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Effects of fenofibrate and ezetimibe, both as monotherapy and in coadministration, on cholesterol mass within lipoprotein subfractions and low-density lipoprotein peak particle size in patients with mixed hyperlipidemia

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Abstract

Coadministration of fenofibrate and ezetimibe (FENO + EZE) produced complementary and favorable effects on the major lipids and lipoproteins, low-density lipoprotein cholesterol (LDL-C), triglycerides, high-density lipoprotein cholesterol (HDL-C), and non–HDL-C levels, and was well tolerated in patients with mixed hyperlipidemia. The current analysis evaluates the effects of FENO and EZE, as monotherapies and in coadministration, on lipoprotein subfractions and LDL particle size distributions in these patients. In a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, patients with mixed hyperlipidemia were randomized in a 1:3:3:3 ratio to one of 4 treatment groups: placebo, FENO 160 mg/day, EZE 10 mg/day, or FENO 160 mg/day + EZE 10 mg/day. At baseline and study end point, the Vertical Auto Profile II method was used to measure the cholesterol associated with 2 very low-density lipoprotein (VLDL) subfractions (VLDL-C1 + 2 and VLDL-C3), intermediate-density lipoproteins (IDL-C), and 4 LDL subfractions (LDL-C1 through LDL-C4, from most buoyant to most dense), lipoprotein (Lp) (a), and 2 HDL-C subfractions (HDL-C2 and HDL-C3). The LDL particle size was determined using segmented gradient gel electrophoresis. Fenofibrate reduced cholesterol mass within VLDL, IDL, and dense LDL (primarily LDL-C4) subfractions, and increased cholesterol mass within the more buoyant LDL-C2 subfraction, consistent with a shift to a more buoyant LDL peak particle size. Ezetimibe reduced cholesterol mass within all of the apolipoprotein B–containing particles (eg, VLDL-C, IDL-C, and LDL-C) but did not lead to a shift in the LDL particle size distribution profile. Coadministration of FENO and EZE promoted more pronounced reductions in VLDL-C, IDL-C, and LDL-C, and a preferential decrease in dense LDL subfractions. Fenofibrate and FENO + EZE promoted similar increases in HDL-C2 and HDL-C3. Coadministration of FENO + EZE produced complementary and favorable changes in lipoprotein fractions and subfractions, as assessed by the Vertical Auto Profile II method, in patients with mixed hyperlipidemia. These changes reflected the combined effects of FENO in reducing triglycerides-rich lipoproteins and promoting a shift in the LDL particle distribution profile toward larger, more buoyant particles and of EZE in promoting reductions in cholesterol mass across the apolipoprotein B particle spectrum.

1. Introduction

In a large clinical trial, coadministration of fenofibrate (FENO) and ezetimibe (EZE) improved the atherogenic lipid profile of patients with mixed hyperlipidemia and was well tolerated for up to 52 weeks [1,2]. Coadministration of FENO + EZE reduced low-density lipoprotein cholesterol (LDL-C) by 20%, total cholesterol by 22%, non–high-density lipoprotein cholesterol (non–HDL-C) by 30%, and apolipoprotein (apo) B by 26%. Changes in HDL-C and triglycerides (TG) were +19% and −44%, respectively, with coadministration [1]. Consistent with the well-known effects of fibrates on lipid metabolism [3], nearly two thirds of the

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patients treated with FENO + EZE shifted from a smaller, more dense to a larger, more buoyant LDL distribution profile [1].

The major lipoprotein classes are comprised of particle subpopulations of varying size, density, chemical composition, and associations with risk of cardiovascular disease [4,5]. Subfractionation of the lipoprotein classes thus provides additional insight into the potential impact of lipid-lowering therapies on disease risk. The Vertical Auto Profile II (VAP II) method is a commercially available and validated ultracentrifugation method for quantification of cholesterol among lipoprotein fractions and subfractions [6]. Recently, changes in cholesterol associated with lipoprotein subfractions were examined using the VAP II method in patients with primary hypercholesterolemia treated with EZE and/or simvastatin [7]. The purpose of the current analysis in patients with mixed hyperlipidemia was to evaluate the effects of FENO and EZE, both as monotherapies and in coadministration, on cholesterol associated with lipoprotein fractions and subfractions as measured by the VAP II method. Additional analyses included lipoprotein particle distribution profiles by gradient gel electrophoresis.

2. Design and methods

Complete details regarding study design and patient entry criteria are published elsewhere [1]. In brief, this was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Eligible patients were men and women aged 18 to 75 years with mixed hyperlipidemia and no coronary heart disease (CHD), CHD-equivalent disease (except for type 2 diabetes mellitus), or CHD risk score >20% as defined by the National Cholesterol Education Program Adult Treatment Panel III. After drug washout and a run-in period with a lipid-altering diet, lipid criteria for randomization were LDL-C of 130 to 220 mg/dL inclusive and TG of 200 to 500 mg/dL inclusive. Patients with type 2 diabetes mellitus 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 4 treatment groups: placebo, EZE 10 mg/day, FENO 160 mg/day, or FENO 160 mg/day + EZE 10 mg/day for 12 weeks. All patients provided written informed consent to participate. The primary efficacy end point of the trial was percentage change in LDL-C from baseline to study end point after treatment with FENO + EZE vs FENO alone [1]. The current predefined analyses evaluated the effects of study treatments on changes in cholesterol mass within the major lipoprotein fractions and subfractions and LDL particle distribution profiles and particle size in archived samples.

2.1. Blood collection and lipid analyses

Lipid and lipoprotein measurements were performed using fasting plasma collected at baseline and study end point (week 12). Cholesterol associated with individual lipoprotein fractions and subfractions was quantified using the VAP II method, a validated ultracentrifugation method that involves direct cholesterol measurements in eluting fractions including very low-density lipoprotein (VLDL-C) and 2 VLDL-C subfractions (VLDL-C1 + 2 and VLDL-C3), intermediate-density lipoprotein (IDL-C), 4 LDL subfractions (LDL-C1 to 4), lipoprotein (Lp) (a)-C, and HDL-C2 and HDL-C3 [6,8,9]. A value for LDL-C, designated *true LDL-C* (LDL-CVAP), was calculated from all fractions containing true LDL particles and excluded the contributions of IDL and Lp(a) typically included in standard LDL-C measurements (ie, from β quantitation) [6]. All VAP II measurements were performed by Atherotech (Birmingham, AL). The LDL particle size was assessed based on segmented gradient gel electrophoresis performed by Berkeley Heartlab (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.

Table 1
Cholesterol associated with lipoprotein subfractions at baseline as quantified by the VAP II method

Variables[a] (mg/dL)	Placebo	EZE 10 mg	FENO 160 mg	FENO 160 mg/EZE 10 mg
	n = 58-59	n = 167-170	n = 170-176	n = 170-171
VLDL-C	34.0 ± 10.2	34.0 ± 12.1	35.0 ± 13.0	34.0 ± 9.3
VLDL-C1 + 2	15.7 ± 6.6	16.0 ± 6.4	15.6 ± 7.1	16.2 ± 6.0
VLDL-C3	18.0 ± 6.5	17.0 ± 5.6	18.0 ± 5.6	18.0 ± 5.6
IDL-C	26.0 ± 14.9	22.0 ± 11.2	24.0 ± 12.1	21.0 ± 9.3
LDL-CR	135.0 ± 26.0	130.0 ± 35.3	138.0 ± 36.3	133.3 ± 36.3
LDL-C1	24.6 ± 9.0	24.3 ± 9.5	25.7 ± 8.1	24.9 ± 7.5
LDL-C2	12.9 ± 14.2	11.9 ± 14.7	13.0 ± 14.3	12.0 ± 17.1
LDL-C3	66.6 ± 18.1	63.6 ± 26.8	66.8 ± 24.7	64.8 ± 24.6
LDL-C4	24.4 ± 16.6	26.3 ± 24.2	26.0 ± 18.5	26.2 ± 23.5
Lp(a)-C	5.0 ± 2.8	5.0 ± 3.7	5.0 ± 2.8	5.0 ± 3.7
HDL-C2	8.0 ± 3.7	8.0 ± 2.8	8.0 ± 2.8	8.0 ± 2.8
HDL-C3	32.0 ± 8.4	34.0 ± 6.5	34.0 ± 7.4	34.0 ± 8.4

[a] Data are presented as median ± standard deviation for median, which are based on the interquartile range.

2.2. Statistical analysis

End points in this analysis included percentage change from baseline to study end point in cholesterol associated with individual lipoprotein fractions (LDL-CVAP, IDL-C, and VLDL-C) and subfractions (LDL-C1 to 4, VLDL-C1 + 2, and VLDL-C3). Lipoprotein (a)-C, HDL-C2, and HDL-C3 and changes in LDL peak particle size were also evaluated. 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. Because the cholesterol results with the VAP II method were not normally distributed, nonparametric statistical methods were used in the analyses. A nonparametric test (analysis of covariance model based on Tukey normalized ranks) was used for inferential testing of between-treatment differences [10]. $P < .05$ was considered statistically significant. Data are expressed as median with robust standard deviations for median or as median change from baseline with standard errors [11].

3. Results

3.1. Baseline characteristics

The treatment groups were generally well-matched with respect to baseline demographics and traditional lipid parameters [1]. Overall, patients had a mean LDL-C of 161 mg/dL (measured by β quantitation), mean HDL-C of 42 mg/dL, and median TG of 275 mg/dL at baseline. There

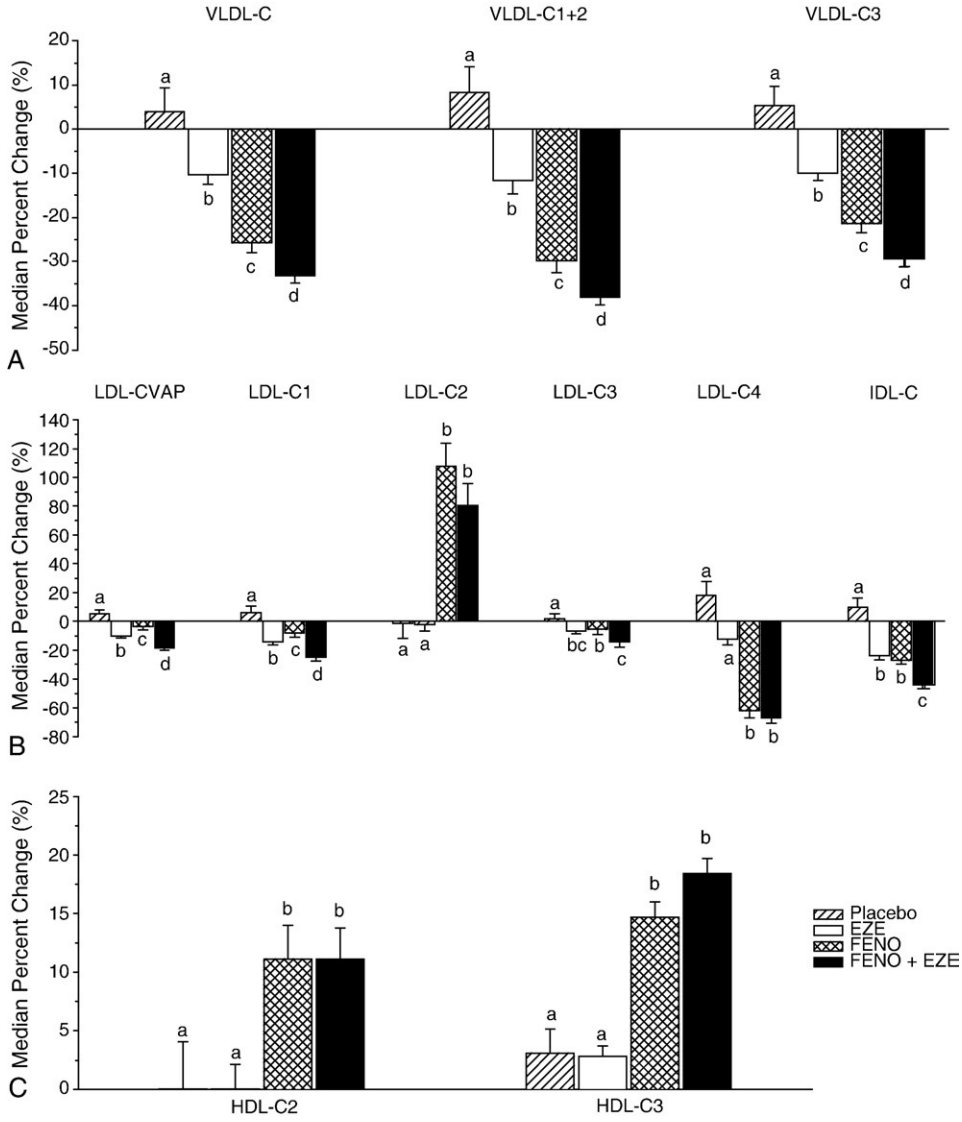

Fig. 1. Median percentage change (standard error) from baseline to study end point for cholesterol associated with lipoprotein fractions and subfractions: (A) VLDL, (B) LDL and IDL, and (C) HDL. For any pairwise comparison within each of the specified lipoprotein classes, a significant ($P < .05$) between-treatment difference is denoted by the presence of a different letter above the bar (eg, for VLDL-C, the different letters [a-d] above each bar indicate that the percentage changes for all groups were significantly different from each other [placebo < EZE < FENO < FENO + EZE]).

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). Because LDL-CVAP does not include cholesterol associated with IDL and Lp(a) [6], LDL-CVAP values were on average approximately 25 mg/dL lower than the standard LDL-C values determined by β quantitation. However, LDL-CVAP was highly correlated with standard LDL-C (Spearman correlation coefficient, $\rho = 0.86$, $P < .001$). Among the LDL subfractions, LDL-C2 exhibited the lowest cholesterol mass and LDL-C3 exhibited the greatest (accounting for about 10% and 50%, respectively, of the total LDL subfraction cholesterol mass).

3.2. Treatment-induced changes in lipoprotein subfractions

Median percentage changes from baseline to study end point for lipoprotein subfractions are shown in Fig. 1A to C. Relative to placebo, EZE, FENO, and FENO + EZE significantly ($P < .05$) changed cholesterol mass in most of the lipoprotein fractions and subfractions, with the largest changes typically observed in the coadministration group. The effects of EZE, FENO, and FENO + EZE on VLDL subfractions were similar to those for VLDL overall (Fig. 1A); effects for all treatments appeared to be slightly more pronounced for VLDL-C1 + 2 than for VLDL-C3. All active treatments reduced IDL-C (Fig. 1B). For EZE, the most pronounced (percentage) change was a reduction in IDL-C.

Although FENO produced relatively small reductions in LDL-CVAP, its effects on cholesterol mass within the individual LDL subfractions were pronounced, with significant reductions in LDL-C1, LDL-C3, and LDL-C4 and significant increases in LDL-C2 relative to placebo (Fig. 1B). The 10% reduction in LDL-CVAP with EZE treatment was primarily accounted for by reductions in the most buoyant and most dense subfractions (LDL-C1 and LDL-C4, respectively) (Fig. 1B). A modest, but significant, reduction was observed for LDL-C3, whereas no changes were observed for LDL-C2 after EZE treatment. When coadministered, FENO + EZE produced a pattern of changes similar to those of FENO alone; but the reductions in LDL-C1 and LDL-C3 were greater because of the added effects of EZE.

There were no meaningful changes in cholesterol associated with Lp(a) (median change = 0% in all treatment

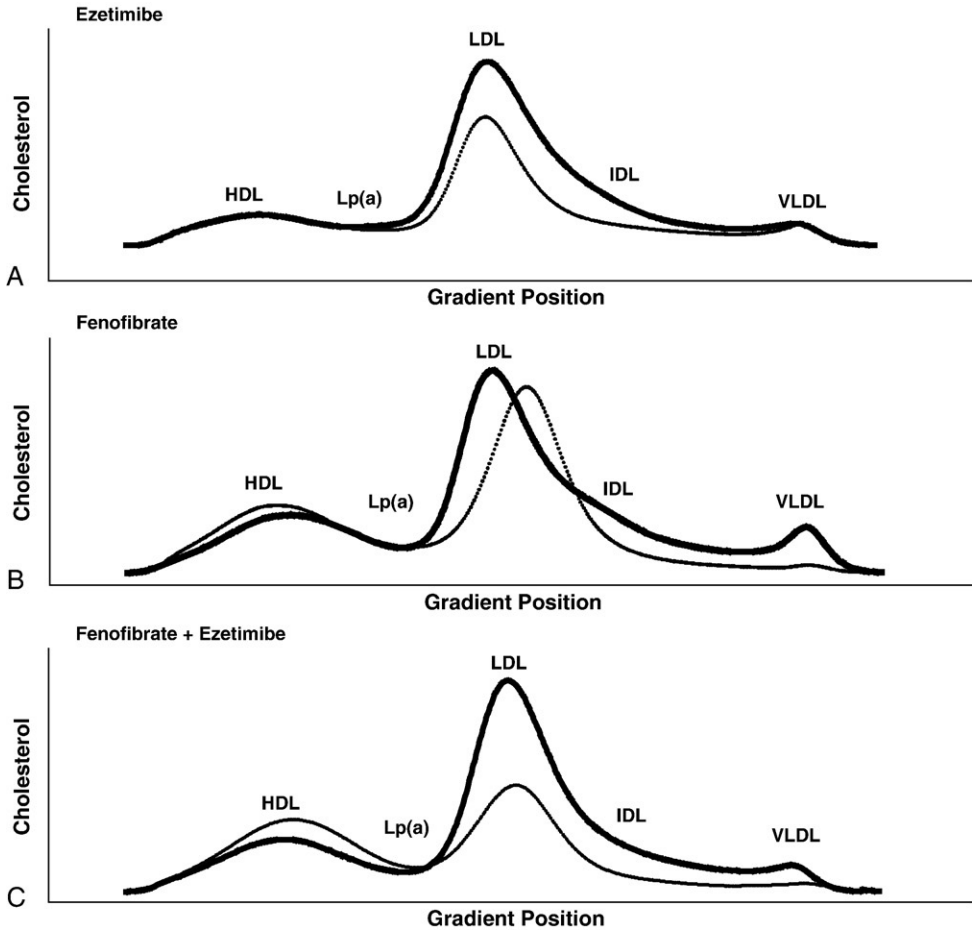

Fig. 2. The VAP II lipid distributions at baseline (solid thick line) and at study end point (dotted thin line) for a representative subject in each active treatment group: (A) EZE, (B) FENO, and (C) FENO + EZE.

Table 2
Low-density lipoprotein peak particle diameter at baseline and at study end point as measured by segmented gradient gel electrophoresis

	Placebo	EZE 10 mg	FENO 160 mg	FENO 160 mg/ EZE 10 mg
	n = 59/58	n = 165/165	n = 170/167	n = 165/159
LDL peak particle diameter[a] *(Å) at:*				
Baseline	253.0 ± 6.5	253.7 ± 5.4	254.9 ± 5.2	254.0 ± 4.7
Study end point	253.1 ± 11.8	255.0 ± 10.2	268.0 ± 10.2 *	268.0 ± 6.4 *

[a] Data are presented as median ± standard deviation; n = number of patients included in baseline/study end point measurements.
* $P < .05$ for change from baseline relative to placebo.

groups). Fenofibrate and FENO + EZE similarly increased median HDL-C2 and HDL-C3 compared with EZE and placebo (Fig. 1C).

The effects of treatment are further illustrated in overlaid baseline (dotted lines) and end point (solid lines) VAP II scans for representative subjects (Fig. 2). The EZE-treated subject exhibited reductions within the VLDL-C, IDL-C, and LDL-C density ranges without a shift in LDL density distributions or changes in the HDL-C range (Fig. 2A). In the FENO-treated subject, VLDL-C and IDL-C were markedly reduced, HDL-C was increased, and there was a pronounced shift in the distribution of LDL toward larger, more buoyant LDL particles with a small effect on LDL-C values overall (Fig. 2B). 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 subfractions (Fig. 2C).

3.3. Treatment-induced changes in LDL particle size

The size of the predominant LDL peak was similar among the treatment groups at baseline. Ezetimibe did not significantly affect LDL peak particle size, whereas FENO and FENO + EZE increased LDL peak particle size (Table 2). These effects are consistent with VAP II results for the individual LDL subfractions.

4. Discussion

Mixed (or combined) hyperlipidemia is characterized by elevated TG, TG-rich lipoproteins, and LDL-C and reduced HDL-C, generally with a preponderance of smaller, dense LDL particles characteristic of the high-risk LDL subclass pattern B phenotype [12]. In view of the complex nature of mixed hyperlipidemia, the National Cholesterol Education Program Adult Treatment Panel III guidelines acknowledge the frequent need to treat mixed hyperlipidemia patients with a combination of lipid-lowering agents [13]. We previously demonstrated that coadministration of FENO + EZE was well tolerated for up to 52 weeks and produced complementary, favorable effects on LDL-C, TG, and HDL-C in patients with mixed hyperlipidemia [1,2]. Although the influence of fibrates on lipoprotein subfractions and LDL particle size has been characterized previously [14], the effects of EZE or the coadministration of FENO + EZE on lipoprotein subfractions have not been previously evaluated in patients with mixed hyperlipidemia. The present report provides the first information on the effects of FENO and EZE alone compared with their use in combination on cholesterol levels in lipoprotein subfractions assessed by the VAP II method.

In this cohort of patients with mixed hyperlipidemia, FENO had only modest effects on overall LDL-C [1], but led to a marked redistribution of cholesterol among the LDL subfractions, characterized by a decrease in cholesterol mass in the smaller, more dense LDL-C3 and LDL-C4 and an increase in cholesterol mass in the larger, more buoyant LDL-C2. These results are generally consistent with previous observations with FENO using the nonequilibrium density ultracentrifugation methodology [15]. Ezetimibe monotherapy produced significant reductions in cholesterol mass across apo-B–rich lipoproteins (LDL, IDL, and VLDL). In particular, the percentage reduction in IDL-C was pronounced with EZE alone. These effects are noteworthy in light of evidence that IDL-C may be an independent predictor of cardiovascular disease risk [16]. With all active treatments, changes in LDL-C were primarily accounted for by reductions of cholesterol within the most buoyant and most dense subfractions (LDL-C1 and LDL-C4, respectively). The effects of coadministration of FENO + EZE were greater for VLDL-C including VLDL-C1 + 2 and VLDL-C3, IDL-C, LDL-CR, LDL-C1, and LDL-C3 compared with the monotherapies. The changes in LDL-C2 and LDL-C4 were similar with FENO + EZE and FENO. Changes in HDL2 and HDL3 were primarily influenced by FENO and consistent with those noted for overall HDL-C and apo A-I [1].

Treatment with FENO + EZE and FENO increased LDL peak particle size to a similar extent. Although this effect was mainly due to FENO, EZE monotherapy also produced a small, nonsignificant increase in LDL peak particle size relative to placebo. This change in LDL size has been previously demonstrated with fibrates [14] and is consistent with the dramatic decrease in the proportion of patients with the LDL pattern B phenotype after treatment with FENO + EZE and FENO. As previously published, the proportions of patients exhibiting LDL pattern B at baseline were 69.5%, 77.6%, 74.7%, and 74.5% in the placebo, EZE, FENO, and FENO + EZE groups, respectively [1]. At study end point, the percentages of patients with LDL pattern B were 71.2%, 66.1%, 21.8%, and 18.2% in the placebo, EZE, FENO, and FENO + EZE groups, respectively.

Although LDL-C is the most commonly used lipoprotein parameter to define cardiovascular risk and determine treatment needs [13], evaluations of other lipoproteins and lipoprotein size and subfraction composition may allow refinement of that risk and the beneficial effects of treatments [16-24]. Epidemiologic and prospective interventional studies have demonstrated a strong association between the LDL size and pattern B phenotype and risk of coronary

events [25]. The causal basis of this association remains uncertain but has been suggested to reflect a greater atherogenicity of smaller, more dense LDL particles or their precursors because of differences in particle properties (eg, oxidizability, ability to penetrate the artery wall, or affinity for the LDL receptor) and/or other aspects of metabolism that give rise to these particles [5]. Patients with the mixed hyperlipidemia or lipid triad (ie, elevated LDL-C and TG and low HDL-C levels) have demonstrated clinical benefit with simvastatin [26] or fibrate [27,28] treatment. This benefit may be conferred primarily by changes in major lipoprotein and lipid concentrations. However, more subtle changes in cholesterol content, size, and other properties of lipoprotein subclasses are also believed to contribute. There are no data available at present that specifically relate on-treatment changes in cholesterol within lipoprotein subfractions using the VAP II methodology with reduction in risk for cardiovascular events.

In summary, coadministration of FENO and EZE produced substantial reductions in cholesterol associated with VLDL, IDL, and LDL and a redistribution of cholesterol from small, dense to larger, more buoyant LDL subfractions in patients with mixed hyperlipidemia. These changes reflected the combined effects of FENO in reducing TG-rich lipoproteins and promoting a shift in the LDL particle distribution profile toward larger, more buoyant particles and of EZE in promoting reductions in cholesterol mass across the apo B particle spectrum. Although these changes would be expected to have favorable effects on the atherosclerotic process to which mixed hyperlipidemic patients are vulnerable, clinical outcomes studies are needed to definitively establish benefit.

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