# Lack of Interaction of Apolipoprotein E Phenotype With the Lipoprotein Response to Lovastatin or Gemfibrozil in Patients With Primary Hypercholesterolemia

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**The magnitude of serum lipid changes in response to hypolipidemic drugs varies considerably between individuals. These differences may be due to interactions between genetic and environmental factors that effect drug bioavailability or the capacity of the lipid-regulating enzyme and receptor targets to be affected. The apolipoprotein E (apoE) gene locus has been examined in this regard, but reports are conflicting on the effect of its variability on the response to hypolipidemic drugs. We investigated the effect of apoE polymorphism on the serum lipid response to the hepatic hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitor lovastatin and the fibric acid derivative gemfibrozil. Lipoprotein changes were assessed after 12 weeks of therapy in 106 patients with primary hypercholesterolemia and combined hyperlipidemia treated with lovastastin and in 63 given gemfibrozil therapy. No significant effect of the apoE phenotypes E3/2, E3/3, or E4/3 on the heterogeneity of lipid responses to either drug was found.**



THE MAGNITUDE OF SERUM lipid changes in response to therapy with hypolipidemic drugs varies considerably between individuals. As with many other drugs,[1] these differences may be due to interactions between multiple genetic and environmental factors that affect drug bioavailability or the capacity of the lipid-regulating enzyme and receptor targets to be effected. The apolipoprotein E (apoE) gene locus has been examined in this regard, but reports are conflicting on the effect of its variability on the response to hypolipidemic drugs.[2-10]

Human apoE is a genetically polymorphic, arginine-rich protein controlled by three alleles, ε2, ε3, and ε4, at a single gene locus in chromosome 19; these code for three isoforms (E2, E3, and E4) that differ by an amino acid substitution at residues 112 and 158, and thus determine the six phenotypes resulting from the combination of any two of them.[11] The most common isoform, E3, has cysteine at site 112 and arginine at site 158, whereas E2 has cysteine and E4 has arginine, respectively, at the two residues.[12] These three isoforms differ by their isoelectric point, E4 being the most basic and E2 the most acidic, and can thus be separated by isoelectrofocusing in acrylamide.[13] ApoE acts as the ligand between triglyceride-rich lipoprotein particles and hepatic low-density lipoprotein (LDL) and chylomicron-remnant receptors.[14]

The polymorphism of apoE influences hepatic cholesterol content because lipoproteins with the E4 isoform, particularly chylomicrons and very–low-density lipoprotein (VLDL), are taken up with greater affinity than those with the common E3 isoform, which in turn are cleared more efficiently than those with the E2 isoform.[12] Indeed, homozygous and heterozygous E4 subjects have been shown both to absorb[15] and to deliver[16] to the liver more intestinal cholesterol than E2/E2, E3/E2, or E3/E3 subjects. Accelerated VLDL and chylomicron-remnant clearance leads to downregulation of hepatocyte LDL receptors,[17] which underlies the well-known hypercholesterolemic effect of the ε4 allele, with its attendant high risk of atherosclerosis and cardiovascular mortality.[18-22] On the other hand, the ε2 allele causes a delayed clearance of triglyceride-rich lipoproteins with a subsequent decrease in hepatic cholesterol and upregulation of LDL receptors,[17] with its attendant hypocholesterolemic effect.[18]

In the present study, we have evaluated the influence of apoE polymorphism on the serum lipid and lipoprotein response to treatment with two different, widely used lipid-regulating drugs, lovastatin and gemfibrozil, in patients with primary hypercholesterolemia and combined hyperlipidemia.

## SUBJECTS AND METHODS

### *Subjects*

A hyperlipidemic population sample was drawn from the outpatient Lipid Clinic of our tertiary-care, university-affiliated medical center. Patients referred to the Lipid Clinic undergo a routine protocol with a medical history, dietary questionnaire, tests to rule out secondary lipid disorders, lipoprotein studies including apoE phenotyping, and periodic dietary-compliance assessments during intervention.[23] In a retrospective study, outpatients with primary lipid disorders (isolated hypercholesterolemia or combined hyperlipidemia) and known apoE phenotype who had shown long-term compliance with a hypolipidemic diet[23] and required drug treatment to meet recommended target levels of LDL cholesterol and/or triglycerides[24,25] were preselected. To achieve comparable patient groups, those with the rare phenotypes E2/2, E4/2, and E4/4 were excluded. The final study population consisted of 169 subjects who had been given monotherapy with either lovastatin or gemfibrozil and had taken the full prescribed dosage without side effects for at least 12 weeks. There were 112 men and 57 women (45 postmenopausal) aged 53 ± 12 years. None of the postmenopausal women were receiving estrogen replacement therapy. A total of 16 patients were diagnosed with familial hypercholesterolemia (FH) on the basis of severe hypercholesterolemia associated with tendon xanthomas and/or a family history indicative of FH.

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There were 86 patients with isolated hypercholesterolemia (World Health Organization [WHO] type IIa), defined as LDL cholesterol more than 160 mg/dl, or more than 130 mg/dL when previous coronary heart disease was present, and triglycerides less than 200 mg/dL; 83 patients had combined hyperlipidemia (WHO type IIb), defined as LDL cholesterol more than 130 mg/dL in patients with prior coronary heart disease, or more than 160 mg/dL in those without, together with triglycerides more than 200 mg/dL. Sixty-six patients (39%) had been previously diagnosed with coronary heart disease. Only patients with primary hyperlipidemia were considered for the purposes of this study, and hence, patients with alcoholism, hepatic or renal disease, overt diabetes, or other endocrine disorders were excluded. Concomitant treatment with drugs capable of affecting lipid metabolism (β-blockers and diuretics) was used at baseline and throughout the study period.

One hundred six patients, including all 16 patients with FH, received lovastatin 40 mg/d, and 63 patients were treated with gemfibrozil 1.2 g/d.

### *Laboratory Methods*

Blood samples for lipid analysis were obtained after an overnight fast at baseline and after 12 weeks of pharmacological treatment. Lipid and apolipoprotein determinations were performed as previously described.[23] Briefly, serum cholesterol and triglyceride levels were measured by enzymatic methods (Trinder; Bayer Diagnostics, Tarrytown, NY) adapted to a Cobas-Mira automated analyzer (Hoffmann-LaRoche, Basel, Switzerland). High-density lipoprotein (HDL) cholesterol was obtained after precipitation of apoB-containing lipoproteins with phosphotungstate/magnesium. The VLDL fraction was isolated by ultracentrifugation at 45,000 rpm and 15°C for 18 hours in a Kontron ultracentrifuge using a fixed-angle rotor (50.3 Ti; Kontron Instruments, Zurich, Switzerland) according to the method of Havel et al.[26] LDL cholesterol was determined by subtracting HDL and VLDL cholesterol from total cholesterol. Serum concentrations of apoAI and apoB were determined by an immunoturbidimetric method (Unimate 3; Roche Diagnostic Systems, Basel, Switzerland).

ApoE phenotypes were determined in a delipidated aliquot of the VLDL fraction by a modification of the method of Eto et al.[27] The procedure was performed in a flat-bed apparatus using an ultrathin layer of freshly prepared polyacrylamide gel (T5, C6) containing 6 mol/L urea, 8% ampholytes (Pharmalyte 4-6,5M; Pharmacia Fine Chemicals, Uppsala, Sweden), and 1.55 mol/L glycerol. After a 30-minute period for prefocusing (3W), samples of apo VLDL were redissolved on 0.01 mol/L Tris, pH 8.2, containing 25% (by volume) nonionic detergent (Nonidet P-40; LKB, Bromma, Sweden), 8 mol/L urea, and 65 mmol/L dithiothreitol. Samples were focused at 6W for 2 hours at 4°C, fixed on 1.22 mol/L trichloroacetic acid, equilibrated in alcohol:acetic acid: water (20:6:74 vol/vol), stained with Coomassie brilliant blue G-250 at 60°C for 30 minutes, destained in alcohol:acetic acid:water (24:9:67) overnight, and assessed by densitometry.

### *Statistical Analyses*

Values are expressed as the mean ± SD. The Statistical Package for the Social Sciences (SPSS-PC)[28] was used for statistical analyses. Assessments of normality and skewness were made by graphical methods. The data were normally distributed. Differences in categorical variables (sex, previous coronary heart disease, and use of β-blocking agents and diuretics) between groups were analyzed by the Pearson chi-square test. Differences between baseline and drug treatment were compared using paired *t* tests, whereas unpaired *t* tests were used for comparison of lipid changes between HF and non-HF subgroups. Percent lipid changes among apoE groups were compared by the Kruskal-Wallis test. On-treatment lipid and lipoprotein concentrations among the three apoE groups were compared by ANOVA controlling for sex and WHO phenotype, with basal values as covariates. All statistical tests were two-tailed.

## RESULTS

### *Baseline Data by ApoE Phenotype*

The distribution of apoE phenotypes and the clinical characteristics of patients in the two treatment groups are shown in Table 1. There were no statistically significant differences between apoE subgroups with regard to demographic, anthropometric, and clinical data, or the proportion of patients with hypercholesterolemia and mixed hyperlipidemia or who were using β-blockers or diuretics.

Data for baseline lipid and lipoprotein levels are summarized in Tables 2 and 3. For simplicity and because the possible confounding effects were controlled for in the statistical analysis, data on men and women, and on hyperlipidemia types IIa and IIb were combined for each of the two drugs tested. Furthermore, the IIa or IIb phenotype blunted the usual effect of apoE polymorphism observed in the general population. Thus, mean LDL cholesterol levels in type IIa E2, E3, and E4 subjects were 205, 219, and 215 mg/dL ($P = .624$), respectively, whereas respective values for type IIb subjects were 184, 186, and 190 mg/dL ($P = .435$). Likewise, no differences in baseline levels for the three apoE phenotypes considered were apparent in the lovastatin treatment group (Table 2). Although total and LDL cholesterol levels tended to be lower and triglycerides higher in apoE 3/2 subjects in comparison to the 3/3 and 4/3 groups,

**Table 1. Distribution and Clinical Characteristics of the Patients According to ApoE Phenotype**

| Characteristic | ApoE Phenotype 3/2 | 3/3 | 4/3 |
|---|---|---|---|
| Lovastatin group | | | |
| No. of subjects (men/women) | 15 (7/8) | 62 (42/20) | 29 (19/10) |
| Age (yr) | 55 ± 11 | 53 ± 12 | 54 ± 12 |
| Body mass index (kg/m²) | 26 ± 3 | 25 ± 3 | 26 ± 3 |
| Prior CHD, n (%) | 5 (33) | 23 (37) | 12 (41) |
| Concomitant drugs, n (%) | | | |
| β-Blockers | 4 (27) | 15 (24) | 8 (28) |
| Diuretics | 1 (7) | 8 (13) | 5 (17) |
| WHO type (IIa/IIb) | 10/5 | 37/25 | 16/13 |
| Gemfibrozil group | | | |
| No. of subjects (men/women) | 12 (10/2) | 35 (23/12) | 16 (11/5) |
| Age (yr) | 50 ± 9 | 53 ± 11 | 53 ± 9 |
| Body mass index (kg/m²) | 28 ± 4 | 26 ± 3 | 26 ± 3 |
| Prior CHD, n (%) | 4 (33) | 16 (46) | 6 (38) |
| Concomitant drugs, n (%) | | | |
| β-Blockers | 5 (42) | 10 (29) | 6 (38) |
| Diuretics | 1 (8) | 5 (14) | 2 (13) |
| WHO type (IIa/IIb) | 4/8 | 12/23 | 7/9 |

NOTE. All differences between the apoE phenotypes were nonsignificant.

Abbreviation: CHD, coronary heart disease.

**Table 2. Lipid, Lipoprotein, and Apolipoprotein Concentrations (mg/dL) According to ApoE Phenotype in 106 Subjects With Primary Hypercholesterolemia Before and After 12 Weeks of Treatment with Lovastatin 40 mg/d**

| Parameter | ApoE Phenotype | No. | Baseline | Treatment | Percent Change | Range | P* | P† | P‡ | P§ |
|---|---|---|---|---|---|---|---|---|---|---|
| Total cholesterol | 3/2 | 15 | 299 ± 50 | 229 ± 42 | −23 ± 13 | −41-3 | | | | |
| | 3/3 | 62 | 294 ± 48 | 218 ± 42 | −25 ± 10 | −46-−2 | .748 | .646 | .904 | .694 |
| | 4/3 | 29 | 301 ± 42 | 224 ± 42 | −26 ± 9 | −46-−5 | | | | |
| LDL cholesterol | 3/2 | | 221 ± 51 | 151 ± 42 | −31 ± 17 | −51-2 | | | | |
| | 3/3 | | 214 ± 48 | 140 ± 42 | −34 ± 13 | −63-2 | .778 | .508 | .711 | .390 |
| | 4/3 | | 221 ± 42 | 147 ± 39 | −33 ± 12 | −57-−3 | | | | |
| HDL cholesterol | 3/2 | | 47 ± 13 | 50 ± 11 | 12 ± 30 | −25-94 | | | | |
| | 3/3 | | 43 ± 10 | 49 ± 14 | 13 ± 22 | −24-90 | .375 | .534 | .842 | .152 |
| | 4/3 | | 42 ± 10 | 46 ± 10 | 11 ± 20 | −23-75 | | | | |
| Triglycerides | 3/2 | | 158 ± 44 | 147 ± 78 | −9 ± 28 | −37-76 | | | | |
| | 3/3 | | 180 ± 85 | 152 ± 87 | −13 ± 32 | −66-144 | .479 | .976 | .703 | .450 |
| | 4/3 | | 190 ± 98 | 153 ± 80 | −18 ± 20 | −67-30 | | | | |
| ApoAI | 3/2 | | 153 ± 23 | 161 ± 24 | 7 ± 18 | −16-52 | | | | |
| | 3/3 | | 146 ± 25 | 151 ± 23 | 3 ± 13 | −20-56 | .499 | .170 | .874 | .567 |
| | 4/3 | | 144 ± 23 | 148 ± 22 | 3 ± 12 | −19-31 | | | | |
| ApoB | 3/2 | | 172 ± 25 | 130 ± 25 | −24 ± 10 | −43-−11 | | | | |
| | 3/3 | | 174 ± 39 | 126 ± 25 | −25 ± 15 | −55-21 | .740 | .792 | .612 | .502 |
| | 4/3 | | 179 ± 37 | 129 ± 29 | −28 ± 13 | −50-5 | | | | |

NOTE. Data are the mean ± SD.
*ANOVA analysis for basal levels.
†ANOVA analysis for treatment levels.
‡Kruskall-Wallis test for percent change.
§ANOVA analysis for apoE effect controlled for sex, WHO phenotype, and basal value.

baseline levels were not significantly different between apoE phenotypes in the gemfibrozil treatment group (Table 3).

*Effect of ApoE Polymorphism on Response to Lovastatin*

Besides controlling for sex in the statistical analysis, there were no sex-related differences in the magnitude of the hypolipidemic response within each apoE subgroup. Therefore, the responsiveness to lovastatin treatment was analyzed together for men and women.

Table 2 shows basal and posttreatment lipid and lipoprotein levels, as well as the respective percent changes, in subjects with apoE phenotypes 3/2, 3/3, and 3/4. Statistically significant

**Table 3. Lipid, Lipoprotein, and Apolipoprotein Concentrations (mg/dL) According to ApoE Phenotype in 63 Subjects With Primary Hypercholesterolemia Before and After 12 Weeks of Treatment with Gemfibrozil 1.2 g/d**

| Parameter | ApoE Phenotype | No. | Baseline | Treatment | Percent Change | Range | P* | P† | P‡ | P§ |
|---|---|---|---|---|---|---|---|---|---|---|
| Total choleserol | 3/2 | 12 | 252 ± 30 | 236 ± 32 | −6 ± 11 | −22-13 | | | | |
| | 3/3 | 35 | 270 ± 28 | 244 ± 32 | −9 ± 13 | −37-15 | .246 | .649 | .661 | .341 |
| | 4/3 | 16 | 270 ± 42 | 250 ± 48 | −7 ± 12 | −34-17 | | | | |
| LDL cholesterol | 3/2 | | 163 ± 37 | 158 ± 27 | 1 ± 22 | −29-49 | | | | |
| | 3/3 | | 187 ± 31 | 172 ± 30 | −6 ± 20 | −40-31 | .125 | .366 | .734 | .523 |
| | 4/3 | | 187 ± 39 | 178 ± 40 | −3 ± 20 | −41-30 | | | | |
| HDL cholesterol | 3/2 | | 41 ± 14 | 49 ± 13 | 26 ± 17 | 7-67 | | | | |
| | 3/3 | | 40 ± 11 | 47 ± 12 | 22 ± 19 | −27-62 | .786 | .619 | .754 | .690 |
| | 4/3 | | 38 ± 9 | 45 ± 11 | 19 ± 14 | −5-46 | | | | |
| Triglycerides | 3/2 | | 245 ± 103 | 147 ± 46 | −34 ± 23 | −71-2 | | | | |
| | 3/3 | | 228 ± 79 | 126 ± 41 | −41 ± 17 | −67-−1 | .768 | .458 | .595 | .490 |
| | 4/3 | | 223 ± 81 | 135 ± 69 | −40 ± 17 | −76-−4 | | | | |
| ApoAI | 3/2 | | 142 ± 17 | 147 ± 21 | 4 ± 11 | −14-19 | | | | |
| | 3/3 | | 137 ± 28 | 147 ± 27 | 9 ± 22 | −32-78 | .832 | .815 | .863 | .293 |
| | 4/3 | | 138 ± 22 | 143 ± 14 | 5 ± 14 | −23-34 | | | | |
| ApoB | 3/2 | | 152 ± 12 | 141 ± 21 | −7 ± 11 | −33-8 | | | | |
| | 3/3 | | 167 ± 22 | 148 ± 27 | −11 ± 14 | −45-13 | .107 | .706 | .565 | .719 |
| | 4/3 | | 170 ± 32 | 151 ± 38 | −11 ± 18 | −34-26 | | | | |

NOTE. Data are the mean ± SD.
*ANOVA analysis for basal levels.
†ANOVA analysis for treatment levels.
‡Kruskall-Walllis test for percent change.
§ANOVA analysis for ApoE effect controlled for sex, WHO phenotype, and basal value.

($P < .001$) differences were found between basal and treatment levels of total cholesterol, LDL cholesterol, and apoB in each apoE subgroup, but the extent of lipid changes was similar. Serum triglycerides decreased 9% in apoE 3/2 subjects, 13% in those with apoE 3/3, and 18% in the apoE 4/3 group, but these differences were not statistically significant. Within each apoE phenotype, large variations were observed with regard to lipid, lipoprotein, and apolipoprotein percent changes in response to the drug (Table 2); however, covariate analysis showed these to be unrelated to apoE polymorphism.

A subanalysis of the overall results of therapy in patients with and without HF showed a similar responsiveness to lovastatin of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, apoAI, and apoB, with changes of −26% versus −25%, −33% versus −34%, 13% versus 12%, −15% versus −13%, 4% versus 3%, and −29% versus −25%, respectively.

*Effect of ApoE Polymorphism on Response to Gemfibrozil*

The number of men and women was not comparable within each apoE subgroup (Table 1), and sex was controlled for in the statistical treatment of the data; hence, no subanalysis of gender-related differences in response was attempted and the results are analyzed together.

Lipoprotein changes from baseline after gemfibrozil treatment in the three apoE groups are also shown in Table 3. The triglyceride decrease and HDL cholesterol increase induced by gemfibrozil in each apoE subset were statistically significant ($P < .001$). Triglycerides and LDL cholesterol decreased less in the apoE 3/2 subgroup, whereas HDL cholesterol had the lesser increase in apoE 3/4 subjects; however, no statistically significant differences were found between any pair of apoE subgroup comparisons. Like in lovastatin-treated subjects, large variations occurred in lipid, lipoprotein, and apolipoprotein percent changes in response to gemfibrozil (Table 3), but they were not influenced by apoE polymorphism.

## DISCUSSION

ApoE polymorphism contributes to the variability of serum lipids in many populations. Thus, subjects carrying the ε4 allele have higher total and LDL cholesterol levels than those who are homozygous for the ε3 allele, who in turn show higher levels than subjects possessing the ε2 allele; the latter also tend to have higher serum levels of triglyceride-rich lipoproteins than individuals with the other two apoE subscripts.[14,18] As reported in previous studies of hyperlipidemic patients,[4-7,10,23] baseline levels of lipids and lipoproteins were not significantly different among the different apoE subgroups in the present study. Because our patients were already on a lipid-lowering diet, it could be argued that dietary therapy eliminated any preexisting differences if apoE genetic variation influenced the response to diet in a way that counteracted them.[10] However, reports concerning the effect of apoE polymorphism on the serum lipid response to changes in dietary fat and cholesterol are conflicting.[29] Moreover, in previous studies[23] with patient populations and dietary therapies similar to those described herein, we found that lipoprotein responses to dietary intervention were unrelated to apoE phenotype. Conceivably, the primary metabolic defect leading to hyperlipidemia had an effect on serum lipid concentrations much larger than the small variation due to heterogeneity at the apoE gene locus observed in population studies, therefore blunting any differences.

As customarily noted in trials with hypolipidemic drugs, a wide interindividual variation in treatment responses to both lovastatin and gemfibrozil was observed in the present study. Although diet, an important environmental confounding factor, was kept as constant as possible, it still may have influenced this variation.[30] The treatment responses could also be dependent on variation at the apoE gene locus. Theoretically, the response to hepatic hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors could be impaired in patients carrying the ε4 allele, because apoE4-containing lipoproteins are cleared more effectively by the liver than those with other apoE isoforms, resulting in increased hepatocellular cholesterol and suppression of HMG CoA reductase activity.[16] Accordingly, drugs acting on a partially inhibited enzyme could have a blunted effect. Conversely, the ε2 allele could enhance the response to HMG CoA reductase inhibitors due to decreased triglyceride-rich lipoprotein uptake, reduced hepatic cholesterol content, and compensatory upregulation of HMG CoA reductase activity.[16]

In the present study, total cholesterol, LDL cholesterol, and apoB responses to lovastatin were similar in patients with primary hypercholesterolemia, mostly non-FH, independently of apoE polymorphism. Five previous studies of the interaction between apoE phenotypes and the LDL cholesterol response to HMG CoA reductase inhibitors in hypercholesterolemic patients have been published.[4-7,9] Ojala et al[6] treated FH and non-FH patients with lovastatin and found similar responses among different apoE phenotypes. In patients with FH, O'Malley and Illingworth,[4] with lovastatin, and De Knijff et al,[5] with simvastatin, noted a nonsignificant trend for E4 subjects to have the lesser response. Carmena et al[7] reported that male FH patients carrying the ε4 allele had a significantly lower response to lovastatin than ε3 and ε2 patients. Recently, Ordovas et al[9] have shown that patients with moderate hypercholesterolemia possessing the ε2 allele are more responsive to pravastatin than those in other apoE subgroups. Their study[9] contains a meta-analysis of the combined data of the five studies with HMG CoA reductase inhibitors indicating significant differences in the response of LDL cholesterol in the order ε4 < ε3 < ε2, with respective mean decreases of 33%, 35%, and 37%. These differences are clinically insignificant and do not explain the marked heterogeneity in the LDL cholesterol response to treatment with HMG CoA reductase inhibitors observed in this and other studies.

Like other fibric acid derivatives, gemfibrozil exerts a hypotriglyceridemic effect by decreasing VLDL triglyceride synthesis and accelerating VLDL catabolism via stimulation of lipoprotein lipase activity.[31] Because apoE polymorphism influences triglyceride metabolism, there could be a theoretical basis for an influence on the response of serum triglycerides to gemfibrozil treatment. Particularly, metabolic studies have shown that E2 subjects with hyperlipidemia have increased rates of triglyceride fatty acid synthesis, probably as a compen-

sation by hepatic cells to a low uptake rate of triglyceride-rich lipoproteins.[32] In addition, in vitro studies suggest that VLDL from E2 subjects is not a good substrate for lipase action,[33] and this low efficiency of delipidation leads to reduced formation of LDL.[17,33] Therefore, increased synthesis and reduced degradation of VLDL in E2 subjects could blunt the effect of gemfibrozil on both triglycerides and LDL cholesterol.

In this study, subjects with primary hypercholesterolemia and combined hyperlipidemia treated with gemfibrozil showed significant decreases in triglycerides and increases in HDL cholesterol that were unrelated to apoE polymorphism. As expected in patients with hypertriglyceridemia treated with gemfibrozil,[34] LDL cholesterol decreased only marginally. Nonsignificant trends were noted for a lesser response of triglycerides and LDL cholesterol in patients with the E3/2 phenotype. In three studies with HMG CoA reductase inhibitors,[4,5,9] triglyceride responses also tended to be lower in E2 patients versus E3 and E4 groups. There is only one prior study[10] of the interaction of apoE phenotypes with the lipid response to gemfibrozil, also with negative results.

In summary, this study shows that differences in the lipoprotein response to lovastatin or gemfibrozil in subjects with primary hypercholesterolemia are unrelated to allelic variation at the apoE gene locus.

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