Effects of Long-Term Fenofibrate Treatment on Markers of Renal Function in Type 2 Diabetes

The FIELD Helsinki substudy

CAROL FORSBLOM, DMSC[1,2]
ANNE HIUKKA, MD[3]
EEVA S. LEINONEN, MD, PHD[3]

JOUKO SUNDVALL, MSC[4]
PER-HENRIK GROOP, MD, PHD[1,2]
MARJA-RIITTA TASKINEN, MD, PHD[3]

OBJECTIVE — Although fenofibrate was associated with less progression of albuminuria in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, it is unknown if it has any effect on renal function. We explored if there were changes in commonly available markers of renal function during fenofibrate treatment in the FIELD Helsinki cohort excluding statin users.

RESEARCH DESIGN AND METHODS — One hundred and seventy subjects with type 2 diabetes were randomly assigned to micronized fenofibrate (200 mg/day) or placebo for 5 years. In this substudy, we measured several markers of albumin excretion and renal function.

RESULTS — After intensified treatment, blood pressure and fasting glucose decreased in both groups while A1C remained at 7.2%. Plasma creatinine increased with fenofibrate while urine creatinine remained comparable between the groups, resulting in significant decreases in both creatinine clearance and estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD)-4 and Cockroft-Gault equations in the fenofibrate group. Cystatin C increased during fenofibrate treatment. Urinary albumin-to-creatinine ratio and diurnal urine protein remained unchanged, whereas overnight urinary albumin excretion rate showed minor decreases in both groups.

CONCLUSIONS — We report concomitant decreases in creatinine clearance and eGFR by fenofibrate. These changes complicate the clinical surveillance during fenofibrate treatment. We could not demonstrate the beneficial effects of fenofibrate on albumin excretion. A novel finding is the increase of cystatin C in type 2 diabetic patients during fenofibrate treatment. The clinical relevance of the changes needs to be assessed in a long-term outcome study of renal function.

Diabetes Care **33:215–220, 2010**

D iabetic nephropathy is associated with a marked increase of cardio-vascular disease (CVD) (1,2). Part of this risk has been explained by concomitant dyslipidemia, which is further aggravated in patients who develop diabetic nephropathy. This in particular is reflected in decreased HDL cholesterol and increased triglyceride (TG) levels. Interestingly, hypertriglyceridemia seems to be associated with the development and the progression of nondiabetic (3,4) as well as diabetic kidney disease (5,6).

Fibrates are peroxisome proliferator–activated receptor α agonists, designed to decrease TGs and LDL cholesterol and increase HDL cholesterol. Fenofibrate has been shown to reduce the progression of microalbuminuria in patients with type 2 diabetes in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study and the Diabetes Atherosclerosis Intervention Study (DAIS) (7,8). In these studies, data on albuminuria were analyzed using a change between different albuminuria categories as an indicator of progression or regression. More patients showed regression to a lower level and fewer patients showed progression to a higher level of albuminuria in the fenofibrate group. Such categorical analysis is sensitive to changes in the variance of the data, and thus the results should be interpreted cautiously. In fact, the absolute values of albumin excretion rate (AER) did not change during the DAIS (15.2 vs. 12.7 μg/min, P = not significant [NS]).

Plasma creatinine levels seem to increase with the use of fibrates. The exact mechanism for this increase is not known. In a 2-week study in dyslipidemic subjects (n = 13), there was no effect of fenofibrate on creatinine clearance, explained by an increased urinary excretion of creatinine and, thus, no subsequent change in the creatinine clearance (9). A recent study (10), however, reported that the urinary excretion of creatinine remained unchanged even though para-aminohippurate clearance was decreased and cystatin C was increased. Thus, available data are rather confusing and do not address the important question of whether the fenofibrate-induced increase in plasma creatinine is or is not detrimental.

In this prespecified FIELD Helsinki substudy, we used several markers of albuminuria and renal function, including cystatin C, to further elucidate the existing controversy of fenofibrate therapy.

RESEARCH DESIGN AND METHODS — The FIELD study design has been described in detail (11). Briefly, men and women aged 50–75 years with type 2 diabetes, with or without prior coronary heart disease, were eligible using the following lipid criteria:
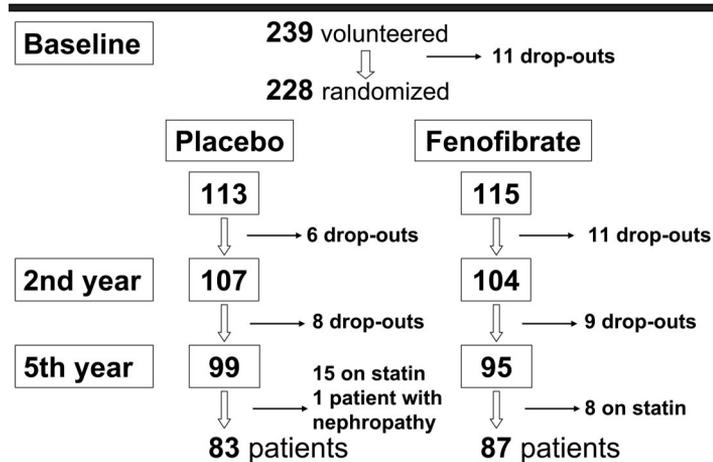
FIELD Helsinki Renal Substudy

Figure 1—*Consort flow of the study patients.*

serum (S-) cholesterol (3.0–5.5 mmol/l) plus either S-TGs (1.0–5.0 mmol/l) or S-cholesterol–to–HDL cholesterol ratio over 4. Patients with hepatic or renal (S-creatinine >130 μmol/l) dysfunction, gallstones, lipid-lowering medication, cyclosporin, alcohol abuse, and other severe mental or physical illnesses were excluded. Patients were randomly assigned to receive in a double-blind design either placebo or micronized fenofibrate (200 mg daily) for 5 years. In randomization, patients were stratified within the country stratum for prognostic factors such as age, sex, previous myocardial infarction, lipid levels, and urinary albumin concentration. A total of 270 type 2 diabetic patients were recruited to the FIELD study at the Helsinki Centre (Finland). Of these patients, 239 volunteered to participate in this substudy and 228 were randomized to the placebo or fenofibrate group (Fig. 1). There were two deaths and 12 serious adverse events in the placebo group and five deaths and 15 serious adverse events in the fenofibrate group. We excluded patients who had statin added to their medication during the study course since this was considered a confounding factor. We further excluded from the analysis one patient who developed diabetic nephropathy and overt proteinuria (3 g/24 h) early in the study and was thus a clear outlier in our study population. Consequently, 170 patients were eligible for the analysis (placebo group = 62 men and 21 women, fenofibrate group = 63 men and 24 women). All patients signed informed consent forms. The ethics committee of the Helsinki University Central Hospital approved the substudy protocol.

This analysis and report have been prepared independent of the FIELD Study Group.

Laboratory analyses
Baseline examinations were performed during the placebo run-in period of the FIELD study before any fenofibrate intervention. Blood samples were obtained after an overnight fast. Serum and EDTA plasma were separated by centrifugation and stored at −80°C until analyzed. Lipids were measured in lipoprotein fractions isolated by ultracentrifugation. Enzymatic colorimetric assays were used to measure cholesterol (Unimate 7 CHOL, Hoffman-La Roche, Basel, Switzerland, for baseline samples and later ABX Diagnostics Cholesterol and ABX Pentra Cholesterol, HORIBA ABX, Montpellier, France) and TG (Unimate 7 TRIG, Hoffman-La Roche, for baseline samples and later ABX Diagnostics Triglycerides and ABX Pentra Triglycerides, HORIBA ABX) concentrations in whole sera or lipoprotein fractions using a Cobas Mira automatic analyzer (Hoffman-La Roche). Plasma glucose concentrations were analyzed by a glucose dehydrogenase method (Precision-G Blood Glucose Testing System; Abbott, Abbott Park, IL). A1C was measured using a commercially available kit (DCA 2000+ Analyzer; Bayer Diagnostics, Tarrytown, NY).
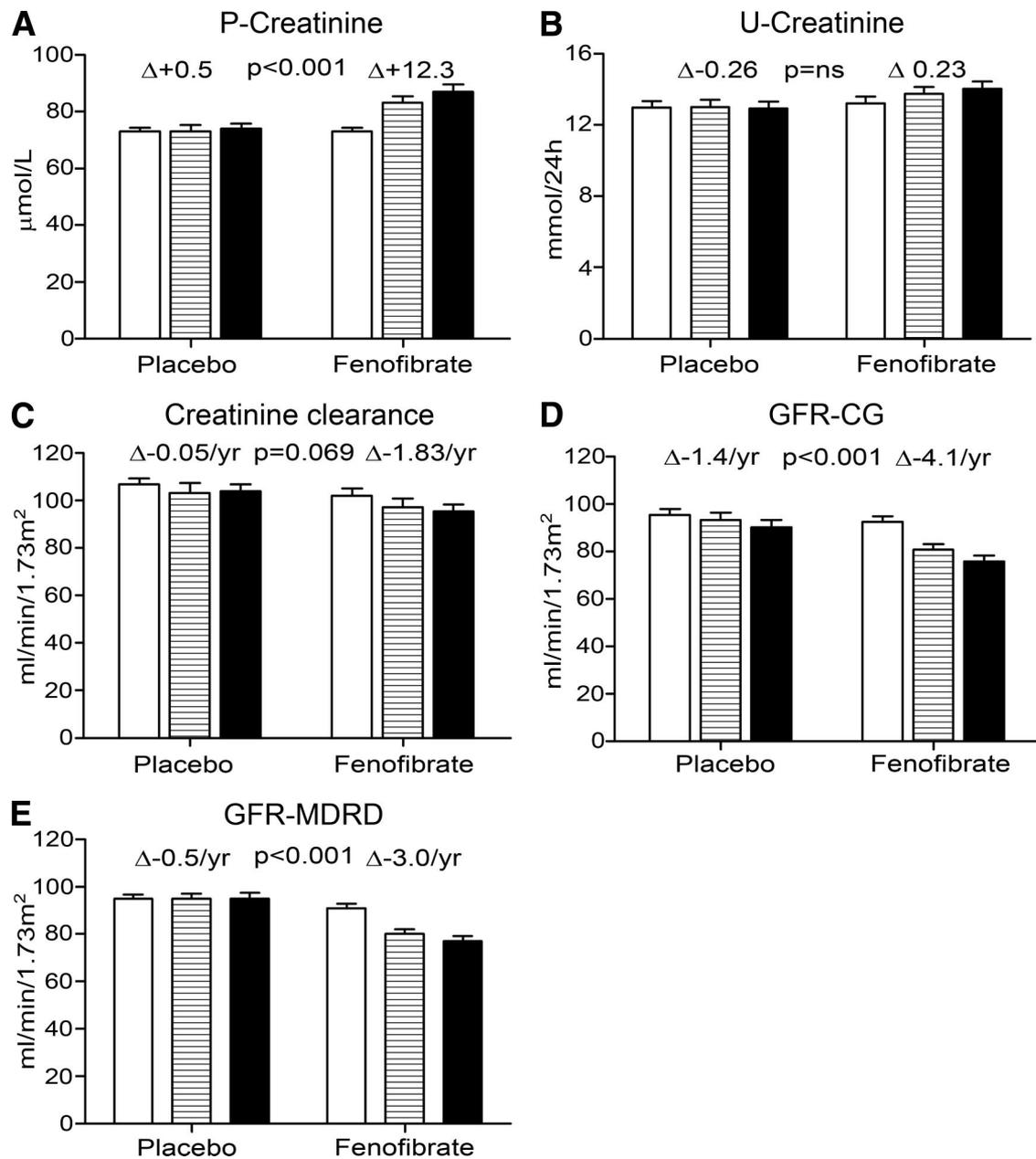
Serum/plasma/urine creatinine was measured using the Jaffe method and later using an enzymatic method in the laboratory of Helsinki University Central Hospital. Samples were randomly selected to perform parallel analyses with the Jaffe and enzymatic methods. The values from the two methods were highly correlated with $R^2 = 0.977$, and their relationship was formulated as serum creatinine (μmol/l, enzymatic method) = 1.07 × serum creatinine (μmol/l, Jaffe method) − 21. Due to ~15% lower levels of creatinine with the enzymatic method, a conversion factor of 0.85 was used for values measured with the Jaffe method. The timed overnight urine samples were analyzed for albumin concentration by an immunoturbidimetric method. At baseline, AER was collected during 3 consecutive nights, and the median of these results was used in the analysis. At the 2nd year and the 5th year, an additional AER was collected. The patients collected a 24-h urine sample at each study visit, and urinary protein excretion rate (measured by a turbidimetric benzetoniumchloride method) and creatinine clearance were calculated from the same sample. The eGFR was calculated both by Cockroft-Gault equation and MDRD-4. The eGFR estimates and the calculated creatinine clearance were normalized to body surface area by the DuBois formula. We also used the data on ACR, which was determined from a spot sample in the main FIELD study. Cystatin C was measured by an immunoprecipitation method (Thermo Fisher Scientific, Vantaa, Finland).

Statistical analysis
The statistical analysis was performed using SPSS 12.0 (SPSS, Chicago, IL) and Confidence Interval Analysis 2.1.2 (www.som.soton.ac.uk/cia/). Most of the variables were non-normally distributed, and their results are shown as median (+ SEM) in Fig. 2 and median with interquartile range in Tables 1 and 2.

For normally distributed variables, mean (+ SEM) is used in Fig. 2 and mean ± SD is used in the tables. We used repeated-measures ANOVA with log-transformed values or the Mann-Whitney U test to compare changes between the treatment groups and Wilcoxon signed-rank test for matched pairs to compare the changes within the groups. When testing variables of renal function, we included covariates of glucose, blood pressure, LDL cholesterol, and TGs to the ANOVA model. Qualitative variables are presented as N (%), and their changes are compared with the 2 × 2 likelihood ratio test for transition probability matrices (www.kttl.helsinki.fi/sarna/Stats/LRtest2x2.xls) or χ^2 test. Correlations were studied using Spearman

A P-Creatinine

Δ+0.5 p<0.001 Δ+12.3

B U-Creatinine

Δ-0.26 p=ns Δ 0.23

C Creatinine clearance

Δ-0.05/yr p=0.069 Δ-1.83/yr

D GFR-CG

Δ-1.4/yr p<0.001 Δ-4.1/yr

E GFR-MDRD

Δ-0.5/yr p<0.001 Δ-3.0/yr

Figure 2—*Creatinine levels in plasma (P-creatinine) and urine (U-creatinine) and markers of renal function during the study in placebo and fenofibrate groups. □, baseline; ☰, 2nd year; ■, 5th-year data (median). The change (Δ) during the study is expressed as total change for P- and U-creatinine and as annual change for the markers of renal function. The changes have been compared with the Mann-Whitney U test. CG, Cockroft-Gault.*

correlation coefficient. A *P* value of <0.05 was considered significant in all analyses.

RESULTS

Characteristics of patients

The mean age of subjects was 61.3 ± 6.7 years in the placebo and 62.5 ± 6.3 years in the fenofibrate groups (NS). Median duration of diabetes was 5 years (2–10) in the placebo group and 6 years (3–11) in the fenofibrate group. The majority of the patients were nonsmokers (42%) or former smokers (43%), and there were no significant differences between the groups during the study. A history of CVD was reported by 25% in the placebo group and 33% in the fenofibrate group (*P* = NS). In both groups, 13% of the patients had retinopathy. Fasting serum glucose values decreased slightly in both groups with no change in A1C (Table 1 and supplemental Table 1 in the online appendix, available at http://care. diabetesjournals.org/cgi/content/full/dc09-0621/DC1). The use of antihypertensive treatment increased in both groups, and systolic blood pressure was decreased in both groups (Table 1). Our study cohort was similar to the entire Finnish FIELD study cohort and had a greater proportion of men and patients with preexisting CVD compared with the entire FIELD study cohort. The use of β-blockers, diuretics, aspi-

Table 1—*Characteristics of the patients at baseline and at the 5th year*

| | Placebo | | Fenofibrate | | |
	Baseline	5th year	Baseline	5th year	*P*§
n	83	83	87	87	
BMI (kg/m^2)	29.7 (26.8–33.0)	29.5 (26.6–32.9)	29.1 (26.3–32.5)	28.6 (26.3–33.4)	NS
Glucose (mmol/l)	7.7 (6.5–8.7)	7.1 (6.0–8.8)	7.9 (6.8–9.1)	7.2 (6.0–8.6)‡	NS
A1C (%)	7.0 (6.3–8.1)	7.0 (6.4–7.7)	7.2 (6.6–8.0)	7.3 (6.6–8.1)	NS
sBP (mmHg)	140 (132–150)	138 (126–148)‡	142 (134–152)	136 (126–142)*	NS
dBP (mmHg)	87 ± 9	80 ± 9*	88 ± 9	78 ± 10*	0.047
S-cholesterol (mmol/l)	4.9 ± 0.7	5.0 ± 0.6	5.2 ± 0.7	4.3 ± 0.8*	<0.001
LDL cholesterol (mmol/l)	3.0 ± 0.6	3.0 ± 0.6	3.3 ± 0.6	2.7 ± 0.7*	<0.001
TG (mmol/l)	1.7 (1.3–2.1)	1.6 (1.2–2.2)	1.5 (1.1–2.2)	1.1 (0.8–1.7)*	<0.001
HDL cholesterol (mmol/l)	1.1 (1.0–1.3)	1.2 (1.0–1.4)*	1.1 (1.0–1.4)	1.1 (1.0–1.4)	NS

Data are means ± SD or median (interquartile range). Between baseline and 5th year within each group, *P* values with Wilcoxon signed-rank test for two related variables. *$P < 0.001$, ‡$P < 0.05$, §*P* value from the repeated-measures ANOVA. dBP, diastolic blood pressure; sBP, systolic blood pressure.

rin, and oral antihyperglycemic agents was more common in our cohort compared with the entire FIELD study cohort (data not shown).

Markers of renal function and albuminuria
Plasma creatinine increased during fenofibrate treatment (Fig. 2*A*), which was similar to the main FIELD study. However, urine creatinine levels remained comparable between the treatment groups (Fig. 2*B*). This obviously resulted in a decrease in calculated creatinine clearance and eGFR (Fig. 2*C–E*) in the fenofibrate treatment group. There were no differences in 24-h urine protein excretion, AER, or ACR between the treatment groups at study close-out (Table 2).

Cystatin C increased in the fenofibrate treatment group by 14.1% during the study, compared with the 3.6% increase in the placebo group ($P < 0.001$). Of the albuminuria markers, AER decreased in both groups whereas ACR remained stable.

CONCLUSIONS — Our study showed that fenofibrate reduces several measures of renal function to a greater extent than placebo.

In addition, our study showed that long-term fenofibrate treatment had no effect on albumin excretion rate. This finding is in agreement with the lack of changes in the mean values of AER attributable to fenofibrate in the DAIS. In the FIELD study, the allegedly beneficial renal outcome was based on 2.6% more patients allocated to fenofibrate than placebo regressing or not progressing in a categorized albuminuria variable ($P = 0.002$). This benefit is rather modest, and the clinical relevance should be evaluated in a long-term outcome study of renal function.

In the placebo group, systolic and diastolic blood pressure decreased by 2 and 8 mmHg, respectively, and in the fenofibrate group by 6 and 8 mmHg, respectively. These changes in blood pressure may explain the decrease in AER in both groups. Furthermore, the increased use of renin-angiotensin system blockers in both groups may have had nephroprotective effects beyond arterial blood pressure lowering. It should also be recognized that glycemic control did not worsen during our 5-year study. These variables, together with TGs and LDL cholesterol, were included in the repeated-measures ANOVA and were found not to account for the changes in renal function. Overall, these factors may explain the modest annual reduction of eGFR seen in the placebo group.

Table 2—*Markers of albuminuria and renal function at baseline and at the 5th year*

| | Placebo | | Fenofibrate | | |
	Baseline	5th year	Baseline	5th year	*P*§
n	83	83	87	87	
P-creatinine (μmol/l)	73 (66–78)	75 (63–85)	73 (68–85)	87 (75–101)*	<0.001
U-creatinine (mmol/24 h)	13.0 (10.8–15.5)	12.9 (10.0–15.5)	13.2 (10.8–15.6)	14.0 (10.0–16.4)	NS
Creatinine clearance (ml/min per 1.73 m^2)	108 (95–119)	104 (89–127)	102 (87–118)	95 (77–112)*	0.027
eGFR-CG (ml/min per 1.73 m^2)	95 (83–109)	90 (75–108)	93 (80–104)	76 (59–89)*	<0.001
eGFR-MDRD (ml/min per 1.73 m^2)	95 ± 15	95 ± 23	91 ± 16	78 ± 20*	<0.001
Cystatin C (mg/l)	0.85 ± 0.13*	0.91 ± 0.17	0.92 ± 0.17	1.05 ± 0.25*	<0.001
AER (μg/min)	6.5 (5–11)	4 (2–11)‡	6 (4–12)	4 (2–13)	NS
dU-Prot (mg/day)	105 (82–190)	100 (70–150)	123 (78–184)	110 (73–190)	NS
ACR (mg/mmol)	1.0 (0.7–2.3)	1.1 (0.4–2.9)	1.1 (0.6–2.8)	1.0 (0.0–3.3)	NS
CPK (u/l)	92 (61–134)	98 (70–150)	84 (60–133)	84 (55–115)	0.05

Data are means ± SD or median (interquartile range). Between baseline and 5th year within each group, *P* values with Wilcoxon signed-rank test for two related variables. *$P < 0.001$, ‡$P < 0.05$, §*P* value from the repeated-measures ANOVA, except for AER for which Mann-Whitney *U* test was used to compare relative changes from baseline to 5th year between the groups. CG, Cockroft-Gault; CPK, creatine phosphokinase; dU-Prot, 24-h urine protein excretion; P-creatinine, plasma creatinine; U-creatinine, urine creatinine.

The increase in plasma creatinine by fenofibrate is a well-established phenomenon. In contrast, the reduction in renal function has been previously observed as a decrease of para-aminohippurate clearance and an increase of cystatin C in nondiabetic subjects (10). Since urinary creatinine levels remained unchanged in both studies, there was an obvious reduction in creatinine clearance. The MDRD-4 and Cockroft-Gault estimates express variability and tend to underestimate renal function in subjects with relatively normal renal function. In these patients, creatinine clearance is a more reliable measure of renal function. As cystatin C is considered the best marker of renal function (12,13), we used it as a creatinine-independent marker of renal dysfunction during fenofibrate treatment. We observed a 14% increase of cystatin C levels in the fenofibrate group, suggesting impairment of renal function.

It has been suggested that fibrates increase the production of creatinine (9) with no adverse effect on renal function. This seems unlikely since an increase of creatinine excretion has not been observed (10), which was confirmed in our study. Thus, we cannot exclude the option that the increase of creatinine is caused by the decrease in creatinine clearance. Another hypothetical option is that fenofibrate might have an inhibitory effect on the excretion of creatinine via the kidneys, requesting higher blood concentration of creatinine to maintain normal excretion. Finally, fenofibrate may increase the flow of creatinine from the muscle. If fenofibrate increases creatinine outflow from the muscle, muscle damage cannot be ruled out. However, creatine phosphokinase levels were lower in the fenofibrate group in this study. Likewise, increased flux of creatinine from muscle should be reflected in increased excretion of creatinine, which was not seen in this study.

This study was a prespecified FIELD Helsinki substudy addressing renal function using several markers but not an intention to treat analysis as several patients were excluded. In this substudy, direct measures of GFR could not be used due to multiple visits and a cumbersome study protocol. However, the size of our study cohort gives enough statistical power despite potential day-to-day variations in the measured variables. The strength of our study is that all used parameters of albumin excretion and renal function

showed parallel results in the fenofibrate group.

In conclusion, our results do not support the benefits of fenofibrate on the progression of albuminuria. Available data do not allow us to conclude whether the fenofibrate-induced increase in creatinine and cystatin C are relevant for the prognoses of these patients, but obviously the changes in the estimates of eGFR impair the follow-up of renal function in clinical practice. The results of the lipid-lowering arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial may clarify the issue (14). Currently, the use of fenofibrate for cardiovascular protection should be considered in the context of the increases of both creatinine and cystatin C.

References

1. Watkins PJ. Cardiovascular disease, hypertension, and lipids. BMJ 2003;326: 874–876
2. Weiner DE, Tighiouart H, Stark PC, Amin MG, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ. Kidney disease as a risk factor for recurrent cardiovascular disease and mortality. Am J Kidney Dis 2004;44:198–206
3. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kidney Int 2000;58:293–301
4. Tozawa M, Iseki K, Iseki C, Oshiro S, Ikemiya Y, Takishita S. Triglyceride, but not total cholesterol or low-density lipoprotein cholesterol levels, predict development of proteinuria. Kidney Int 2002;62:1743–1749
5. Colhoun HM, Lee ET, Bennett PH, Lu M, Keen H, Wang SL, Stevens LK, Fuller JH. Risk factors for renal failure: the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001;44(Suppl. 2):S46–S53
6. Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, Ferris FL 3rd; Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Report No. 26. Kidney Int 2004;66: 1173–1179
7. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005; 366:1849–1861
8. Ansquer JC, Foucher C, Rattier S, Taskinen MR, Steiner G; DAIS Investigators: Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention Study (DAIS). Am J Kidney Dis 2005;45:485–493
9. Hottelart C, El Esper N, Rose F, Achard JM, Fournier A. Fenofibrate increases creatininemia by increasing metabolic production of creatinine. Nephron 2002;92: 536–541
10. Ansquer JC, Dalton RN, Causse E, Crimet D, Le Malicot K, Foucher C. Effect of fenofibrate on kidney function: a 6-week randomized crossover trial in healthy people. Am J Kidney Dis 2008;51:904–913
11. Field Study Investigators. The need for a large-scale trial of fibrate therapy in diabetes: the rationale and design of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [ISRCTN 64783481]. Cardiovasc Diabetol 2004; 3:9
12. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J,

Van Lente F, Bruce RD 3rd, Zhang YL, Greene T, Levey AS. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis 2008;51:395–406

13. Roos JF, Doust J, Tett SE, Kirkpatrick CM. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children: a meta-analysis. Clin Biochem 2007;40:383–391

14. ACCORD Study Group, Buse JB, Bigger JT, Byington RP, Cooper LS, Cushman WC, Friedewald WT, Genuth S, Gerstein HC, Ginsberg HN, Goff DC Jr, Grimm RH Jr, Margolis KL, Probstfield JL, Simons-Morton DG, Sullivan MD. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. Am J Cardiol 2007;99:21i–33i