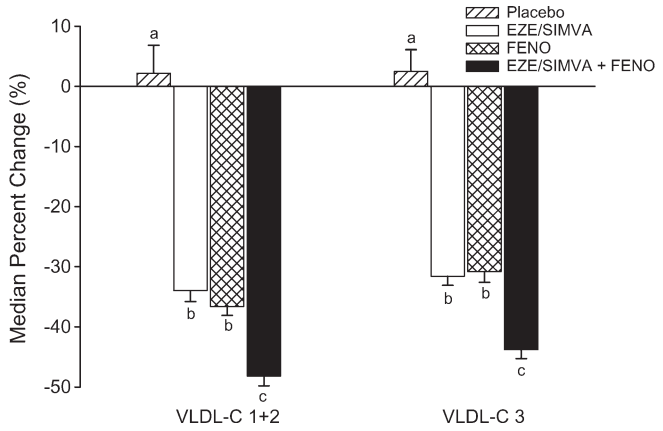

Fig. 2. Median (± SE) percent change from baseline to study endpoint for cholesterol associated with VLDL-C subclasses. For any pair-wise comparison, a significant between-treatment difference is denoted by the presence of a different letter above the bar (e.g., for VDL-C 1+2). Different letters above/below each bar indicate that the changes were significantly different from each other [placebo < ezetimibe (EZE)/simvastatin (SIMVA) = fenofibrate (FENO) < EZE/SIMVA + FENO].

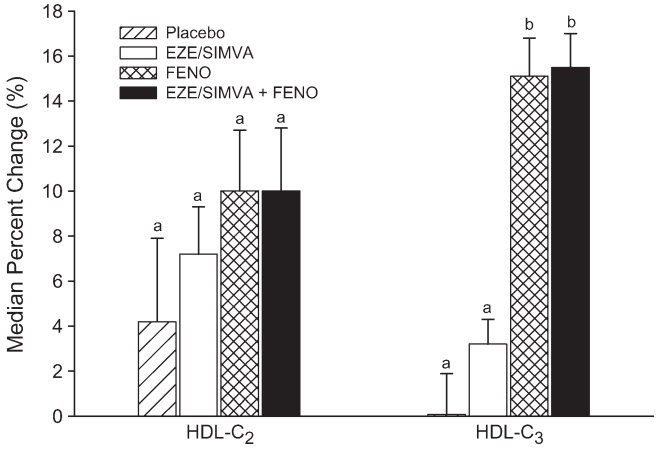

Fig. 4. Median (± SE) percent change from baseline to study endpoint for cholesterol associated with HDL-C subclasses. For any pair-wise comparison, a significant between-treatment difference is denoted by the presence of a different letter above the bar (e.g., for HDL-C_3). Different letters above each bar indicate that the changes were significantly different from each other [placebo = ezetimibe (EZE)/simvastatin (SIMVA) < fenofibrate (FENO) = EZE/SIMVA + FENO].

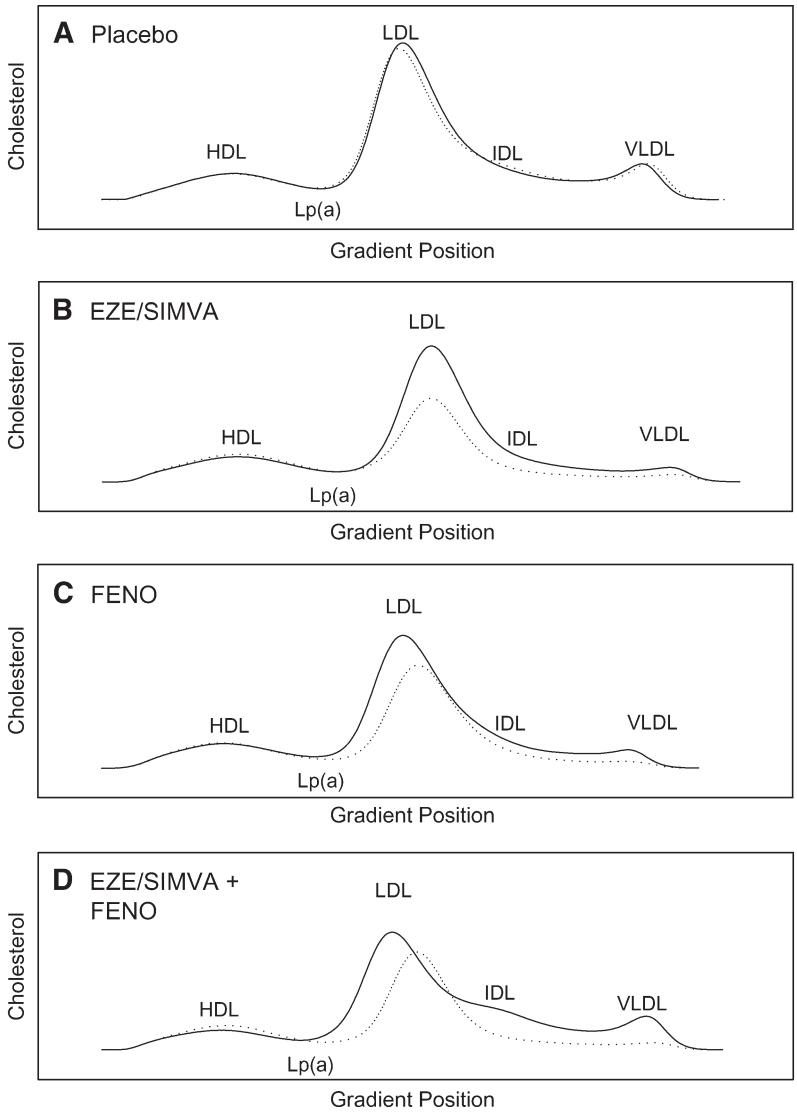

Fig. 5. Representative Vertical Auto Profile II lipid distributions at baseline (solid line) and at study endpoint (dotted line) for each active treatment from patients representing median results: A: Placebo. B: Ezetimibe/simvastatin (EZE/SIMVA). C: Fenofibrate (FENO). D: (EZE/SIMVA + FENO). Error bars indicate ± SE.

statin therapy produced significant reductions in VLDL-C, IDL-C, and LDL-CR mass compared with placebo. Percent reduction in IDL-C mass was particularly pronounced with ezetimibe/simvastatin. Changes in LDL-CR were observed as reductions in all subclasses (LDL-C 1, C 2, C 3, and C 4) as determined by the VAP II method, with the greatest relative change in LDL-C 1 and C 3. The median content of LDL-C 2 was increased by greater than 60% by fenofibrate, whereas this effect was blunted to about a 15% increase by the combination therapy owing to the cholesterol-lowering effect of ezetimibe/simvastatin when added to fenofibrate. The combination of ezetimibe/simvastatin + fenofibrate resulted in greater effects than either separate therapy on VLDL-C subfractions. Thus, changes in TG-rich lipoproteins with ezetimibe/simvastatin + fenofibrate were generally greater than for fenofibrate alone, but they did not reach the sum of the separate therapies.

With all therapies added together, the sum of the effects observed on the lipoprotein subclasses when administered separately was not achieved. From the design of the study, the contribution of the ezetimibe with simvastatin and fenofibrate alone to the cholesterol content of the various

TABLE 2. LDL peak particle size at baseline and at study endpoint

Variables	Placebo	Ezetimibe/simvastatin	Fenofibrate	Ezetimibe/simvastatin + fenofibrate
LDL peak particle size (Å)				
Baseline ± SD	254.0 ± 9.3	254.5 ± 11.2	254.0 ± 11.2	253.0 ± 12.1
Study endpoint ± SD	253.0 ± 11.2	255.0 ± 12.6	265.0 ± 4.7	265.0 ± 5.6

Data are presented as median ± standard deviation; n = number of patients included in baseline/study endpoint measurements. Placebo, n = 56; ezetimibe/simvastatin, 10/20 mg, n = 168; fenofibrate, 160 mg, n = 175; ezetimibe/simvastatin, 10/20 mg + fenofibrate, 160 mg, n = 169.

lipoprotein subfractions has been identified. From a previous study, the combination of ezetimibe and fenofibrate appeared to approach the sum of the individual activities of the individual agents (15). To determine the fenofibrate-related effects when it is administered with simvastatin, it is necessary to extrapolate the effect of fenofibrate alone from other studies (15, 16) and apply it to the previous simvastatin with fenofibrate study (14), because that study did not have a fenofibrate-only arm. The extrapolated results indicate that the use of simvastatin and fenofibrate together appeared not to approach the sum of the separate activities. Therefore, it appears that when simvastatin/ezetimibe is present, the LDL-C reductions seem to be already near maximum, but with an LDL-C subfraction distribution that is characteristic of fenofibrate. This may indicate that the sum of the mechanisms of action when all three agents are present has reached a saturation of major, perhaps interconnected, pathways for the effect of any one of the agents.

Treatment with fenofibrate and ezetimibe/simvastatin + fenofibrate increased LDL peak particle size compared with placebo or ezetimibe/simvastatin. For ezetimibe/simvastatin therapy, the increases in LDL peak particle size were modest compared with placebo. These changes in LDL particle size are reflected in the dramatic change from baseline in the proportion of patients with LDL size pattern B with fenofibrate and ezetimibe/simvastatin + fenofibrate treatments (16). These changes are consistent with greater reductions in VLDL-C, IDL-C, and LDL-C 4 and improvements in the mass of the larger, more-buoyant LDL-C 2 subfraction observed with fenofibrate and ezetimibe/simvastatin + fenofibrate treatments.

Changes in HDL-C subclasses were primarily influenced by fenofibrate, which is in agreement with those noted for HDL-C and apoA-I (16). Changes in TG are interrelated with those in HDL-C. Fenofibrate significantly reduced TG levels about twice the amount observed with ezetimibe/simvastatin alone. The increases in both HDL fractions are approximately inversely proportional to the reduction in TG in these patients with mixed hyperlipidemia (16). It is noted, however, that with ezetimibe/simvastatin added to fenofibrate, there was no additive effect on HDL-C, suggesting that the mechanism driving the increase in HDL-C had reached saturation.

Examinations of treatment effects on lipoprotein subfractions are important because of the association of these with increased cardiovascular risk. VLDL-C measurements have been shown to be predictors of recurrent coronary events (6). VLDL metabolism was demonstrated to be altered in patients with type 2 diabetes and increased adiposity, conditions generally associated with atherogenic dyslipidemia (20). IDL-C was elevated in patients with angiographically determined coronary artery disease (21), and was positively associated with progression of coronary artery disease in hypercholesterolemic men (1). A predominance of smaller, more-dense LDL-C particles, which usually occurs in association with higher concentrations of TG, is associated with increased risk of myocardial infarction (2). Increased levels of HDL-C_2 and HDL-C_3 subclasses have both been reported to be protective against coronary artery disease (5, 22). The results of this exploratory study suggest that there are quantitative and qualitative changes in lipoprotein subclasses and LDL particle size with coadministration of ezetimibe/simvastatin and fenofibrate that result in a more favorable plasma lipid milieu in patients with mixed hyperlipidemia. Whether these changes will result in better health outcomes remains to be established. Comparison of the changes observed here from the prospective of similar changes in LDL-C cholesterol to the improvements in clinical outcomes indicates that the shifts in LDL-C fractions play a role in the improvements in clinical outcomes.

The combination therapy was well tolerated and produced a safety profile that was similar to those of the individual drugs (14–16).

In summary, ezetimibe/simvastatin and fenofibrate, both as separate therapy and in coadministration, produced beneficial changes in the distribution of lipoprotein subclasses within the VLDL-to-LDL density range. The combination of ezetimibe/simvastatin + fenofibrate produced greater reductions in VLDL-C, IDL-C, and LDL-C (relative to other treatment groups) and greater improvements in the distribution of LDL-C subfractions, with a shift from smaller, more-dense to larger, more-buoyant LDL-C particle size in patients with mixed hyperlipidemia.

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