# Reversibility of Fenofibrate Therapy–Induced Renal Function Impairment in ACCORD Type 2 Diabetic Participants

Josyf C. Mychaleckyj, dphil[1]
Timothy Craven, ms[2]
Uma Nayak, phd[1]
John Buse, md[3]
John R. Crouse, md[4]
Marshall Elam, md, phd[5]
Kent Kirchner, md[6]
Daniel Lorber, md[7]
Santica Marcovina, phd[8]
William Sivitz, md[9]
JoAnn Sperl-Hillen, md[10]
Denise E. Bonds, md[11]
Henry N. Ginsberg, md[12]

**OBJECTIVE**—To assess the reversibility of the elevation of serum creatinine levels in patients with diabetes after 5 years of continuous on-trial fenofibrate therapy.

**RESEARCH DESIGN AND METHODS**—An on-drug/off-drug ancillary study to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial to investigate post-trial changes in serum creatinine and cystatin C. Eligible participants were recruited into a prospective, nested, three-group study based on retrospective on-trial serum creatinine levels: fenofibrate case subjects ($n$ = 321, ≥20% increase after 3 months of therapy); fenofibrate control subjects ($n$ = 175, ≤2% increase); and placebo control subjects ($n$ = 565). Serum creatinine and cystatin C were measured at trial end and 6–8 weeks after discontinuation of trial therapy.

**RESULTS**—At trial end, case subjects had the highest adjusted serum creatinine (± SE) mg/dL (1.11 ± 0.02) and the lowest adjusted estimated glomerular filtration rate (eGFR) (± SE) mL/min/1.73 $m^2$ (68.4 ± 1.0) versus control subjects (1.01 ± 0.02; 74.8 ± 1.3) and placebo subjects (0.98 ± 0.01; 77.8 ± 0.7). After 51 days off-drug, serum creatinine in case subjects was still higher (0.97 ± 0.02) and eGFR still lower (77.8 ± 1.0) than control subjects (0.90 ± 0.02; 81.8 ± 1.3) but not different from placebo subjects (0.99 ± 0.01; 76.6 ± 0.7). Changes in serum cystatin C recapitulated the serum creatinine changes.

**CONCLUSIONS**—Participants with significant initial on-trial increases in serum creatinine (≥20%) returned to the same level of renal function as participants receiving placebo while participants who had ≤2% increase in serum creatinine had net preservation of renal function compared with the same unselected placebo reference group. The fenofibrate-associated on-trial increases in serum creatinine were reversible, and the reversal was complete after 51 days off-drug. The similarity of the cystatin C results suggests that the mechanism of this change is not specific for serum creatinine.

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From the [1]Department of Public Health Sciences, University of Virginia School of Medicine, Charlottesville, Virginia; the [2]Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the [3]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina; the [4]Department of Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the [5]Memphis VA Medical Center, Memphis, Tennessee; the [6]G.V. (Sonny) Montgomery VA Medical Center, Jackson, Mississippi; the [7]Lang Center for Research and Education, Division of Endocrinology, New York Hospital, Queens, Flushing, New York; the [8]University of Washington, Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, Washington; the [9]University of Iowa Diabetes Clinical Research, Iowa City, Iowa; the [10]Health Partners Research Foundation, Minneapolis, Minnesota; the [11]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; and the [12]Department of Medicine, Columbia University, New York, New York.
Corresponding author: Josyf C. Mychaleckyj, jcm6t@virginia.edu.
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Fenofibrate therapy is commonly prescribed for the clinical management of elevated triglyceride levels in diabetic patients, but has been noted to cause an elevation in serum creatinine concentrations. In several small studies, creatinine levels increased during fenofibrate treatment but returned to baseline after discontinuation of therapy (1–4). In the Diabetes Atherosclerosis Intervention Study (DAIS) of the effects of fenofibrate on angiographically demonstrated progression of coronary artery disease in 418 individuals with diabetes, serum creatinine rose 16% in the fenofibrate-treated group and 0.2% in the placebo group (5,6). In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study of the effects of fenofibrate on cardiovascular outcomes in 9,795 individuals with diabetes, after the prerandomization 6-week fenofibrate run-in period, serum creatinine returned to baseline levels after 4 months in those participants randomized to receive the non-fenofibrate placebo (7). In a post-FIELD trial wash-out study in 7% of the participants ($n$ = 661), serum creatinine fell by 16% (change in median 1.04–0.87 mg/dL) in the fenofibrate group, but by 4% in the placebo group (0.93–0.89 mg/dL) (7,8).

Although these data suggest that the increase in creatinine is reversible, the effect has not been fully confirmed in large studies or trials, and the mechanism underlying the rapid elevation and subsequent decline on cessation of therapy is not well understood. Given the apparently rapid and complete reversibility in most cases, it has been postulated that the mechanism is an alteration of renal hemodynamics. Increased creatinine production has also been proposed (9) as has decreased creatinine secretion in renal tubules (10). Serum cystatin C, considered to be a specific marker of glomerular filtration rate (GFR), has been reported to be unchanged (10) or increased (11,12) during fenofibrate treatment. Similarly, inulin clearance has been reported to be unchanged in two smaller studies despite increases in serum creatinine (10,13).

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial

offered a rare opportunity in a large cohort to determine if the rise in creatinine seen among some individuals upon starting fenofibrate is reversible after prolonged exposure to the drug.

## RESEARCH DESIGN AND METHODS

—The ACCORD Trial was a double 2 × 2 factorial trial designed to test the effect of *1*) intensive glucose control versus standard control, *2*) intensive blood pressure control versus standard control, and *3*) lipid treatment strategy that used fenofibrate plus a statin compared with statin monotherapy on the composite outcome of myocardial infarction, stroke, or cardiovascular death. Details of the design of the ACCORD Lipid Trial have already been published (14–16). Briefly, 5,518 participants were randomized to either fenofibrate or placebo medication. All participants received simvastatin to assure good LDL control, and participants were started on masked medication (160 mg/day fenofibrate or placebo) at the month 1 visit. All 77 participating clinics obtained approval from their local institutional review board prior to participating. This ACCORD Renal Ancillary Study was conducted among participants of a subset of 40 clinics with a total enrollment of 1,081 participants (mean per clinic enrollment was 27, range 2–91). Participants read and signed an additional informed consent before enrollment in this study.

During the ACCORD Lipid Trial, participants whose GFR fell below 50 mL/min/1.73 $m^2$ for two consecutive visits had their fenofibrate dose reduced to 54 mg/day. Participants whose GFR fell below 30 mL/min/1.73 $m^2$ on two consecutive visits had their fenofibrate discontinued. To maintain masking, placebo arm participants who experienced similar decreases in GFR were provided with equivalent appearing, reduced dose placebo tablets or had their placebo pills discontinued. All GFR estimates for safety reporting used the Modification of Diet in Renal Disease method (17).

### Study population and design

This study used a retrospectively defined, nested, three group, on-drug/off-drug study design. Eligible participants within participating clinics were identified by the Coordinating Center approximately 3 months prior to their ACCORD Lipid Trial close-out visit and reported to clinics while maintaining masking to participant randomization status. Fenofibrate arm case subjects ("cases") were defined as active participants in the fenofibrate arm who had experienced ≥20% increase in serum creatinine from trial baseline to month 4 and remained on study medication at close out (either full or reduced dose). Since the study drug was started 1-month postrandomization, study month 4 was equivalent to 3 months of therapy. Fenofibrate arm control subjects ("controls") were defined as active in the fenofibrate arm who experienced ≤2% increase in creatinine over the same period. Placebo arm control subjects ("placebos") were defined as randomized to placebo but without restriction on their change in serum creatinine. Individuals with baseline renal disease (creatinine >1.5 mg/dL) were excluded from ACCORD. All eligible cases and controls that consented to participate were enrolled in the study, while eligible placebos were enrolled until maximum enrollment was achieved.

The ACCORD Lipid Trial close-out visit served as the baseline visit for the ACCORD Renal Ancillary Study. A follow-up visit for ancillary study participants was held 6–8 weeks after the trial close-out visit, referred to here as the "postclose-out" visit. At both visits, a medication inventory was obtained. At the trial close-out visit, all trial participants were provided with a 3-month supply of simvastatin, as well as their current diabetes medications. No fenofibrate was provided to any trial participant at close out, and participants in the ancillary study were given a letter asking their physician to refrain from starting open label fenofibrate or other medications that could affect serum creatinine or creatinine excretion until after the postclose-out visit. This protocol was approved by the institutional review board at each clinic, at the Coordinating Center, and at the ACCORD Renal Study Center.

### Renal measures

Serum creatinine was measured during the ACCORD Lipid Trial at the baseline visit, every 4 months throughout the trial, and at the close-out visit. An additional blood sample was drawn at the close-out and postclose-out visits to assay serum creatinine and cystatin C. The same ACCORD central laboratory performed all assays.

Serum creatinine was determined using the Roche Creatinine Plus enzymatic assay with spectrometric analysis on a Roche Double Modular P Analytics analyzer (Roche Diagnostics, Indianapolis, IN). The results are traceable to the isotope dilution mass spectrometry reference method. The assay sensitivity was 0.03 mg/dL, and intra-assay coefficients of variation based on analysis of low- and high-quality control samples were 0.8% and 0.7%, respectively, while interassay coefficients of variation were 1.6% and 2.5%. The interassay precision is consistently <1.4% for the high-quality and <2.2% for the low-quality control samples. Serum cystatin C concentrations were determined using the Siemens Diagnostics reagent on a Roche Hitachi P-Module analyzer (Siemens Diagnostics, Deerfield, IL). The interassay precision for the high- and low-quality control samples was 2.5 and 2.6%, respectively. All serum samples were analyzed for creatinine on the day of sample receipt; cystatin C assays were performed in a single batch from plasma previously stored at −80°C. Estimated GFR (eGFR) in this study was computed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) method (18). Serum cystatin C estimated glomerular filtration rate (cGFR) was computed by the method of Stevens et al. (19) (Eq. 2) with adjustments for age, sex, and race.

### Statistical analysis

Descriptive statistics were computed overall and by each group. Pairwise differences between groups were compared using two-sample *t* tests for continuous factors (with Satterthwaite correction for unequal variances where appropriate) and $\chi^2$ tests for categorical factors. Between-group comparisons of renal function measures (serum creatinine, eGFR, serum cystatin C, cystatin C-eGFR) were performed using linear analysis of covariance models. Each measure or outcome was evaluated for normality and appropriately transformed if warranted. All analyses were performed using SAS version 9.2 software (SAS Institute, Cary, NC).

### Study power

The study power was estimated for the change in creatinine levels after the trial postclose-out visit based on two-group *t* tests of differences in the log-transformed serum creatinine. The estimates used Satterthwaite approximation for unequal variances at a Bonferroni-adjusted global significance of 0.05. Based on projected variability estimates prior to study close-out, the power to detect a difference of 1.1 versus 1.0 mg/dL in serum creatinine (i.e., a difference of 0.095 between log means) was 91% for fenofibrate cases versus fenofibrate controls; 99% for fenofibrate cases versus placebo controls; and 94% for fenofibrate controls versus placebo

controls. Observed variability was less than projected, yielding post hoc power estimates of 99% for all three comparisons.

**RESULTS**—We recruited 321 active fenofibrate arm cases (30.2%), 175 active fenofibrate arm controls (16.5%), and 565 active placebo controls (53.3%) plus 20 others (18 ineligible and 2 eligible but missing required study data) for a total ACCORD Renal Ancillary Study enrollment of 1,081 participants. Forty-nine individuals (4.6%) were lost to follow-up between the trial close-out visit (the first Renal Study on-drug visit) and postclose-out (off-drug) visit. Two of the forty-nine were deaths with causes not attributed to this study. The clinical characteristics for the three recruited study groups are listed in Table 1. As expected, the change in serum creatinine between the trial baseline and month 4 visits was significantly different between cases and controls with a mean (± SD) increase of +0.31 ± 0.16 mg/dL in cases, decrease of −0.05 ± 0.08 mg/dL in controls, and was also significantly different between controls and placebos, with placebos showing no change (0.00 ± 0.13 mg/dL). Other differences between the three groups included fewer control participants in the intensive arm of the ACCORD Glycemia Trial (37%) than cases (55%) or placebos (49%); differences among all three groups in the mean follow-up time during the main trial from randomization to close-out visit (5.0 ± 1.0 vs. 5.6 ± 1.6 vs. 5.2 ± 1.2 years); more Asian participants among controls (17%) than in cases (10%) or placebo (10%); a lower triglyceride level at trial close-out among cases (136 ± 14 mg/dL) than either controls (160 ± 227 mg/dL) or placebos (163 ± 93 mg/dL); greater use of insulin by cases at trial close-out (62%) than among controls (49%); and more cases (58%) with a creatinine >1.0 mg/dL at close-out than among either controls (38%) or placebos (36%). There were no significant differences in

**Table 1—*Clinical characteristics of the nested fenofibrate case, fenofibrate control, and placebo control study groups***

| | Fenofibrate cases | | Fenofibrate controls | | Placebo controls | | *P* value | | |
|---|---|---|---|---|---|---|---|---|---|
| | *n* | Mean (SD) or % (count) | *n* | Mean (SD) or % (count) | *n* | Mean (SD) or % (count) | Fenofibrate cases vs. fenofibrate controls | Fenofibrate cases vs. placebo controls | Fenofibrate controls vs. placebo controls |
| Serum creatinine (Lipid Trial month 4 visit—trial baseline) (mg/dL), mean change (SD) | 321 | 0.31 (0.16) | 175 | −0.05 (0.08) | 564 | 0.00 (0.13) | <0.0001 | <0.0001 | <0.0001 |
| Randomized to intensive glycemia control arm | 321 | 55 (177) | 175 | 37 (64) | 565 | 49 (276) | <0.001 | 0.07 | 0.004 |
| Follow-up time, randomization to trial close-out visit, mean years (SD) | 321 | 5.0 (1.0) | 175 | 5.6 (1.6) | 565 | 5.2 (1.2) | <0.0001 | 0.05 | 0.001 |
| Age, mean (SD)* | 321 | 67.2 (6.2) | 175 | 66.9 (6.5) | 565 | 67.3 (7.1) | 0.6 | 0.7 | 0.5 |
| Female sex | 321 | 30 (97) | 175 | 40 (70) | 565 | 35 (197) | 0.02 | 0.2 | 0.2 |
| Total nonwhite race | 321 | 35 (111) | 175 | 46 (80) | 565 | 38 (213) | 0.02 | 0.4 | 0.06 |
| African American | 321 | 13 (43) | 175 | 15 (26) | 565 | 16 (92) | 0.7 | 0.3 | 0.7 |
| Asian | 321 | 10 (33) | 175 | 17 (29) | 565 | 10 (55) | 0.04 | 0.8 | 0.01 |
| Hispanic | 321 | 8 (25) | 175 | 12 (21) | 565 | 9 (52) | 0.1 | 0.5 | 0.3 |
| Duration of diabetes, mean years (SD)* | 318 | 16.1 (7.4) | 173 | 15.2 (7.0) | 559 | 15.4 (7.3) | 0.2 | 0.2 | 0.8 |
| $HbA_{1c}$, mean (SD)* | 320 | 7.6 (1.3) | 174 | 7.6 (1.2) | 561 | 7.6 (1.2) | 0.8 | 0.6 | 0.5 |
| HDL cholesterol (mg/dL), mean (SD)* | 321 | 41.5 (10.3) | 174 | 42.6 (11.1) | 561 | 41.5 (9.1) | 0.3 | 1.0 | 0.2 |
| Triglycerides (mg/dL), mean (SD)* | 321 | 136 (74) | 174 | 160 (227) | 561 | 163 (93) | 0.2 | <0.001 | 0.9 |
| Systolic BP (mm Hg), mean (SD)* | 313 | 129 (16) | 170 | 131 (15) | 558 | 130 (16) | 0.1 | 0.3 | 0.3 |
| Diastolic BP (mmHg), mean (SD)* | 313 | 68 (10) | 170 | 70 (10) | 558 | 70 (10) | 0.07 | 0.09 | 0.5 |
| History of CVD* | 321 | 39 (124) | 175 | 39 (68) | 565 | 41 (233) | 1.0 | 0.4 | 0.6 |
| History of microalbuminuria* | 319 | 43 (136) | 175 | 49 (85) | 563 | 45 (253) | 0.2 | 0.5 | 0.4 |
| History of macroalbuminuria* | 319 | 8 (26) | 175 | 11 (19) | 563 | 8 (42) | 0.3 | 0.7 | 0.2 |
| Use of insulin* | 320 | 62 (198) | 175 | 49 (86) | 565 | 58 (326) | 0.006 | 0.2 | 0.05 |
| Use of ACEI/ARB* | 321 | 67 (215) | 175 | 67 (117) | 565 | 68 (384) | 1.0 | 0.8 | 0.8 |
| Use of TZD* | 320 | 33 (104) | 175 | 30 (53) | 565 | 27 (154) | 0.6 | 0.1 | 0.4 |
| Serum creatinine >1.0* | 321 | 58 (186) | 175 | 38 (66) | 565 | 36 (205) | <0.001 | <0.001 | 0.7 |

Data are % (*n*) unless otherwise stated. *Characteristics are measures at the ACCORD Lipid Trial close-out visit. BP, blood pressure; CVD, cardiovascular disease; ACEI/ARB, ACE inhibitor/angiotensin receptor blocker; TZD, thiazolidinedione.

mean time interval between close-out and postclose-out visits for the three groups (Table 2). Creatinine levels in cases remained higher than controls at study close-out after a mean of 5.2 years of follow-up, although the creatinine levels in cases declined from the month 4 visit to close-out visit, while that of the controls and placebos increased, narrowing the difference in the means between the groups.

Table 2 shows the adjusted mean creatinine and eGFR for the three groups at four time points during the trial and the postclose-out visit. The same data are plotted in Figs. 1*A* and 2*A*. The mean values in Table 2 were adjusted for glycemia treatment arm assignment, age, diabetes duration, sex, nonwhite race, insulin use, and systolic and diastolic blood pressure; the change in values were additionally adjusted for the time interval between visits (trial baseline to month 4, or trial close-out to postclose-out visit). All subsequent results in the main text refer to these adjusted values (unadjusted values are included for comparison in Supplementary Table 1). The mean serum creatinine levels in the three study groups were not significantly different at baseline or month 4 from the other participants in the main lipid trial who would have satisfied the retrospective percent change in serum creatinine inclusion criterion and were thus representative of the entire eligible ACCORD Lipid Trial cohort at month 4.

In the retrospectively defined nested groups, the mean (± SE) serum creatinine at the month 4 visit was greater in cases (1.16 ± 0.01 mg/dL) than in controls (0.90 ± 0.01 mg/dL) or placebos (0.90 ± 0.01 mg/dL). No difference was seen between controls and placebos ($P$ = 0.9). At the trial close-out visit after a mean trial follow-up period of 5.2 years (range 5.0–5.6 years in the three groups), serum creatinine was still greater in cases than controls or placebos (1.11 ± 0.02 mg/dL versus 1.01 ± 0.02 mg/dL and 0.98 ± 0.01 mg/dL, respectively) although the difference in the means of the three groups decreased.

**Table 2—*Time course of primary renal outcomes for the 3 study groups in ACCORD Lipid Trial and Renal Ancillary Study***

| | Fenofibrate cases | | Fenofibrate controls | | Placebo controls | | *P* value | | |
|---|---|---|---|---|---|---|---|---|---|
| | *n* | Mean (SE) | *n* | Mean (SE) | *n* | Mean (SE) | Fenofibrate cases vs. fenofibrate controls | Fenofibrate cases vs. placebo controls | Fenofibrate controls vs. placebo controls |
| Interval between close-out (end of trial) and postclose-out (follow-up), days | 309 | 50.3 (0.6) | 164 | 51.2 (0.9) | 539 | 50.9 (0.4) | 0.4 | 0.4 | 0.8 |
| Adjusted serum creatinine (mg/dL) | | | | | | | | | |
| Trial baseline | 321 | 0.85 (0.01) | 175 | 0.94 (0.01) | 564 | 0.90 (0.01) | <0.0001 | <0.0001 | 0.005 |
| Trial month 4 visit | 321 | 1.16 (0.01) | 175 | 0.90 (0.02) | 565 | 0.90 (0.01) | <0.0001 | <0.0001 | 0.9 |
| Trial close-out visit | 321 | 1.11 (0.02) | 175 | 1.01 (0.02) | 565 | 0.98 (0.01) | <0.0001 | <0.0001 | 0.2 |
| Trial postclose-out visit† | 308 | 0.97 (0.02) | 164 | 0.90 (0.02) | 536 | 0.99 (0.01) | 0.008 | 0.3 | 0.0002 |
| Mean change, trial baseline-to-4 month | 321 | 0.31 (0.01) | 175 | −0.05 (0.01) | 564 | 0.0 (0.01) | <0.0001 | <0.0001 | 0.0002 |
| Mean change, trial close-out to postclose-out visit | 308 | −0.13 (0.01) | 164 | −0.09 (0.01) | 536 | 0.02 (0.01) | 0.002 | <0.0001 | <0.0001 |
| Adjusted eGFR (mL/min/1.73 $m^2$) | | | | | | | | | |
| Trial baseline | 321 | 90.0 (0.8) | 175 | 82.0 (1.1) | 564 | 85.9 (0.6) | <0.0001 | <0.0001 | 0.002 |
| Trial month 4 visit | 321 | 66.9 (0.9) | 175 | 86.0 (1.2) | 565 | 86.1 (0.6) | <0.0001 | <0.0001 | 0.9 |
| Trial close-out visit | 321 | 68.4 (1.0) | 175 | 74.8 (1.3) | 565 | 77.8 (0.7) | 0.0002 | <0.0001 | 0.05 |
| Trial postclose-out visit† | 308 | 77.7 (1.0) | 164 | 81.8 (1.4) | 536 | 76.6 (0.7) | 0.02 | 0.4 | 0.001 |
| Mean change, trial baseline-to-4 month visit | 321 | −23.1 (0.5) | 175 | 4.0 (0.7) | 564 | 0.2 (0.4) | <0.0001 | <0.0001 | <0.0001 |
| Mean change, trial close-out to postclose-out visit | 308 | 9.0 (0.5) | 164 | 6.3 (0.7) | 536 | −1.3 (0.4) | 0.002 | <0.0001 | <0.0001 |
| Adjusted cystatin C (mg/dL) | | | | | | | | | |
| Trial close-out visit | 315 | 1.03 (0.02) | 171 | 0.95 (0.02) | 537 | 0.95 (0.01) | 0.002 | <0.0001 | 0.5 |
| Trial postclose-out visit† | 299 | 0.96 (0.02) | 158 | 0.88 (0.02) | 520 | 0.97 (0.01) | 0.003 | 0.9 | <0.0001 |
| Mean change, trial close-out to postclose-out visit | 293 | −0.07 (0.01) | 155 | −0.06 (0.01) | 497 | 0.02 (0.01) | 0.4 | <0.0001 | <0.0001 |
| Adjusted cGFR (mL/min/1.73 $m^2$) | | | | | | | | | |
| Trial close-out visit | 315 | 76.0 (1.3) | 171 | 84.7 (1.8) | 537 | 85.6 (1.0) | 0.0001 | <0.0001 | 0.6 |
| Trial postclose-out visit† | 299 | 83.1 (1.4) | 158 | 91.4 (1.9) | 520 | 83.1 (1.0) | 0.0003 | 0.9 | <0.0001 |
| Mean change, trial close-out to postclose-out visit | 293 | 7.3 (0.7) | 155 | 6.6 (0.9) | 497 | −2.0 (0.5) | 0.6 | <0.0001 | <0.0001 |

Participants were off masked study medication at the visit. Means were adjusted for glycemia treatment arm assignment, age, diabetes duration, sex, nonwhite race, insulin use, systolic blood pressure, and diastolic blood pressure. Means of differences were also adjusted for individual time interval between visits. †The postclose-out visit was the visit for ancillary study participants only that occurred 6–8 weeks post Lipid Trial close-out visit.

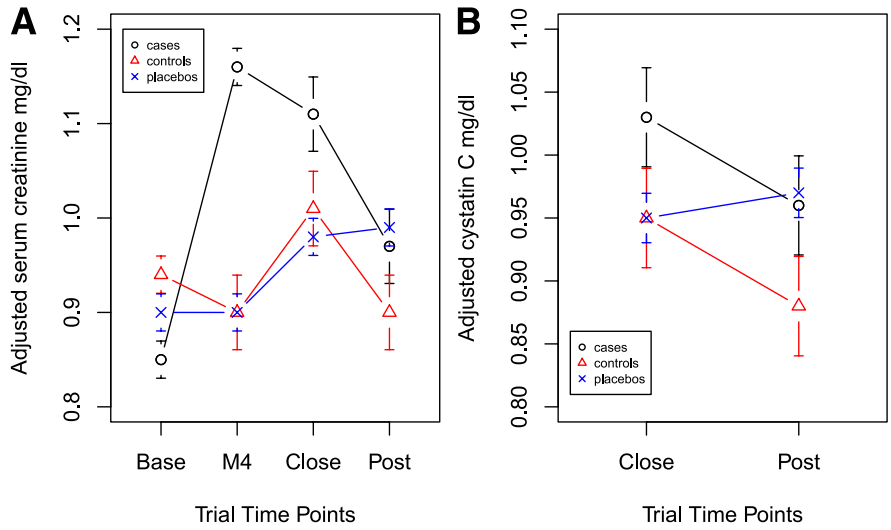


**Figure 1**—*Time course values of adjusted serum creatinine and cystatin C by ACCORD Renal Study Group.* A: *The changes in serum creatinine in units of mg/dL.* B: *Changes in cystatin C in units of mg/dL. The horizontal trial time point axis is not shown to scale. The study group trends are shown as: black circles, fenofibrate cases; red triangles, fenofibrate controls; blue crosses, placebo controls. Base, baseline visit; M4, month 4 visit; Close, close-out visit; Post, postclose-out visit. (A high-quality color representation of this figure is available in the online issue.)*

At the postclose-out visit after discontinuation of the fenofibrate study drug for 51 days, the mean creatinine had decreased markedly in both cases (average decrease −0.13 ± 0.01 mg/dL) and controls (average decrease −0.09 ± 0.01 mg/dL), but showed a slight increase in placebos (average increase +0.02 ± 0.01 mg/dL). The absolute magnitude of reduction in serum creatinine was significantly greater in cases than in controls ($P = 0.002$), and also different in both cases and controls compared with a slight rise in placebos ($P < 0.0001$ for both comparisons). After discontinuation of the study drug for 6–8 weeks, cases had a mean serum creatinine of 0.12 mg/dL above trial baseline mean, while controls were 0.04 mg/dL below their baseline mean, although identical to their mean value at trial month 4. Similar between-group trends were observed in eGFR. At postclose-out, the mean eGFR of cases was 1.1 mL/min/1.73 $m^2$ greater than placebos but not significant ($P = 0.4$), while controls were 5.2 mL/min/1.73 $m^2$ greater than placebos ($P < 0.0001$). These results did not change substantially after removing participants who stopped taking nonfenofibrate, renal function–altering medications between close-out and postclose-out visits (further details in the Supplementary Data online). The Supplementary Data also includes analyses that suggest that the reduction in serum creatinine was essentially complete after 51 days.

Changes in adjusted serum cystatin C levels between close-out and postclose-out visits recapitulated those of serum creatinine, Table 2, and Figs. 1*B* and 2*B*. In cases, cystatin C dropped from a mean (± SE) of 1.03 ± 0.02 to 0.96 ± 0.02 mg/dL and was not significantly different from placebos at postclose-out ($P = 0.9$). Controls likewise dropped from 0.95 ± 0.02 to 0.88 ± 0.02 mg/dL. The mean change in cases and controls was not significantly different ($P = 0.4$). Trends in adjusted cGFR were similar to eGFR with mean cGFR in controls at postclose-out (91.4 ± 1.9 mL/min/1.73 $m^2$) greater than either cases (83.1 ± 1.4) or placebos (83.1 ± 1.0), which were not significantly different ($P = 0.9$). The mean recovery of cGFR was also greater in cases and controls on drug cessation compared with placebos.

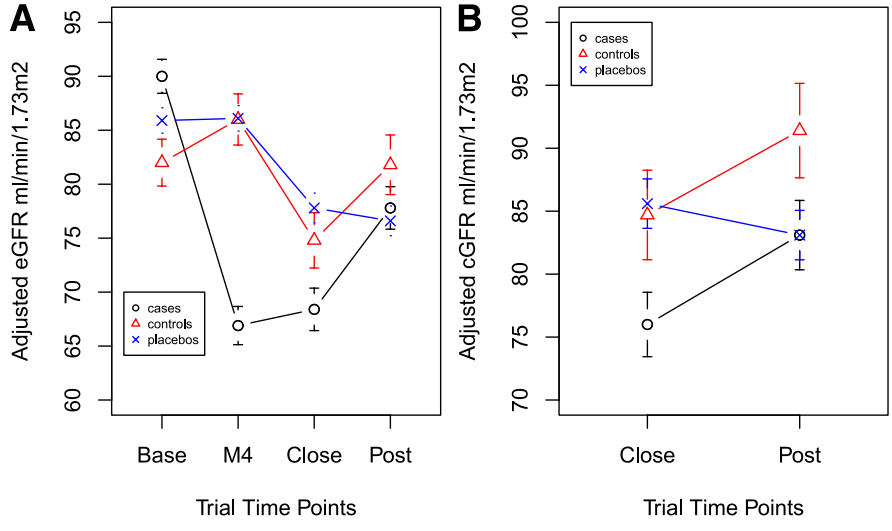


**Figure 2**—*Time course values of adjusted eGFR and cGFR by ACCORD Renal Study Group.* A: *The changes in eGFR in units of mL/min/1.73 $m^2$.* B: *Changes in cGFR in units of mL/min/1.73 $m^2$. The horizontal trial time point axis is not shown to scale. The study group trends are shown as: black circles, fenofibrate cases; red triangles, fenofibrate controls; blue crosses, placebo controls. Base, baseline visit; M4, month 4 visit; Close, close-out visit; Post, postclose-out visit. (A high-quality color representation of this figure is available in the online issue.)*

**CONCLUSIONS**—We investigated the potential reversibility of the rapid serum creatinine increase observed on starting fenofibrate therapy. The fenofibrate cases (participants who experienced a 20% or more increase in serum creatinine after 3 months of fenofibrate; 47.4% of all participants randomized to fenofibrate in the ACCORD Lipid Trial) had a mean serum creatinine decrease on cessation of fenofibrate to a value that was no different than the mean creatinine of the placebo reference group, suggesting no residual loss of GFR after 5 years of therapy. This reversal of serum creatinine elevation was complete after 51 days off therapy. By contrast, for the control subgroup of fenofibrate participants (participants who experienced <2% change in creatinine; 24.6% of all participants randomized to fenofibrate), the mean serum creatinine was lower than the placebo reference group after

51 days off therapy, suggesting a net preservation of GFR and renal function. The serum cystatin C results showed similar trends.

Fenofibrate was also found to have a protective effect on the albuminuria levels in ACCORD Lipid Trial participants. Fewer participants randomized to fenofibrate progressed to frank microalbuminuria or proteinuria postrandomization than placebos (16). This result is consistent with the reduced progression found in the DAIS and FIELD Trials (5,7), and the greater reduction in mean urinary albumin/creatinine ratio in the fenofibrate arm compared with placebo over 5 years of follow-up in FIELD (7). The ACCORD Lipid Trial albuminuria results will be reported in detail elsewhere.

Previous studies support our key finding about the reversibility of serum creatinine levels postfenofibrate therapy. Early comparative studies in patients who had undergone renal transplant and were on fenofibrate therapy demonstrated a reversible increase in creatinine if no chronic renal failure was present at baseline (1,2). A limitation of these early reports is that they were all retrospective case studies in a limited number of patients with pre-existing renal disease or transplant. The FIELD Trial reported results from a large study of reversibility of renal function in patients with diabetes on fenofibrate therapy. After a 6-week prerandomization run-in period of all FIELD study participants on fenofibrate therapy, mean levels of serum creatinine increased, but returned to baseline in those subjects randomized to placebo within 4 months of cessation of therapy. Furthermore, a posttrial fenofibrate wash-out substudy at the conclusion of the 5-year trial demonstrated an acute decline in creatinine values during the wash-out period of 52 days resulting in a net protective effect of fenofibrate (7,8). Similar to ACCORD, the FIELD Trial examined a broad population of type 2 diabetic participants who had normal renal function at study entry.

Our results suggest the presence of two distinct clinical effects of fenofibrate therapy. The first is the previously studied rise in serum creatinine levels shortly after starting therapy. Based on the ACCORD results, this can be expected to occur in 47% of type 2 diabetic patients with a similar cardiovascular and renal function profile to the participants in the ACCORD Lipid Trial. This rise appears to be wholly reversible after 5 years of therapy. The second effect is a preservation of GFR in patients who experience little or no rise in serum creatinine immediately after initiating therapy, which is expected in about 25% of patients with a similar profile to ACCORD Lipid. A similar protective effect on GFR was also seen in fenofibrate participants more generally at the conclusion of the FIELD Trial (7). Whether this preservation is maintained or whether it reduces the long-term macro- or microvascular disease risk after the initial 5 years of therapy is unknown. The ACCORDION (ACCORD Follow-Up) Study, which is currently underway, will help to answer the second question. ACCORDION is a posttrial, prospective, observational study of 8,000 ACCORD participants over 3.5 years to elucidate the long-term effects of the ACCORD treatment strategy and will include additional measurements of serum creatinine, urinary creatinine, and albumin.

The underlying mechanism for the increase in creatinine is not understood. Potential mechanisms include increased muscular production of creatinine, decreased secretion from renal tubules, and a change in the glomerular filtration through altered hemodynamics. Hottelart et al. (9) postulated that increased serum creatinine levels result from increased creatinine production. The investigators performed a crossover study of 15 patients with renal insufficiency (average creatinine clearance 69 mL/min) that had experienced at least a 10% increase in serum creatinine with fenofibrate therapy. Renal function was assessed following discontinuation of fenofibrate therapy and following rechallenge. Serum creatinine increased with fenofibrate therapy, but indices of both GFR (creatinine clearance, inulin clearance) and renal blood flow (*p*-aminohippuric acid clearance) were unaffected. A similar, small, cross-over study in healthy individuals found that while creatinine clearance was reduced by fenofibrate, neither GFR as measured by inulin clearance nor the rate of creatinine secretion changed (10). Similar changes have been seen in some but not all drugs in this class. Fifty-five patients treated with ciprofibrate showed similar results but no significant change was observed in 15 patients taking gemfibrozil. Similar results were observed by Westphal et al. (11) in a cross-over study of 22 men with hypertriglyceridemia and normal renal function randomized to either micronized fenofibrate 200 mg/day or gemfibrozil 900 mg/day.

The cystatin C results in the ACCORD Renal Study are consistent with the FIELD Helsinki substudy, which showed that an increase in cystatin C levels accompanied the initial increase in serum creatinine with fenofibrate (12). The results suggest that the physiological mechanism for the rapid increase in serum creatinine on initiation of fenofibrate therapy (and the reversion on cessation) is not specific for creatinine and rule out increased creatinine production or secretion as a plausible mechanism. However, more work needs to be done to confirm and elaborate these findings.

An unexpected benefit of this design was that it highlighted the differences in changes in serum creatinine and cystatin C in major subgroups of trial participants once these subgroups ceased on-trial therapy. These different responses would typically not have been identified in an on-drug/off-drug study that recruited without regard to the magnitude of the initial serum creatinine increase and analyzed the mean of the single active fenofibrate group, such as in the FIELD Trial (7,8). The selection of the case and control subgroups in this study also had its limitations, however. Interpretation of the serum marker trends in these groups during the trial and posttrial is complicated by the effect of single point-in-time selection of the extremes of percent change of serum creatinine and statistical regression to the mean. This study did not analyze the changes in the 28% of patients with intermediate response in percent serum creatinine after 3 months (2–20% change in serum creatinine). Furthermore, the choice of 20% and 2% as thresholds for change in serum creatinine was arbitrary, albeit that they are clinically meaningful levels of change/no change. Finally, participants who had significant worsening of renal function and required discontinuation of study medication are not included in this substudy. Despite these limitations, these results can assist clinical decision making for type 2 diabetic patients with comparable cardiovascular and renal profile according to their percent serum creatinine change in response to initiation of fenofibrate therapy.

This study found that about 50% of ACCORD type 2 diabetic participants experienced an increase of 20% or more in serum creatinine levels immediately upon starting fenofibrate therapy, while approximately 25% had no increase. For those participants with a creatinine increase of 20% or more, the increase was reversible and not associated with an adverse effect—compared with placebo—on renal function over 5 years. Those with no increase in creatinine upon starting fenofibrate appeared to have

less renal function loss compared with placebo over 5 years of therapy. More work needs to be done to test these findings over longer durations of therapy, to determine if this apparent renal protection is also seen among the low HDL/high triglyceride subgroup that had apparent cardiovascular benefit in the main ACCORD Lipid Study, and to determine the duration of the apparent renal protective effects.

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**References**

1. Broeders N, Knoop C, Antoine M, Tielemans C, Abramowicz D. Fibrate-induced increase in blood urea and creatinine: is gemfibrozil the only innocuous agent? Nephrol Dial Transplant 2000;15:1993–1999
2. Lipscombe J, Lewis GF, Cattran D, Bargman JM. Deterioration in renal function associated with fibrate therapy. Clin Nephrol 2001;55:39–44
3. Boissonnat P, Salen P, Guidollet J, et al. The long-term effects of the lipid-lowering agent fenofibrate in hyperlipidemic heart transplant recipients. Transplantation 1994; 58:245–247
4. Rössner S, Orö L. Fenofibrate therapy of hyperlipoproteinaemia. A dose-response study and a comparison with clofibrate. Atherosclerosis 1981;38:273–282
5. 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
6. Genest J, Frohlich J, Steiner G. Effect of fenofibrate-mediated increase in plasma homocysteine on the progression of coronary artery disease in type 2 diabetes mellitus. Am J Cardiol 2004;93: 848–853
7. Davis TM, Ting R, Best JD, et al.; Fenofibrate Intervention and Event Lowering in Diabetes Study investigators. Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. Diabetologia 2011;54:280–290
8. Keech A, Simes RJ, Barter P, et al.; 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
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, Caussé 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. Westphal S, Dierkes J, Luley C. Effects of fenofibrate and gemfibrozil on plasma homocysteine. Lancet 2001;358:39–40
12. Forsblom C, Hiukka A, Leinonen ES, Sundvall J, Groop PH, Taskinen MR. Effects of long-term fenofibrate treatment on markers of renal function in type 2 diabetes: the FIELD Helsinki substudy. Diabetes Care 2010;33:215–220
13. Hottelart C, el Esper N, Achard JM, Pruna A, Fournier A. Fenofibrate increases blood creatinine, but does not change the glomerular filtration rate in patients with mild renal insufficiency. Nephrologie 1999;20:41–44 [in French]
14. Buse JB, Bigger JT, Byington RP, et al.; ACCORD Study Group. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. Am J Cardiol 2007;99:21i–33i
15. Ginsberg HN, Bonds DE, Lovato LC, et al.; ACCORD Study Group. Evolution of the lipid trial protocol of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol 2007;99:56i–67i
16. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–1574
17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461–470
18. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612
19. Stevens LA, Coresh J, Schmid CH, et al. 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