Relationships of HDL Cholesterol, ApoA-I, and ApoA-II With Homocysteine and Creatinine in Patients With Type 2 Diabetes Treated With Fenofibrate

Marja-Riitta Taskinen, David R. Sullivan, Christian Ehnholm, Malcolm Whiting, Diana Zannino, R. John Simes, Anthony C. Keech, Philip J. Barter, for the FIELD study investigators

Objective—The purpose of this study was to determine fenofibrate-induced changes in plasma high-density lipoprotein cholesterol (HDL-C), apolipoprotein (apo) A-I, and apolipoprotein (apo) A-II and how they relate to changes in plasma homocysteine and creatinine.

Methods and Results—FIELD was a double-blind placebo-controlled trial done in Australia, New Zealand, and Finland. All FIELD subjects were included except those who started statin therapy or permanently discontinued fenofibrate. Patients were randomized to receive daily micronised fenofibrate (200 mg) or matching placebo and were followed up for a median of 5 years. Plasma HDL-C, apoA-I, apoA-II, homocysteine, and creatinine were measured. There was an inverse relationship between baseline homocysteine levels and HDL-C in the placebo (P = 0.07 for linear trend) and fenofibrate groups (P < 0.0001) and apoA-I (P < 0.001, both groups). The increases in homocysteine and creatinine in the fenofibrate group correlated positively (P < 0.0001). The greater the increase in homocysteine induced by fenofibrate, the smaller the increases in HDL-C and apoA-I (P < 0.0001 for linear trends). There was a highly significant and positive relationship between fenofibrate-induced changes in homocysteine and apoA-II levels.

Conclusions—PPARα agonists that have a more robust effect on HDL-C and apoA-I would be desirable. (Arterioscler Thromb Vasc Biol. 2009;29:950-955.)

Key Words: type 2 diabetes ■ lipid and lipoprotein metabolism ■ fibrates ■ homocysteine ■ HDL

Fibrates have been used for many years as lipid-modifying agents, decreasing plasma triglyceride concentrations and, to a variable extent, increasing high-density lipoprotein cholesterol (HDL-C) concentrations. Their effect on low-density lipoprotein cholesterol (LDL-C) is variable but generally small. Fibrates increase plasma HDL-C by increasing the expression of genes for apoA-I and apoA-II, the 2 main apolipoproteins of HDL. The increase in plasma apoA-II tends to be greater than that of apoA-I, increasing the proportion of HDL particles containing both apoA-I and apoA-II, at the expense of those containing apoA-I without apoA-II.

Treatment with fibrates is associated with an increase in homocysteine levels, which previous studies have suggested may influence the metabolism of apoA-I. Homocysteine reduces apoA-I synthesis in the liver. In human studies the plasma concentrations of both apoA-I and HDL-C negatively correlate with plasma homocysteine levels. It is possible, therefore, that the potential HDL-C-raising effect of fibrates may be opposed by the accompanying increase in plasma homocysteine levels.

Elevated homocysteine occurs on treatment with most fibrates, although the increase varies with different fibrates. Fenofibrate increases homocysteine by 36% to 55%, gemfibrozil by up to 18% and bezafibrate by 18% to 19%. Although in mice the fenofibrate-induced increase in homocysteine has seemed to be dependent on PPARα, the mechanism by which fibrates increase homocysteine and its clinical importance are not known. Fibrates also increase plasma creatinine levels, again by an unknown mechanism.

The Fibrates Intervention and Event Lowering in Diabetes (FIELD) study showed that fenofibrate induced substantial increases in the concentrations of plasma homocysteine and creatinine. This posthoc analysis of FIELD investigates whether fibrate-induced elevations of homocysteine and creatinine affect HDL-C, apoA-I, and apoA-II responses. Here we report: (1) the relationship of plasma HDL-C, apoA-I, and apoA-II with levels of homocysteine and creatinine in samples collected before treatment; and (2) the relationships of fenofibrate-induced changes in concentrations of HDL-C, apoA-I, and apoA-II with fenofibrate-induced changes in plasma levels of homocysteine and creatinine.

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### Methods

#### Setting and Participants

Details of the FIELD study design and baseline characteristics have been published. Patients from the study who did not take statins and who did not permanently discontinue fenofibrate treatment were included in this substudy. Of the 5428 who met the inclusion criteria and had all required measurements, 2363 were allocated to placebo and 3065 to fenofibrate (Figure 1). All patients provided written consent, and the study protocol was approved by local and national ethics and procedures committees according to the Declaration of Helsinki and Good Clinical Practice guidelines.

#### Laboratory Measurements

Plasma apolipoproteins were measured by automated immunologic methods at central laboratories at Flinders Medical Centre, Adelaide, South Australia, and the National Public Health Institute, Helsinki, Finland. Assay performance was monitored over time by internal quality control procedures and participation in local external quality assurance programs. To ensure alignment of results and traceability to WHO reference material SP1-01 for apoA-I, the same quality control procedures and participation in local external quality assurance programs were used if the data were not normally distributed, and geometric means and corresponding 95% confidence intervals (95% CI) are reported. Trend probability values across quintiles were calculated on transformed data, unless indicated otherwise. Numbers in quintiles were unequal for some variables because of high numbers of tied values. All analyses used SAS software (version 9.1).

### Results

#### Baseline Characteristics

In this substudy, the 2 treatment groups were well matched for general characteristics (Table 1), including history of cardiovascular disease (CVD) and the use of CVD and glucose-lowering therapies (data not shown). Given that statin treatment was an exclusion criterion for the substudy and that more subjects in the placebo group were excluded on these grounds, baseline levels of total cholesterol, LDL-C, and apoB levels were higher in the fenofibrate group than in the placebo group. Baseline homocysteine, creatinine, HDL-C, apoA-I, and apoA-II levels, however, did not differ between the 2 groups (test for heterogeneity across treatment groups was not significant). Levels of most lipids were significantly worse in excluded patients than patients in this subset (data not shown).

#### Relationships of Baseline HDL-C, ApoA-I, and ApoA-II With Baseline Homocysteine and Creatinine

Baseline homocysteine and creatinine concentrations correlated positively and significantly in both groups (r=0.41, P<0.0001, and r=0.43, P<0.0001 in the fenofibrate and placebo groups, respectively). Baseline HDL-C and apoA-I concentrations correlated inversely with homocysteine in

### Table 1. Mean Concentrations (95% CI) at Baseline and Study Close and Mean Percentage Changes, by Treatment Group in the FIELD Study*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>HDL-C (mmol/L)</th>
<th>ApoA-I (g/L)</th>
<th>ApoA-II (g/L)</th>
<th>Homocysteine (µmol/L)</th>
<th>Creatinine (µmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=2363)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.09 (1.08–1.10)</td>
<td>1.28 (1.27–1.29)</td>
<td>0.35 (0.35–0.35)</td>
<td>9.57 (9.46–9.68)</td>
<td>75.3 (74.7–75.9)</td>
</tr>
<tr>
<td>Study close</td>
<td>1.09 (1.08–1.10)</td>
<td>1.29 (1.28–1.29)</td>
<td>0.35 (0.35–0.35)</td>
<td>11.33 (11.19–11.46)</td>
<td>80.6 (79.9–81.4)</td>
</tr>
<tr>
<td>Mean change (%)</td>
<td>0.6</td>
<td>0.3</td>
<td>−0.2</td>
<td>18.4</td>
<td>7.1</td>
</tr>
<tr>
<td>Fenofibrate (n=3065)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.09 (1.08–1.10)</td>
<td>1.29 (1.28–1.30)</td>
<td>0.35 (0.35–0.35)</td>
<td>9.55 (9.46–9.65)</td>
<td>75.0 (74.5–75.5)</td>
</tr>
<tr>
<td>Study close</td>
<td>1.12 (1.11–1.13)</td>
<td>1.32 (1.31–1.33)</td>
<td>0.46 (0.46–0.46)</td>
<td>15.83 (15.66–16.01)</td>
<td>91.4 (90.5–92.3)</td>
</tr>
<tr>
<td>Mean change (%)</td>
<td>2.2</td>
<td>2.2</td>
<td>31.5</td>
<td>65.7</td>
<td>21.8</td>
</tr>
</tbody>
</table>

*Analyses used log-transformed data. Results are reported on the original scale.
†Data were included if values were available for both baseline and study close.
‡Difference = study close concentration–baseline concentration (means of individual patient differences).
both treatment groups (Figure 2; P<0.001 for linear trend of HDL-C in the fenofibrate group and P=0.07 for the placebo group; P<0.0001 for linear trends of apoA-I in both groups). In contrast, baseline apoA-II levels did not correlate with levels of homocysteine (Figure 2). Likewise, there was no significant correlation between baseline levels of apoB, triglyceride, or HbA1c with either homocysteine or creatinine (data not shown).

Baseline HDL-C and apoA-I concentrations correlated inversely and significantly with creatinine (Figure 2). There was also a significant negative linear trend relating baseline apoA-II levels to creatinine in each treatment group. 

Effects of Fenofibrate on HDL-C, ApoA-I, ApoA-II, Homocysteine, and Creatinine
At study close, HDL-C concentrations had increased by 0.6% in the placebo group and 2.2% in the fenofibrate group. The respective increases in apoA-I and apoA-II were 0.3% and −0.2% in the placebo group and 2.2% and 31.5% in the fenofibrate group (Table 1). There were also increases in homocysteine (65.7%) and creatinine (21.8%) concentrations in the fenofibrate group and smaller increases (18.4% and 7.1%, respectively) in the placebo group (Table 1). The increases in homocysteine and creatinine in the fenofibrate group also correlated positively and significantly (r=0.31, P<0.0001; supplemental Figure I).

Relationship Between Changes in HDL-C, ApoA-I, and ApoA-II and Changes in Homocysteine and Creatinine With Fenofibrate Treatment
The changes in HDL-C and apoA-I concentrations during the 5 years of fenofibrate treatment were markedly influenced by the degree of fenofibrate-induced increase in plasma homocysteine (Table 2). The greater the increase in homocysteine induced by fenofibrate, the smaller the increases in HDL-C and apoA-I. These relationships remained significant after adjustment for changes in creatinine and baseline homocysteine concentrations (both P<0.0001 for linear trend).

The increase in HDL-C concentrations in the fenofibrate group over the course of the study was also less in those who had the greatest increase in creatinine, a relationship that remained significant after adjustment for changes in homocysteine. However, changes in apoA-I were not related to changes in creatinine, with or without adjustment for changes in homocysteine (Table 2).

In marked contrast to the significant relationship between changes in apoA-I and homocysteine with fenofibrate treatment, the relationship between changes in apoA-II and homocysteine was positive and significant (Table 2). This relationship persisted after adjustment for changes in creatinine (P<0.0001 for linear trend; Table 2).

The increase in apoA-II in the fenofibrate-treated group was also marginally greater in those who had the greatest increase in creatinine, although this relationship disappeared after adjustment for changes in homocysteine (Table 2).

Discussion
The aim of this FIELD substudy was to explore the interactions between concentrations of HDL-C, apoA-I, and apoA-II with those of homocysteine and creatinine in a large cohort of people with diabetes treated with fenofibrate. The observed inverse relationship between homocysteine levels and those of HDL-C and apoA-I is consistent with previous reports from smaller cohorts.9–13 By contrast, the finding of a substantial and highly significant positive relationship between fenofibrate-induced changes in homocysteine and apoA-II concentrations was both new and unexpected. Thus, the relationships of HDL-C and apoA-I with homocysteine are fundamentally different from the relationship of apoA-II with homocysteine. Notably, analyses that included the whole cohort of the FIELD study gave similar results, indicating that the relationships observed in this subset are robust (data not shown).

Fibrates, which activate the nuclear transcription factor PPARα, could influence HDL metabolism by several mechanisms. They increase the synthesis of apoA-I and apoA-II by upregulating APOA1 and APOA2 gene expression.45 In addition, PPARα activators increase expression of lipoprotein lipase, ABCA1, SR-BI, and PLTP genes.30–33
fenofibrate is the most effective in raising HDL-C, with the populations studied or may be fibrate-specific. In general, that may be secondary to upregulation of SR-B1 expression although in PPAR by which fibrates increase homocysteine are not known, a fibrate-induced increase in homocysteine. The mechanism may be a consequence of the differences in the magnitude of possibility that the variation in the HDL response to fibrates people with type 2 diabetes. This study raises the explanation for the differing results. The differences may reflect variations in the HDL cholesterol and apoA-I metabolism are unresolved, but recent studies have provided interesting insights. Recently, Velez-Corrasco et al reported that mice that homocysteine inhibits the hepatic synthesis of apoA-I. Furthermore, supraphysiological concentrations of homocysteine reduce PPARα and apoA-I protein levels in HEP G2 cells. Whether homocysteine also impairs hepatic transcriptional regulation of apoA-I synthesis remains uncertain.

Metabolic conversion of homocysteine to homocysteine-thiolactone (Hcy-thiolactone) is mediated by homocysteine thiolactonase (HTase). Importantly, plasma Hcy-thiolactone levels are elevated in subjects with high homocysteine owing to mutation of cystathionine β synthase (CBS) and methylene tetrahydrofolate reductase (MTHFR). Emerging evidence indicates that protein N-homocysteinylatation is detrimental because it modifies proteins, including LDL, HDL, and fibrinogen with lysine residues. In addition, the antiatherogenic function of HDL is impaired in subjects with high homocysteine levels. Recently, Yang et al reported that plasma Hcy-thiolactone was associated with risk of coronary heart disease. However, whether an effect of homocysteine on HDL cholesterol and apoA-I has clinical relevance is unclear from this substudy.

Interestingly, fenofibrate-induced increases in HDL cholesterol and apoA-I were absent in subjects whose homocysteine was in the highest quintile at study close (homocysteine >20.1 μmol/L) (Figure 3). In general, homocysteine levels above 15 mmol/L are considered to be elevated, indicating that about 40% of subjects in the fenofibrate group would be classified as having hyperhomocysteinemia at the end of the study. Fenofibrate-induced increases of HDL-C and apoA-I classified as having hyperhomocysteinemia at the end of the study. Fenofibrate-induced increases of HDL-C and apoA-I were absent in subjects whose homocysteine levels were less than 16.7 μmol/L. This raises the possibility of a threshold effect for the interaction between homocysteine and the changes in HDL cholesterol and apoA-I concentration in people on fenofibrate.

### Table 2. Changes in HDL-C, ApoA-I, and ApoA-II by Quintile of Change in Homocysteine and Creatinine Between Baseline and Study Close

<table>
<thead>
<tr>
<th>Quintile Ranges</th>
<th>Increase in homocysteine, μmol/L</th>
<th>Increase in HDL-C (mmol/L)</th>
<th>Increase in ApoA-I (g/L)</th>
<th>Increase in ApoA-II (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted*</td>
<td>Unadjusted</td>
<td>Adjusted*</td>
</tr>
<tr>
<td>Increase in homocysteine, μmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.1</td>
<td>608</td>
<td>0.04</td>
<td>0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>3.1–5</td>
<td>618</td>
<td>0.06</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>5–7.1</td>
<td>607</td>
<td>0.05</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>7.1–9.6</td>
<td>619</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>&gt;9.6</td>
<td>613</td>
<td>−0.00</td>
<td>0.01</td>
<td>−0.01</td>
</tr>
<tr>
<td>Linear trend P†</td>
<td>&lt;0.0001</td>
<td>&lt;0.01</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Correlation (P)‡</td>
<td>−0.06 (&lt;0.01)</td>
<td>−0.10 (&lt;0.001)</td>
<td>0.21 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Increase in creatinine, μmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>612</td>
<td>0.04</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>3.5–10.5</td>
<td>606</td>
<td>0.04</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>10.5–18.25</td>
<td>621</td>
<td>0.06</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>18.25–30</td>
<td>612</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>≥30</td>
<td>614</td>
<td>−0.01</td>
<td>−0.00</td>
<td>0.02</td>
</tr>
<tr>
<td>Linear trend P†</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Correlation (P)‡</td>
<td>−0.07 (&lt;0.001)</td>
<td>0.00 (0.9)</td>
<td>0.07 (&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

*Analyses adjusted for change in homocysteine and change in creatinine and transformed baseline values.
†Wherever P for trend is significant, comparison of quintile 1 against quintile 5 is also statistically significant, and the slope in the regression equation for increases in homocysteine or creatinine is also significant.
‡All Spearman correlations were derived from concentrations as continuous variables.
In contrast to the well-documented relationship between homocysteine and apoA-I, a relationship between apoA-II and homocysteine has not been reported. The observation that the fenofibrate-induced increase in homocysteine predicted the fenofibrate-induced elevation of apoA-II was unexpected. The increase in apoA-I that was dampened by the rise in homocysteine may explain the known (but previously unexplained) observation that fibrates increase apoA-II concentrations to a greater extent than apoA-I.6–8 The relationship between homocysteine and apoA-II in the present study is complex. Whereas it was evident that the fenofibrate-induced increase in homocysteine was a positive and powerful predictor of the increase in apoA-II, there was no evidence of a significant relationship between homocysteine and apoA-II concentrations in the baseline samples. This apparent inconsistency is not immediately clear, nor is it known whether the differential effects of the fenofibrate-induced elevation of homocysteine on apoA-I and apoA-II are clinically relevant. One view holds that apoA-II is less antiatherogenic than apoA-I.45,46 However, the reported relationship between apoA-II and CVD has been inconsistent, with one study suggesting that apoA-II levels are predictive of a reduced risk of future CVD.47

The relationship between homocysteine and renal function is well established.48,49 Homocysteine concentrations correlated significantly and positively with baseline creatinine as did the increases in levels of these substances with fenofibrate treatment. It was apparent, however, that the significant relationships between fenofibrate-induced changes in homocysteine, HDL-C, apoA-I, and apoA-II concentrations were independent of changes in creatinine. Potter et al50 reported that adjusting for renal function eliminated elevated homocysteine as a predictor of vascular injury. These observations raised the question whether elevated homocysteine levels are a surrogate marker for renal impairment but not an independent CVD risk factor.50 However, these data cannot exclude the possibility that elevated homocysteine levels may also promote atherothrombosis directly.51 It must be emphasized, however, that posthoc analyses of clinical trials such as reported here are hypothesis generating and do not address mechanisms.

It could be speculated that a fenofibrate-induced increase in homocysteine blunted what might otherwise have been a robust increase in HDL-C and apoA-I and that this, in turn, contributed to the smaller than predicted CVD benefits of fenofibrate in the FIELD study. However, in the absence of any mechanistic approach, this suggestion is speculation. It could, however, support the value of developing selective PPARα agonists and SPARMS that do not raise homocysteine52 but have a robust effect on HDL-C and apoA-I concentrations.

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Disclosures
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References


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Table I: Baseline characteristics of patients in the FIELD trial substudy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=2363)</th>
<th>Fenofibrate (n=3065)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1487 (63%)</td>
<td>1852 (60%)</td>
</tr>
<tr>
<td>White</td>
<td>2230 (94%)</td>
<td>2863 (93%)</td>
</tr>
<tr>
<td>Age at visit 1 (years, mean [SD])</td>
<td>61.7 (6.9)</td>
<td>61.9 (6.8)</td>
</tr>
<tr>
<td>Diabetes duration (years, median [IQR])</td>
<td>5 (2–9)</td>
<td>5 (2–9)</td>
</tr>
<tr>
<td>BMI (kg/m², median [IQR])</td>
<td>30.0 (26.9–33.7)</td>
<td>29.7 (26.8–33.6)</td>
</tr>
<tr>
<td>Waist-hip ratio (median [IQR])*</td>
<td>0.94 (0.88–0.98)</td>
<td>0.93 (0.88–0.98)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg, mean [SD])</td>
<td>140 (15)</td>
<td>140 (15)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg, mean [SD])</td>
<td>82 (9)</td>
<td>82 (8)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>188 (8%)</td>
<td>247 (8%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1187 (50%)</td>
<td>1501 (49%)</td>
</tr>
</tbody>
</table>

**Laboratory data**

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Placebo (n=2363)</th>
<th>Fenofibrate (n=3065)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L, mean [SD])†</td>
<td>4.87 (0.67)</td>
<td>5.01 (0.67)</td>
</tr>
<tr>
<td>LDL-C (mmol/L, mean [SD])†</td>
<td>2.92 (0.63)</td>
<td>3.04 (0.63)</td>
</tr>
<tr>
<td>HDL-C (mmol/L, mean [SD])</td>
<td>1.11 (0.26)</td>
<td>1.12 (0.26)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L, median [IQR])</td>
<td>1.66 (1.31–2.20)</td>
<td>1.69 (1.33–2.24)</td>
</tr>
<tr>
<td>HbA1c (% median [IQR])</td>
<td>6.9 (6.1–7.8)</td>
<td>6.8 (6.1–7.7)</td>
</tr>
<tr>
<td>Creatinine (µmol/L, mean [SD])</td>
<td>76.7 (14.8)</td>
<td>76.5 (15.2)</td>
</tr>
<tr>
<td>Homocysteine (µmol/L, median [IQR])</td>
<td>9.5 (7.9–11.3)</td>
<td>9.4 (7.8–11.3)</td>
</tr>
<tr>
<td>ApoA-I (g/L, mean [SD])</td>
<td>1.26 (0.22)</td>
<td>1.27 (0.21)</td>
</tr>
<tr>
<td>ApoA-II (g/L, mean [SD])</td>
<td>0.36 (0.07)</td>
<td>0.36 (0.07)</td>
</tr>
<tr>
<td>ApoB (g/L, mean [SD])†</td>
<td>0.93 (0.16)</td>
<td>0.96 (0.16)</td>
</tr>
</tbody>
</table>

* P=0.02; † P<0.0001.
Correlation of changes in homocysteine and changes in creatinine between baseline and study close for individual patients assigned to fenofibrate ($r = 0.3$, $P < 0.001$).

* Outliers for value of change in homocysteine.