Statin and fibrate treatment of combined hyperlipidemia: the effects on some novel risk factors

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Summary
The effects of cerivastatin and fenofibrate on proteins involved in haemostasis and on markers of inflammation were investigated in otherwise healthy middle-aged males with combined hyperlipidemia. Besides classical risk factors, other so-called novel risk factors for coronary artery disease are seen to be playing an increasingly important role in the development and progression of atherosclerosis. Thirty-eight males, aged 49 ± 5 years were randomised to 12 weeks treatment either with cerivastatin at a daily dose of 0.2 mg to 0.4 mg to achieve the LDL cholesterol goal of <3.0 mM, or with fenofibrate 250 mg daily. Fasting serum lipids, homocysteine, total and free tissue factor pathway inhibitor (TFPI), plasminogen activator inhibitor (PAI-1) and tissue plasminogen activator (t-PA) antigen and activity, C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured. No change in homocysteine level was observed in the cerivastatin group, while after fenofibrate administration it increased (p <0.0001). Total TFPI decreased significantly after cerivastatin (p = 0.002), but not after fenofibrate. Free TFPI did not decrease after either drug. Neither drug affected (t-PA) antigen and activity, while fenofibrate increased PAI-1 antigen (p <0.05) and activity (p <0.05). Cerivastatin decreased serum CRP values by 49.5% (p = 0.001), and fenofibrate by 29.8% (p = 0.03). The decreases of CRP in the two groups differed significantly (p = 0.04). IL-6 levels decreased significantly in the fenofibrate group (39%; p <0.0001), but not in the cerivastatin group (15%; p = 0.24). No significant decreases were observed for TNF-α. Cerivastatin had neutral effects on fibrinolysis, homocysteine or coagulation. On the other hand, fenofibrate increased PAI-1 antigen and activity and homocysteine, and did not affect coagulation. Both cerivastatin and fenofibrate reduced CRP levels, the decrease being significantly greater after cerivastatin. Fenofibrate also significantly decreased IL-6.

Keywords
Novel risk factors, fenofibrate, cerivastatin

Prepublished online August 3, 2004 DOI:10.1160/TH03-04-0250

Introduction
Conventional risk factors such as hyperlipidemia, hypertension, and cigarette smoking do not account for all cases of cardiovascular diseases (1). Novel coronary artery disease risk factors, including homocysteine (2, 3), inflammatory (4-7) and haemostatic proteins (6) have been found to be independent predictors of future coronary artery events in apparently healthy males as well as in patients with coronary artery disease.

Atherogenic propensity, associated with hyperhomocysteinaemia, results from endothelial dysfunction and injury followed by platelet activation and thrombus formation (8). The increase of homocysteine, even within physiological limits, impairs endothelial function (9). Elevated concentrations of the acute
phase reactant, C-reactive protein (CRP), predict the development of clinical coronary heart disease over many years, suggesting that inflammation makes a contribution to the earlier stages of the atherosclerotic process (10). Increased levels of interleukin (IL)-6, which is a central mediator of the acute-phase response and a primary determinant of hepatic production of CRP (11), were found to be associated with increased risk of future myocardial infarction among apparently healthy men (6). Tumor necrosis factor-α (TNF-α), which is a multifunctional circulating cytokine derived from endothelial cells and macrophages associated with coronary atheroma, is elevated in patients with previous myocardial infarction who are at increased risk of recurrent coronary events (7). Levels of TNF-α, the principal mediator of the acute inflammatory response, and IL-6, the cytokine that together with TNF-α stimulates the synthesis of the acute-phase proteins (12), correlate closely with CRP serum levels (13).

Disruption of an atherosclerotic plaque, with resultant intraluminal thrombosis, is a crucial mechanism in the pathogenesis of acute coronary events (14). Exposure of tissue factor (TF) to blood initiates the extrinsic clotting cascade, and is considered to be a major regulator of coagulation (15). Tissue factor pathway inhibitor (TFPI) is an anticoagulant, which regulates TF induced blood coagulation (16). Most of the circulating TFPI is bound to lipoproteins such as LDL cholesterol, HDL cholesterol and lipoprotein (a) (17). The free form of TFPI, which might be physiologically important, is released from endothelial cells as a compensatory mechanism of endothelial cell damage (18). Fibrinolysis involves the action of tissue plasminogen activator (t-PA) on plasminogen to produce plasmin, which in turn degrades the cross-linked fibrin of the thrombus. One of the major inhibitors of fibrinolysis is plasminogen activator inhibitor-1 (PAI-1), which inhibits t-PA (19). Both t-PA and PAI-1 have been found to predict future coronary events in patients with coronary artery disease (20, 21).

Our aim was to compare the effects of cerivastatin, a representative of statins, and fenofibrate, a well established representative of fibrates, on these novel atherogenic risk factors, in asymptomatic, overweight middle-aged males with combined hyperlipidemia which, according to recommendations (22), may be treated either by statins or fibrates which have different lipid lowering effects.

Methods

Subjects and study design

Healthy male volunteers, non-smokers, aged between 40 and 60 years, with combined hyperlipidemia (a 12-hour fasting level of serum total cholesterol above 6.0 mM, LDL cholesterol above 4.0 mM and triglycerides between 2.2 and 4.6 mM) were eligible for the study if they were not receiving cholesterol-lowering drugs or any other medication. No participants should have a history of hypertension, diabetes mellitus, coronary heart disease, heart failure or any other systemic or inflammatory disease.

After initial screening of 134 men, 38 of them were found to fulfill these criteria and were included in this prospective, randomized, double blind, parallel study. After 6 weeks run-in period, during which the subjects received a lipid-lowering diet (American Heart Association step I diet), they were randomly assigned to a 12-week treatment with either fenofibrate (250 mg daily) or cerivastatin. Cerivastatin was given in a daily dose of 0.2 mg for 6 weeks, increased to 0.4 mg daily if the LDL cholesterol did not decrease below 3.0 mM. Before randomization and after 6 and 12 weeks of treatment, clinical examinations and laboratory blood analyses were performed. No adverse clinical (nausea, diarrhea, headache, myopathy) or laboratory (increase of liver tests or creatinin kinase) effects were noted during the study. Since there were no drop outs after run-in period or after randomization all patients were included in the statistical analysis.

The study protocol was approved by the State Ethics Committee and each subject gave written informed consent.

Clinical examination

At the clinical examination systolic and diastolic blood pressures were measured with a mercury sphygmomanometer after a minimum of 10 minutes rest in sitting position. The average of three measurements was taken. Anthropometric parameters were determined and body mass index (BMI) was calculated as body weight in kilograms divided by the square of the height in metres.

Laboratory procedures

Blood for laboratory analyses was collected in the morning after a 12-hour overnight fast. Samples were drawn from the antecubital vein. Blood for lipid analysis and CRP measurement was collected without additives. For analysis of homocysteine and haemostatic variables, nine volumes of blood were allowed to flow directly into precooled siliconized glass vacuum tubes, containing one volume of 0.11 M trisodium citrate. For t-PA activity measurements, blood was collected in vacuum tubes with strong acid citrate anticoagulant (Stabilyte TM; Biopool, Umeå, Sweden). Tubes were transported in ice water and centrifuged for 30 min at 2000 g and 4°C. Serum and plasma were transferred to small plastic vials and stored at -70°C until analysed.

Concentrations of total cholesterol, HDL cholesterol, triglycerides and creatinine were determined by standard colorimetric assays (Ektachem 250 Analyzer, Eastman Kodak Company, Rochester, USA). LDL cholesterol was calculated using Friedewald’s formula (23). Fasting total plasma homocysteine was measured with an enzyme-linked immunosorbent assay (ELISA) as instructed by the manufacturer (Axis-Shield AS,
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Oslo, Norway). Serum CRP was measured with a fully automat-
ed, latex-enhanced nephelometric immunoassay (N High Sensitivity CRP, Dade Behring Marburg, Germany) on the BN ProSpec® System (Dade Behring, Germany). For calibration we used multiple dilutions of a human calibrator, traceable to the international reference preparation for plasma proteins BCR-CRM 470 (24). The detection limit of the assay was 0.2 mg/l. Serum TNF-α (Quantikine® HS Human TNF-α Immunoassay, R&D Systems, USA) and IL-6 (Quantikine® Human IL-6 Immunoassay, R&D Systems, USA) were determined with enzyme-linked immunosorbent assays according to the manufacturer’s instructions.

T-PA, PAI-1 antigens and total and free TFPI in plasma were determined by ELISA, using commercially available kits (Imulyse t-PA and Imulyse PAI-1; Biopool, Umeå, Sweden, Asserachrom® total TFPI, Stago, Asserachrom® free TFPI, Stago respectively). Plasma PAI-1 activity and t-PA activity were determined by chromogenic substrate assays (Spectrolyse/ pl, Biopool, Umeå, Sweden).

Statistical analysis
The variables showing a normal distribution, as determined by the Kolmogorov-Smirnov test, were expressed as means and standard deviations. Other variables were described by median and range. Differences between groups before the intervention period were tested for significance by Student’s t-test for unpaired data for normally distributed variables, and the Mann-Whitney U test for non-normally distributed variables. The change of each variable after the intervention period in each group was tested by ANOVA for repeated measurements. Post hoc comparisons were made by the Tukey HSD test. For correlation analysis, Pearson’s correlation coefficient was calculated for normally distributed variables and Spearman’s rank-correlation coefficient for non-normally distributed variables. The criterion for statistical significance was a P value of less than 0.05.

All calculations were performed by the Statistica computer program (StatSoft Inc., Tulsa, Oklahoma, USA, 1995).

Results
Clinical characteristics
At baseline the two groups were similar for age (47 ± 8 years in the fenofibrate group and 50 ± 2 years in the cerivastatin group), body-mass index (28.0 ± 2.8 and 28.6 ± 2.2 kg/m², respectively), systolic (123 ± 9 and 121 ± 8 mm Hg, respectively) and dia-
stolic (77 ± 5 and 77 ± 4 mm Hg, respectively) blood pressure. These parameters were unchanged after the treatment period.

Biochemical parameters
Laboratory results for each group are presented in table 1. There were no differences in serum lipids between the two groups at baseline. After 6 weeks of treatment significant decreases in total and LDL cholesterol were observed for both groups (p >0.0001), while significant changes in triglycerides and HDL cholesterol were observed only in the fenofibrate group. No further significant changes in lipid parameters were observed at 12 weeks. In the cerivastatin group the decrease of triglycerides over the whole treatment period was significant (p = 0.002).

The decreases in total and LDL cholesterol were significantly greater after cerivastatin treatment (p = 0.03, p = 0.0008, respectively), while the decrease in triglycerides and the increase in HDL cholesterol were significantly greater in patients receiving fenofibrate (p = 0.05 for both).

In the cerivastatin group we found no changes in creatinine, while in the fenofibrate group it increased significantly in the first 6 weeks (p <0.0001), and even more in the next 6 weeks (p = 0.01).

There was no change in homocysteine values in the cerivastatin group, while in the fenofibrate group they increased after

Table 1: Biochemical parameters at baseline and after 6 and 12 weeks treatment with cerivastatin (group C) or fenofibrate (group F). Mean values ± SD or medians with ranges between 1st and 3rd quartile are shown.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Baseline</th>
<th>After 6 weeks</th>
<th>After 12 weeks</th>
<th>ANOVA p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>C</td>
<td>6.8±0.8</td>
<td>5.4±0.9</td>
<td>5.2±0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(mmol/l)</td>
<td>F</td>
<td>6.9±0.9</td>
<td>6.1±1.0</td>
<td>5.9±1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>C</td>
<td>4.2±0.7</td>
<td>3.0±0.8</td>
<td>2.9±0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(mmol/l)</td>
<td>F</td>
<td>4.3±0.7</td>
<td>4.0±1.0</td>
<td>3.8±1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>C</td>
<td>0.97±0.2</td>
<td>0.97±0.2</td>
<td>1.0±2.1</td>
<td>ns</td>
</tr>
<tr>
<td>(mmol/l)</td>
<td>F</td>
<td>1.0±0.2</td>
<td>1.2±0.2</td>
<td>1.2±0.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>C</td>
<td>3.7(2.7-4.1)</td>
<td>2.4(1.9-4.5)</td>
<td>2.2(1.7-3.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>(mmol/l)</td>
<td>F</td>
<td>3.6(2.9-4.1)</td>
<td>2.1(1.6-2.2)</td>
<td>2.1(1.6-2.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>C</td>
<td>10.7(8.3-13.3)</td>
<td>10.7(7.4-11.8)</td>
<td>10.4(7.9-12.8)</td>
<td>ns</td>
</tr>
<tr>
<td>(µmol/l)</td>
<td>F</td>
<td>10.7(8.6-12.5)</td>
<td>13.6(11.6-17.4)</td>
<td>16.1(14.7-18.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>C</td>
<td>87±8</td>
<td>89±10</td>
<td>88±11</td>
<td>ns</td>
</tr>
<tr>
<td>(µmol/l)</td>
<td>F</td>
<td>87±9</td>
<td>98±11*</td>
<td>104±15*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Post hoc comparison:

1P<0.001 comparing with baseline value of the same group, 1P<0.01 comparing with baseline value of the same group ns -not significant
6 weeks of treatment by 22.4% (p = 0.002) and in the following 6 weeks by another 18.4% (p = 0.005). Altogether homocysteine in the fenofibrate group increased by 44.9% (p >0.0001) (Table 1).

**Markers of coagulation and fibrinolysis**

Of the haemostatic parameters, there were no differences between the two groups at baseline in total and free TFPI, PAI-1 activity and antigen, and t-PA activity and antigen (Table 2). After therapy with cerivastatin, the median value of total TFPI was significantly lower than the value before therapy (p <0.05), although the levels of free TFPI did not change. After therapy with fenofibrate, plasma values of total and free TFPI did not change. On the other hand, values of PAI-1 antigen and activity increased significantly (p <0.05 for both) under fenofibrate therapy. Both changes took place after 6 weeks of therapy and there were no statistically significant changes after the next 6 weeks of therapy. Cerivastatin treatment did not change PAI-1 antigen and activity. Neither drug affected t-PA antigen or activity.

Simple regression analyses on correlations between changes in haemostatic and lipid parameters were performed. The decrease of total cholesterol (r = 0.48; p = 0.003) and LDL cholesterol (r = 0.45; p = 0.004) correlated with the decrease of total TFPI, while no correlations were found between the decrease of other haemostatic and lipid parameters in any of the patients. In the cerivastatin group we found no correlations between changes in lipid and haemostatic parameters, while in the fenofibrate group the increase of PAI-1 antigen and activity correlated with decrease of triglycerides (r = -0.52; p = 0.02 for both), and changes of PAI-1 antigen also correlated with changes in HDL cholesterol (r = -0.48; p = 0.04).

**Markers of inflammation**

At entry, no significant differences between the two treatment groups were seen in serum level of CRP, IL-6 and TNF-α. However, a statistically significant decrease in serum CRP levels was observed in both groups after treatment. In the cerivastatin group serum CRP values decreased by 49.5% (p = 0.001), while in the fenofibrate group they decreased by 29.8% (p = 0.03). The decreases of CRP in the two groups differed significantly (p = 0.04). IL-6 levels decreased significantly in the fenofibrate group (39%; p <0.0001), while the decrease was not significant in the cerivastatin group (15%; p = 0.24) No significant decreases were observed for TNF-α (Table 3).

We performed additional statistical analyses to assess whether the observed changes in markers of inflammation might be related to changes in lipid levels associated with each treatment group. In the cerivastatin group the decrease of IL-6 correlated with the decrease of total cholesterol (r = 0.47; p = 0.05). In the fenofibrate group the decrease of TNF-α correlated with a decrease of total and LDL cholesterol (r = -0.79,

<table>
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<tr>
<th>Parameter</th>
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<th>Baseline</th>
<th>After 6 weeks</th>
<th>After 12 weeks</th>
<th>ANOVA p</th>
</tr>
</thead>
<tbody>
<tr>
<td>total TFPI (µg/l)</td>
<td>C</td>
<td>80.3</td>
<td>74.0</td>
<td>72.7</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>79.2</td>
<td>81.3</td>
<td>75.9</td>
<td>ns</td>
</tr>
<tr>
<td>free TFPI (µg/l)</td>
<td>C</td>
<td>9.3</td>
<td>8.4</td>
<td>8.7</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>9.4</td>
<td>9.5</td>
<td>8.8</td>
<td>ns</td>
</tr>
<tr>
<td>PAI-1 antigen (ng/ml)</td>
<td>C</td>
<td>27.8</td>
<td>28.4</td>
<td>31.4</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>22.3</td>
<td>26.8</td>
<td>27.6</td>
<td>0.05</td>
</tr>
<tr>
<td>PAI-1 activity (IE/ml)</td>
<td>C</td>
<td>25.2</td>
<td>25.4</td>
<td>29.3</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>18.9</td>
<td>18.3</td>
<td>15.5</td>
<td>ns</td>
</tr>
<tr>
<td>t-PA antigen (ng/ml)</td>
<td>C</td>
<td>10.6</td>
<td>9.5</td>
<td>9.4</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>9.5</td>
<td>9.0</td>
<td>9.7</td>
<td>ns</td>
</tr>
<tr>
<td>t-PA activity (IE/ml)</td>
<td>C</td>
<td>0.40</td>
<td>0.41</td>
<td>0.41</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>0.42</td>
<td>0.36</td>
<td>0.50</td>
<td>ns</td>
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</table>

Post hoc comparison: p<0.05 comparing with baseline value of the same group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Baseline</th>
<th>After 6 weeks</th>
<th>After 12 weeks</th>
<th>ANOVA p</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>C</td>
<td>2.2</td>
<td>1.9</td>
<td>0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>1.6</td>
<td>1.4</td>
<td>1.1</td>
<td>0.03</td>
</tr>
<tr>
<td>IL-6 (ng/ml)</td>
<td>C</td>
<td>1.6</td>
<td>1.7</td>
<td>1.3</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>1.9</td>
<td>1.7</td>
<td>1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TNF-α (ng/ml)</td>
<td>C</td>
<td>1.0</td>
<td>0.9</td>
<td>1.0</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>1.0</td>
<td>0.9</td>
<td>0.9</td>
<td>ns</td>
</tr>
</tbody>
</table>

Post hoc comparison: p<0.05 comparing with baseline value of the same group

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Table 2: Plasma levels of markers of fibrinolysis and coagulation, at baseline and after 6 and 12 weeks of treatment with cerivastatin (C) or fenofibrate (F). Medians with ranges between 1st and 3rd quartile are shown.

Table 3: Plasma levels of markers of inflammation at baseline and after 6 and 12 weeks of treatment with cerivastatin (C) or fenofibrate (F). Medians with ranges between 1st and 3rd quartile are shown.
Discussion

To the best of our knowledge, this is the first prospective, randomized trial to compare the effects of statins and fibrates on coagulation, fibrinolysis and inflammation. The advantage of our study was that we chose subjects with no clinically evident atherosclerosis and with no other atherosclerotic risk factors except being overweight. This made it possible to eliminate the influence of other variables that could affect the changes in markers of inflammation.

In our study cerivastatin did not change homocysteine level, while fenofibrate increased it. This is in agreement with results of others who found that simvastatin, another statin, had no influence on homocysteine level, while fenofibrate and bezafibrate increased homocysteine level (25, 26). They assume that the increase after fibrates is not dependent on the vitamin B6, B12 and folate status, since their levels did not change during the fenofibrate treatment (26). An alteration of renal function measured by the increment of cystatin C and creatinine (26), the later also observed in the present study, could be a possible explanation for the increase of homocysteine after fenofibrate treatment. Whether the increase in homocysteine outweighs the benefit of fenofibrate on lipids needs to be assessed.

The levels of total and free TFPI have been observed to be elevated in patients with hyperlipidemia (18). It can be assumed that this increase constitutes a compensatory mechanism for maintaining a normal haemostatic balance, since tissue factor, the major regulator of coagulation, is also elevated in such patients (18). Similar to our results after cerivastatin treatment, decreases in total but not free TFPI after treatment with simvastatin, atorvastatin or lovastatin were observed in patients with combined hyperlipidemia (18, 27). The fall in total TFPI is believed to be due mainly to the lowering of the amount of TFPI bound to LDL cholesterol. This suggests that the lowering of total TFPI does not reduce the anticoagulant potential of TFPI in plasma, since it is dependent on free TFPI only (18), which did not change. Much lower decrease of LDL cholesterol after fenofibrate than after cerivastatin might be the reason why we found no effects of fenofibrate on total or free TFPI.

The effects of statins and fibrates on haemostatic variables appear to be much less uniform than their lipid effects. Similarly to the lack of effect of cerivastatin in our study, fluvastatin had no effect on PAI-1 antigen in patients with coronary artery disease and moderate hypercholesterolemia (28). On the other hand pravastatin reduced PAI-1 and t-PA antigen levels in patients with hypercholesterolemia independently of its cholesterol lowering effect (29). Contrary to these results, in the Oxford cholesterol study patients with moderate hypercholesterolemia treated with simvastatin showed increased levels of PAI-1 antigen compared to patients receiving a placebo (30). The differences between the studies could be attributed to different effects of statins on endothelium, since decrease of PAI-1 antigen is considered as an indicator of improved endothelium-related fibrinolysis (29). Gemfibrozil, bezafibrate and ciprofibrate did not affect PAI-1 antigen in patients with type II b hyperlipidemia (31, 32). In the present study an increase in PAI-1 antigen and activity was observed after treatment with fenofibrate, while in study of Durrington et al. (31) bezafibrate increased only PAI-1 activity. Gemfibrozil however, decreased PAI-1 antigen only in patients with hypertriglyceridemia in whom triglycerides decreased to almost normal levels (33). It is possible that the effects of fibrates on fibrinolytic parameters are different in patients with type IV and V hyperlipoproteinemia from those with II b hyperlipoproteinemia. This variability in effects may also reflect the different actions of different fibrates.

Cerivastatin (34), pravastatin (35), simvastatin and atorvastatin (36, 37) reduced CRP levels significantly. In all studies, except that of Strandberg et al. (36), the reductions of CRP levels were independent of the changes in lipid parameters, which is in agreement with our results. Strandberg et al. (36) found that the decrease of CRP correlated with an increase of HDL cholesterol. In contrast to these findings, the FACT study did not find any changes of CRP levels after treatment with fluvastatin, bezafibrate or a combination of these drugs in patients with coronary artery disease and combined hyperlipidemia (38). The specific pathways by which statins reduce CRP and exert anti-inflammatory effects remain uncertain. Proteins secreted by activated leukocytes and activated vascular endothelial cells, including IL-6, which is the cytokine that stimulates hepatocytes to produce CRP, could be important. However, we could not confirm this possibility, since in our study cerivastatin had no effect on IL-6, similarly to atorvastatin in the MIRACL study (37). In both studies no correlation between the magnitude of CRP and IL-6 changes was observed. Using transgenic animals it was shown that the regulation of CRP in mice is similar to that in humans. In these experiments IL-6 dependent and independent induction of CRP production was found (39). No data is available on the effects of statins on TNF-α. In our study cerivastatin did not affect its level, suggesting that the decrease of CRP after this treatment is also not dependent on TNF-α decrease.

In addition to the FACT study (38), the effects of fibrates on CRP were investigated in two other studies (40, 41). In both studies they found that fenofibrate decreased CRP in hyperlipemic patients. In one study (40) IL-6 levels were also decreased, although the association between decrease in CRP...
and IL-6 was not investigated. In our study fenofibrate treatment significantly decreased IL-6 and this decrease correlated with the decrease in CRP. The CRP decrease also correlated with reduction of TNF-\(\alpha\), although the latter did not change significantly during the observation period. We assumed that the decrease of CRP after fenofibrate treatment was dependent on IL-6 and TNF-\(\alpha\) decrease and therefore different from the effect of cerivastatin. Only one study (41) compared the effects of statins and fibrates on CRP. They found that both, simvastatin and fenofibrate decreased CRP levels with no differences between groups, despite having different effects on lipoprotein profiles, but in their group there were also patients with other atherosclerotic risk factors and clinically manifested atherosclerosis, while our patients had no other atherosclerotic risk factors, except combined hyperlipidemia and being overweight, and CRP levels in their patients were lower compared to values in our patients. Whether combination of statin and fibrate would, due to the evidently different pathway of CRP decrease, induce greater decrease of CRP levels than statin alone is yet to be studied, since it might be clinically relevant.

In conclusion, cerivastatin had no effects on homocysteine or fibrinolytic parameters and showed no pro-coagulatory effects judged from TFPI levels. Fenofibrate had different effects: it increased homocysteine and decreased fibrinolysis, but showed no influence on pro-coagulatory activity. Both drugs exerted beneficial effects on inflammation, which were more pronounced after cerivastatin, while only fenofibrate decreased some proinflammatory cytokines. Further prospective studies, with a larger number of patients are needed to answer the question whether these differences in the effect of statins and fibrates on novel risk factors are clinically important.

**Acknowledgement**

We are grateful to Prof. Dr. Janez Stare from the Institute of Biomedical Informatics, Ljubljana, for statistical advice.

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**References**


