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Comparison of Gemfibrozil Versus Simvastatin in Familial Combined Hyperlipidemia and Effects on Apolipoprotein-B-Containing Lipoproteins, Low-Density Lipoprotein Subfraction Profile, and Low-Density Lipoprotein Oxidizability

Sebastian J.H. Bredie, MD, Tjerk W.A. de Bruin, MD, Pierre N.M. Demacker, PhD, John J.P. Kastelein, MD, and Anton F.H. Stalenhoef, MD

We evaluated in a double-blind, placebo-controlled, randomized trial of 45 well-defined patients with familial combined hyperlipidemia, the effect of gemfibrozil (1,200 mg/day) or simvastatin (20 mg/day) on apolipoprotein-B (apo-B)-containing lipoproteins, low-density lipoprotein (LDL) subfraction profile, and LDL oxidizability. Although both drugs reduced plasma cholesterol and triglyceride concentrations, gemfibrozil reduced plasma triglycerides more effectively and simvastatin reduced plasma cholesterol more effectively. LDL cholesterol was reduced with simvastatin. With both drugs, total serum apo-B concentration decreased. With gemfibrozil, this was due to an exclusive reduction (-46%) of very low/intermediate-density lipoprotein (VLDL + IDL) apo-B, whereas simvastatin decreased apo-B in both VLDL + IDL and LDL (34% and 15%, respectively). Initially, a dense LDL subfraction profile was present in

all patients. The decrease in LDL cholesterol with simvastatin was due to a decrease in all isolated LDL subfractions except LDL₂; gemfibrozil increased LDL₁ and LDL₂ cholesterol ($p = 0.001$) and reduced LDL₄ cholesterol, resulting in a more buoyant LDL subfraction profile compared with simvastatin. In both groups, a predominance of small dense LDL remained despite therapy. LDL fatty acid composition showed a shift from oleic acid to linoleic acid after gemfibrozil; arachidonic acid increased after simvastatin. Vitamin E was lower after gemfibrozil. In the measurements of LDL oxidation, only the oxidation rate was significantly reduced with simvastatin. Thus, quantitative and qualitative changes of LDL cholesterol had only a small effect on total *in vitro* LDL oxidizability in this population with familial combined hyperlipidemia.

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Familial combined hyperlipidemia is a metabolically and genetically heterogeneous lipid disorder,¹⁻³ with affected persons exhibiting elevations of total cholesterol, triglycerides, or both, at least partially caused by very-low-density lipoprotein (VLDL)-apolipoprotein-B (apo-B) overproduction.⁴ Its prevalence is estimated to be 0.5% to 1.0%,² and the trait predisposes to premature cardiovascular complications.^{1,5} Because of the absence of a specific metabolic parameter characteristic of familial combined hyperlipidemia, family studies are pivotal for diagnosis. The current diagnosis is based on the following criteria^{1,6}: prevalence of multiple lipoprotein phenotypes in first-degree relatives, premature atherosclerosis, decreased high-density lipoprotein (HDL) cho-

lesterol levels, elevated plasma levels of apo-B,⁷ impaired clearance of VLDL remnants,⁸ and an increased prevalence of small dense low-density lipoprotein (LDL).⁷ A predominance of small LDL and its enhanced susceptibility to copper-mediated oxidative modification⁹ is associated with atherogenesis.^{10,11} Because of the reported increased risk for premature atherosclerosis, treatment with lipid-lowering drugs is frequently indicated.^{12,13} In this report we described the baseline lipoprotein concentrations, LDL subfraction profiles, and LDL oxidizability of well-defined patients with familial combined hyperlipidemia, and compared the effectiveness of treatment with gemfibrozil or simvastatin on these parameters in a double-blind, placebo-controlled fashion.

METHODS

Subjects: In all, 81 outpatients with familial combined hyperlipidemia were selected by 3 participating centers to evaluate the effect of treatment with either gemfibrozil or simvastatin on serum lipids. Forty-five patients from the 3 centers were randomly assigned for more extensive biochemical studies. They participated after informed consent was obtained. At entry into the placebo baseline period, patients met the following inclusion criteria: total serum cholesterol >6.5 mmol/L and triglyceride level between 2.3 and 5.6 mmol/L; at least 1 first-

From the Department of Medicine, Division of General Internal Medicine, University Hospital Nijmegen, Nijmegen; the Departments of Internal Medicine and Endocrinology, University Hospital Utrecht; and the Centre for Vascular Medicine, Academic Medical Centre, University of Amsterdam, The Netherlands. This study was supported by Research Grant 92.056 from the Netherlands Heart Foundation, The Hague, and a grant from Merck Sharp & Dohme, The Netherlands. Drs. de Bruin and Kastelein are senior clinical investigators of the Netherlands Heart Foundation. Manuscript received August 22, 1994; revised manuscript received and accepted October 17, 1994.

Address for reprints: Sebastian J. H. Bredie, MD, Department of Medicine, Division of General Internal Medicine, University Hospital Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

degree relative with significant hypercholesterolemia, hypertriglyceridemia, or both; a positive family history of premature coronary artery disease; total apo-B 100 levels >1,200 mg/dl; and age >30 years. Patients with secondary causes for dyslipidemia or with apolipoprotein phenotype E 2/2 were excluded.

Study design: This study was a double-blind, placebo-controlled trial with a double-dummy design, divided into 3 consecutive periods over 20 weeks. During the first period (weeks -8 to -5), selected patients who had taken no lipid-lowering drugs for ≥ 4 weeks received a standard lipid-lowering diet. The second period (weeks -4 to day 0) was a baseline placebo period. Each patient received 2 bottles, 1 containing placebo matching gemfibrozil and 1 containing placebo matching simvastatin. During the third period of active treatment (day 0 to week 12), patients were randomly assigned to receive either simvastatin 20 mg/day together with placebo matching gemfibrozil ($n = 23$) or gemfibrozil 1,200 mg/day together with placebo matching simvastatin ($n = 22$). In the present study, data obtained at the end of the placebo period (day 0) were compared with results obtained at the end of the period of active treatment (day 84).

Plasma: Blood samples were obtained after an overnight fast and collected in vacutainers containing 1 mg/ml of ethylenediaminetetraacetic acid. Plasma was isolated immediately and a saccharose solution (600 mg/ml H₂O) was added to prevent denaturation of LDL during freezing; samples were stored at -80°C for 4 to 15 weeks. All measurements were obtained in the lipid research laboratory of the University Hospital Nijmegen.

Analytic methods: VLDL + intermediate-density lipoprotein (IDL) (density [d] ≤ 1.019 g/ml) were isolated by ultracentrifugation for 16 hours at 40,000 rpm in a fixed angle rotor (TFT 45.6 rotor, Kontron, Zürich) in a Beckman L7-55 ultracentrifuge (Beckman, Palo Alto, California).¹⁴ After removal of VLDL + IDL, cholesterol and triglycerides were measured in the remaining plasma and in total plasma. HDL was isolated from whole plasma by the polyethylene glycol method.¹⁵ All cholesterol and triglyceride measurements were determined by enzymatic methods (Boehringer-Mannheim, Mannheim, Germany [catalog no. 237574], and Sera Pak, Miles, Tournai, Belgium [catalog no. 6669], respectively) with a centrifugal analyzer (Multistat III, Instrumentation Laboratory, Lexington, Massachusetts). VLDL + IDL cholesterol and triglycerides were calculated by subtraction. Apo-B concentrations in total plasma and in fractions that remained after VLDL + IDL removal were determined by nephelometry.¹⁶ To improve the accuracy of the results, the values obtained in our laboratory were recalculated on the basis of values determined by radioimmunoassay, standardized by the International Union of Immunological Societies, in 40 specially selected fresh frozen control sera provided by Dr. S. Marcovina (Northwest Lipid Research Laboratory, Seattle, Washington). VLDL + IDL apo-B was calculated by subtraction.

Low-density lipoprotein subfractionation: LDL subfraction analysis before and after treatment was performed by density gradient ultracentrifugation.¹⁴ For

each patient at both occasions, this analysis was performed in the same run. After ultracentrifugation, the LDL subfractions were visible as distinct bands in the middle of the tube. Up to 5 LDL subfractions could be distinguished concentrated in the following density ranges: LDL1 (1.030 to 1.033 g/ml), LDL2 (1.033 to 1.040 g/ml), LDL3 (1.040 to 1.045 g/ml), LDL4 (1.045 to 1.049 g/ml), and LDL5 (1.049 to 1.054 g/ml). The ultracentrifugation tubes, containing LDL subfractions stained with Coomassie Brilliant Blue R, were placed in a specially designed rack and photographed. Accurate documentation of the different LDL subfraction patterns was obtained by scanning the slides in triplicate on an LKB 2202 ultrascan laser densitometer (Pharmacia LKB, Uppsala, Sweden). The mean relative peak heights (h1 to h5) of the LDL subfractions (LDL1 to LDL5) on the 3 scans were used to calculate parameter K as a continuous variable, to describe each individual LDL subfraction pattern.¹⁷ When LDL4 or LDL5, or both, were detected, their relative peak heights were included in the formula $LDL[100\%] = LDL1[\%h1] + LDL2[\%h2] + LDL3[\%h3]$ by converting $\%h3$ into $\%h3'$ in which $\%h3' = (\%h3 + \%h4 + \%h5)$. Variable K was calculated by: $K = (\%h1 - \%h3') / (\%h2 - \%h1 + 1)$.¹⁷ A negative value ($-1 < K < 0$) reflects a dense subfraction profile, an intermediate subfraction profile is described by $K = 0$, and a complete buoyant profile delivers a positive K value ($0 < K < 1$). After photography, the LDL subfractions were accurately isolated by aspiration with a rubber bulb pipet, and total cholesterol content of each subfraction was determined.

Determination of fatty acids and vitamin E in low-density lipoprotein: Analysis of fatty acids, extracted from LDL by vortex mixing with 3 ml n-hexane, was performed by gas chromatography (Varian 3400 GC, Houten, The Netherlands).¹⁸ Vitamin E concentrations were determined by high-performance liquid chromatography (HPLC Spectra Physics model 8800, Breda, The Netherlands), with fluorescence detection.¹⁴ For extraction of vitamin E, 0.2 ml LDL was vortex-mixed with 2 ml acetone and 2 ml petroleum ether.

Oxidation of low-density lipoproteins: The oxidation experiments were performed as described by Esterbauer et al,¹⁹ with modifications by Kleinveld et al.²⁰

Statistics: Results are expressed as mean \pm SD. Statistical analysis of alterations within 1 group of treatment was performed with Wilcoxon's signed rank test. Differences in percentages between the 2 groups of treatment were analyzed with Wilcoxon's rank sum test. A 2-tailed probability value < 0.05 was considered significant. Statistical analyses were performed with procedures available in the SPSS PC+ (Statistical Package for the Social Sciences) software package version 4.0.

RESULTS

Patients: At entry into the placebo period, all 45 patients described in this study met the inclusion criteria. Therefore, all patients had hyperlipidemia phenotype IIB. The groups consisted of 5 women and 17 men in the gemfibrozil group and 18 men and 5 women in the simvastatin group (mean age 53.9 ± 9.8 vs 53.1 ± 10.3 years, respectively; body mass index 27.4 ± 3.1 vs 26.6

$\pm 2.9 \text{ kg/m}^2$, respectively). Both age and body mass index were similar in both groups. The lipid and lipoprotein levels, body mass index, and age of the 45 patients were equal compared with the initial population.

Effect of treatment on plasma lipid and lipoprotein levels: The lipid and lipoprotein levels of the patients with familial combined hyperlipidemia before and after treatment with gemfibrozil ($n = 22$) or simvastatin ($n = 23$) are summarized in Table I. There were no significant differences in lipid concentrations between the 2 groups at

baseline. Gemfibrozil significantly affected total triglyceride levels in plasma as well as in the VLDL + IDL fraction, whereas simvastatin induced the largest reduction in total plasma cholesterol. On the other hand, VLDL + IDL cholesterol was reduced with both therapies to the same extent. The largest contribution to the reduction in total cholesterol and triglycerides was generated by a decrease in the VLDL + IDL fraction. LDL cholesterol only decreased with simvastatin, and even tended to increase after gemfibrozil. HDL cholesterol levels increased with both drugs.

Effect of treatment on apolipoprotein-B lipoproteins: A significant correlation was found between apo-B and total apo-B-related cholesterol (total cholesterol minus HDL cholesterol) (Pearson's correlation coefficient 0.91; $p = 0.001$) (Figure 1). The concentrations of VLDL + IDL cholesterol and LDL cholesterol also correlated with their related apo-B content (correlation coefficient 0.70; $p = 0.001$; 0.63; $p = 0.001$, respectively). Both therapies reduced total apo-B to a similar extent. Gemfibrozil reduced apo-B only in the VLDL + IDL fraction, whereas simvastatin reduced apo-B in the VLDL + IDL and in the LDL fraction (Figure 2).

Effect of therapy on low-density lipoprotein subfraction profile and K value: Initially in all patients, LDL consisting of a limited number of LDL subfractions, with a predominance of intermediate dense (LDL2) and small dense (LDL3 and LDL4) subfractions. In 3 of 45 LDL subfraction profiles, a clear, very dense LDL5 band could be distinguished, which in all cases completely disappeared after treatment (1 after gemfibrozil and 2 after simvastatin). This sporadic LDL5 appearance, in 3 patients with lipoprotein levels comparable to the other subjects, was excluded from further statistical analysis. Gemfibrozil treatment induced a less dense LDL subfraction profile, without a reduction in total LDL cholesterol, consisting of LDL1 to LDL4, with a predominance of LDL1 to LDL3 as the main LDL subfractions (Figure 3). The ratio of cholesterol/triglyceride within the LDL particle increased, whereas that of triglyceride/apo-B decreased, probably due to a reduction in triglycerides per LDL particle. The ratio of cholesterol/apo-B did not change (Table II). Simvastatin treatment reduced total LDL, but did not induce a major shift to a less dense LDL subfraction profile as seen with gemfibrozil. The amount of cholesterol in all LDL subfractions, except LDL2, was significantly reduced (Figure 3). Neither the ratio of cholesterol/triglyceride nor the ratio of cholesterol/apo-B or triglyceride/apo-B

	Before	After	Change (%)	p Value
Total cholesterol				
G	7.54 \pm 1.13	6.51 \pm 0.91	-12.9 \pm 11.7	<0.001
S	7.15 \pm 0.87	5.58 \pm 1.12	-22.2 \pm 9.4*	<0.001
Triglycerides				
G	2.90 \pm 0.91	1.42 \pm 0.41	-48.1 \pm 18.0	<0.001
S	3.27 \pm 1.19	2.61 \pm 0.86	-15.9 \pm 25.8†	0.003
VLDL + IDL triglycerides				
G	2.24 \pm 0.77	0.96 \pm 0.38	-54.5 \pm 20.0	<0.001
S	2.58 \pm 1.02	2.04 \pm 0.74	-15.1 \pm 24.2†	0.005
VLDL + IDL cholesterol				
G	2.26 \pm 0.76	0.99 \pm 0.47	-55.3 \pm 30.3	<0.001
S	2.65 \pm 0.90	1.50 \pm 0.51	-40.9 \pm 18.1*	<0.001
LDL cholesterol				
G	4.36 \pm 0.86	4.59 \pm 0.92	+9.3 \pm 36.6	NS
S	3.68 \pm 1.01	3.12 \pm 0.98	-13.3 \pm 21.6*	<0.001
HDL cholesterol				
G	0.92 \pm 0.18	1.06 \pm 0.26	+15.3 \pm 20.9	0.003
S	0.82 \pm 0.21	0.94 \pm 0.21	+16.8 \pm 13.1	<0.001
Apo-B				
G	2,136 \pm 410	1,644 \pm 388	-21.1 \pm 20.7	<0.001
S	2,029 \pm 413	1,522 \pm 406	-25.2 \pm 9.9	<0.001

* $p < 0.01$, † $p < 0.001$; gemfibrozil versus simvastatin.
 Values are presented in mmol/L as mean \pm SD.
 Apo-B = apolipoprotein-B; G = gemfibrozil ($n = 22$); HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; S = simvastatin ($n = 23$); VLDL = very-low-density lipoprotein.

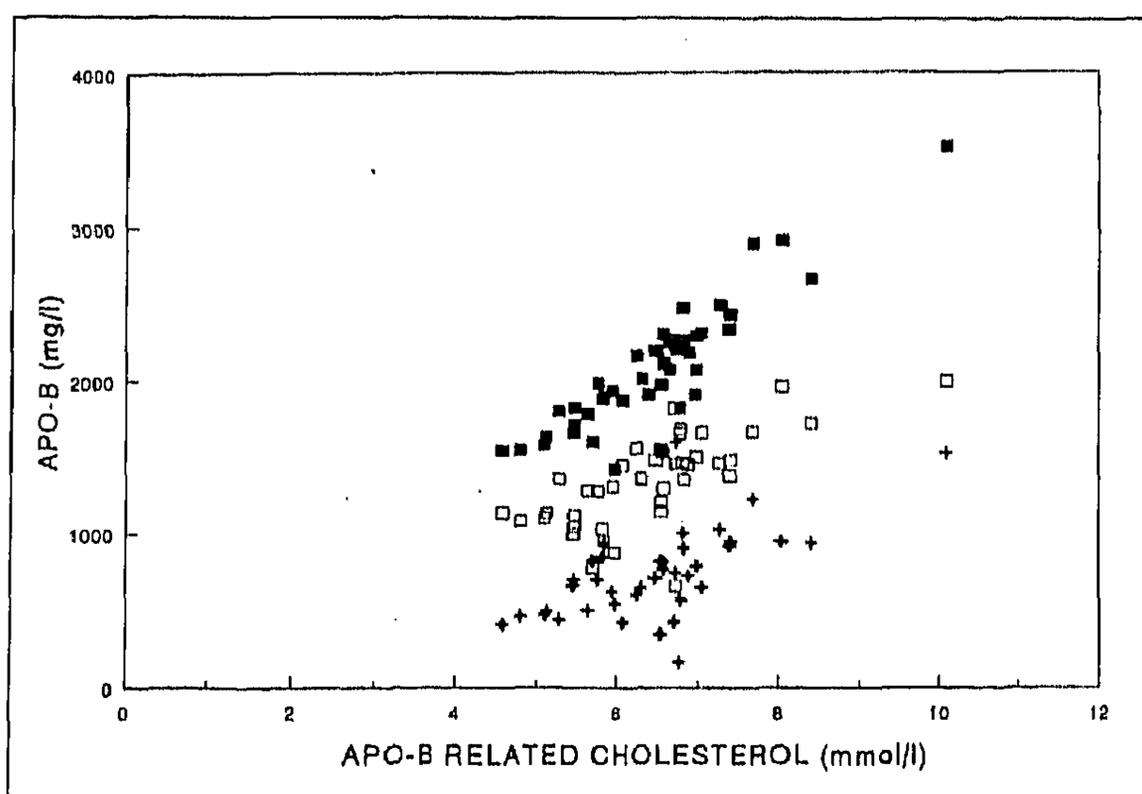


FIGURE 1. Correlation between total apolipoprotein-B (apo-B)-related cholesterol (total plasma cholesterol minus high-density lipoprotein cholesterol) (in mmol/L) and total plasma apo-B (closed squares), very-low-density lipoprotein + intermediate-density lipoprotein apo-B (plus signs), and low-density lipoprotein apo-B (open squares) (in mg/L) in 45 patients with familial combined hyperlipidemia.

changed significantly (Table II). The value of parameter K increased more after gemfibrozil (-0.55 ± 0.18 to -0.32 ± 0.21 ; $p < 0.001$) than after simvastatin (-0.55 ± 0.16 to -0.47 ± 0.22 ; $p = 0.04$; gemfibrozil vs simvastatin; $p < 0.05$). In 5 of 45 patients treated with gemfibrozil, the dense subfraction profile was altered into an intermediate subfraction profile, with an equal amount of buoyant and dense LDL particles. The other patients retained a dense subfraction profile, expressed as a negative value for parameter K, despite lipid-lowering therapy.

Fatty acid composition and vitamin E content of low-density lipoprotein: The fatty acid composition of each isolated LDL was determined (Table III). For technical reasons, only the results of 14 patients treated with gemfibrozil and 15 patients with simvastatin could be analyzed. This

reduction had no effect on lipid levels, apo-B levels, or the value of parameter K before and after therapy in this subset when compared with the initial 45 patients. In the gemfibrozil group, the relative amount of stearic acid (18:0) and oleic acid (18:1) decreased, whereas that of linoleic acid (18:2) increased. In the simvastatin group,

the relative contribution of linoleic acid (18:2) decreased, with an increase in arachidonic acid (20:4). Vitamin E in LDL decreased significantly with gemfibrozil and was unaffected with simvastatin. The ratio of polyunsaturated fatty acids/vitamin E tended to increase after gemfibrozil, whereas simvastatin did not affect this ratio.

	Before	After	Change (%)	p Value
Cholesterol/triglyceride				
G	7.73 ± 2.27	10.26 ± 2.62	53.7 ± 67.0	0.001
S	6.14 ± 1.75	6.14 ± 1.87	1.6 ± 20.9*	
Cholesterol/apo-B				
G	1.48 ± 0.17	1.54 ± 0.21	5.8 ± 22.0	
S	1.34 ± 0.16	1.36 ± 0.16	0.5 ± 12.9	
Triglyceride/apo-B				
G	0.47 ± 0.11	0.36 ± 0.08	-17.5 ± 19.3	<0.001
S	0.53 ± 0.13	0.55 ± 0.17	5.0 ± 20.2†	
Total cholesterol/HDL cholesterol				
G	8.4 ± 2.0	6.5 ± 2.2	-22.1 ± 16.5	<0.001
S	9.3 ± 2.6	6.1 ± 1.5	-32.7 ± 10.4‡	<0.001

*p < 0.01, †p < 0.001, ‡p < 0.05; gemfibrozil versus simvastatin. Values are presented as mean ± SD. Abbreviations as in Table I.

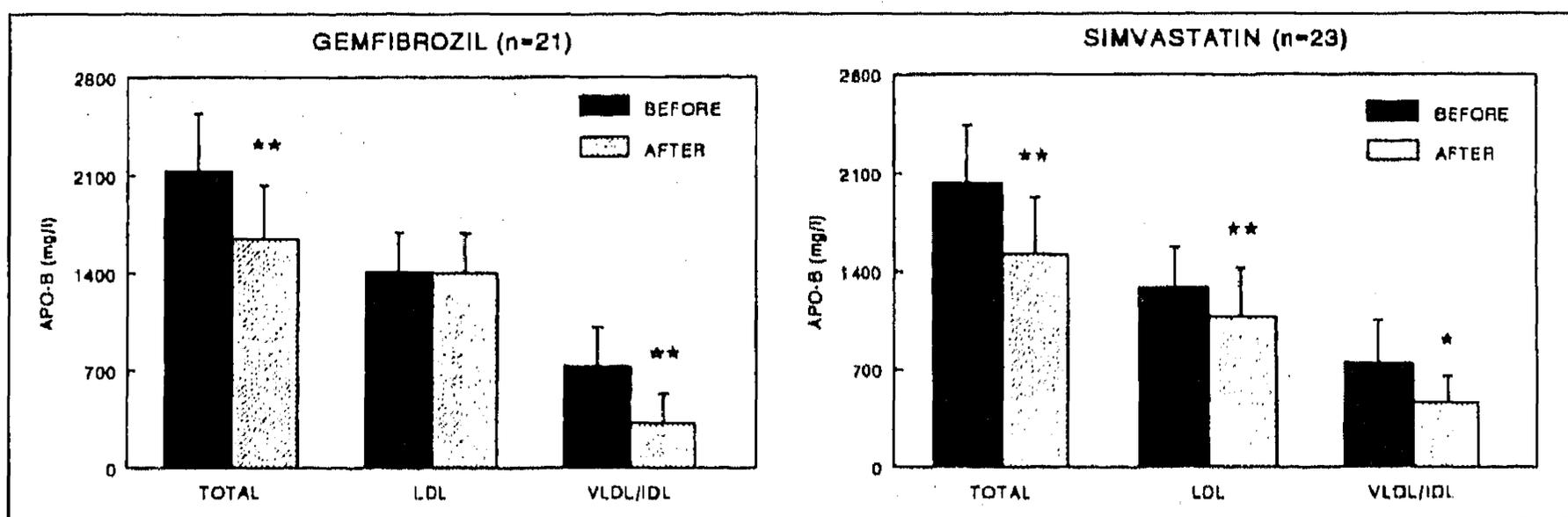


FIGURE 2. Effect of treatment with either gemfibrozil (n = 21) or simvastatin (n = 23) on apolipoprotein-B (apo-B)-containing lipoproteins in total plasma (TOTAL), low-density lipoprotein (LDL) fraction, and the very-low-density lipoprotein + intermediate-density lipoprotein (VLDL/IDL) fraction in patients with familial combined hyperlipidemia. *p = 0.003; **p < 0.001.

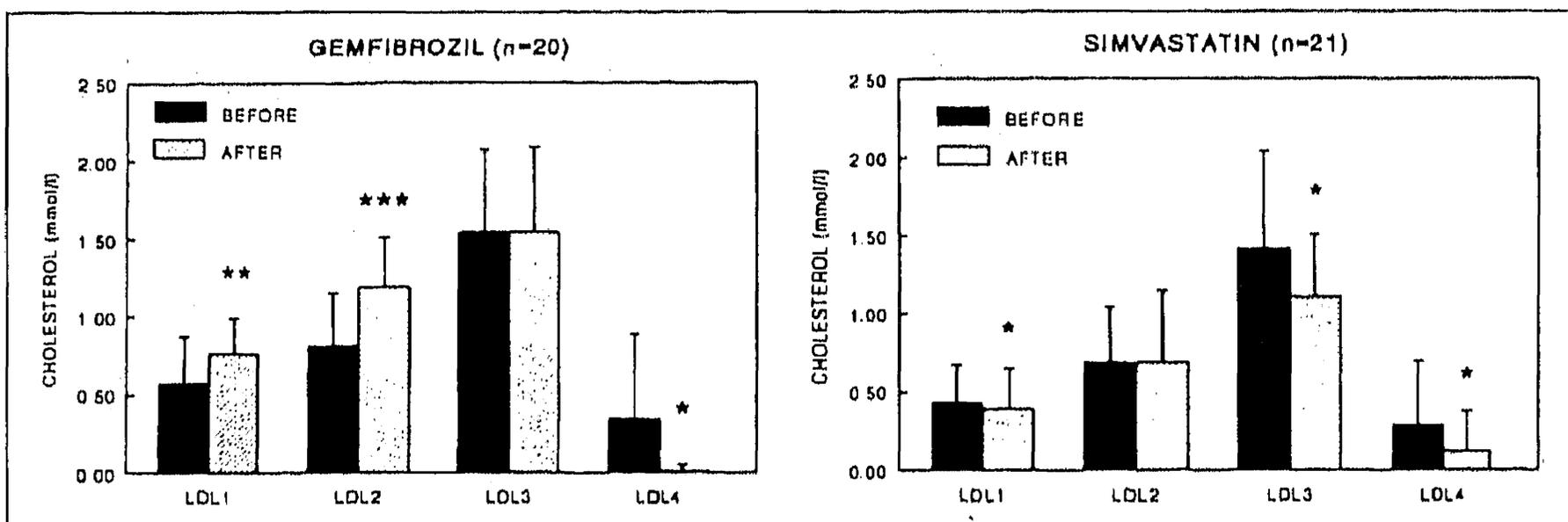


FIGURE 3. Effect of treatment with either gemfibrozil (n = 20) or simvastatin (n = 21) on the cholesterol content (in mmol/L) of 4 low-density lipoprotein subfractions (LDL1 to LDL4) in patients with familial combined hyperlipidemia. *p < 0.05; **p = 0.001; ***p < 0.001.

TABLE III Change in Fatty Acid Composition and Vitamin E Content of Total LDL After Treatment With Gemfibrozil (n = 14) or Simvastatin (n = 15) in Patients With Familial Combined Hyperlipidemia

Fatty Acids	Before	After	Change (%)	p Value
Palmitic acid (16:0)				
G	22.3 ± 1.9	21.7 ± 1.6	-2.8 ± 6.2	
S	23.4 ± 2.2	23.5 ± 2.4	+0.2 ± 5.7	
Stearic acid (18:0)				
G	6.6 ± 0.8	6.3 ± 0.7	-3.1 ± 5.9	0.04
S	6.6 ± 0.6	6.8 ± 0.7	+2.8 ± 6.3*	
Oleic acid (18:1)				
G	18.7 ± 1.9	17.8 ± 1.6	-4.8 ± 5.7	0.01
S	18.8 ± 1.8	19.0 ± 2.2	+0.9 ± 8.6*	
Linoleic acid (18:2)				
G	44.1 ± 3.7	45.8 ± 3.2	+4.1 ± 4.3	0.01
S	43.4 ± 3.6	41.6 ± 4.1	-4.0 ± 6.0 [†]	0.04
Arachidonic acid (20:4)				
G	8.2 ± 1.7	8.4 ± 1.6	+3.0 ± 14.5	
S	7.8 ± 1.4	9.1 ± 1.4	+20.1 ± 21.0 [‡]	0.01
Vitamin E [§]				
G	4.06 ± 1.65	3.42 ± 1.66	-16.5 ± 18.2	0.004
S	3.65 ± 1.76	3.82 ± 1.68	+14.0 ± 45.9*	
PUFA/Vit. E [¶]				
G	846 ± 596	1,102 ± 673	+42 ± 83	
S	801 ± 538	727 ± 339	-6 ± 52	

*p <0.05, [†]p <0.001, [‡]p <0.01; gemfibrozil versus simvastatin.

Values of fatty acids are presented in percentage of total fatty acids as mean ± SD.

[§]Vitamin E in mg/g low-density lipoprotein.

[¶]Ratio of polyunsaturated fatty acids/vitamin E in μmol/mg.

PUFA = polyunsaturated fatty acids (μmol/mg); Vit. = vitamin; other abbreviations as in Table I.

Total low-density lipoprotein oxidizability: Because of technical reasons, the results of only 17 patients treated with gemfibrozil versus 18 patients with simvastatin could be analyzed. This reduction had no effect on lipid and apo-B levels, or the value of parameter K before and after therapy in this subset when compared with the initial 45 patients. Although the lag time at the preoxidative phase tended to increase, the differences were not significant in any of the treatment groups. Oxidation rate decreased after simvastatin (p = 0.01), in contrast to gemfibrozil. Total amounts of produced conjugated dienes (malon dialdehyde reactive products) per milligram of LDL protein were similar before and after treatment in both groups.

DISCUSSION

The underlying cause of the increased tendency toward cardiovascular diseases in patients with familial combined hyperlipidemia is probably related to increased levels of small dense LDL and other atherogenic lipoprotein remnant particles.^{8,14,21} A predominance of small dense LDL is observed either as a physiologic response to lipid abnormalities,²² or as a distinct characteristic of the disease with a possible genetic basis.^{17,23} These small dense subfractions are associated with atherosclerosis because of enhanced susceptibility to copper-induced oxidative modification.¹⁴ In the present study, we therefore investigated the apo-B-containing lipoprotein concentrations, LDL subfraction profiles, and LDL oxidizability of 45 affected patients, and evaluated the effects of pharmacologic intervention on these parameters.

The observed reduction of total plasma cholesterol and plasma triglyceride concentrations with simvastatin (-22.2% and -15.9%, respectively) and gemfibrozil

(-12.9% and -48.1%, respectively) after 12 weeks of treatment are in accordance with previous reports.^{24,25} Isolation of VLDL and IDL particles together (d <1.019 g/ml), instead of isolating IDL together with LDL (d >1.006 g/ml), explains the relatively large contribution of VLDL + IDL cholesterol and the relatively small contribution of LDL cholesterol to total plasma cholesterol, and also the large impact of the 2 therapies on this VLDL + IDL fraction. The increase in HDL cholesterol with simvastatin similar to gemfibrozil, despite a less pronounced reduction of triglyceride concentration after simvastatin, is larger than previously reported.^{25,26} The decrease and increase in LDL cholesterol with simvastatin and gemfibrozil, respectively, are also in line with other reports.^{12,13,26} A depletion in triglycerides in the VLDL fraction with gemfibrozil, leading to small, more dense VLDL + IDL particles that are more likely to be converted into LDL particles, is suggested to be a cause of the observed increase in LDL cholesterol after gemfibrozil.^{26,27}

All patients had moderate to severe elevations of apo-B levels in accordance with their elevation of lipid levels. In normolipidemic subjects, total apo-B-related cholesterol concentration correlates highly with serum apo-B. In hypertriglyceridemic states, this correlation is less pronounced because of possible underestimation of apo-B,²⁸ although the correlation between total cholesterol minus HDL cholesterol and apo-B in these patients was still significant. Both therapies reduced total apo-B to a similar extent, but just like the reduction in VLDL + IDL cholesterol/triglyceride and LDL cholesterol, gemfibrozil reduced only VLDL + IDL apo-B-containing particles and simvastatin reduced both VLDL + IDL and LDL apo-B-containing particles.

Initially, all patients had a dense LDL subfraction profile, both determined by cholesterol content in isolated LDL subfractions and described by a continuous variable, parameter K. This method of approach provides the opportunity to obtain more detailed information about small alterations in the LDL subfraction profile than the often-used dichotomous classification in pattern A (light) and pattern B (heavy).¹⁷ The increase in cholesterol in the buoyant LDL1 and LDL2 subfractions after gemfibrozil could be explained by the observed decrease in the ratio of triglyceride/protein of the LDL particle only after gemfibrozil, reflecting an overall reduction in triglycerides in the LDL particles. This triglyceride reduction, not observed after simvastatin, is associated with more buoyant LDL subfractions.¹⁴ It is remarkable that despite the substantial reduction in plasma triglyceride concentrations, no patient with a dense LDL subfraction profile had complete conversion to a buoyant LDL subfraction profile. Only 5 patients had conversion to an intermediate profile. These results are

supported by a recent study by Hokanson et al²⁹ in which they proposed that in familial combined hyperlipidemia, small dense LDL and hypertriglyceridemia appear as interrelated but separate characteristics and regulated as separate processes.

In general, the observed LDL fatty acid composition in this group with familial combined hyperlipidemia was similar to that found in normal subjects.¹⁸ After both therapies, only small alterations in this composition were seen. The total amount of polyunsaturated fatty acids (linoleic and arachidonic acids), most susceptible for oxidative modification,¹⁸ did not change. On the contrary, vitamin E as the major antioxidant in LDL was reduced only with gemfibrozil. This may have implications for total LDL oxidizability.

Our data show only little effect on LDL oxidizability after treatment, less than suspected on the basis of a more buoyant LDL subfraction profile.¹⁴ However, some explanations for this lack of change in LDL oxidizability are possible: We determined LDL oxidizability in total LDL, which is the addition of maximal 5 LDL subfractions, so small changes might be undetected. Despite treatment, these patients still had a predominance of small dense LDL particles. The ratio of cholesterol/protein of LDL particles correlating with LDL oxidizability³⁰ was unaffected after both therapies. Finally, the ratio of polyunsaturated fatty acids/vitamin E increased only with gemfibrozil. This implies that the expected diminished susceptibility to copper-induced oxidation because of a more buoyant LDL subfraction profile¹⁴ could be offset by a reduced protection of polyunsaturated fatty acids from oxidation by vitamin E.

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