Pravastatin Effectively Lowers LDL Cholesterol in Familial Combined Hyperlipidemia Without Changing LDL Subclass Pattern

Guido Franceschini, Michela Cassinotti, Giuseppe Vecchio, Gemma Gianfranceschi, Franco Pazzucconi, Toru Murakami, Marina Sirtori, Antonio L. D'Acquarica, Cesare R. Sirtori

Abstract Familial combined hyperlipidemia (FCHL) is the most common familial form of hyperlipidemia among young survivors of myocardial infarction. Affected patients can present with variable lipid and lipoprotein phenotypes, including hypercholesterolemia alone, hypertriglyceridemia alone, or both hypercholesterolemia and hypertriglyceridemia. These phenotypes can vary among different members of the same family and even in the same subject when analyzed at different times.

The hyperlipidemia in FCHL patients is characterized by elevations of both very-low-density and low-density lipoproteins (VLDL and LDL), whereas high-density lipoprotein (HDL) levels in plasma are often reduced. A striking feature of this syndrome is the presence of small and dense LDL particles, with a low cholesterol-to-protein ratio. In case-control studies, an LDL subclass pattern similarly characterized by the predominance of small, dense LDL particles (pattern B) was associated with an increased risk of coronary heart disease (CHD). Thus, the accumulation of small LDL, enriched in apolipoprotein B (apoB) and possibly consequent to an overproduction of apoB in either VLDL or LDL, might be partly involved in the increased CHD risk of FCHL patients. FCHL was initially proposed to be an autosomal dominant disorder; however, the underlying genetic defect has yet to be identified. Molecular alterations in several human genes, including the lipoprotein lipase gene, the cholesteryl ester hydrolase gene, and the apoA-I/C-III/A-IV gene cluster, may potentially account for the hyperlipidemia in some FCHL patients, suggesting that FCHL is actually a heterogeneous condition. Indeed, a recent analysis of the plasma apoB levels in a large group of FCHL patients showed a bimodal distribution caused by a subset of individuals with small LDL (pattern B) and disproportionate elevations of plasma apoB levels. Since no single genetic or clinical marker identifying FCHL has been yet described, the diagnosis is essentially based on the occurrence of hyperlipidemia in close relatives. However, lipid and lipoprotein profiles very close to those found in FCHL are often detectable also in hyperlipidemic patients in whom a familial origin of the lipoprotein disorder cannot be ascertained because family data are either not available or not sufficiently informative. This syndrome, identified as mixed or combined hyperlipidemia, is also associated with an increased CHD risk.

Since FCHL patients are at significant risk for premature CHD, treatments aimed at lowering lipids and correcting the LDL abnormality are mandatory for reducing coronary risk. Nicotinic acid, which decreases the production of VLDL in the liver, should be the

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drug of choice, but because of a variety of subjective and objective side effects, it is seldom prescribed and is not available in most European nations. Gemfibrozil alone or combined with colesteolip orlovastatin has been proposed as drug therapy for FCHL patients but does not normalize the LDL subclass pattern.

Lovastatin was effective in lowering blood lipids in patients with mixed/combined hyperlipidemia, through either a stimulation of the receptor-mediated LDL catabolism or a normalization of the hepatic production of apoB-containing lipoproteins. The present study evaluated the lipid-lowering efficacy of pravastatin, a competitive inhibitor of hydroxymethylglutaryl coenzyme A (HMG CoA) reductase with an improved liver selectivity, in FCHL patients. In addition to the standard lipid-lipoprotein parameters, special attention was given to changes in LDL structure because of its close relation with cardiovascular risk. The LDL particle distribution and structure were carefully examined by electrophoretic and ultracentrifugal techniques. Moreover, the activities of two major factors involved in the determination of plasma LDL structure, ie, lecithin-cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP), were also evaluated.

Methods

Patients and Experimental Design

Twelve FCHL patients were selected among those referred to the E. Grossi Paoletti Lipid clinic. Patients were diagnosed as having FCHL when they fulfilled the following criteria: (1) a primary combined hyperlipidemia, defined as plasma triglyceride levels greater than 200 mg/dL, LDL cholesterol (LDL-C) greater than 130 mg/dL, and lipoprotein(a) less than 25 mg/dL at the first visit to the lipid clinic, (2) varying lipoprotein phenotype expression during a follow-up of at least 1 year, (3) at least one first-degree relative with a different lipoprotein phenotype than the index patient and a history of premature cardiovascular disease, and (4) presence of small Hpoprotein phenotype than the index patient and a history of premature cardiovascular disease. None of the selected patients was overweight; all were homozygotes for apoE3, except two with an apoE2/E3 phenotype; none of the recruited patients had an apoE2/E2 phenotype; all were monitored at each visit. LDL and HDL characterization and measurement of enzyme activities were performed at 0 and 12 weeks. A standard battery of biochemical and hematologic analyses was also carried out at 0 and 12 weeks.

Laboratory Procedures

Blood samples were collected after an overnight fast. Both serum and plasma (Na,EDTA, 1 mg/mL) were prepared by low-speed centrifugation at 4°C. Plasma aliquots were stored at -80°C for LCAT and CETP activity determinations; serum aliquots were immediately mixed with EDTA (1 mg/dL) and NaBr (5.1 mol/L) and stored at 4°C for a maximum of 1 week before LDL and HDL subtraction separation by rate zonal ultracentrifugation. Lipid analyses were performed during the same day of blood collection, and lipoprotein fractionation was started within 2 days.

Plasma total cholesterol and triglyceride levels were determined by enzymatic methods standardized within a World Health Organization Quality Control Program. HDL-C levels were measured after precipitation of the apoB-containing lipoproteins by dextran sulfate/MgCl2. ApoA-I, A-HDL, and B levels were determined by immunoturbidimetry. ApoE phenotyping was performed as in Reference 32.

Plasma lipoproteins were separated by sequential ultracentrifugation using a TL 100 ultracentrifuge equipped with a TL 100.3 rotor (Beckman Instruments). The total cholesterol (TC), free cholesterol (FC), triglyceride, and phospholipid contents of lipoprotein fractions were determined by enzyme methodologies; the CE mass was then calculated as (TC–FC)×1.68. Protein contents were measured by the method of Lowry et al using bovine serum albumin as standard.

LDL and HDL subfractions were separated by rate zonal ultracentrifugation in a swinging bucket rotor; mean elution profiles were described by plotting mean absorbances calculated from individual runs against elution volume (Ve). The flotation rates of both LDL and HDL were evaluated as the Ve of the major peaks from the density gradient. LDL and HDL particle size distributions were analyzed by nondenaturing polyacrylamide gradient gel electrophoresis using 2% to 16% and 4% to 30% acrylamide gels, respectively. The gels were scanned by an LKB XL laser densitometer, and particle sizes were calculated with LKB 2400 GELOG software using latex particles (38 nm), thyroglobulin, apoferritin, lactate dehydrogenase, and bovine serum albumin as calibrators. Mean particle distributions were calculated within ranges of 7.2 to 12.9 nm (HDL) and 18.0 to 30.0 nm (LDL) by plotting mean absorbance values against particle diameter with the GELOG software.

Substrate-dependent LCAT activity was analyzed as cholesteryl esterification rate in whole plasma by a modification of the radioassay method described by Stokke and Norum. Substrate-independent LCAT activity was determined by a common substrate method using an apoa-I/egg phosphatidylcholine/cholesterol (0.8:250:12.5) proteoliposome containing [14C]cholesterol prepared by the cholate dialysis technique. Substrate-independent CETP activity was measured by using 10 µL plasma as the CETP source and [3H]CE-HDL2 as donor lipoproteins and unlabeled LDL as acceptor particles.

Statistical Analyses

Results are given as mean±SD. Values were compared for every patient by using repeated-measures ANOVA followed by the Newman-Keuls multiple comparison test; ANCOVA was used to compare treatment groups with respect to changes in lipid and lipoprotein concentrations from baseline values. Correlation coefficients (r) were calculated, and the significance of the correlation was determined by the F parameter. A probability value of less than .05 was considered significant.

Results

Twelve patients with FCHL (Table 1) participated in the study. In line with the selection criteria, all patients showed, in addition to elevated plasma cholesterol and triglyceride levels, smaller and less buoyant LDL compared with control subjects or patients with familial hypercholesterolemia.
TABLE 1. Baseline Characteristics of Selected Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>TG</th>
<th>TC</th>
<th>VLDL-C</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>ApoB</th>
<th>LDL Size, nm</th>
<th>LDL Vₜₜ, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.L.</td>
<td>30</td>
<td>M</td>
<td>226</td>
<td>313</td>
<td>46</td>
<td>219</td>
<td>48</td>
<td>177</td>
<td>24.3</td>
<td>4.36</td>
</tr>
<tr>
<td>N.M.</td>
<td>65</td>
<td>F</td>
<td>204</td>
<td>283</td>
<td>40</td>
<td>203</td>
<td>40</td>
<td>157</td>
<td>24.0</td>
<td>4.71</td>
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<tr>
<td>R.E.</td>
<td>45</td>
<td>M</td>
<td>288</td>
<td>296</td>
<td>53</td>
<td>178</td>
<td>38</td>
<td>148</td>
<td>24.6</td>
<td>4.21</td>
</tr>
<tr>
<td>P.T.</td>
<td>50</td>
<td>F</td>
<td>416</td>
<td>337</td>
<td>77</td>
<td>216</td>
<td>44</td>
<td>193</td>
<td>23.8</td>
<td>4.07</td>
</tr>
<tr>
<td>C.I.</td>
<td>55</td>
<td>M</td>
<td>225</td>
<td>322</td>
<td>50</td>
<td>225</td>
<td>47</td>
<td>204</td>
<td>25.0</td>
<td>4.32</td>
</tr>
<tr>
<td>M.G.</td>
<td>56</td>
<td>F</td>
<td>247</td>
<td>299</td>
<td>53</td>
<td>202</td>
<td>44</td>
<td>175</td>
<td>24.0</td>
<td>4.12</td>
</tr>
<tr>
<td>U.M.</td>
<td>41</td>
<td>M</td>
<td>231</td>
<td>417</td>
<td>56</td>
<td>323</td>
<td>38</td>
<td>270</td>
<td>25.1</td>
<td>4.60</td>
</tr>
<tr>
<td>S.B.</td>
<td>57</td>
<td>M</td>
<td>221</td>
<td>253</td>
<td>56</td>
<td>157</td>
<td>40</td>
<td>144</td>
<td>23.8</td>
<td>4.39</td>
</tr>
<tr>
<td>B.M.</td>
<td>34</td>
<td>M</td>
<td>346</td>
<td>401</td>
<td>75</td>
<td>258</td>
<td>68</td>
<td>214</td>
<td>24.8</td>
<td>4.13</td>
</tr>
<tr>
<td>B.E.</td>
<td>54</td>
<td>M</td>
<td>206</td>
<td>311</td>
<td>53</td>
<td>200</td>
<td>58</td>
<td>146</td>
<td>25.3</td>
<td>4.38</td>
</tr>
<tr>
<td>P.G.</td>
<td>44</td>
<td>F</td>
<td>238</td>
<td>260</td>
<td>55</td>
<td>155</td>
<td>50</td>
<td>139</td>
<td>24.9</td>
<td>4.10</td>
</tr>
<tr>
<td>B.P.</td>
<td>42</td>
<td>M</td>
<td>202</td>
<td>254</td>
<td>47</td>
<td>192</td>
<td>55</td>
<td>143</td>
<td>24.1</td>
<td>4.58</td>
</tr>
</tbody>
</table>

TG indicates triglycerides; TC, total cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; apo, apolipoprotein; and Vₜₜ, elution volume.

All selected patients completed the study. Pravastatin was well tolerated; monitoring of drug intake by pill counting indicated that compliance with treatment was satisfactory (>90%). Weight changes were minimal, as were variations in blood pressure and routine hematologic tests. During the 4 weeks preceding the study, no significant changes were noted in the major lipid-lipoprotein parameters; the baseline (time 0) levels were thus considered for comparative evaluations.

A prompt reduction of plasma total cholesterol, LDL-C, and apoB levels was observed after 4 weeks of treatment (Table 2) and was maintained throughout the study. By contrast, plasma triglycerides and VLDL-C did not change; HDL-C concentrations showed a small, nonsignificant increase at 4 weeks (+10%), returning to baseline values at the end of the study.

Mean values during pravastatin administration were calculated and are reported in Table 2. Pravastatin lowered total cholesterol and LDL-C levels by 21% and 32%, respectively; a slight increase (+6%) of HDL-C levels was also observed. Because of these changes, the ratio of LDL-C to HDL-C decreased significantly from 4.57±1.35 to 3.14±0.81. The increase in total HDL-C levels was due to a significant 73% rise of HDL₂-C concentrations (from 6.0±2.7 to 10.4±3.0 mg/dL) associated with a minor, nonsignificant decrease of HDL₃-C levels (from 41.5±4.4 to 38.2±3.9 mg/dL); therefore, the ratio of HDL₂-C to HDL₃-C increased significantly from 0.15±0.08 to 0.26±0.17. Plasma triglyceride and VLDL-C levels were reduced by 6% and 3%, respectively, during pravastatin treatment. ApoB levels decreased by 9%; minor, nonsignificant changes were recorded for both apoA-I and A-II levels (Table 2).

LDL particle distribution was analyzed after separation by nondenaturing gradient gel electrophoresis and rate zonal ultracentrifugation. As expected, the electrophoresis profiles at baseline showed the presence of a single major LDL subpopulation of relatively small size (24.5±0.5 nm), with very minor additional components (Table 1, Fig 1). The mean diameter of the major LDL subpopulation decreased after pravastatin treatment to 23.8±0.6 nm (P=0.013), with no difference in the size or contribution of minor components (Fig 1). An LDL subclass pattern B persisted after treatment in all examined patients.

TABLE 2. Plasma Lipid and Lipoprotein Levels During Pravastatin Treatment in 12 Patients With Familial Combined Hyperlipidemia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
<th>12 Weeks</th>
<th>Mean on Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>313.2±49.2</td>
<td>247.2±34.2*</td>
<td>250.8±43.8</td>
<td>246.5±39.8*</td>
<td>248.1±35.8*</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>55.1±10.6</td>
<td>52.7±9.1</td>
<td>49.3±11.7</td>
<td>57.8±19.4</td>
<td>53.3±15.9</td>
</tr>
<tr>
<td>LDL-C</td>
<td>210.6±43.3</td>
<td>143.0±29.0*</td>
<td>146.2±39.0*</td>
<td>140.4±29.3*</td>
<td>143.2±29.7*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>47.5±8.7</td>
<td>52.2±6.2</td>
<td>50.4±6.9</td>
<td>48.3±7.6</td>
<td>50.3±6.3</td>
</tr>
<tr>
<td>TG</td>
<td>249.1±62.7</td>
<td>239.7±95.6</td>
<td>206.0±58.5</td>
<td>254.0±97.2</td>
<td>233.2±68.7</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>144.6±16.6</td>
<td>156.2±11.3</td>
<td>152.7±19.7</td>
<td>153.9±11.6</td>
<td>154.3±10.4</td>
</tr>
<tr>
<td>ApoA-II</td>
<td>39.5±7.5</td>
<td>37.0±4.7</td>
<td>40.7±6.8</td>
<td>36.6±3.8</td>
<td>36.1±2.8</td>
</tr>
<tr>
<td>ApoB</td>
<td>175.8±37.5</td>
<td>162.7±27.3*</td>
<td>165.5±22.9</td>
<td>151.9±31.5*</td>
<td>160.1±19.3*</td>
</tr>
</tbody>
</table>

Definitions are as in Table 1. Results are expressed as mean±SD in milligrams per deciliter.

*Significantly different from baseline.
At baseline, a single monodisperse LDL component was detectable by rate zonal ultracentrifugation (Fig 2); these LDL were significantly less buoyant ($V_c = 4.33 \pm 0.21$ mL) compared with those of hypercholesterolemic patients ($V_c = 5.40 \pm 0.38$ mL). The height of the LDL peak was reduced slightly after pravastatin, with minor, nonsignificant changes in shape and flotation rate ($V_c = 4.46 \pm 0.20$ mL), indicative of a reduced number of circulating LDL particles. Fractions corresponding to the LDL peak were collected, and LDL composition was determined as described in "Methods." LDL became CE poor after pravastatin, as demonstrated by the significant reduction of the CE-apoB ratio (from 1.64±0.40 to 1.27±0.52); minimal, nonsignificant variations were recorded in other LDL components. The reduction of LDL diameter after pravastatin was significantly correlated with the decrease in the LDL-CE content (r=.65).

The HDL subfraction distribution was analyzed by rate zonal ultracentrifugation and nondenaturing polyacrylamide gel electrophoresis. The flotation rate of both major HDL subtractions, HDL$_2$ and HDL$_3$, increased significantly after pravastatin treatment (Fig 3). This increase was mostly due to an enhanced CE content, with minor changes in other HDL constituents. The protein staining of the HDL bands separated by gradient gel electrophoresis did not change after pravastatin, suggesting that treatment does not affect HDL particle number in plasma.

To investigate whether the changes in LDL and HDL structure and composition after pravastatin were consequent to changes in cholesterol esterification and transfer in plasma, we measured the activities of CETP and LCAT both by substrate-dependent methods, evaluating the interaction of the endogenous lipoprotein substrates with either LCAT or CETP, and by substrate-independent methods, evaluating the concentration and activity of each single factor independent of the endogenous lipoprotein substrates (Table 3). The substrate-dependent CETP activity decreased after pravastatin by 28%, despite a minimal, nonsignificant 4% reduction of the substrate-independent activity. The reduction of substrate-dependent CETP activity was significantly correlated with the decrease in plasma total cholesterol (r=.57) and LDL-C (r=.63) levels. LCAT activity was minimally affected by pravastatin treatment (Table 3).

**Discussion**

FCHL is a relatively common genetic disorder characterized by elevations of plasma VLDL and/or LDL levels and by the accumulation of small and dense LDL.

<table>
<thead>
<tr>
<th>Table 3. CETP and LCAT Activities in 12 Patients With Familial Combined Hyperlipidemia Before and After Pravastatin Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>CETP</td>
</tr>
<tr>
<td>substrate-dependent</td>
</tr>
<tr>
<td>CETP</td>
</tr>
<tr>
<td>substrate-independent</td>
</tr>
<tr>
<td>LCAT</td>
</tr>
<tr>
<td>substrate-dependent</td>
</tr>
<tr>
<td>LCAT</td>
</tr>
<tr>
<td>substrate-independent</td>
</tr>
</tbody>
</table>

CETP indicates cholesteryl ester transfer protein; LCAT, lecithin-cholesterol acyltransferase. Results are expressed as mean±SD in nanomoles per milliliter per hour.

*Significantly different from baseline.
particles poor in cholesterol and relatively enriched in apoB. Despite the undoubted genetic origin of the disease, the molecular defect has yet to be identified, the most recent evidence suggesting that FCHL is a heterogeneous condition. Overproduction of apoB in the liver appears to be the underlying metabolic defect in many FCHL patients; the accumulation of VLDL or LDL may then depend on the individual capacity to drive the excess apoB into triglyceride- or cholesterol-rich particles or to efficiently metabolize the various lipoprotein species.

Because of the strong association between FCHL and an increased risk of premature CHD, therapeutic approaches to reduce blood lipids and favorably modify the LDL pattern in affected individuals are mandatory. Nicotinic acid should be the drug of choice because of its capacity to inhibit lipoprotein synthesis in the liver, but it is seldom prescribed because of significant side effects. Alternative therapeutic approaches have been proposed, the most effective being the combination of gemfibrozil with lovastatin, which, however, is also of poor clinical applicability because of the high risk of severe muscular syndromes. Gemfibrozil alone, although effective in lowering plasma VLDL-C and triglyceride levels and raising HDL-C, tends to increase plasma LDL-C concentrations without affecting the small LDL size.

Lovastatin, the first HMG CoA reductase inhibitor marketed in the United States, proved effective in potentiating the lipid-lowering activity of gemfibrozil in FCHL patients. A lovastatin derivative, simvastatin, lowered plasma lipid and lipoprotein levels and induced significant changes in LDL subfraction distribution in patients with combined hyperlipidemia or moderate hypercholesterolemia. However, the effect of lovastatin or simvastatin on LDL levels and structure in FCHL patients has not yet been investigated. In the present study pravastatin, an HMG CoA reductase inhibitor with an improved liver selectivity, effectively lowered plasma total cholesterol, LDL-C, and apoB levels in patients with FCHL but did not affect either plasma triglyceride concentrations or LDL subclass pattern. Instead, LDL particles tended to become even smaller and richer in apoB after pravastatin, mostly because of a reduction in the CE content.

The mechanism or mechanisms responsible for the prevalence of small LDL particles in FCHL patients are still largely undefined. Small, dense LDL may accumulate in plasma because of an increased production of apoB in either VLDL or LDL or a defective VLDL lipolysis. Both of these mechanisms seem to be poorly affected by pravastatin treatment. Plasma lipolytic activities are minimally modified by HMG CoA reductase inhibitors, consistent with evidence from kinetic studies that failed to show a modification of the VLDL to LDL conversion in vivo.

Lipoprotein synthesis in the liver apparently did not change after pravastatin treatment in these FCHL patients, as indicated by the lack of variation in plasma triglyceride and VLDL levels as well as in VLDL composition. Pravastatin was instead able to inhibit the hepatic secretion of VLDL in patients with moderate hypercholesterolemia, resulting in decreased input rates for LDL-apoB in most patients. Similarly, lovastatin treatment in patients with nonfamilial combined hyperlipidemia caused a reduction of LDL-apoB, mainly due to an inhibited entry of apoB-containing lipoproteins into plasma. However, in the latter study patients were heterogeneous; some had mainly hypertriglyceridemia and others, moderate hypertriglyceridemia. Some of them responded to lovastatin treatment with an increase in the LDL fractional catabolic rate instead of a decreased input rate. In patients with mixed hyperlipidemia, lovastatin lowered LDL-C and apoB concentrations mainly through an increased fractional catabolic rate. These earlier studies did not examine changes in LDL particle structure or distribution. Indeed, in the present study the abnormal structure of LDL, typically small and dense, enriched in apoB compared with control or hypercholesterolemic LDL, was not affected by pravastatin treatment. These findings, together with evidence from in vivo kinetic studies, suggest that in patients with mixed hyperlipidemia and with FCHL, pravastatin acts mainly through a stimulation of LDL receptor expression in the liver, resulting in an accelerated removal of LDL from plasma. The number of circulating LDL particles will thus decrease, without changes in size or density distribution.

In the present study LDL became even smaller after pravastatin treatment. The reduction of LDL size was mostly related to a decreased CE content. A decrease of either plasma CETP or LCAT activity should contribute to the decreased concentration of CE within LDL. The measurement of both of these activities by substrate-independent methods, evaluating the activity of LCAT and CETP independently of the endogenous lipoprotein substrates and reflecting plasma concentrations, failed to show any change after pravastatin treatment. Instead, the in vitro net mass transfer of CE from HDL to lower density lipoproteins was significantly reduced.

This measurement evaluates the in vitro interaction between CETP and the endogenous substrates, either acceptor or donor lipoproteins. In the absence of changes in the concentrations of plasma CETP and HDL, the reduced CE transfer seems to be mostly related to the decreased pool of acceptor lipoproteins. If this mechanism also operates in vivo, it should explain both the reduction of LDL-CE and the accumulation of large, fast-floating, and CE-rich HDL. Similarly, elevated plasma HDL-C levels have been reported after prolonged treatment with simvastatin, consistent with the described increase of apoA-I-containing particles after both simvastatin and pravastatin.

In conclusion, the present study demonstrates that pravastatin effectively lowers plasma total cholesterol and LDL-C levels in patients with FCHL, thus reducing the CHD risk in these otherwise high-risk patients. However, the postulated metabolic defects, ie, an overproduction of apoB in either VLDL or LDL as well as the abnormal LDL size, are not affected by treatment. Gemfibrozil administration to a similar group of FCHL patients effectively lowered plasma triglyceride but raised LDL-C and again did not affect LDL size distribution. These findings confirm that the LDL subclass pattern in FCHL patients is largely controlled by genetic factors and independently of plasma lipid levels. In view of the intrinsic high CHD risk associated with the predominance in plasma of small LDL, typically found in FCHL patients, and of the apparent resistance of these abnormal LDL to drug-induced modifications,
a maximal lipid-lowering effect is mandatory for reducing CHD risk in these patients. The combination of an HMG CoA reductase inhibitor with gemfibrozil or niacin should provide the best lipid-lowering results, reducing plasma triglyceride and LDL-C while raising HDL-C levels. It remains to be seen whether this or other treatments may correct the LDL abnormality characteristic of FCHL.

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