Comparison of the Effect of Fluvastatin, an Hydroxymethyl Glutaryl Coenzyme A Reductase Inhibitor, and Cholestyramine, a Bile Acid Sequestrant, on Lipoprotein Particles Defined by Apolipoprotein Composition

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In a double-blind, parallel-group, randomized study, the effects of fluvastatin (FLUV) 20 and 40 mg/d on lipoprotein particle levels were compared with those of cholestyramine (CME) 16 g/d. Lipoparticles were defined by apolipoprotein composition as either those containing both apolipoprotein (apo) B and apo E or CIII (lipoprotein [Lp] E-B or Lp CIII-B) or those containing apo AI alone (Lp AI) or in association with apo AII (Lp AI-AII). After an 8-week dietary stabilization period, 100 hypercholesterolemic patients were treated with FLUV 20 mg/d for 6 weeks and 40 mg/d for an additional 6 weeks and were compared with 48 hypercholesterolemic subjects treated with CME 16 g/d. Treatment with FLUV (40 mg/d) or CME (16 g/d) for 12 weeks was associated with a significant reduction in plasma cholesterol and low-density lipoprotein (LDL) cholesterol and a significant increase in high-density lipoprotein (HDL) cholesterol. However, plasma triglyceride levels decreased following FLUV treatment, whereas they increased with CME. These changes were associated with a significant reduction in the levels of apo B (FLUV, −24%, $P < .001$; CME, −26%, $P < .001$), apo E (FLUV, −36%, $P < .001$; CME, −32%, $P < .001$), and apo CIII (FLUV, −21%, $P < .001$; CME, −6%, NS). The decreased levels of apo E and apo CIII were mainly due to a decrease in the apo B–containing fraction as assessed by the decrease in apo E (FLUV, −40%, $P < .001$; CME, −24.4%, $P < .001$) and apo CIII (FLUV, −50%, $P < .05$; CME, −33%, NS) that coprecipitated with apo B–containing lipoproteins and by the decrease in plasma levels of Lp E-B (FLUV, −25.8%, $P < .001$; CME, 2.3%, NS) and Lp CIII-B (FLUV, −48.8%, $P < .001$; CME, −34.1%, $P < .001$). With regard to apo AI–containing particles, significant effects were observed. Treatment with FLUV or CME increased plasma levels of apo AI (FLUV, +4.7%, $P < .001$; CME, +8.7%, $P < .001$) and Lp AI (FLUV, +10%, $P < .001$; CME, +25.5%, $P < .001$) and decreased Lp AI-AII (FLUV, −5.7%, NS; CME, −11.5%, $P < .05$). FLUV or CME decreased apo E bound to HDL (−36.8%, $P < .001$, and −50%, $P < .001$, respectively). In summary, treatment with FLUV or CME was associated with beneficial changes in plasma lipid, lipoprotein, apolipoprotein, and lipoparticle levels. FLUV is more efficient in reducing levels of atherogenic apo B–containing particles, whereas CME has a greater effect in increasing the levels of Lp AI.

IT IS NOW CLEARLY established that reduction of plasma low-density lipoprotein (LDL) cholesterol diminishes the risk of atherosclerosis.[1] In addition, recent epidemiological studies have found that lipoproteins defined by apolipoprotein content could serve as markers of cardiovascular risk.[2] The development of immunological methods has clearly established that density classes represent, in fact, a mixture of particles with the same density but different apolipoprotein composition. According to a new concept developed by Alaupovic,[3] lipoproteins may be separated into simple lipoprotein particles containing one apolipoprotein (lipoprotein [Lp] B, and Lp AI) and complex lipoprotein particles containing two or more apolipoproteins (Lp E-B, Lp CIII-B, Lp CIII-E-B, Lp AI-AII, etc.). It has been suggested that all the apo AI–containing particles may not have the same role in promoting reverse cholesterol transport,[4,5] and that Lp AI but not Lp AI-AII may be protective against atherosclerosis development. In addition, different apo B–containing particles do not behave the same way as regards the LDL receptor pathway.[6] In several cases, the association of these markers with cardiovascular risk was greater than the association with the classic lipoprotein defined by density range.[2]

Thus, lipoproteins should be classified according to apolipoprotein composition rather than density.[7]

Therapies that increase LDL receptor activities have been used as a means of decreasing plasma LDL cholesterol levels. Two families of drugs increase LDL receptor activity: bile acid sequestrants and inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase). Cholestyramine (CME) is a bile acid sequestrant, and fluvastatin (FLUV) is a new HMG CoA reductase inhibitor, the first synthetic compound of this category. Previously, the effects of cholesterol-lowering drugs have been studied on lipoproteins defined by physical properties[8] and classified by hydrated density (very–low-density lipoprotein [VLDL], LDL, and high-density lipoprotein [HDL]). Little is known of the effects of hypolipidemic drugs on levels of lipoparticles.[9,10]

This study compares the effects of FLUV and CME in primary hypercholesterolemia, with a particular regard to lipoprotein particles defined by apolipoprotein composition.

SUBJECTS AND METHODS

A total of 250 male or female patients aged 18 to 75 years with primary hypercholesterolemia were recruited in a single-center study (Norway). The main exclusion criteria were as follows: myocardial infarction in the 6 months preceding the study, unstable angina pectoris, diabetes, impaired liver or renal function, homozygous or compound heterozygous familial hypercholesterolemia, or type I, III, IV, or V hyperlipoproteinemia. Patients with excessive alcohol consumption (defined as consumption >50 mL pure alcohol per week) were excluded from the study. Ingestion of any

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agent specifically intended to reduce plasma lipid levels within 4 weeks before the study or of probucol within 1 year before the study also resulted in exclusion.

At the first clinical visit, each patient was prescribed a cholesterol-lowering diet (American Heart Association phase I or National Cholesterol Education Program spect I). Patients were advised to eat no more than 350 mg cholesterol daily and that 30% of energy intake should be in the form of fat. Patients were counseled by a certified dietician at week −14 or before. Dietary compliance was evaluated using a 3-day food record kept by the patient before week −6, 0, and 12 visits. Total calories, fat, polyunsaturated to saturated fat ratio, and cholesterol intake were calculated using a computerized version of the official Norwegian food tables.

After 8 weeks of a cholesterol-lowering diet, 168 subjects entered the 6-week placebo phase. Patients were included in the active treatment phase according to lipid levels at the start of and 3 weeks into placebo periods. Only those with LDL cholesterol levels of at least 160 mg/dL (4.1 mmol · L^{-1}), triglycerides less than 300 mg/dL (3.4 mmol · L^{-1}), premature coronary heart disease and/or two associated risk factors (as defined by the European Atherosclerosis Society)[11] or those with LDL cholesterol levels of at least 190 mg/dL (4.9 mmol · L^{-1}), triglycerides less than 300 mg/dL (3.4 mmol · L^{-1}), no premature coronary heart disease, and less than two associated risk factors after adherence to a lipid-lowering diet were included. One hundred fifty-one patients fulfilled these criteria and were randomized to receive either FLUV or CME.

Study Design

The study was designed to compare the effects of two dosages (20 mg/d, then 40 mg/d) of FLUV with the effect of CME 16 g/d on lipoprotein particles over a 12-week treatment period. The study was a double-blind, double-dummy, parallel-group, randomized trial with three phases: phase 1, an 8-week, prestudy diet stabilization period (weeks −14 to −6); phase 2, a 6-week, single-blind, placebo period (weeks −6 to 0); and phase 3, a 12-week, double-blind, active monotherapy period (weeks 0 to 12).

Two thirds of the patients took FLUV 20 mg at bedtime for 6 weeks, increasing to 40 mg for 6 weeks, plus CME placebo before breakfast and before dinner.

One third of the patients took CME 8 g/d in two equal doses before breakfast and before dinner, increasing to 16 g/d after the first week, plus FLUV placebo at bedtime.

FLUV and its placebo were provided by Sandoz Pharma (Basel, Switzerland), and CME and its placebo were provided by Bristol-Myers Squibb (Paris, France) labeled specifically for the study and provided to the investigators by Sandoz Pharma.

Analytical Methods

The patients visited the Lipid Clinic every third week during the study. At each visit, drug compliance was registered and new medication was provided. All lipid analyses were performed by a central laboratory within 48 hours of venesection (SEP, Institut Pasteur, Lille, France).

Blood samples were taken after subjects had fasted for at least 12 hours at each visit, in tubes containing sodium/potassium EDTA at a concentration of 1 mg/mL.

Lipid and Lipoprotein Lipid Measurement

Levels of total cholesterol, VLDL cholesterol, HDL cholesterol, and triglycerides were determined on a Hitachi 717 analyzer by enzymatic methods (Boehringer, Mannheim, Germany) with microenzymatic procedures standardized using the methods of the National Heart, Lung, and Blood Institute (Bethesda, MD)/Centers for Disease Control (Atlanta, GA) Lipid Standardization Program.

HDL cholesterol was isolated using the modified heparin–2-mol/L $MnCl_2$ procedure to precipitate VLDL and LDL. VLDL was separated by ultracentrifugation for 48 hours at a density of 1.006 kg/L, and cholesterol level was measured. LDL cholesterol was determined by Friedewald's formula[12] and was separated (by ultracentrifugation) and then measured (ß quant).[13]

Apolipoprotein Measurement

Apolipoprotein (apo) AI and apo B were analyzed by immunonephelometric assays on a laser reader (Behring, Rueil Malmaison, France) using commercial polyclonal antibodies (Behring).

Apo CIII[14] and apo E[15] were determined by immunoenzymometric assays as previously described.

Lipoprotein Particle Measurement

Lipoproteins containing apo AII and AI (Lp AI-AII), apo CIII and B (Lp CIII-B), apo E and B (Lp E-B), and apo (a) and B (Lp (a)-B) were measured using a two-site immunoenzymometric assay.[16-18] These methods measure the totality of particles containing apolipoproteins recognized by the antibodies used in the assay. For instance, Lp E-B assay does not distinguish between Lp E-B free of apo CIII and Lp CIII-E-B. All the antibodies used in immunoenzymometric assays were prepared by the laboratory (SERLIA) of Pasteur Institute (Lille, France).

Lipoproteins containing apo AI but free of apo AII (Lp AI) were quantified at the same sampling times using a differential electroimmunoassay (Sebia, Issy-les-Moulineaux, France).[19]

HDLs were isolated by precipation of VLDL and LDL by phosphotungstate. Apo CIII and apo E levels were measured by immunoenzymometric assays[14-15] in the supernatant leading to the assay of Lp CIII HDL and Lp E HDL. Lp CIII non-HDL and Lp E non-HDL were calculated by differences between apo CIII and Lp CIII HDL and apo E and Lp E HDL, respectively.

Statistical Analysis

Efficiency parameters were estimated using an all-patients-treated approach. Baseline was defined as the mean of weeks −3 and 0 for all lipid parameters except VLDL cholesterol and LDL cholesterol (ß quant), for which the baseline was week 0.

For total cholesterol, LDL cholesterol (ß quant), LDL cholesterol (Friedewald), triglycerides, VLDL cholesterol, and HDL cholesterol, the mean ± SD are given for the baseline, at each visit, and for the percentage change from baseline. Paired *t* tests were used to detect significant mean percentage change from baseline. Two-sample Student's *t* tests were performed to detect differences between treatment groups. For apolipoproteins and lipoprotein particles (apo B, apo E, apo AI, Lp (a)-B, apo CIII, Lp CIII-B, Lp E-B, Lp AI, Lp AI-AII, Lp CIII HDL, Lp CIII non-HDL, Lp E HDL, and Lp E non-HDL), the median and interquartile range are presented at baseline, at each visit, and for the percentage change from baseline to each visit. Wilcoxon signed-rank tests were used to detect significance of the median percentage change from 0. In addition, a Kruskal-Wallis test was performed to detect differences between treatment groups. In computing medians and quartiles, no adjustment is made for equal values. Hence, it is possible to observe a median change of zero that is significant.

RESULTS

Placebo Period (phase 2)

None of the lipid, lipoprotein, apolipoprotein, and particle levels changed during the placebo period.

Table 1. Summary of Comparative Results (mean ± SD) in FLUV and CME Groups for Main Lipid Parameters at the End of the Placebo Period

Parameter (mg/dL)	FLUV (n = 101)	CME (n = 50)
Total cholesterol	325.1 ± 58.3	325 ± 45.7
LDL cholesterol (Friedewald)	249.4 ± 58.5	247.2 ± 46.2
Triglycerides	131.7 ± 53.9	136.8 ± 55.2
HDL cholesterol	49.4 ± 12.6	50.4 ± 12.3

Active Treatment Period (phase 3)

At the end of the placebo period, there was no significant difference between FLUV and CME groups with respect to the studied parameters (Table 1).

Effects of FLUV and CME on lipids and lipoproteins. Table 2 compares the effects of both therapies on plasma lipids. The two drugs decreased total cholesterol, and CME was more effective (FLUV 40 mg/d *v* CME 16 g/d, $P < .01$). FLUV decreased triglycerides, whereas CME increased this parameter (FLUV 40 mg/d *v* CME 16 g/d, $P < .001$).

Tables 3 and 4 summarize the effects of the two drugs on cholesterol carried by the various lipoprotein fractions. FLUV (20 and 40 mg/d) decreased VLDL cholesterol by 20.5% ($P < .001$) and 23.5% ($P < .001$), respectively, but 12 weeks of treatment with CME did not modify this parameter.

LDL cholesterol (ß quant and Friedewald) was decreased by both drugs. The two methods of determination of LDL cholesterol produced similar results. FLUV 20 mg/d decreased LDL cholesterol (Friedewald) by 24.5% ($P < .001$), and at 40 mg/d the reduction was 28% ($P < .001$). Twelve weeks of treatment with CME 16 g/d reduced this cholesterol fraction by 35% ($P < .001$). CME was more efficient than FLUV ($P < .001$).

FLUV (20 and 40 mg/d) induced a slight but significant increase ($P < .001$) in HDL cholesterol (+3.6% and +3.7%, respectively). CME also increased this parameter (+3.7%, $P < .05$).

Effects of FLUV and CME on apolipoproteins. Tables 5 and 6 list the results obtained on apolipoproteins. Both drugs were efficient in reducing apo B. FLUV (20 and 40 mg/d) decreased apo B by 20.2% ($P < .001$) and 23.8% ($P < .001$), respectively, and CME decreased this parameter by 24.6% ($P < .001$) at week 6 and by 25.8% ($P < .001$) at week 12. CME 16 g/d was more efficient than FLUV 20 mg/d.

Apo E was significantly reduced by both drugs, and no difference was observed between the two therapies (FLUV 40 mg/d, −35.7%, $P < .001$; CME, −32.2%, $P < .001$).

FLUV 20 mg/d did not modify the apo CIII level, but FLUV 40 mg/d decreased it by 21.6% ($P < .001$). CME did not significantly change this parameter.

Both therapies slightly but significantly increased apo AI (FLUV 20 mg/d, +2.9%, $P < .05$; FLUV 40 mg/d, +4.7%, $P < .001$; CME for 12 weeks, +8.7%, $P < .001$).

Effects of FLUV and CME on lipoprotein particles. Effects of the two tested drugs on lipoprotein particles defined by apolipoprotein composition are reported in Tables 7 and 8. FLUV (20 and 40 mg/d) decreased Lp CIII-B by 30.6% ($P < .001$) and 48.2% ($P < .001$), respectively. CME also decreased this parameter (week 12, −34.1%, $P < .001$), but was less potent than FLUV 40 mg/d ($P < .01$). Lp E-B was decreased by FLUV 20 and 40 mg/d by −20%

Table 2. Comparison of the Effects of Low- and High-Dose FLUV and CME 16 g on Lipid Parameters (mean ± SD)

Parameter/Treatment Group	No. of Patients*	Baseline†	Week 6	% Change	*P* Value‡ A	*P* Value‡ B
Low-dose						
Total cholesterol (mg/dL)						e
20 mg FLUV	100	325.4 ± 58.5	263.6 ± 50.6	−18.8 ± 8.1	c	
16 g CME	48	327.2 ± 45.4	246.9 ± 41.0	−24.1 ± 11.2	c	
Total	148					
Triglycerides (mg/dL)						e
20 mg FLUV	100	131.6 ± 54.2	120.3 ± 55.8	−6.7 ± 26.5	a	
16 g CME	48	133.4 ± 53.6	143.2 ± 72.4	7.4 ± 28.6		
Total	148					
			Week 12			
High-dose						
Total cholesterol (mg/dL)						d
40 mg FLUV	99	325.0 ± 58.6	253.4 ± 50.4	−21.7 ± 8.1	c	
16 g CME	48	325.7 ± 46.8	242.7 ± 43.0	−25.1 ± 10.9	c	
Total	147					
Triglycerides (mg/dL)						f
40 mg FLUV	99	131.0 ± 54.1	117.8 ± 82.7	−10.1 ± 28.2	c	
16 g CME	48	136.0 ± 53.8	150.9 ± 69.5	12.6 ± 28.9	b	
Total	147					

*Sample size discrepancies are due to missing data.

†Baseline: mean of weeks −3 and 0.

‡(A) *P* values from Student's *t* test comparing treatment groups: [a]$P < .05$, [b]$P < .01$, [c]$P < .001$. (B) *P* values from paired *t* test for mean percent change equal to 0: [d]$P < .05$, [e]$P < .01$, [f]$P < .001$.

Table 3. Comparison of the Effects of FLUV 20 mg and CME 16 g on Different Cholesterol Fractions (mean ± SD)

Parameter/Treatment Group	No. of Patients*	Baseline†	Week 6	% Change	*P* Value‡ A	*P* Value‡ B
LDL-C, Friedewald (mg/dL)						f
20 mg FLUV	100	249.7 ± 58.7	188.6 ± 51.5	−24.5 ± 10.4	c	
16 g CME	48	249.9 ± 45.2	164.2 ± 44.7	−34.1 ± 14.8	c	
Total	148					
LDL-C, direct β quant (mg/dL)						f
20 mg FLUV	100	252.0 ± 59.6	191.7 ± 48.7	−23.4 ± 11.2	c	
16 g CME	48	251.5 ± 44.0	167.9 ± 42.2	−32.9 ± 14.5	c	
Total	148					
VLDL-C (mg/dL)						d
20 mg FLUV	100	28.7 ± 14.2	21.0 ± 9.1	−20.5 ± 28.2	c	
16 g CME	48	27.6 ± 11.2	25.0 ± 10.6	−6.7 ± 25.3		
Total	148					
HDL-C (mg/dL)						
20 mg FLUV	100	49.4 ± 12.7	50.9 ± 12.9	3.6 ± 11.8	b	
16 g CME	48	50.6 ± 12.4	54.0 ± 14.8	6.8 ± 11.9	c	
Total	148					

*Sample size discrepancies are due to missing data.

†Baseline: week 0 for LDL-C (direct β quant) and VLDL-C, and mean of weeks −3 and 0 for all other main lipid parameters.

‡(A) *P* values from Student's *t* test comparing treatment groups: [a]$P < .05$, [b]$P < .01$, [c]$P < .001$. (B) *P* values from paired *t* test for mean percent change equal to 0: [d]$P < .05$, [e]$P < .01$, [f]$P < .001$.

($P < .05$) and −25.8% ($P < .001$), respectively, but not by CME. Lp (a)-B was slightly decreased by FLUV 20 mg/d (−2%, $P < .001$) but not by FLUV 40 mg/d, and was also slightly decreased by CME (week 12, −15%, $P < .01$).

Lp AI was increased by FLUV 40 mg/d (+10%, $P < .001$) and CME (week 12, +25.5%, $P < .001$). The effect of CME was significantly more potent on this parameter than FLUV ($P < .001$). FLUV 40 mg/d and CME decreased Lp AI-AII by −5.7% (NS) and −11.5% ($P < .001$), respectively, with CME being significantly more active ($P < .05$).

Lp E HDL was significantly reduced by FLUV 40 mg/d (−36.8%, $P < .001$) or CME (week 12, −50%, $P < .001$). Lp E non-HDL was also decreased by FLUV 40 mg/d (−40%, $P < .001$) or CME (week 12, −24.4%, $P < .001$).

FLUV did not modify Lp CIII HDL, whereas 6 weeks of treatment with CME increased this parameter (+13.8%, $P < .001$).

Lp CIII non-HDL was decreased by FLUV and CME, but only the treatment with FLUV 40 mg/d was significantly active (−50%, $P < .05$).

DISCUSSION

The aim of the present study was to compare the effects of CME or FLUV on lipoprotein particle levels. The results show that both CME and FLUV reduced levels of apo B–containing particles. However, this effect was associated with a significant increase in plasma triglyceride levels in the group treated with CME.

Table 4. Comparison of the Effects of FLUV 40 mg and CME 16 g on Different Cholesterol Fractions (mean ± SD)

Parameter/Treatment Group	No. of Patients*	Baseline†	Week 12	% Change	*P* Value‡ A	*P* Value‡ B
LDL-C, Friedewald (mg/dL)						f
40 mg FLUV	99	249.5 ± 59.0	179.2 ± 48.5	−28.0 ± 10.5	c	
16 g CME	48	248.5 ± 46.5	160.8 ± 44.8	−35.0 ± 13.9	c	
Total	147					
LDL-C, direct β quant (mg/dL)						e
40 mg FLUV	99	252.0 ± 59.9	182.2 ± 47.6	−27.1 ± 11.7	c	
16 g CME	48	250.1 ± 45.2	164.4 ± 42.5	−34.0 ± 13.4	c	
Total	147					
VLDL-C (mg/dL)						f
40 mg FLUV	99	28.5 ± 14.2	20.6 ± 11.3	−23.5 ± 25.2	c	
16 g CME	48	27.6 ± 11.2	26.7 ± 11.3	0.1 ± 30.2		
Total	147					
HDL-C (mg/dL)						
40 mg FLUV	99	49.2 ± 12.6	50.6 ± 12.2	3.7 ± 11.3	b	
16 g CME	48	50.0 ± 11.3	51.6 ± 12.8	3.7 ± 12.0	a	
Total	147					

*Sample size discrepancies are due to missing data.

†Baseline: week 0 for LDL-C (direct β quant) and VLDL-C, and mean of weeks −3 and 0 for all other main lipid parameters.

‡(A) *P* values from Student's *t* test comparing treatment groups: [a]$P < .05$, [b]$P < .01$, [c]$P < .001$. (B) *P* values from paired *t* test for mean percent change equal to 0: [d]$P < .05$, [e]$P < .01$, [f]$P < .001$.

Table 5. Comparison of the Effects of FLUV 20 mg and CME 16 g on Different Apolipoproteins

Parameter/Treatment Group	No. of Patients*	Baseline†		Week 6		% Change		P Value‡	
		Median	IQR	Median	IQR	Median	IQR	A	B
Apo B (mg/dL)									e
20 mg FLUV	100	192.5	48.0	156.0	39.0	−20.2	15.8	c	
16 g CME	48	202.0	35.0	147.0	36.5	−24.6	16.4	c	
Total	148								
Apo E (mg/dL)									
20 mg FLUV	100	5.3	2.8	4.4	1.6	−18.5	51.0	b	
16 g CME	48	5.0	2.8	4.5	2.2	−20.3	52.2		
Total	148								
Apo AI (mg/dL)									e
20 mg FLUV	100	133.5	35.0	132.5	36.0	2.9	13.9	a	
16 g CME	48	133.0	33.0	142.0	35.0	8.7	11.7	c	
Total	148								
Apo CIII (mg/dL)									
20 mg FLUV	100	3.0	1.7	2.9	1.3	1.8	43.9		
16 g CME	48	3.2	2.3	3.4	1.4	10.9	49.2		
Total	148								

Abbreviation: IQR, interquartile range.

*Sample size discrepancies are due to missing data.

†Baseline: mean of weeks −3 and 0.

‡(A) *P* values from Student's *t* test comparing treatment groups: $^{a}P < .05$, $^{b}P < .01$, $^{c}P < .001$. (B) *P* values from paired *t* test for mean percent change equal to 0: $^{d}P < .05$, $^{e}P < .01$, $^{f}P < .001$.

This was a comparative study dealing with two parallel groups treated with either FLUV (20 mg/d followed by 40 mg/d) or CME (16 g/d). Because of the absence of a placebo-only group, within-group analysis is given as an indicator only. Absolute changes in any parameter within each group must be viewed with caution, since some of the observed changes might have occurred in a placebo-only group.

Treatments with CME or FLUV were both associated with a significant reduction in plasma cholesterol, LDL cholesterol, and apo B levels. These results are consistent with the known effect of both drugs on cholesterol metabolism. Both hypolipidemic drugs increased LDL receptor expression, but by two different mechanisms. CME binds bile acids in the intestinal lumen and thus interrupts their enterohepatic circulation, increasing the excretion of acidic steroids and cholesterol in the feces. This drain results in depletion of the hepatic pool of cholesterol and stimulation of LDL receptor activity on hepatocytes.[20] It is important to note that this agent stimulates VLDL production in the liver and may therefore increase triglyceride concentration. FLUV is a new inhibitor of HMG CoA reductase, the rate-limiting enzyme of cholesterol biosynthesis. Inhibition of cellular cholesterol production results in depletion of the intracellular pool of sterol and, as a consequence, in an increase of LDL receptor activity.[20]

Table 6. Comparison of the Effects of FLUV 40 mg and CME 16 g on Different Apolipoproteins

Parameter/Treatment Group	No. of Patients*	Baseline†		Week 12		% Change		P Value‡	
		Median	IQR	Median	IQR	Median	IQR	A	B
Apo B (mg/dL)									NS
40 mg FLUV	99	192.0	48.0	145.0	38.0	−23.8	14.0	c	
16 g CME	48	202.0	36.0	143.0	38.0	−25.8	15.0	c	
Total	147								
Apo E (mg/dL)									NS
40 mg FLUV	99	5.3	2.8	3.0	1.8	−35.7	43.4	c	
16 g CME	48	4.9	2.5	3.5	1.6	−32.2	39.7	c	
Total	147								
Apo AI (mg/dL)									NS
40 mg FLUV	99	132.0	34.0	136.0	35.0	4.7	16.1	c	
16 g CME	48	133.0	33.0	144.0	36.0	8.7	15.2	c	
Total	147								
Apo CIII (mg/dL)									NS
40 mg FLUV	99	3.0	1.7	2.3	0.8	−21.6	41.6	c	
16 g CME	48	3.2	2.2	2.8	1.2	−5.9	43.4		
Total	147								

*Sample size discrepancies are due to missing data.

†Baseline: mean of weeks −3 and 0.

‡(A) *P* values from Student's *t* test comparing treatment groups: $^{a}P < .05$, $^{b}P < .01$, $^{c}P < .001$. (B) *P* values from paired *t* test for mean percent change equal to 0: NS, not significant.

Table 7. Comparison of the Effects of FLUV 20 mg/d and CME 16 g on Different Lipoprotein Particles

Parameter/Treatment Group	No. of Patients*	Baseline†		Week 6		% Change		*P* Value‡	
		Median	IQR	Median	IQR	Median	IQR	A	B
Lp (a)-B (mg/dL)									e
20 mg FLUV	95	8.0	17.5	7.0	19.7	−2.1	28.0	c	
16 g CME	47	9.0	33.4	6.0	25.2	−27.1	44.9	c	
Total	142								
Lp CIII-B (mg/dL)									
20 mg FLUV	100	15.5	13.0	12.5	7.5	−30.6	61.9	c	
16 g CME	48	16.0	17.5	14.0	10.0	−15.6	52.8	a	
Total	148								
Lp E-B (mg/dL)									d
20 mg FLUV	100	53.5	49.5	42.5	26.5	−20.0	58.5	a	
16 g CME	48	52.0	53.0	49.5	48.0	1.1	61.4		
Total	148								
Lp AI (mg/dL)									f
20 mg FLUV	100	42.0	23.5	43.0	19.5	2.0	23.3		
16 g CME	48	44.0	16.0	56.0	20.5	23.9	25.2	c	
Total	148								
Lp AI-AII (mg/dL)									d
20 mg FLUV	100	74.5	28.0	75.5	21.5	−3.4	27.9		
16 g CME	48	82.5	27.0	73.5	21.0	−13.6	27.0	b	
Total	148								
Lp CIII HDL (mg/dL)									
20 mg FLUV	100	1.8	0.7	1.9	0.6	4.3	51.3		
16 g CME	48	1.6	0.6	2.0	0.7	13.8	56.3	c	
Total	148								
Lp CIII non-HDL (mg/dL)									
20 mg FLUV	100	1.1	1.5	0.9	1.2	−17.4	112.6		
16 g CME	47	1.2	1.7	1.0	1.6	−27.3	127.1		
Total	147								
Lp E HDL (mg/dL)									
20 mg FLUV	100	1.1	1.2	1.0	0.9	−9.5	73.4		
16 g CME	48	1.4	1.0	0.9	0.7	−14.3	67.4		
Total	148								
Lp E non-HDL (mg/dL)									
20 mg FLUV	100	3.7	2.5	3.1	1.8	−21.6	66.8		
16 g CME	48	3.8	2.6	3.4	2.0	−16.5	67.1		
Total	148								

*Sample size discrepancies are due to missing data.

†Baseline: mean of weeks −3 and 0.

‡(A) *P* values from Student's *t* test comparing treatment groups: $^{a}P < .05$, $^{b}P < .01$, $^{c}P < .001$. (B) *P* values from paired *t* test for mean percent change equal to 0: $^{d}P < .05$, $^{e}P < .01$, $^{f}P < .001$.

In addition to its effect on plasma cholesterol, CME or FLUV treatment was significantly associated with a significant reduction in levels of plasma apo B–containing particles. Both drugs significantly reduced plasma apo B levels to the same extent. The effects were clearly distinct when apo B–containing particle levels were analyzed in detail. Particles containing both apo B and E and apo B and CIII were decreased after FLUV treatment. In contrast, Lp E-B levels were not different from the pretreatment value with CME. Among the apo B–containing lipoproteins, apo E is mainly associated with VLDL and IDL, and to a lesser extent with LDL. Apo E is necessary for the binding of triglyceride-rich particles on the LDL (B-E) receptor and therefore plays a critical role in the clearance of these lipoproteins.[21] The reduction in Lp E-B particles observed with FLUV certainly reflects the increased LDL (B-E) receptor-mediated catabolism of Lp E-B particles. In subjects treated with CME, the increased LDL (B-E) receptor-mediated clearance is certainly balanced by increased synthesis of triglyceride-rich particles, resulting in no effect on the overall Lp E-B concentration. Like apo E, most apo CIII of apo B–containing particles is associated with VLDL and IDL.[22] The observed decrease in Lp CIII-B level in the FLUV group probably reflects the increased LDL receptor-mediated clearance of apo B–containing particles. The less marked decrease in Lp CIII-B in the CME group than in the FLUV group ($P < .001$) and the nonsignificant decrease of Lp CIII non-HDL in the resin-treated group could be linked to an oversynthesis of VLDL by the liver, as indicated by the increase in triglyceride. Recent epidemiological studies have demonstrated an association between levels of plasma Lp CIII-B and Lp E-B and the risk of myocardial infarction.[23] Therefore, the observation of a major significant reduction in plasma Lp CIII-B and Lp E-B particles with FLUV treatment indicated a potential beneficial protective effect on the risk of myocardial infarction.

Lp (a) is an important cardiovascular risk factor.[24] In this study, Lp (a) level was measured as Lp (a)-B^{18} particles.

Table 8. Comparison of the Effects of FLUV 40 mg/d and CME 16 g on Different Lipoprotein Particles

Parameter/Treatment Group	No. of Patients*	Baseline†		Week 12		% Change		*P* Value‡	
		Median	IQR	Median	IQR	Median	IQR	A	B
Lp (a)-B (mg/dL)									
40 mg FLUV	96	8.0	17.4	7.0	22.6	0.0	46.5		
16 g CME	47	8.0	29.5	6.0	28.1	−15.0	37.5	b	
Total	143								
Lp CIII-B (mg/dL)									e
40 mg FLUV	99	15.0	13.0	9.0	6.0	−48.2	31.5	c	
16 g CME	48	16.0	17.0	11.0	8.0	−34.1	44.1	c	
Total	147								
Lp E-B (mg/dL)									f
40 mg FLUV	99	53.0	50.0	40.0	24.0	−25.8	58.2	c	
16 g CME	48	53.5	53.0	54.0	44.0	2.3	70.2		
Total	147								
Lp AI (mg/dL)									f
40 mg FLUV	99	42.0	24.0	46.0	21.0	10.0	28.3	c	
16 g CME	48	44.0	16.0	59.5	31.0	25.5	40.8	c	
Total	147								
Lp AI-AII (mg/dL)									d
40 mg FLUV	99	74.0	28.0	75.0	21.0	−5.7	38.6		
16 g CME	48	82.0	26.5	69.0	18.0	−11.5	27.0	a	
Total	147								
Lp CIII HDL (mg/dL)									
40 mg FLUV	99	1.8	0.7	1.7	0.9	−4.8	49.6		
16 g CME	48	1.7	0.6	1.9	0.8	7.2	52.4		
Total	147								
Lp CIII non-HDL (mg/dL)									
40 mg FLUV	99	1.1	1.5	0.6	0.7	−50.0	95.0	a	
16 g CME	47	1.2	1.7	1.0	5.6	−33.3	86.6		
Total	146								
Lp E HDL (mg/dL)									
40 mg FLUV	99	1.2	1.3	0.7	0.7	−36.8	54.8	c	
16 g CME	48	1.3	0.9	0.5	0.4	−50.0	36.3	c	
Total	147								
Lp E non-HDL (mg/dL)									
40 mg FLUV	99	3.7	2.6	2.1	1.6	−40.0	60.6	c	
16 g CME	48	3.8	2.7	2.5	1.4	−24.4	45.4	c	
Total	147								

*Sample size discrepancies are due to missing data.

†Baseline: mean of weeks −3 and 0.

‡(A) *P* values from Student's *t* test comparing treatment groups: $^{a}P < .05$, $^{b}P < .01$, $^{c}P < .001$. (B) *P* values from paired *t* test for mean percent change equal to 0: $^{d}P < .05$, $^{e}P < .01$, $^{f}P < .001$.

FLUV 40 mg/d did not decrease Lp (a)-B whereas CME did moderately. It has been proposed that activation of the LDL receptor pathway could induce this decrease.[25] This study could indicate that CME would be more appropriate than FLUV to treat hypercholesterolemic patients with additional high Lp (a) levels. However, the explanation for this difference in the effect of these two drugs leading to an activation of the receptor pathway is missing. Furthermore, we have no explanation for the fact that low-dose FLUV decreased Lp (a)-B but not high-dose FLUV.

HDL cholesterol and apo AI were slightly but significantly increased by both therapies. CME and FLUV increased Lp AI, but the effects of the resin were more important than those of FLUV. FLUV did not modify and CME decreased Lp AI-AII. Recent clinical and epidemiological studies[4,23] have shown that Lp A-I is associated with a lesser risk of cardiovascular disease. These findings were confirmed in transgenic mice for apo AI and apo AII. Mice that received the human apo AI gene were protected against atherosclerosis, whereas mice receiving the apo AII gene were not protected.[26] Thus, the finding of higher levels of Lp AI following treatment with FLUV and CME indicated a potential beneficial effect of these treatments. Plasma levels of Lp E HDL were significantly decreased after treatment with both drugs. Apo E–enriched HDL are highly recognized by the LDL receptor.[27] Therefore, one may speculate that stimulation of the LDL receptor pathway by FLUV and CME could increase degradation of such HDLs and decrease Lp E HDLs. In this case, apo E–enriched HDL would certainly represent a minor fraction of HDL particles,[28] since FLUV and CME increased rather than decreased HDL cholesterol level. This HDL fraction could be important in reverse cholesterol transport and in catabolism of peripheral cholesterol by the liver. An alternative possibility is that both therapies could reduce the apo E concentration in the entire HDL spectrum[29] or facilitate the shift of apo E from HDL to VLDL, thus explaining the reduction in Lp E HDL.

Six weeks of treatment with CME increased Lp CIII HDL, but not 12 weeks. This may be related to a transitory effect of CME that disappears when the steady-state action of CME on lipoprotein metabolism is achieved.

The results of the present comparative study show that FLUV 40 mg and CME 16 g reduce equally well cholesterol and LDL cholesterol and increase HDL cholesterol levels. However, FLUV significantly reduces levels of plasma triglycerides and Lp E-B and Lp CIII-B particles, whereas CME does not. The overall resultant effect is an improvement in the atherogenic profile of hypercholesterolemic patients.

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