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Benefits and Safety of Long-Term Fenofibrate Therapy in People With Type 2 Diabetes and Renal Impairment

The FIELD Study

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ON BEHALF OF THE FIELD STUDY INVESTIGATORS*

OBJECTIVE—Diabetic patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] 30–59 mL/min/1.73 m^2) are at particular cardiovascular risk. Fenofibrate's safety in these patients is an issue because it may elevate plasma creatinine. Furthermore, guidelines regarding fenofibrate dosing in renal impairment vary internationally. We investigated fenofibrate's effects on cardiovascular and end-stage renal disease (ESRD) events, according to eGFR, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study.

RESEARCH DESIGN AND METHODS—Type 2 diabetic patients (aged 50–75 years) with eGFR ≥30 mL/min/1.73 m^2 were randomly allocated to a fixed dose of fenofibrate (200 mg daily) (n = 4,895) or placebo (n = 4,900) for 5 years. Baseline renal function (Modification of Diet in Renal Disease equation) was grouped by eGFR (30–59, 60–89, and ≥90 mL/min/1.73 m^2). The prespecified outcome was total cardiovascular events (composite of cardiovascular death, myocardial infarction, stroke, and coronary/carotid revascularization). Serious adverse events and instances of ESRD (plasma creatinine >400 μmol/L, dialysis, renal transplant, or renal death) were recorded. Analysis was by intention to treat.

RESULTS—Overall, fenofibrate reduced total cardiovascular events, compared with placebo (hazard ratio 0.89 [95% CI 0.80–0.99]; P = 0.035). This benefit was not statistically different across eGFR groupings (P = 0.2 for interaction) (eGFR 30–59 mL/min/1.73 m^2: 0.68 [0.47–0.97], P = 0.035; eGFR ≥90 mL/min/1.73 m^2: 0.85 [0.70–1.02], P = 0.08). ESRD rates were similar between treatment arms, without adverse safety signals of fenofibrate use in renal impairment.

CONCLUSIONS—Patients with type 2 diabetes and moderate renal impairment benefit from long-term fenofibrate, without excess drug-related safety concerns compared with those with no or mild renal impairment. Fenofibrate treatment should not be contraindicated in moderate renal impairment, suggesting that current guidelines may be too restrictive.

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Cardiovascular disease (CVD) is projected to remain the single leading cause of death (1) and is a major cause of morbidity and premature mortality in people with diabetic kidney disease, independent of other risk factors (2,3). The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study was a 5-year trial of fenofibrate versus placebo involving type 2 diabetic patients. Although there was no significant benefit from fenofibrate for the primary end point of coronary heart disease (CHD) events, the secondary end points of CVD events and nonfatal myocardial infarction were significantly reduced, as were hospitalizations for acute coronary syndromes and coronary and carotid revascularization procedures (4). Fenofibrate also significantly reduced the microvascular complications of type 2 diabetes (5–7), including nephropathy.

Set against its potential benefits, there have been safety concerns associated with fenofibrate administration in the setting of renal impairment, with current guidelines recommending dose reduction in patients with even mildly abnormal renal function (8,9). The rise in plasma creatinine in response to fenofibrate is well documented, but this does not reflect true renal injury or an actual fall in glomerular filtration rate (GFR) (4,7,10). Although renal impairment is an independent risk predictor of CVD and end-stage renal disease (ESRD) (2,11,12), it has been unclear whether the fenofibrate-associated rise in plasma creatinine might also confer excess risk, especially in patients with pretreatment renal impairment. We therefore investigated the impact of fenofibrate on prespecified cardiovascular and renal end points of the FIELD Study in patients with impaired renal function at baseline.

RESEARCH DESIGN AND METHODS

—The FIELD Study was a double-blinded placebo-controlled trial conducted in Australia, New Zealand, and Finland. The registered study (clinical trial no. ISRCTN64783481) had ethics committee approval in accordance with the

Declaration of Helsinki and Good Clinical Practice Guidelines. Study design and patient characteristics have been published elsewhere (4). In brief, 9,795 patients with type 2 diabetes, aged 50–75 years, were randomly allocated to receive 200 mg comicronized fenofibrate or placebo daily for an average of 5 years. There was no dose adjustment for any degree of renal impairment. Subjects had mild dyslipidemia, with no immediate indication at study entry for lipid-modifying therapy. Exclusion criteria included plasma creatinine >130 μmol/L, liver or symptomatic gallbladder disease, or a CVD event within 3 months before recruitment. All patients with National Kidney Foundation chronic kidney disease stage 5 (estimated GFR [eGFR] <15 mL/min/1.73 m^2), stage 4 (eGFR 15–29 mL/min/1.73 m^2), and some with stage 3 (eGFR 30–59 mL/min/1.73 m^2) of the disease were therefore excluded (13). All patients provided informed consent and then completed a 16-week run-in period comprising 4 weeks of diet, 6 weeks of single-blinded placebo, and 6 weeks of single-blinded fenofibrate before being randomly assigned. Eligibility was confirmed during the run-in period independently of adherence or biochemical changes.

A telephone computer randomization service using dynamic balancing to stratify patients by prognostic variables was used; all investigators, except one statistician, were masked to treatment allocation. Patients were seen every 4–6 months against a background of usual care, and information concerning treatment tolerability and complications was obtained.

eGFR was calculated by the Modification of Diet in Renal Disease (MDRD) Study four-variable equation (14) and was grouped as eGFR ≥90, 60–89, and 30–59 mL/min/1.73 m^2. Baseline eGFR was taken as the mean of two measurements before the active run-in phase (visits 1 and 3, median 72 days apart).

All major CVD events and all other deaths were adjudicated by an outcomes assessment committee using prespecified definitions and while unaware of treatment allocation. The safety- and data-monitoring committee reviewed the safety data at regular intervals every 6 months and undertook two formal interim analyses of the numbers of deaths from CHD.

The primary end point was CHD events (the first occurrence of either a nonfatal myocardial infarction or death from CHD). Secondary outcomes included total mortality, CVD deaths, total stroke, coronary revascularization procedures, and total CVD events (CHD events, total stroke, coronary and carotid revascularization, and other CVD death combined). Prespecified tertiary end points included ESRD (plasma creatinine >400 μmol/L), dialysis, renal transplant, or death from renal disease.

Statistical analysis

Differences in baseline characteristics were assessed by comparing the 30–59 mL/min/1.73 m^2 group with the combined ≥60 mL/min/1.73 m^2 group using χ^2 tests for categorical variables and *t* tests or nonparametric tests, as appropriate, for continuous variables. Tests for linear trend across the three prespecified eGFR groups also were performed. Cox proportional hazards models were applied within each eGFR group to assess the effect of treatment on primary and secondary outcomes, with an interaction term between treatment and group used to test for the heterogeneity of the treatment effect. χ^2 Tests were used to test for a difference between the number of patients experiencing each type of nonfatal serious adverse event within each eGFR group and the logistic regression used to test for an interaction between treatment and eGFR groups. All analyses were performed on an intention-to-treat basis, with inferences drawn on a two-sided significance level of 0.05, unadjusted for multiple comparisons. SAS software (version 9.2; SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Baseline characteristics

The placebo and fenofibrate groups were well matched for baseline characteristics (4) (Table 1). The 519 participants with eGFR <60 mL/min/1.73 m^2 were older, had a longer duration of diabetes, and had higher systolic blood pressure than the others. A smaller proportion had a history of smoking. They were more likely to have elevated urinary albumin-to-creatinine ratios (ACRs), elevated total cholesterol and triglyceride levels, and a history of previous CVD events.

Lipid and blood pressure effects of fenofibrate by eGFR

The early (over ~6 weeks) lipid-modifying effects of fenofibrate (increased HDL cholesterol and lower LDL cholesterol and triglycerides) were independently significant within each category of eGFR, with significantly greater improvement in lipid profile in the lowest eGFR group (Supplementary Table 1). However, the differences between eGFR groups in lipid effects were lost over 5 years (Supplementary Table 2). In addition, over the 6-week fenofibrate run-in period, there was a small but significantly greater reduction in systolic blood pressure in patients with eGFR 30–59 mL/min/1.73 m^2 (5.1 mmHg) compared with those with eGFR ≥90 mL/min/1.73 m^2 (3.4 mmHg) (Supplementary Table 3).

Cardiovascular risk by eGFR and fenofibrate treatment

Among placebo-allocated patients, all CVD outcomes (CHD events, coronary revascularization, CVD death, total CVD events, stroke, and total mortality) were more frequent in those with renal impairment compared with those without (Table 2). The number of CVD events in placebo-treated patients with eGFR 30–59 mL/min/1.73 m^2 was more than double that of those with eGFR ≥90 mL/min/1.73 m^2 (Fig. 1), and CVD and all-cause death were more than six- and fourfold higher, respectively (Table 2, Fig. 1).

Consistent with the highest absolute risks for CVD events being in those with the greatest renal impairment, fenofibrate offered the greatest absolute risk reductions in these individuals. Patients with a baseline eGFR of 30–59 mL/min/1.73 m^2 who received fenofibrate had independently significant absolute risk reductions compared with those allocated to the placebo group in coronary revascularization, total CVD events, and CVD mortality (Table 2). However, the relative risk reductions with fenofibrate were similar to those for other patients such that there were no statistically significant trends for varying treatment effects across eGFR groups ($P > 0.05$ for interaction), even after adjustment for on-study statin use. For example, fenofibrate reduced CVD risk overall by 11% (hazard ratio [HR] 0.89 [95% CI 0.80–0.99]; $P = 0.035$) irrespective of eGFR grouping (Fig. 2; $P = 0.22$ for interaction), with an overall number needed to treat of 70 (95% CI 36–1,112) to avoid one event. Among those with an eGFR of 30–59 mL/min/1.73 m^2, there was neither significantly greater benefit nor greater harm, with an estimated total CVD risk reduction of 32% (0.68 [0.47–0.97]; $P = 0.035$) and number needed to treat of 14 (7–834). These observed benefits on total CVD (as also was true for reduced albuminuria) were independent of

Table 1—*Clinical and metabolic characteristics of the FIELD Study population at baseline, by eGFR group*

	Baseline eGFR (mL/min/1.73 m^2)				
	≥90	60–89	30–59	*P* for trend	*P* contrast*
n	4,058	5,218	519		
Fenofibrate allocated [*n* (%)]	2,039 (50.2)	2,561 (49.1)	295 (56.8)		
Male [*n* (%)]†	2,693 (66.4)	3,231 (61.9)	214 (41.2)	<0.001	<0.001
Age (years) [mean (SD)]†	60.20 (6.66)	63.38 (6.66)	66.51 (5.92)	<0.001	<0.001
Diabetes duration (years) [geometric mean (95% CI)]†‡	4.81 (4.68–4.95)	5.06 (4.93–5.19)	6.02 (5.55–6.54)	<0.001	<0.001
Smoking status [*n* (%)]				<0.001	<0.001
Never†	1,462 (36.0)	2,201 (42.2)	266 (51.3)		
Previous†	2,120 (52.2)	2,607 (50.0)	217 (41.8)		
Current†	476 (11.7)	410 (7.9)	36 (6.9)		
BMI (kg/m^2) [geometric mean (95% CI)]					
Women‡	32.2 (31.9–32.5)	31.2 (31.0–31.5)	31.5 (30.9–32.2)	0.07	0.74
Men‡	29.7 (29.5–29.9)	29.1 (29.0–29.3)	29.2 (28.6–29.8)	0.11	0.56
Systolic blood pressure (mmHg) [geometric mean (95% CI)]†	138.5 (138.1–139.0)	140.2 (139.7–140.6)	143.4 (142.0–144.8)	<0.001	<0.001
HbA_{1c} (%) [geometric mean (95% CI)]‡	6.97 (6.93–7.02)	6.91 (6.88–6.94)	7.02 (6.91–7.13)	0.44	0.15
Total cholesterol (mmol/L) [mean (SD)]§	5.02 (0.70)	5.04 (0.70)	5.11 (0.71)	<0.01	0.02
Triglycerides (mmol/L) [geometric mean (95% CI)]‡	1.76 (1.74–1.78)	1.79 (1.77–1.81)	1.91 (1.85–1.98)	<0.001	<0.001
HDL cholesterol (mmol/L) [geometric mean (95% CI)]‡	1.07 (1.06–1.07)	1.07 (1.06–1.08)	1.06 (1.03–1.08)	0.33	0.24
Dyslipidemia [*n* (%)]	1,492 (36.8)	1,971 (37.8)	247 (47.6)	<0.001	<0.001
Hemoglobin (g/dL) [mean (SD)]†	14.62 (1.19)	14.51 (1.23)	13.86 (1.37)	<0.001	<0.001
ACR [*n* (%)]				<0.001	<0.001
Normal†	3,026 (74.9)	3,927 (75.4)	307 (59.2)		
Microalbuminuria†	890 (22.0)	1,068 (20.5)	146 (28.2)		
Macroalbuminuria†	126 (3.1)	213 (4.1)	65 (12.5)		
Use of RAAS inhibitors [*n* (%)]†	1,518 (37.4)	1,987 (38.1)	286 (55.1)	<0.001	<0.001
Use of aspirin [*n* (%)]†	1,012 (24.9)	1,621 (31.1)	196 (37.8)	<0.001	<0.001
Previous CVD [*n* (%)]†	680 (16.8)	1,245 (23.9)	206 (39.7)	<0.001	<0.001

Microalbuminuria: urine ACR ≥2.5 mg/mmol (male subjects) and ≥3.5 mg/mmol (female subjects). Macroalbuminuria: urine ACR >25 mg/mmol (male subjects) and >35 mg/mmol (female subjects). RAAS, renin-angiotensin-aldosterone system. *P for eGFR <60 vs. ≥60 mL/min/1.73 m^2. †$P < 0.001$ for trend. Smoking status and ACR are for overall values. ‡Analyses performed on log-transformed data. §$P < 0.05$ for trend.

the background use or nonuse of ACE inhibitors, the extent of glycemic control (by HbA_{1c}), and systolic blood pressure levels (all *P* interactions were not significant).

The CVD mortality risk in those with an eGFR of 30–59 mL/min/1.73 m^2 allocated to fenofibrate was significantly reduced by 49% (95% CI 7–72; $P = 0.03$) compared with placebo, with greater benefit among those with lower eGFR than others ($P = 0.03$ for interaction) (Table 2). However, this pattern was no longer significant after adjustment for other baseline variables (sex, age, diabetes duration, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, HbA_{1c}, hemoglobin, urine ACR, previous retinopathy, previous CVD, renin-angiotensin-aldosterone blocker use, β-blocker use, and aspirin use).

Plasma creatinine concentrations rose by ~12% soon after commencement of fenofibrate (7), but there was no loss of CVD benefit among those with the greatest creatinine rise. In fact, the greatest absolute benefit was seen in this group (7).

Analysis by eGFR group showed a significant inverse association between baseline eGFR and the extent of fenofibrate-associated plasma creatinine rise, with the greatest rises seen in the lowest eGFR group, although the strength of this relationship was weak ($r^2 = 0.03$, $P < 0.001$). The average rise in plasma creatinine in the lowest eGFR group was approximately twice that in the highest eGFR group (17.9 vs. 8.4 μmol/L, $P < 0.001$ for trend across all three eGFR groups).

Analysis by the presence of different lipid abnormalities (low HDL cholesterol [male subjects <1.03 mmol/L, female subjects <1.29 mmol/L], high triglycerides [≥1.7 mmol/L], and dyslipidemia [low HDL cholesterol and high triglycerides]), older age (≥65 years), previous CVD, or sex within each eGFR group did not reveal any statistically significant interactions. Among those with eGFR 30–59 mL/min/1.73 m^2, those with low HDL cholesterol or marked dyslipidemia (low HDL cholesterol plus triglycerides ≥2.3 mmol/L) had independently significant total CVD risk reductions (data not shown).

Safety of fenofibrate use in renal impairment: ESRD events overall and by eGFR

Overall, there were 26 compared with 21 ESRD events over 5 years in the placebo compared with fenofibrate group, respectively. The greatest rate of ESRD events occurred among those with baseline eGFR 30–59 mL/min/1.73 m^2 (stratified by treatment). There was no increase in ESRD events with fenofibrate use compared with placebo either overall (data previously

Table 2—*Effect of treatment on primary and secondary outcomes by baseline eGFR*

	Placebo		Fenofibrate				
	n	%	*n*	%	HR (95% CI)	*P*	Interaction
Outcome*							
Coronary events							
eGFR (mL/min/1.73 m^2)							
30–59	25	11.2	23	7.8	0.67 (0.38–1.18)	0.17	0.60
60–89	168	6.3	148	5.8	0.91 (0.73–1.14)	0.42	
≥90	95	4.7	85	4.2	0.89 (0.66–1.19)	0.42	
Coronary revascularization							
eGFR (mL/min/1.73 m^2)							
30–59	25	11.2	15	5.1	0.43 (0.23–0.81)	0.01	0.10
60–89	204	7.7	171	6.7	0.87 (0.71–1.07)	0.18	
≥90	134	6.6	104	5.1	0.77 (0.59–0.99)	0.04	
CVD mortality							
eGFR (mL/min/1.73 m^2)							
30–59	26	11.6	18	6.1	0.51 (0.28–0.93)	0.03	0.03
60–89	65	2.4	78	3.0	1.25 (0.90–1.74)	0.18	
≥90	36	1.8	44	2.2	1.22 (0.78–1.89)	0.38	
Total stroke							
eGFR (mL/min/1.73 m^2)							
30–59	20	8.9	23	7.8	0.85 (0.47–1.55)	0.60	0.33
60–89	91	3.4	89	3.5	1.02 (0.76–1.36)	0.90	
≥90	64	3.2	46	2.3	0.71 (0.49–1.04)	0.08	
Total CVD events							
eGFR (mL/min/1.73 m^2)							
30–59	60	26.8	57	19.3	0.68 (0.47–0.97)	0.03	0.22
60–89	387	14.6	352	13.7	0.94 (0.81–1.08)	0.38	
≥90	236	11.7	203	10.0	0.85 (0.70–1.02)	0.08	
Total mortality							
eGFR (mL/min/1.73 m^2)							
30–59	41	18.3	43	14.6	0.77 (0.50–1.18)	0.23	0.23
60–89	182	6.8	195	7.6	1.12 (0.91–1.37)	0.27	
≥90	100	5.0	118	5.8	1.17 (0.90–1.53)	0.24	
Renal end points†							
Creatinine >400 μmol/L							
eGFR (mL/min/1.73 m^2)							
30–59	2	0.9	2	0.7	—	—	
60–89	1	0.0	4	0.2	—	—	
≥90	0	0.0	0	0.0	—	—	
Peritoneal or hemodialysis							
eGFR (mL/min/1.73 m^2)							
30–59	3	1.3	5	1.7	—	—	
60–89	13	0.5	7	0.3	—	—	
≥90	5	0.2	4	0.2	—	—	
Renal transplant							
eGFR (mL/min/1.73 m^2)							
30–59	0	0.0	0	0.0	—	—	
60–89	0	0.0	0	0.0	—	—	
≥90	0	0.0	0	0.0	—	—	
Death from renal disease							
eGFR (mL/min/1.73 m^2)							
30–59	1	0.4	0	0.0	—	—	
60–89	1	0.0	1	0.0	—	—	
≥90	2	0.1	0	0.0	—	—	
Total number of patients with ESRD							
eGFR (mL/min/1.73 m^2)							
30–59	5	2.2	7	2.4	—	—	
60–89	14	0.5	10	0.4	—	<0.0001‡	
≥90	7	0.3	4	0.2	—	—	

*Event categories are not mutually exclusive. †Most end points had insufficient numbers for statistical comparison. ‡*P* for trend in the rate of ESRD events across eGFR groups, stratified by treatment.

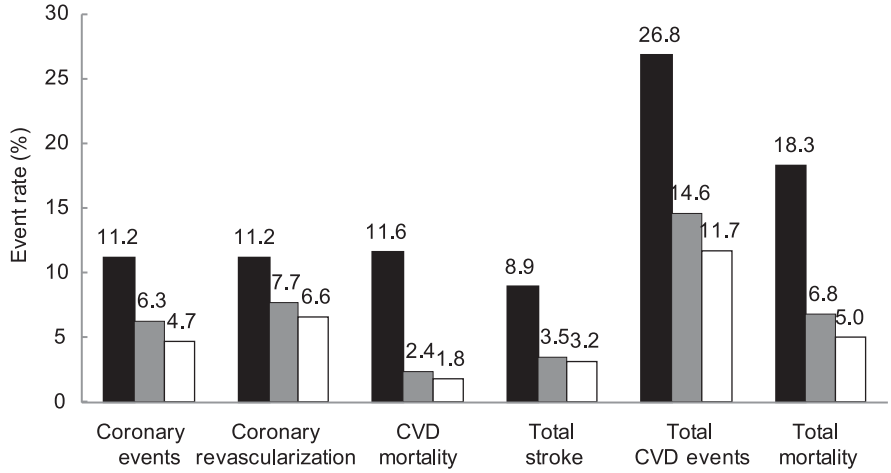

Figure 1—*Percentage event rate of subtypes of vascular events and mortality within each category of eGFR.* ■, *30–59 mL/min/1.73 m*^{2}; ■, *60–89 mL/min/1.73 m*^{2}; □, *≥90 mL/min/1.73 m*^{2}.

published [7]) or within any eGFR group (Table 2; $P = 0.75$ for interaction). Within the group with eGFR 30–59 mL/min/1.73 m^2, the rates were 1.7 vs. 1.3% (dialysis), 0.7 vs. 0.9% (plasma creatinine >400 μmol/L), and 0.0 vs. 0.4% (death from renal disease) in the fenofibrate- versus placebo-allocated patients. The extent of the plasma creatinine rise with fenofibrate did not predict the occurrence of ESRD events ($P = 0.60$ for interaction).

Other serious adverse events

For approximately one-half of the categories of adverse events, the greater the renal impairment the higher the rates of occurrence (Supplementary Table 4). However, adverse event rates generally were no higher among those receiving fenofibrate than those on placebo, including within the eGFR 30–59 mL/min/1.73 m^2 group. The only category with a statistically significant interaction was nonfatal gastrointestinal events, with more events in the fenofibrate- than placebo-allocated patients with normal renal function (20.5 vs. 17.3% in the placebo group, $P = 0.01$, unadjusted for multiple comparisons) but no significant difference for patients with eGFR 30–59 or 60–89 mL/min/1.73 m^2 (Supplementary Table 4). Those allocated to fenofibrate had a statistically significant, but only marginally greater, overall risk of pancreatitis and pulmonary embolism than those allocated to placebo, but there was no difference in risk across groups by eGFR (P for interaction for both events not significant). Overall, there was no increased risk of myopathy (2 vs. 1 subjects) or rhabdomyolysis (3 vs. 1 subjects) attributed to fenofibrate, compared with placebo, with too few events to assess whether treatment effect differed by baseline renal function.

CONCLUSIONS—Fenofibrate may be an especially appropriate therapy to reduce CVD risk in the setting of renal impairment because it raises apolipoprotein A1 and HDL cholesterol levels and influences HDL particle size (15,16). However, its use has been limited by concerns that the typical drug-induced rise in plasma creatinine might adversely affect CVD risk and renal outcomes. In the FIELD Study, we found no evidence that the use of a standard dose of fenofibrate in patients with moderate renal impairment had adverse effects on either CVD or renal outcomes. In fact, the greatest absolute risk reductions for CVD events with fenofibrate were seen in those with eGFR 30–59 mL/min/1.73 m^2, and no excess ESRD events were seen in fenofibrate-treated patients in any eGFR group. Of interest, although the number of subjects in the low-eGFR group was relatively small, there was an independently significant CVD reduction with fenofibrate in patients with low HDL cholesterol or marked dyslipidemia. The relative CVD benefits of fenofibrate were statistically equivalent across eGFR groups, except for CVD mortality, for which fenofibrate was associated with a significantly greater risk reduction in those with lower baseline renal function.

In general, higher baseline serum creatinine is associated with an increased risk of ESRD (12), with findings confirmed in the FIELD Study. However, the fenofibrate-induced increase in circulating creatinine levels does not carry the same risk of ESRD events because these events were nonsignificantly fewer in those allocated to fenofibrate than to placebo.

The reasons behind the initial fenofibrate-associated plasma creatinine rise have yet to be fully elucidated, and there are various hypotheses apart from reduced glomerular filtration. These include increased muscle production of creatinine, changes in active tubular creatinine secretion, and altered renal plasma flow (7,10,17). Several of these mechanisms may be involved, but regardless of the underlying physiology, the early creatinine rise is fully reversible even after 5 years of fenofibrate treatment (7) and is concurrently associated with significant reductions in total CVD events and preservation of renal function.

In both the Diabetes Atherosclerosis Intervention Study (DAIS) (18) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (19), as well as in the FIELD Study, fenofibrate was associated with a reduction in albuminuria despite similar elevations in serum creatinine to those seen in the FIELD Study (7). In a recent U.S. Food and Drug Administration hearing, the ACCORD trial reported that after fenofibrate withdrawal eGFR returned to placebo-matched levels, with some patients having an overall improvement in renal function (20). The ACCORD trial (19) and other studies (21–23) also show that fenofibrate is not associated with excess kidney-related adverse events and is, overall, safe to use even in combination with statins. However, none of these previous study reports have investigated if there is any relationship between outcomes and the drug-induced creatinine rise or examined the safety and efficacy of fenofibrate use in renal impairment. To our knowledge, this article is the first to do so, looking at both cardiovascular and renal outcomes. It provides added reassurance, demonstrating that the drug is not only safe but also just as efficacious in patients with moderate renal impairment compared with those with normal function.

Clinical implications

Diabetes is a significant risk factor for CVD events and mortality, requiring intensive treatment of conventional CVD risk factors. Unfortunately, the implementation of established preventive treatment recommendations remains incomplete (24), and even with intensive multifactorial risk reduction, the CVD complication rate in type 2 diabetic patients remains unacceptably high (25). The FIELD Study confirms that type 2 diabetic patients

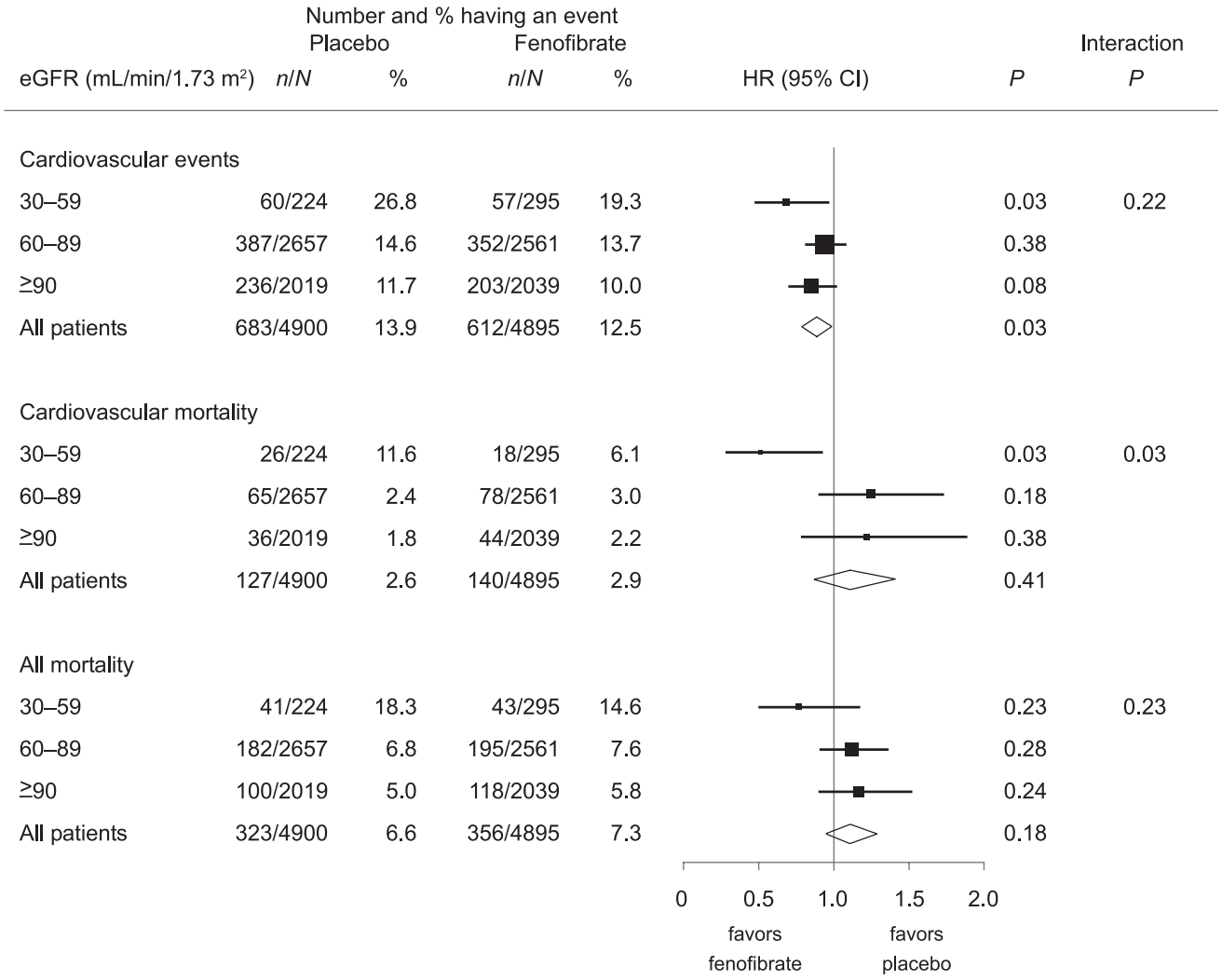

Figure 2—*HRs (95% CIs) for total CVD events, cardiovascular mortality, and total mortality risk by treatment allocation within different categories of eGFR.* ■*, relative weights of the outcome event in each group;* ◇*, summary HR with 95% CI.*

with reduced eGFR (<90 mL/min/1.73 m^2) are at exceptionally high risk of CVD (>5% per year). This underscores the need for better implementation of proven treatments, especially in those with coexistent renal impairment.

These FIELD Study findings should help allay previous concerns regarding the safety of fenofibrate use in patients with renal impairment, indicating that neither moderately poor renal function nor an initial rise in plasma creatinine with fenofibrate is a contraindication to such treatment. Furthermore, treatment benefits at least as great as those seen in patients with normal renal function could be expected. The benefits reported here support the long-term use of standard doses of fenofibrate in such patients to reduce both CVD events and death from CVD. These benefits occur despite a reversible and modest increase in plasma creatinine, with evidence of renoprotection (eGFR preservation and albuminuria reduction) that was similar across the eGFR groups (7). The benefits of fenofibrate on CVD and albuminuria are both in addition to and independent of established proven measures, such as glycemic control, antihypertensive treatment in general, and use of the renin-angiotensin system blockade in particular (7,26–33). In this context, the results would support the use of fenofibrate being in addition to, rather than an alternative to, the above current established strategies.

Fenofibrate therapy in those in the group with low eGFR produced the greatest estimated absolute reduction in CVD risk despite the greatest early plasma creatinine rise. Therefore, not only does this early drug-induced plasma creatinine rise fail to portend any adverse cardiac or renal outcomes, but it may in fact be a surrogate marker of drug benefit. This latter finding is hypothesis generating and will require further clinical investigation.

Current guidelines for fenofibrate use in Western countries recommend a substantial dose reduction (between 30 and 69%) when renal function is impaired but with significant variation in the threshold at which this should be implemented. Dose reduction is recommended when creatinine clearance is <100 mL/min in Canada (9,34) to <80 mL/min in the U.S. (35) and <60 mL/min in the U.K. and Australia (8,36). Recommendations for dose reduction also vary by manufacturer, which may cause confusion and undue concern about fenofibrate use in patients with any level of renal impairment (34–37). Our current findings suggest that these thresholds may be too restrictive and that fenofibrate

dose reductions may not be required until eGFR falls below 30 mL/min/1.73 m^2.

Study limitations

Our study had limitations. The MDRD Study four-variable formula may underestimate true GFR, particularly when eGFR is ≥90 mL/min/1.73 m^2, but is more accurate at lower levels (38). However, our findings essentially were unchanged if analyzed using the Chronic Kidney Disease Epidemiology Collaboration (EPI-CKD) formula for derived GFR (7). The severity classification of eGFR is somewhat arbitrary, and within-individual variation in eGFR may have incorrectly allocated patients who were close to category cutoffs. However, baseline plasma creatinine and eGFR values in the FIELD Study were averaged over two pretreatment visits, and samples were analyzed at a central laboratory. In addition, the eGFR categories were based on standard clinical groupings to facilitate comparison with other studies. The number of patients in the group with eGFR 30–59 mL/min/1.73 m^2 was low compared with the other two groups, with fewer events. Despite this, there was a general pattern of greater risk reduction secondary to fenofibrate in this group compared with the other two across a wide range of individual and composite end points, although these were not statistically significant except for CVD mortality. Although there was a slight imbalance in the numbers of individuals with eGFR 30–59 mL/min/1.73 m^2 between treatment groups, this was minor and unlikely to have confounded the effect of fenofibrate on total CVD reduction because it did not differ consistently across groups of renal function. Patients with eGFR <30 mL/min/1.73 m^2 were excluded; therefore, the study cannot address the safety issues for this group, for whom reduced clearance of fenofibrate and its metabolites has been reported (39). In a previous study, patients with severe renal impairment had a greater unbound fraction of active fenofibrate metabolites than those with normal renal function. This increase is balanced by greater renal clearance, except when creatinine clearance falls below 20 mL/min, at which point the unbound concentration increases accordingly and dose reduction becomes necessary (39).

CONCLUSIONS—In the FIELD Study, fenofibrate did not increase CVD or renal risk in the setting of mild or moderate renal impairment in type 2 diabetes, despite causing an elevation in plasma creatinine. In those with pre-existing moderate renal impairment, the CVD benefits of fenofibrate were at least as great as in those with normal renal function, without any additional safety concerns. Therefore, fenofibrate at standard doses should be considered as an additional therapeutic option, along with conventional risk factor management, to further reduce CVD events and mortality and afford renoprotection in patients with type 2 diabetes, even in patients with moderate renal impairment.

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R.-D.T. researched data, contributed to the discussion, and wrote the manuscript. A.C.K. is the study guarantor, researched data, contributed to the discussion, and wrote the manuscript. P.L.D., A.J.J., T.M.E.D., R.J.S., and K.S. researched data, contributed to the discussion, and reviewed and edited the manuscript. M.W.D. and K.R. researched data and reviewed and edited the manuscript. J.H. researched data. S.L. reviewed and edited the manuscript. D.C. contributed to the discussion and reviewed and edited the manuscript. The authors had full access to all study data.

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The study was designed by an independent management committee and was coordinated by the NHMRC Clinical Trials Centre, University of Sydney. Two nonvoting representatives of the main sponsor attended meetings of the management committee.

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