Comparative Effects of Cerivastatin and Fenofibrate on the Atherogenic Lipoprotein Phenotype in Proteinuric Renal Disease

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Abstract. Patients with nephrotic-range proteinuria have impaired clearance of triglyceride-rich lipoproteins. This results in the atherogenic lipoprotein phenotype (mild hypertriglyceridemia, low high-density lipoproteins [HDL], and excess small, dense low-density lipoproteins [LDLIII]). Excess remnant lipoproteins (RLP) are linked to hypertriglyceridemia and may contribute to the atherogenicity of nephrotic dyslipidemia. A randomized crossover study compared the effects of a statin (cerivastatin) and a fibrate (fenofibrate) on LDLIII and RLP in 12 patients with nephrotic-range proteinuria. Cerivastatin reduced cholesterol (21%, P < 0.01), triglyceride (14%, P < 0.05), LDL cholesterol (LDL-C; 23%, P < 0.01), total LDL (18%, P < 0.01), and LDLIII concentration (27% P < 0.01). LDLIII, RLP-C, and RLP triglyceride (RLP-TG) were unchanged. Plasma LDLIII reduction with cerivastatin treatment correlated with plasma triglyceride reduction (LDLIII r² = 67%, P < 0.001; RLP cholesterol r² = 58%, P < 0.005). Serum creatinine increased with fenofibrate treatment (14%, P < 0.01); however, creatinine clearance was unchanged. LDLIII concentration was 187 ± 85 mg/dl after cerivastatin treatment and 133 ± 95 mg/dl after fenofibrate treatment. Cerivastatin and fenofibrate reduce LDLIII concentration in nephrotic-range proteinuria. However, atherogenic concentrations of LDLIII remain prevalent after either treatment. Fenofibrate but not cerivastatin reduces remnant lipoproteins. The two treatments seem to reduce LDLIII by different mechanisms, suggesting a potential role for combination therapy to optimize lowering of LDLIII and RLP.

Patients with proteinuria have an increased incidence of cardiovascular disease (1). Those with nephrotic-range proteinuria experience a 5.5-fold increase in the relative risk of myocardial infarction, even after correction for hypertension and smoking (2). More than two thirds of patients with nephrotic syndrome have at least two risk factors for the development of atherosclerosis (3), and the dyslipidemia that is prevalent in this population is likely to contribute to the increased incidence of cardiovascular disease.

Lipoproteins exhibit heterogeneity. Low-density lipoproteins (LDL) can be divided into large, light LDLI (d 1.025 to 1.034 g/ml) and LDLII (d 1.034 to 1.044 g/ml), and small, dense LDL (LDLIII; d 1.044 to 1.063 g/ml). LDLIII is considered to be the most atherogenic LDL species. Prospective and retrospective studies have demonstrated a link between LDLIII and increased risk of coronary artery disease (4,5), and a plasma level of LDLIII > 100 mg/dl confers a sevenfold increase in the risk of myocardial infarction (6). We recently demonstrated that patients with nephrotic-range proteinuria possess atherogenic quantities of LDLIII (7). Very low-density lipoprotein (VLDL) can similarly be divided into large, light VLDL1 and smaller, denser VLDL2. VLDL1 and VLDL2 are thought to be regulated independently. VLDL1 is increased in patients with raised triglycerides (6), whereas excess VLDL2 is found in patients with increased LDL cholesterol (LDL-C) (6). In nephrotic-range proteinuria, VLDL1 clearance is delayed and VLDL2 production is increased (8). As a result, both subfractions are found in increased quantities (8).

Pharmacological lipid lowering with either hepatic 3-methylglutaryl coenzyme A reductase inhibitors (statins) or fibrates reduces cardiovascular morbidity and mortality (9–11). However, the majority of patients with coronary artery disease do not have hypercholesterolemia, and a large proportion have a pattern of mild hypertriglyceridemia, low HDL, and excess LDLIII (12), known as the atherogenic lipoprotein phenotype (6). In the normal populations, statins reduce LDLIII by lowering all three LDL subfractions in concert (13). Fibrates...
promote a shift in LDL size toward larger, lighter particles, with or without a change in total LDL (14,15). Recent evidence suggests that remnants of triglyceride-rich lipoproteins may also be implicated in the pathogenesis of atherosclerosis (16). Elevated lipoprotein remnants (RLP) are found in patients with raised plasma triglyceride (17) and therefore may contribute to the increased cardiovascular risk of the atherogenic lipoprotein phenotype.

In addition to hypercholesterolemia, raised plasma triglyceride is well recognized in nephrotic-range proteinuria (18), with reports of 67% (8) and 71% (3) of patients having a plasma triglyceride greater than 2 mmol/L and 2.3 mmol/L, respectively. Statins have been shown to reduce cholesterol and LDL-C in patients with nephrotic dyslipidemia (8); however, this cholesterol-lowering effect is also accompanied by plasma triglyceride reduction and increased receptor-mediated LDL clearance (19). LDLII formation is a consequence of mild increases in plasma triglyceride (6), and therefore the triglyceride-lowering effect of statins may have a beneficial effect not only on LDLII concentration but also on the relative proportions of each LDL subfraction and on remnant lipoproteins. The aim of this study, therefore, was to compare the ability of a statin (cerivastatin) and a fibrate (fenofibrate) to lower levels of these atherogenic lipoproteins in patients with nephrotic-range proteinuria. A secondary aim was to assess changes in VLDL subfractions and plasma apolipoproteins to help identify mechanisms that underlie any changes.

Materials and Methods

Patients

Twelve patients (10 male, 2 female) were recruited from the Glasgow Royal Infirmary Renal Unit. Inclusion criteria were (1) biopsy-proven glomerular disease, (2) urinary albumin >1.5 g/24 h (equivalent to 3 g proteinuria/24 h), (3) serum creatinine <250 μmol/L, (4) cholesterol >6.5 mmol/L, and (5) triglyceride >1.5 mmol/L. Exclusion criteria were (1) significant deterioration in renal function in the previous 6 mo and (2) having diseases or receiving treatment that influenced lipid profile (specifically, diabetes mellitus or amyloid, thiazide diuretics, fat-soluble β-blockers, corticosteroids, or other immunosuppressants). Treatment with other antihypertensives was permitted. All lipid-lowering therapy was stopped for 4 wk before the study.

The study had a randomized, crossover design and lasted 5 mo. Six patients received 100 μg of cerivastatin for 1 mo and 200 μg for the second month. Six patients received fenofibrate 200 mg for 2 mo. This was followed by a month washout period off lipid-lowering treatment and then the alternative treatment for 2 mo. Patients were seen monthly, after an overnight fast, and samples were taken for creatinine, albumin, liver function tests (LFT), creatine kinase (CK), lipids and lipoproteins, VLDL and LDL subfractions, 24-h creatinine clearance, and urinary albumin. The study was approved by the Ethics Committee of Glasgow Royal Infirmary. All patients gave written consent before participating.

Plasma lipids and lipoproteins were measured according to the Lipid Research Clinic’s protocol. VLDL₁ (S₃ 60 to 400), VLDL₂ (S₃ 20 to 60), and intermediate-density lipoprotein (IDL; S₃ 10 to 20) were isolated from plasma by cumulative-gradient ultracentrifugation (20). LDL (d 1.019 to 1.063 g/ml) was isolated from fresh plasma by sequential ultracentrifugation. The triglyceride, free cholesterol, cholesterol ester, phospholipid, and protein contents of all lipoproteins were assayed, and lipoprotein concentrations were calculated as the sum of these components. Three LDL subfractions (LDL₁, d 1.025 to 1.034 g/ml; LDLII, d 1.034 to 1.044 g/ml; and LDLIII, d 1.044 to 1.063 g/ml) were isolated from fresh plasma by nonequilibrium density gradient ultracentrifugation as described previously (21). The individual subfraction areas were quantified and expressed as percentage of total LDL. The lipoprotein concentration of LDL was used to generate individual subfraction concentrations. The cholesteryl and triglyceride content of remnant lipoproteins (RLP-C, RLP-TG) was measured using a diagnostic reagent kit from Japan Immunoresearch Laboratories (JIMRO; Takasaki, Japan). RLP were separated from other lipoproteins by an immunoaffinity gel containing monoclonal antibodies to human apoB100 and human apoA1 (22). The cholesterol and triglyceride contents of the unbound fraction were measured using enzymatic spectrophotometric assays. Apolipoproteins B, CIII, CIV, and E were analyzed from ethylenediaminetetraacetate plasma using kits purchased from Wako Pure Chemical Industries (Osaka, Japan).

Statistical Analyses

Statistical analysis was performed using MINITAB 11 for Windows (Minitab Inc., State College, PA) and SPSS statistical package. Results are shown as means ± SD. Baseline and end point data were compared using repeated measures ANOVA, with the two treatment modalities further compared using paired t test if the ANOVA showed a significant difference. Pre- and posttreatment data were compared using paired t test. Regression analysis identified significant correlations.

Results

Baseline Data

The diagnoses of the study population were IgA nephropathy (four), membranous nephropathy (three), minimal change nephropathy (two), mesangiocapillary glomerulonephritis (two) and focal and segmental glomerulosclerosis (one). Baseline data obtained before treatment are shown in Tables 1 to 3. Values at the beginning of each treatment phase (baseline and washout) did not differ for any parameter. The median age of the study patients was 52 yr (range, 18 to 66). Average BP was 143/87 mmHg (nine treated with antihypertensives). The mean body mass index was 27.7 ± 3.6, with a serum albumin of 35.8 ± 5.5 g/L (<32 g/L in three patients). Only one patient had significant edema. Serum creatinine was >150 μmol/L in 3 of 12 patients before cerivastatin treatment and 2 of 12 before fenofibrate treatment. Compared with normal reference values, concentrations of total VLDL, VLDL₁, and VLDL₂ were increased four- to fivefold (23), and IDL and total LDL were increased twofold (Table 2) (23). LDLII was the most prevalent LDL particle (Table 3) with a concentration >100 mg/dl in 10 of 12 patients in each group. RLP-C and RLP-TG both were raised at baseline (Table 3) (24).
Table 1. Basic lipid and lipoproteins: Cerivastatin versus fenofibrate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (mg/dl)</th>
<th>Cerivastatin</th>
<th>% Decrease (95% CI)</th>
<th>Final Result (mg/dl)</th>
<th>% Decrease (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Creatinine (μmol/l)</td>
<td>128 ± 38</td>
<td>127 ± 38</td>
<td>2 (–2, 7)</td>
<td>145 ± 49&lt;sup&gt;d&lt;/sup&gt;</td>
<td>–14 (–22, –6)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>71 ± 27</td>
<td>74 ± 31</td>
<td>–4 (–20, 12)</td>
<td>70 ± 30</td>
<td>1 (–12, 13)</td>
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<tr>
<td>UAE (g/24 h)</td>
<td>2.7 ± 1.4</td>
<td>2.8 ± 1.3</td>
<td>–4 (–31, 24)</td>
<td>2.3 ± 1.1</td>
<td>2 (–20, 24)</td>
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<tr>
<td>Plasma cholesterol (mmol/L)</td>
<td>7.7 ± 1.0</td>
<td>6.0 ± 0.9</td>
<td>–21 (15, 27)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.3 ± 1.0</td>
<td>19 (10, 27)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma triglyceride (mmol/L)</td>
<td>3.6 ± 2.6</td>
<td>2.8 ± 2.0</td>
<td>14 (1, 27)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.2 ± 1.7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>41 (31, 51)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>VLDL-C (mmol/L)</td>
<td>1.6 ± 1.1</td>
<td>1.1 ± 0.8</td>
<td>16 (–4, 36)</td>
<td>0.7 ± 0.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>52 (32, 73)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>5.2 ± 1.2</td>
<td>3.9 ± 0.8</td>
<td>23 (17, 30)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.4 ± 0.8</td>
<td>8 (–11, 28)</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>0.96 ± 0.21</td>
<td>0.99 ± 0.23</td>
<td>–4 (–15, 7)</td>
<td>1.12 ± 0.26&lt;sup&gt;e&lt;/sup&gt;</td>
<td>–19 (–25, –13)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ApoB (mg/dl)</td>
<td>178 ± 34</td>
<td>134 ± 33</td>
<td>21 (13, 29)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>135 ± 38</td>
<td>27 (16, 37)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ApoCII (mg/dl)</td>
<td>8.6 ± 3.8</td>
<td>7.3 ± 3.4</td>
<td>10 (0, 21)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.4 ± 3.4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>29 (23, 35)&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>ApoCIII (mg/dl)</td>
<td>35.1 ± 8.8</td>
<td>31.7 ± 7.8</td>
<td>7 (1, 14)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>26.7 ± 7.5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>26 (21, 30)&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>ApoE (mg/dl)</td>
<td>6.7 ± 3.8</td>
<td>5.0 ± 3.0</td>
<td>20 (5, 34)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.5 ± 2.6</td>
<td>32 (22, 42)&lt;sup&gt;b&lt;/sup&gt;</td>
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<sup>a</sup> UAE, urine albumin excretion; VLDL-C, very low-density lipoprotein cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; APO, apolipoprotein.

<sup>b</sup> P < 0.01 for response to treatment with cerivastatin and fenofibrate.
<sup>c</sup> P < 0.05 for response to treatment with cerivastatin and fenofibrate.
<sup>d</sup> P < 0.01 for final result of cerivastatin versus fenofibrate.
<sup>e</sup> P < 0.05 for final result of cerivastatin versus fenofibrate.

Table 2. Plasma lipoprotein concentrations: Cerivastatin versus fenofibrate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (mg/dl)</th>
<th>Cerivastatin</th>
<th>% Decrease (95% CI)</th>
<th>Final Result (mg/dl)</th>
<th>% Decrease (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VLDL (mg/dl)</td>
<td>433 ± 291</td>
<td>311 ± 232</td>
<td>26 (16, 35)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>220 ± 214&lt;sup&gt;c&lt;/sup&gt;</td>
<td>55 (42, 68)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>VLDL&lt;sub&gt;1&lt;/sub&gt; (mg/dl)</td>
<td>287 ± 281</td>
<td>200 ± 217</td>
<td>18 (–7, 44)</td>
<td>135 ± 184&lt;sup&gt;d&lt;/sup&gt;</td>
<td>57 (40, 74)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>VLDL&lt;sub&gt;2&lt;/sub&gt; (mg/dl)</td>
<td>147 ± 61</td>
<td>112 ± 62</td>
<td>14 (–14, 43)</td>
<td>85 ± 53&lt;sup&gt;d&lt;/sup&gt;</td>
<td>47 (34, 60)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>IDL&lt;sup&gt;+&lt;/sup&gt; (mg/dl)</td>
<td>97 ± 29</td>
<td>77 ± 38</td>
<td>20 (–1, 41)</td>
<td>84 ± 23</td>
<td>8 (–6, 23)</td>
</tr>
<tr>
<td>Total LDL concentration (mg/dl)</td>
<td>447 ± 90</td>
<td>349 ± 48</td>
<td>18 (9, 26)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>382 ± 80</td>
<td>14 (–1, 29)</td>
</tr>
</tbody>
</table>

<sup>a</sup> IDL, intermediate-density lipoprotein.

<sup>b</sup> P < 0.01 for response to treatment with cerivastatin and fenofibrate.
<sup>c</sup> P < 0.01 for final result of cerivastatin versus fenofibrate.
<sup>d</sup> P < 0.05 for final result of cerivastatin versus fenofibrate.

Table 3. LDL subfractions and plasma lipoprotein remnants: Cerivastatin versus fenofibrate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (mg/dl)</th>
<th>Cerivastatin</th>
<th>% Decrease (95% CI)</th>
<th>Final Result (mg/dl)</th>
<th>% Decrease (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLI concentration</td>
<td>42 ± 42</td>
<td>36 ± 35</td>
<td>24 (–5, 53)</td>
<td>67 ± 45&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–137 (–249, –26)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>LDLII concentration</td>
<td>145 ± 93</td>
<td>125 ± 62</td>
<td>–2 (–34, 31)</td>
<td>183 ± 68</td>
<td>–87 (–191, 61)</td>
</tr>
<tr>
<td>LDLIII concentration</td>
<td>259 ± 105</td>
<td>187 ± 85</td>
<td>27 (12, 41)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>133 ± 95&lt;sup&gt;c&lt;/sup&gt;</td>
<td>49 (30, 68)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>RLP-C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>45 (32 – 67)</td>
<td>31 (24 – 57)</td>
<td>–2 (–48, 43)</td>
<td>32 (19 – 42)</td>
<td>21 (22, 48)</td>
</tr>
<tr>
<td>RLP-TG&lt;sup&gt;a&lt;/sup&gt;</td>
<td>83 (41 – 119)</td>
<td>44 (27 – 152)</td>
<td>–65 (–220, 91)</td>
<td>39 (18 – 69)</td>
<td>32 (22, 66)</td>
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</table>

<sup>a</sup> Median + interquartile range. RLP-C, remnant lipoprotein cholesterol; RLP-TG, remnant lipoprotein triglyceride.

<sup>b</sup> P < 0.05 for response to treatment with cerivastatin and fenofibrate.
<sup>c</sup> P < 0.05 for final result of cerivastatin versus fenofibrate.
<sup>d</sup> P < 0.01 for response to treatment with cerivastatin and fenofibrate.
observed, with a similar decrease in apoCII (20%). Smaller reductions were seen in plasma apoCIII (10%) and apoCIII (7%). No change in serum creatinine, creatinine clearance, LFT, or CK was observed with cerivastatin treatment; however, one patient developed myalgia while receiving 200 μg of cerivastatin, which resolved on decreasing to a 100-μg dosage. No increment in CK was found.

Fenofibrate treatment resulted in large reductions in plasma triglyceride (41%) and VLDL-C (52%). A significant decrease in plasma cholesterol (19%) was also seen, with a 19% increase in HDL-C. Plasma apoCII (27%), apoE (32%), apoCIII (29%), and apoCIII (26%) all were significantly reduced. No consistent change in LDL-C was observed. Fenofibrate treatment was associated with a 14% increase in serum creatinine (P < 0.01); however, there was no change in creatinine clearance. One patient developed abnormal LFT and a rise in CK after 2 mo of fenofibrate treatment. These values returned to normal after stopping the drug as planned. Overall, there was no significant change in CK after fenofibrate treatment (mean increase, 78 μL/L; 95% confidence interval [CI], −105:261).

VLDL, VLDL Subfractions, IDL, and LDL Concentration

Cerivastatin produced a significant reduction in the concentration of total VLDL (26%) and total LDL (18%; Table 2). Changes in VLDL subfractions and IDL were more heterogeneous (Table 2) with an 18% reduction in VLDL1 (mean decrease, 80 mg/dL; 95% CI, 19:141), a 14% reduction in VLDL2 (mean decrease, 29 mg/dL; 95% CI, −4:61), and a nonsignificant reduction in IDL concentration (mean decrease, 21 mg/dL; 95% CI, −2:43). Fenofibrate induced large reductions in total VLDL, VLDL1, and VLDL2 (Table 2). The LDL reduction showed marked heterogeneity (mean decrease, 74 mg/dL; 95% CI, 1:146). IDL concentration did not change.

LDL Subfractions and Lipoprotein Remnants

Plasma LDLIII concentration fell by 27% with cerivastatin treatment (Table 3). LDLI concentration was very low, and a negligible change in LDLII was observed. The relative percentage of each LDL subfraction did not change (pre-cerivastatin %LDLI, 9 ± 7; %LDLII, 31 ± 16; %LDLIII, 60 ± 23; post-cerivastatin %LDLI, 10 ± 9; %LDLII, 36 ± 16; %LDLIII, 54 ± 24). Cerivastatin treatment failed to reduce levels of either RLP-C (mean decrease, 9 mg/dL; 95% CI, −8:26) or RLP-TG (mean decrease, 20 mg/dL; 95% CI, −32:73; Table 3).

Fenofibrate reduced LDLIII concentration (mean decrease, 131 mg/dL; 95% CI, 77:184; P < 0.0005; Table 3), with a corresponding increase in LDLI (26 mg/dL; 95% CI 5:46; P < 0.02; Table 3). The relative proportions of each LDL subfraction therefore changed with a shift in particle size toward larger, lighter particles. Thus, %LDLIII decreased from 60 to 33% (95% CI, 12:41; P < 0.01), whereas %LDLI and %LDLII both increased (%LDLI, 8 to 19%; 95% CI, 3:19; %LDLII, 32 to 48%; 95% CI, 1:30; both P < 0.05, all absolute change). A significant reduction in both RLP-C (16 mg/dL; 95% CI, 8:25) and RLP-TG (43 mg/dL; 95% CI, 9:77) was observed.

Cerivastatin versus Fenofibrate

Clinical Data, Lipids, Lipoproteins, and Apolipoproteins.

Lipoprotein and apolipoprotein concentrations after each treatment were compared. Despite the greater reduction in LDL-C with cerivastatin treatment, no difference in cholesterol or LDL-C was observed (Table 1). Plasma triglyceride (P < 0.01) and VLDL-C (P < 0.05) were lower with fenofibrate treatment; the absolute reduction in triglycerides and VLDL-C also was greater after fenofibrate treatment compared with cerivastatin treatment (mean difference: TG, 0.8 mmol/L; 95% CI, 0:4:1:3; VLDL-C, 0.5 mmol/L; 95% CI, 0:1:0:9). HDL-C was higher with fenofibrate treatment (P < 0.05); there was a greater increment with fenofibrate treatment compared with cerivastatin treatment (difference, 0.15 mmol/L; 95% CI, 0:06:25). With treatment, plasma apoB and apoE concentrations did not differ. Plasma apoCII (P < 0.01) and apoCIII (P < 0.01) were lower with fenofibrate treatment. Serum creatinine was higher with fenofibrate treatment, but no difference in creatinine clearance was observed (Table 1).

Lipoproteins, LDL Subfractions, and Lipoprotein Remnants. Total VLDL (P < 0.01), VLDL1 (P < 0.05), and VLDL2 (P < 0.05) all were lower with fenofibrate treatment compared with cerivastatin treatment (Table 2). The absolute reduction in total VLDL and VLDL2 was also greater with fenofibrate treatment (difference: total VLDL, 118 mg/dL; 95% CI 29:207; VLDL2, 39 mg/dL; 95% CI, 12:66). The difference in VLDL1 reduction did not reach significance (79 mg/dL; 95% CI, −13:170). With treatment, IDL and LDL concentrations were not different.

LDLIII concentration was lower (P < 0.05) and LDL concentration was higher (P < 0.01) with fenofibrate treatment compared with cerivastatin treatment. The absolute changes in LDLI and LDLIII concentration also differed. Fenofibrate increased whereas cerivastatin decreased LDLI concentration (mean difference, 33 mg/dL; 95% CI, 4:62). The reduction in LDLIII with fenofibrate treatment was greater than with cerivastatin treatment (mean difference, 63 mg/dL; 95% CI, −7:134; P < 0.07). The increase in %LDLI and the decrease in %LDLIII both were greater with fenofibrate treatment compared with cerivastatin treatment (Figure 1; both P < 0.03). A greater reduction in RLP-C and RLP-TG was found with

Figure 1. Absolute change in percentage of low-density lipoprotein (%LDL) subfraction: Cerivastatin versus Fenofibrate (mean ± SEM).
fenofibrate treatment; however, the final RLP-C and RLP-TG concentrations did not differ.

**Factors Correlated with LDLIII and RLP Reduction.** The plasma triglyceride reduction after fenofibrate treatment correlated with decreases in both VLDL₁ (r² = 70.5%, P < 0.001) and LDLIII concentration (r² = 67.5%, P < 0.001; Figure 2). The correlation between VLDL₁ and plasma LDLIII reduction just failed to reach significance (r² = 30%, P < 0.07). No correlation was noted between changes in LDLIII and either LDL-C (Figure 2) or total LDL concentration. In contrast, after cerivastatin treatment, no relationship was observed between plasma triglyceride reduction and decreases in plasma LDLIII (Figure 2) or VLDL₁. However, an association was observed between the reduction in LDL-C and the decrease in LDLIII (r² = 33.7%, P < 0.05; Figure 2).

The reduction in RLP after fenofibrate treatment was associated with decreases in VLDL₁ (RLP-C r² = 60.7%, P < 0.004 [Figure 3]; RLP-TG r² = 68.3%, P < 0.002) and plasma triglyceride (RLP-C r² = 58.2%, P < 0.005 [Figure 3]; RLP-TG r² = 55.5%, P < 0.005). With cerivastatin treatment, the change in RLP was also associated with the change in VLDL₁ (RLP-C r² = 39.5%, P < 0.03 [Figure 3]; RLP-TG r² = 40.0%, P < 0.04) but not in plasma triglyceride (RLP-C r² = 15.0%, P = NSD [Figure 3]; RLP-TG r² = 12.1%, P = NSD). In addition, plasma LDLIII reduction with fenofibrate treatment correlated with both RLP-C (r² = 44.6%, P < 0.02; Figure 4) and RLP-TG (r² = 35.0%, P = 0.05) reduction.

**Discussion**

The main findings of this study are that in patients with nephrotic-range proteinuria, both fenofibrate and cerivastatin significantly reduce plasma concentration of LDLIII; fenofibrate but not cerivastatin lowers atherogenic RLP. The data show that cerivastatin reduces plasma cholesterol, LDL-C, and triglyceride, whereas fenofibrate reduces plasma triglyceride with a lesser decrease in cholesterol and a significant increase in HDL-C. It is noteworthy that the two treatments seem to differ in the mechanism by which they reduce LDLIII; cerivastatin lowers LDLIII concentration by reducing the total LDL, independent of any effect on the LDL pattern. In contrast, the marked reduction in LDLIII with fenofibrate treatment results from a shift in LDL size toward larger, lighter particles without any effect on total LDL. Fenofibrate produced a lower final LDLIII concentration compared with cerivastatin and proved
more effective in lowering potentially atherogenic remnants of triglyceride-rich lipoproteins. However, despite successful lipid reduction (27% reductions in LDLIII with cerivastatin treatment and 49% reduction with fenofibrate treatment), atherogenic levels of LDLIII remain with both drug regimens.

The finding that fenofibrate improved plasma triglyceride, VLDL-C, and HDL-C without a reduction in LDL-C is similar to that found in nonproteinuric populations, in which the ability of fibrates to lower LDL-C is known to be related to baseline triglyceride concentrations. As a result, the greatest decreases in LDL are seen in patients with normal plasma triglyceride levels (14,25), whereas in mixed hyperlipidemia, as here, fibrates often fail to reduce LDL-C (25,26). This response has been reported with other fibrates in nephrotic dyslipidemia (27). In contrast, cerivastatin reduced cholesterol and LDL-C, with a lesser but still significant effect on triglycerides. This lipid-lowering effect is similar to that found in nonproteinuric

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**Figure 3.** Percentage change in plasma TG and very low-density lipoprotein (VLDL) concentration versus remnant lipoprotein cholesterol (RLP-C) for fenofibrate and cerivastatin.

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**Figure 4.** Percentage change in RLP-C versus LDLIII concentration for fenofibrate.
populations and with other statins in large-scale intervention studies (9,10).

A dramatic shift in the quality of LDL was seen after fenofibrate treatment. At the beginning of therapy, the predominant LDL subfraction was LDLIII. After treatment, the proportion that was LDLIII fell so that larger, lighter LDLII became the major species present. This response was markedly uniform; the concentration of LDLIII fell in all 12 patients. In contrast, cerivastatin did not shift the particle size distribution, despite a reduction in both plasma triglyceride and VLDL1. This is possibly because the reduction in VLDL1, which according to published models (6) is critical in determining LDLIII, was less than that seen with fenofibrate treatment. Nevertheless, a consistent change was seen with cerivastatin treatment, with a reduction in LDLIII concentration in 11 of 12 patients. Overall, fenofibrate treatment resulted in a larger reduction in LDLIII and lower final LDLIII concentration compared with cerivastatin treatment.

Potential mechanisms that underlie the changes in LDLIII after treatment with fenofibrate and cerivastatin are further elucidated by examining the relationship between the changes in plasma triglycerides, LDL-C, VLDL subfractions, and LDLIII. After fenofibrate therapy, triglyceride reduction is associated with the decrease in both VLDL1 and LDLIII concentration. A weak relationship is also seen between the reduction in VLDL1 and LDLIII. Excess triglycerides (in the form of VLDL1) promote LDLIII formation by allowing triglyceride enrichment of LDL (via cholesterol ester transfer protein–mediated exchange). This makes LDL a better substrate for lipolysis by hepatic lipase (6). Thus, the association between triglyceride reduction and LDLIII reduction with fenofibrate treatment supports the role of hypertriglyceridemia in LDLIII formation. With cerivastatin treatment, the reduction in LDL-C is associated with the decrease in LDLIII. It is likely that the drug reduces LDLIII by reducing the amount of LDL available for conversion to LDLIII and therefore lowering LDLIII by a different mechanism to fenofibrate. We suggest that there may be a future role for combined therapy to achieve greater reductions in plasma concentration of LDLIII.

The changes in RLP after treatment parallel changes seen with the LDL phenotype. It is recognized that plasma triglyceride is the best marker for high levels of RLP (17). Fenofibrate, by improving lipolysis, reduces remnants by 35 to 45%, with a close association between triglyceride reduction and RLP reduction. This hypothesis is supported by the association between fenofibrate-induced RLP reduction and the decrease in VLDL1, apolipoprotein CII, and apolipoprotein CIII after fenofibrate treatment. A clear link is also established between RLP reduction and a decrease in LDLIII. This is not surprising given the common link of hypertriglyceridemia but does suggest that some of the cardiovascular risk attributed to the atherogenic lipoprotein phenotype may result from excess lipoprotein remnants. Metabolic studies suggest that the effect of statins on VLDL subfractions is partly dependent on the dyslipidemia present. In hypercholesterolemic populations (with raised VLDL2 but not VLDL1), statins increase the fractional catabolic rate of VLDL2, reducing VLDL2 with VLDL1 metabolism unchanged (13). However, in mixed hyperlipidemia, of which proteinuria is an example, statins increase catabolism of both VLDL-TG and VLDL-C (28). Our study is in keeping with this hypothesis with cerivastatin reducing triglyceride-rich VLDL1, with a modest (but not quite significant) reduction in cholesterol ester–enriched VLDL2. That the statin failed to reduce remnant lipoproteins significantly is surprising because these drugs are effective in type III hyperlipidemia, where remnants accumulate in the circulation (29). It is noteworthy, however, that changes in RLP after statin treatment were associated with the changes in VLDL1. Thus, the failure of cerivastatin to reduce RLP may result from the heterogeneity of the change in VLDL1 (ranging from a 70% decrease to a 63% increase).

Although fenofibrate treatment was associated with an increase in serum creatinine, no change in creatinine clearance was observed. An increase in serum creatinine has been reported in patients who have impaired renal function and who are treated with fenofibrate, without any change in either creatinine clearance or GFR (30). However, the precise effect of fenofibrate on renal function is not clear and will require more detailed study. It is noteworthy that most fibrin acid derivatives are protein bound and may accumulate in patients with impaired renal function.

In conclusion, it is evident that simply looking at the plasma cholesterol and LDL-C does not allow full assessment of the cardiovascular risk posed by dyslipidemia in patients with nephrotic-range proteinuria. The atherogenic lipoprotein phenotype is a common finding that is not necessarily expressed as an increase in LDL. RLP are a component of the phenotype, which respond to fibrate but not to statin therapy, and atherogenic concentrations of LDLIII continued to be prevalent after treatment. We suggest that cardiovascular protection should aim to reduce not only total cholesterol but also LDLIII and RLP.

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