After the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study: Implications for Fenofibrate

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The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study provides an extensive evidence base for the efficacy and tolerability of fenofibrate treatment in patients with type 2 diabetes mellitus, predominantly in a primary prevention setting. The FIELD study did not show a significant effect with fenofibrate on the primary end point, coronary artery disease death or nonfatal myocardial infarction ($p = 0.16$). Treatment with fenofibrate did reduce all cardiovascular disease (CVD) events, the secondary end point (by 11%, $p = 0.035$). The primary end point was reduced by the same percentage. The modest percent reduction in the primary and secondary end points is probably a result of a number of study confounders, notably an excess of statin drop-in therapy and disproportionate treatment with other drugs for CVD prevention in the placebo arm. Estimates of relative risk reduction used by the FIELD investigators to equalize the use of statins in the fenofibrate and placebo groups suggest a true benefit of treatment on reduction of CVD events of 17%–21%. There was no excess of elevated serum liver enzymes and no cases of rhabdomyolysis in patients receiving both fenofibrate and a statin. Prevention of microvascular disease, specifically, reduction in the rate of laser treatment for retinopathy (by 30%, $p = 0.0003$), progression of albuminuria ($p = 0.002$), and nontraumatic amputations (by 38%, $p = 0.011$), may well be the most innovative finding of the FIELD study, especially in view of the current lack of effective preventative treatments for diabetic retinopathy and the need for additional treatments that slow the progression of diabetic nephropathy. These findings also give impetus to investigate mechanisms by which fenofibrate and peroxisome proliferator-activated receptor–α activation may protect the endothelium of small blood vessels in patients with type 2 diabetes. **(Am J Cardiol 2008;102[suppl]:34L–40L)**

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[1] was designed to investigate whether fenofibrate was broadly therapeutic in patients with type 2 diabetes mellitus, regardless of lipid profile. The pharmacologic profile of fenofibrate indicates activity against atherogenic dyslipidemia typically observed in type 2 diabetes or metabolic syndrome (ie, elevated triglyceride levels and low high-density [HDL] lipoprotein cholesterol levels).

The design of the FIELD study was modeled on the Heart Protection Study. In the latter study, simvastatin, a drug that primarily lowers LDL cholesterol, was given to patients defined only by high risk of cardiovascular disease (CVD) and not by elevated plasma LDL cholesterol.[2] Thus, in the FIELD study, patients were enrolled if they had type 2 diabetes, a condition associated with high risk of CVD events, and not according to specific threshold concentrations of triglycerides or HDL cholesterol. They were randomized to treatment with fenofibrate or placebo against a background of usual care, including the option to add other lipid-lowering agents and drugs for CVD prevention.[1] This ethical approach was necessitated by findings from several studies before and during the FIELD study that showed that statins were beneficial in this setting.[3–5] The decision to initiate lipid-modifying therapy was based on the clinical judgment of the personal physician of each patient.

A Low-Risk Patient Population

Among populations of patients with type 2 diabetes, the FIELD study sample was considered to be at relatively low cardiovascular risk. At the start of the trial, most patients had been diagnosed with type 2 diabetes relatively recently (within a median of 5 years) and had a low prevalence of macrovascular and microvascular complications (22% and 21%, respectively).[1] The study population had good glycemic control at baseline, and this was maintained throughout the study (glycosylated hemoglobin was 6.9% at entry and at the end of study in the placebo group and 6.9% at entry

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Table 1
Baseline characteristics of patients with diabetes mellitus included in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, the Collaborative Atorvastatin Diabetes Study (CARDS), and the Heart Protection Study (HPS)

	FIELD (n = 9,795)	CARDS (n = 2,838)	HPS (n = 5,963)
Median duration of diabetes (yr)	5	8	9
Cardiovascular disease (%)	22	0	50
Microvascular complications (%)			
Retinopathy	8	30	NA
Albuminuria	3	17	NA
HbA_{1c} (%)	6.9	7.8	7.1
Lipid parameters (mean)			
LDL cholesterol (mg/dL)*	120	107	124
HDL cholesterol (mg/dL)*	43	54	41
Triglycerides (mg/dL)†	150	150	204
Mixed dyslipidemia (%)‡	38	NA	NA

HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not available.
* For cholesterol, 1 mg/dL = 0.02586 mmol/L.
† For triglycerides, 1 mg/dL = 0.0113 mmol/L.
‡ Mixed dyslipidemia was characterized by elevated triglycerides (≥150 mg/dL and HDL cholesterol <40 mg/dL in men and <50 mg/dL in women.

and 7.0% at the end of study in the fenofibrate group).[1] Such good glycemic control was achieved at baseline by either diet (24%) or a single hypoglycemic drug (34%), and only 14% required insulin.[1] There was also a low prevalence of mixed dyslipidemia at baseline. Only 38% of patients had elevated triglycerides (>150 mg/dL [1 mg/dL = 0.0113 mmol/L]) and low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women [1 mg/dL = 0.02586 mmol/L]), common clinical criteria for the consideration of lipid-modifying treatment.[6] In contrast, patients with diabetes included in the Heart Protection Study and the Collaborative Atorvastatin Diabetes Study had a longer duration of diabetes, and higher glycosylated hemoglobin values at baseline (Table 1).[4,5]

Confounding of Outcome Benefits

The primary end point in the FIELD study was a composite of coronary artery disease (CAD) death and nonfatal myocardial infarction (MI). The effect of fenofibrate on this end point was nonsignificant (relative risk reduction [RRR], 11%; p = 0.16). Although fenofibrate treatment significantly reduced the risk of nonfatal MI (by 24%, p = 0.01), there was a nonsignificant excess of cardiac mortality (relative risk +19%, p = 0.22). There was, however, a significant reduction in the secondary outcome, total CVD events (from 13.9% with placebo to 12.5% with fenofibrate; RRR, 11%; p = 0.035).[1] This effect was largely driven by a significant RRR for nonfatal MI and the need for coronary revascularization (by 21%, p = 0.003).[1]

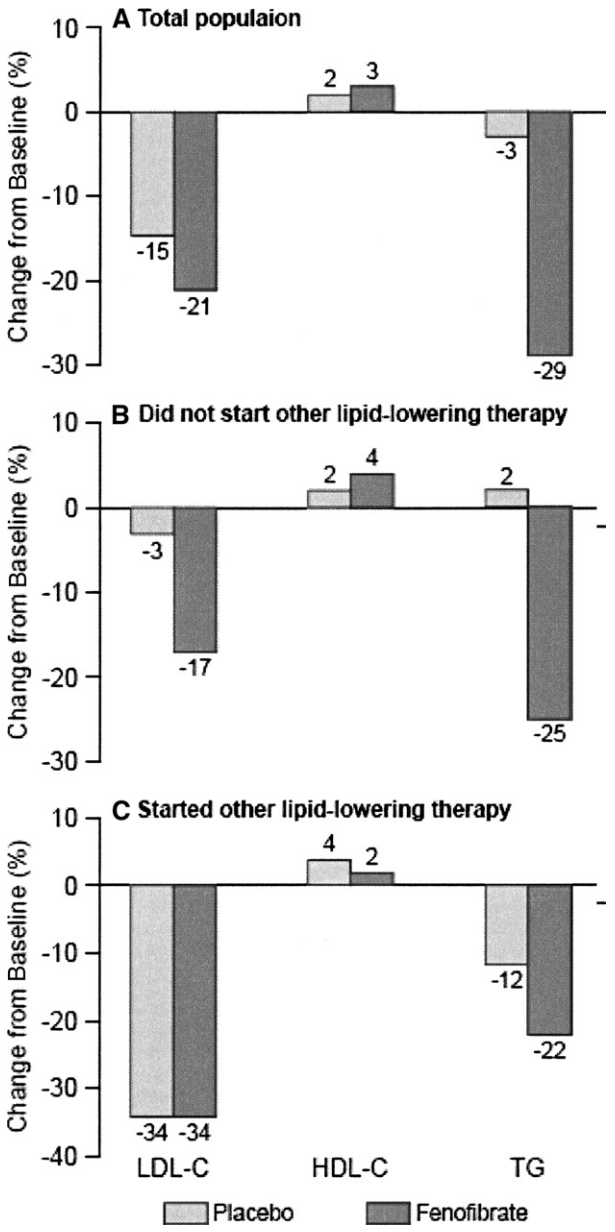

Figure 1. Changes in lipids in (*A*) the total Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study population, and in patient subgroups who (*B*) did not start and (*C*) did start lipid-lowering therapy. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides. (Adapted from *Lancet*.[1])

It is possible that the higher than anticipated drop-in rate for other lipid-lowering treatment may have masked the effect of fenofibrate on the primary end point and contributed to the observed effect on cardiac mortality. The FIELD Investigators had planned for a 10% drop-in rate in the placebo group during the study. Instead, the use of nonstudy lipid-lowering therapy (>90% statins) exceeded this; at study closure, 36% in the placebo group compared with 19% in the fenofibrate group were also receiving a statin.[1] In both treatment groups, patients who received add-on statin therapy showed a greater reduction in LDL cholesterol levels than those who did not (Figure 1).[1]

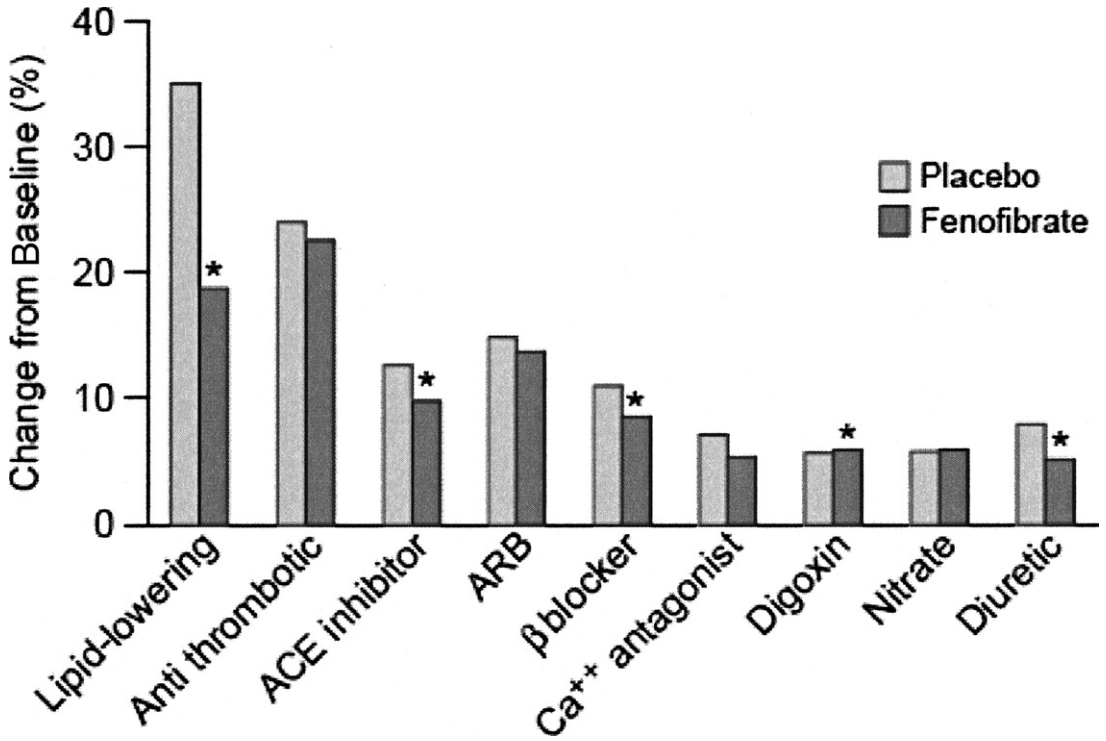

Figure 2. Changes in cardiovascular medication during the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker. *Significant differences at study close: lipid-lowering therapy, $p < 0.0001$; ACE inhibitor, $p = 0.003$; β-blocker, $p = 0.011$; digoxin, $p = 0.045$; diuretic, $p = 0.006$. (Adapted from *Lancet*.[1])

Concomitant medication data suggest that the standard of care was better for patients in the placebo group than the fenofibrate group. Along with greater use of lipid-modifying therapy, there was also more use of angiotensin-converting enzyme inhibitors, β-blockers, diuretics, and antiplatelet drugs in the placebo group compared with the fenofibrate group (Figure 2).[1] It is possible that the improved management of patients in the placebo group may have accounted for the smaller number of coronary deaths in the placebo group than in the fenofibrate group (93 vs 110, respectively).[1]

There was also a much greater use of statins in the patients who had a CVD event before starting the study, the "secondary prevention cohort," compared with the "primary prevention cohort."[1] Prescribing statins is a reasonable action by the patients' primary care physicians in light of the beneficial results in patients with type 2 diabetes in large statin trials of secondary prevention published while the FIELD study was in progress. In contrast, statin use in the placebo group in the primary prevention cohort of the FIELD study was modest. It seems likely that this explains the significant reduction in CVD risk in the primary prevention cohort in which the placebo group was only minimally confounded by statin use. Taken together, it is likely that the combination of these factors may have obscured the full effect of fenofibrate. Modeling to take account of these confounders suggested a real underlying effect of fenofibrate on the primary outcome of 17%–21%.[1]

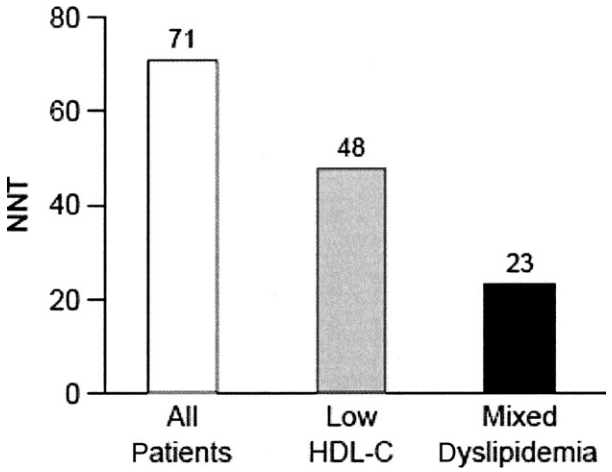

Figure 3. The effect of fenofibrate, as defined by the number of patients needed to treat to prevent 1 adverse outcome (NNT), was greater in patients with mixed dyslipidemia than in those without. HDL-C = high-density lipoprotein cholesterol. (Adapted from *Lancet*[1] and *Circulation*.[8])

Pronounced Benefit in the Primary Prevention Setting

As mentioned, subgroup analyses of the FIELD study data, including adjustment for statin use, showed that the benefit of fenofibrate was greater in patients with no prior CVD, both in the primary outcome (RRR, 25%; $p = 0.014$), as well as total CVD events (RRR, 19%; $p = 0.004$), compared with effects observed in patients with established CVD.[1]

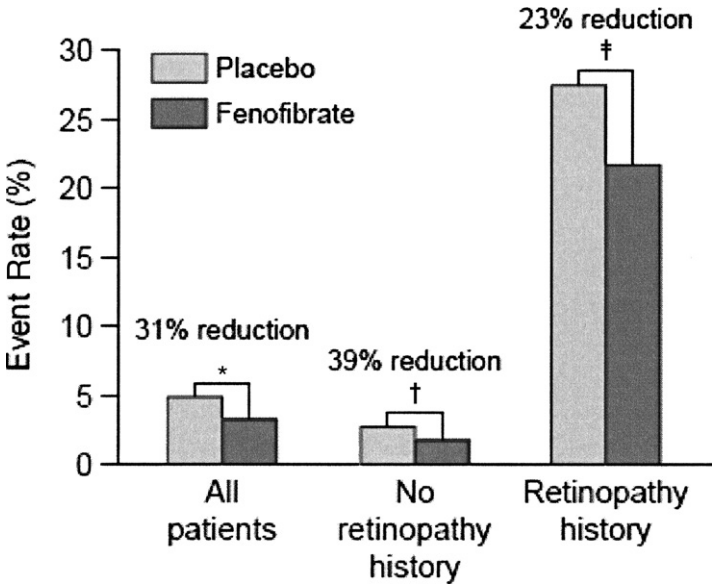

Figure 4. Effect of fenofibrate on laser treatment for diabetic retinopathy in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *p = 0.0002; †p = 0.0008; ‡p = 0.06. (Adapted from *Lancet*.[20])

These findings were consistent with those observed in the Heart Protection Study, in which statin treatment of patients without prior CVD was associated with a greater proportional reduction in the risk of first major vascular events over 5 years than that observed among those with established CVD (33% vs 19%).[4] These findings support recommendations for early initiation of lipid-modifying treatment, in addition to lifestyle intervention, in patients with type 2 diabetes in order to prevent a first CVD event.[7]

Greater Benefit in Mixed Dyslipidemia

Only 38% of patients in the FIELD study had mixed dyslipidemia, defined by increased triglycerides (≥150 mg/dL) and low HDL cholesterol.[6] Subgroup analyses showed that treatment with fenofibrate was particularly beneficial in this subgroup of patients (absolute risk reduction, 2.3%; RRR, 14%; p = 0.06).[1] In patients with mixed dyslipidemia, defined by elevated triglyceride (≥200 mg/dL) and low HDL cholesterol levels (<40 mg/dL in men and <50 mg/dL in women), the benefit of treatment was even greater (absolute risk reduction, 4.3%; RRR, 26%; p = 0.01).[8] It is especially notable that clinical benefit, expressed as the number needed to treat (the inverse of the absolute risk reduction), was >2-fold greater in each of these dyslipidemic subgroups (Figure 3).[1,8]

Results from other fibrate studies are consistent with this finding. For example, in the Helsinki Heart Study, a primary prevention study, the benefit of gemfibrozil treatment (1,200 mg/day) in patients with mixed dyslipidemia (triglycerides >204 mg/dL and LDL/HDL ratio >5) was twice that observed in the total study population, with an RRR for major coronary events of 71% (p <0.005) compared with 34% (p <0.02 in all patients).[9,10] Additionally, subgroup analysis of the Bezafibrate Study, a secondary prevention trial, showed enhanced benefit with bezafibrate in patients with the metabolic syndrome and mixed dyslipidemia (baseline HDL cholesterol, 33 mg/dL; and triglycerides, 170 mg/dL), with a 25% RRR (p = 0.03) for cardiovascular events compared with a nonsignificant effect in all study patients.[11] Moreover, there was even greater benefit in patients with triglycerides ≥200 mg/dL (RRR, 39.5%; p = 0.02).[12] The Veterans Affairs HDL Intervention Trial (VA-HIT) also demonstrated significantly greater reduction in cardiovascular risk with gemfibrozil treatment in CAD patients with diabetes and mixed dyslipidemia (RRR, 32%; p = 0.004) compared with those without diabetes (RRR, 18%; p = 0.07).[13] Thus, evidence of improved clinical benefit with fibrate therapy in patients with mixed dyslipidemia associated with type 2 diabetes or metabolic syndrome in the FIELD study and other fibrate trials reinforces current therapeutic practice to target fibrate treatment to these patient groups.[8,14,15]

Other Findings from the Fenofibrate Intervention and Event Lowering in Diabetes Study

Treatment with fenofibrate also led to reduction in hospitalization for angina pectoris (from 5.1% with placebo to 4.3%; RRR, 18%; p = 0.04).[16] Acute coronary syndromes, including unstable angina, are prevalent and confer substantial adverse prognosis in patients with diabetes. Subgroup analyses from 11 Thrombolysis in Myocardial Infarction (TIMI) study group clinical trials conducted from 1997–2006 showed that of 62,036 patients admitted with acute coronary syndromes, 17% had diabetes. Mortality at 30

days was significantly higher in these patients than in those without diabetes (2.1% vs 1.1%, p <0.001). The 1-year mortality was also 65% higher in patients with diabetes and acute coronary syndromes (hazard ratio, 1.65; 95% confidence interval, 1.30–2.10).[17] The finding that fenofibrate was effective in reducing hospitalization for unstable angina in this predominantly low-risk population is promising and warrants further investigation.

Microvascular Effects

Although macrovascular atherosclerotic disease is the main cause of mortality in patients with type 2 diabetes, microvascular complications are also common and associated with substantial morbidity. In the United States, diabetes is the leading cause of blindness and vision loss, end-stage renal disease, and nontraumatic amputations.[18] Moreover, given the increasing prevalence of diabetes (and metabolic syndrome) among an aging population,[19] the burden attributable to microvascular complications is likely to increase considerably in the future.

The FIELD study has demonstrated, for the first time for any lipid-modifying therapy, a significant reduction in the progression of diabetes-related retinopathy. There was a 30% reduction in the rate of laser treatment for retinopathy with fenofibrate treatment (from 5.2% to 3.6%, p = 0.0003). This effect was evident within the first year of treatment, and it increased over the 5-year period of the study.[1] In a recent analysis of the FIELD study retinopathy data, treatment with fenofibrate was shown to have a significant effect in reducing first laser treatment in patients with macular edema (from 3.4% to 2.4%; RRR, 31%; p = 0.002), as well as those with proliferative retinopathy (from 2.2% to 1.5%; RRR, 30%; p = 0.015). In patients without prior retinopathy, there was an even greater benefit (RRR, 39%; p = 0.0008) (Figure 4).[20] These positive findings gain validity from the fact that the investigators hypothesized benefit during the planning of the study and included retinopathy as a prospectively specified end point in the protocol. This hypothesis in part stemmed from early reports of favorable effects on diabetic eye disease with another fibrate, clofibrate.[21]

Fenofibrate treatment was also associated with other microvascular benefits. There was significant reduction in the evolution of albuminuria (with a decrease by 14% in the proportion of patients showing progression and an increase by 15% in those showing regression of albuminuria, p = 0.002).[1] These data support preliminary findings from the Diabetes Atherosclerosis Intervention Study (DAIS), in which treatment with fenofibrate significantly attenuated the worsening of albumin excretion in patients with type 2 diabetes,[22] discussed elsewhere in this supplement in an article by Dr. George Steiner.[23]

In addition, treatment with fenofibrate significantly reduced the number of nontraumatic amputations for peripheral artery disease by 38% (p = 0.011), which reflects both macrovascular and microvascular benefits.[16] These data suggest that fenofibrate may have favorable effects on small vessel repair and/or protect against capillary damage or leakage. In fact, recent in vitro data indicate that fenofibrate regulates retinal endothelial cell survival via the adenosine monophosphate–activated protein kinase signal transduction pathway, suggesting an effect on retinal leakage independent of lipid effects.[24] As alluded to by Keech et al,[20] further studies are clearly required to investigate the mechanism(s) of these effects reported by the FIELD study.

Tolerability Profile

Consistent with available evidence,[25] the FIELD study data show that fenofibrate is a well-tolerated treatment. Although there was a small increase in rare adverse events of pancreatitis (0.8% vs 0.5%, p = 0.031) and pulmonary embolism (1.1% vs 0.7%, p = 0.022), there were no other significant adverse events.[1] Findings relating to pancreatitis are not inconsistent with the activity of fibrates, which have all been shown to stimulate increased biliary excretion of cholesterol, leading in turn to a substantial increase in the biliary cholesterol saturation index.[26] The effect of fenofibrate on pulmonary embolism, however, has not been reported in other studies of fenofibrate or fibrates in general and is still under investigation by the FIELD Study Scientific Committee.

The potential for myopathy is a concern in fibrate therapy, although evidence suggests that the risk is much lower with fenofibrate than with other fibrates, such as gemfibrozil. Data from the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) over the period 1999–2002 showed that the rate of rhabdomyolysis was >10-fold lower with fenofibrate monotherapy compared with gemfibrozil monotherapy (5.5 vs 59.6 per million prescriptions dispensed for each agent). In addition, the rate of myopathy (excluding rhabdomyolysis) was about 2-fold lower with fenofibrate compared with gemfibrozil (8.8 vs 15.7 per million prescriptions dispensed).[27] Data from the FIELD study are consistent with this favorable tolerability profile. There was no significant difference between the placebo and fenofibrate groups in the incidence of elevation in creatine phosphokinase (>10 × upper limit of normal, 3 vs 4 patients, respectively) or rhabdomyolysis (1 vs 3 patients, respectively).[1]

In patients with mixed dyslipidemia common in type 2 diabetes or metabolic syndrome, the combination of a fibrate and a statin is a recommended strategy for achieving all lipid targets.[7,14] Concern about the risk of myopathy when these agents are administered together may, however, limit the use of this combination. The evidence supports a lower potential risk for myopathy with the combination of fenofibrate and a statin compared with gemfibrozil and a statin. Data from the FDA AERS show that when administered with a statin, fenofibrate combination therapy was

associated with a 15-fold lower risk of rhabdomyolysis than gemfibrozil statin combination therapy (8.6 vs 0.58 cases per million prescriptions dispensed) (data for cerivastatin excluded).[28] Furthermore, there were no cases of rhabdomyolysis in about 1,000 patients in the FIELD study who received both fenofibrate and statin.[1] Experimental studies show that, unlike fenofibrate, gemfibrozil and statins are both metabolized by the same family of glucuronidases.[29] These data suggest a much higher likelihood of pharmacokinetic drug interaction when gemfibrozil rather than fenofibrate is administered with a statin, as confirmed in recent pharmacokinetic interaction studies.[30]

During the FIELD study, plasma creatinine levels were on average higher by 10–12 μmol/L in the fenofibrate than placebo groups, although in a subset of patients restudied 8 weeks after discontinuing study treatment, plasma creatinine levels had decreased to levels below those observed in the placebo group.[1] However, fenofibrate was associated with significant reduction in progression of albuminuria in the FIELD and DAIS studies[1-3] (see above), indicating no impairment of renal function during the 5 years of fenofibrate treatment.

There was also a small nonsignificant excess of non-CVD deaths with fenofibrate. This was investigated by the FIELD study investigators. However, because there was no evidence that this finding was attributable to any specific cause of death or linked to any significant increase in any specific nonfatal non-CVD event, such as invasive cancer, the FIELD study investigators concluded that this was a chance finding.

Taken together, the FIELD study adds to the available evidence supporting guideline recommendations[7,31] that fenofibrate is a well-tolerated treatment option in dyslipidemia management in type 2 diabetes, most likely in combination with a statin. Moreover, a recent health economic analysis of the FIELD study conducted from the perspective of the third party payer, showed that fenofibrate therapy resulted in an approximate 10% reduction in healthcare costs driven mainly from decreases in nonfatal MI risk and coronary revascularization, or supplementary statin therapy.[32] These data suggest potential longer-term cost advantages associated with initiation of fenofibrate therapy in this patient population. Although the FIELD study provides some data on the combination of fenofibrate with a statin, there is also a clear need for data from ongoing outcomes studies to evaluate the efficacy and tolerability of this combination.

Conclusion

The FIELD study aimed to evaluate the role of fenofibrate therapy in reducing CVD risk in patients with type 2 diabetes, predominantly in a primary prevention setting. In this study population, fenofibrate treatment was associated with significant macrovascular and microvascular benefits. Although it is acknowledged that the study failed to show a significant beneficial effect on the primary outcome (major coronary events), a number of confounders may have contributed to this finding.

The FIELD study data need to be considered within the context of statin therapy, which is the main focus of dyslipidemia management in patients with diabetes or metabolic syndrome. Although statins are effective in lowering LDL cholesterol, a substantial proportion of patients fail to achieve all recommended lipid targets, most notably those for triglycerides, HDL cholesterol, and non-HDL cholesterol, and they remain at higher cardiovascular risk. The FIELD study data suggest that the addition of fenofibrate to statin therapy may be a logical, well-tolerated option for reducing this residual risk. Furthermore, the FIELD study indicates that early initiation of fenofibrate treatment may prevent or limit the development of diabetes-related microvascular complications, specifically, retinopathy and nephropathy, which confer substantial disease morbidity. Clearly, further study is needed to evaluate whether this combination provides outcome benefits and is safe. We await with interest the results of ongoing studies, the first of which (ACCORD)[33] are expected in 2009.

Key points:

- Fenofibrate may be effective in reducing cardiovascular risk in patients with type 2 diabetes, particularly in those with mixed dyslipidemia
- Fenofibrate is well tolerated
- Treatment with fenofibrate provides microvascular benefits; these effects require further study
- Early initiation of fenofibrate (most likely in addition to a statin) is likely to be of greatest benefit in the primary prevention setting

Author Disclosures

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