Optimizing Cardiovascular Outcomes in Patients with Type 2 Diabetes—Clinical Implications of the FIELD Results

a report by
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High Residual Cardiovascular Risk in Diabetic Patients Treated with Statins

According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), diabetes is a coronary heart disease (CHD) risk equivalent.[1] One major factor contributing to the excess risk of cardiovascular disease (CVD) in patients with type 2 diabetes mellitus (T2DM) is atherogenic dyslipidemia, characterized by high triglycerides, 'average' low-density lipoprotein (LDL)-cholesterol with an increased number of small, dense LDL particles, and low high-density lipoprotein (HDL)-cholesterol.[1] The NCEP ATPIII guidelines indicate that lowering LDL-cholesterol is the first priority of lipid-lowering therapy.[1] Elevated triglycerides and low HDL-cholesterol are independent risk factors for CVD,[1] and statin therapy does not eliminate the residual CVD risk associated with high triglycerides[4,5] or low HDL-cholesterol.[4–6]

Recent statin trials such as the Heart Protection Study (HPS), which included a subgroup of 5,963 diabetic patients,[7] and the Collaborative Atorvastatin Diabetes Study (CARDS), which enrolled 2,838 T2DM patients,[8] revealed that lowering LDL-cholesterol reduced any major CVD event by 22–32%; however, residual CVD risk remained in these patients after statin therapy (see *Figure 1*).

While this concept of residual CVD risk is true in all patients treated with statins, after diabetic patients are treated with statins their CVD event rates remain higher than the CVD event rates of untreated patients without diabetes (see *Figure 2*). Lipid-modifying therapies that improve triglyceride and HDL-cholesterol abnormalities may reduce the residual CVD risk remaining after optimal statin therapy, especially in patients with diabetes.

Increasing the Evidence Base for Fibrate Use

Clinical trials have demonstrated that fibrate therapy can reduce CVD risk, particularly for patients with atherogenic dyslipidemia and/or diabetes. Among the subgroup of highest-risk subjects (triglyceride levels >204 mg/dl and an LDL/HDL ratio >5) in the Helsinki Heart Study (HHS), gemfibrozil provided a significant 71% reduction in CHD events.[9] In HHS patients with diabetes, gemfibrozil reduced CHD events by 68% ($p = 0.19$).[10] The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) revealed that gemfibrozil significantly reduced CHD events by 32%, CHD death by 41%, and stroke by 40% in the subgroup of patients with diabetes, and this occurred with no significant reduction in LDL-cholesterol.[11] The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was the largest placebo-controlled clinical CVD outcomes study conducted with lipid-modifying therapy in patients with T2DM ($n = 9,795$)[12–14] and has contributed important information about the clinical utility of fenofibrate in this patient population.

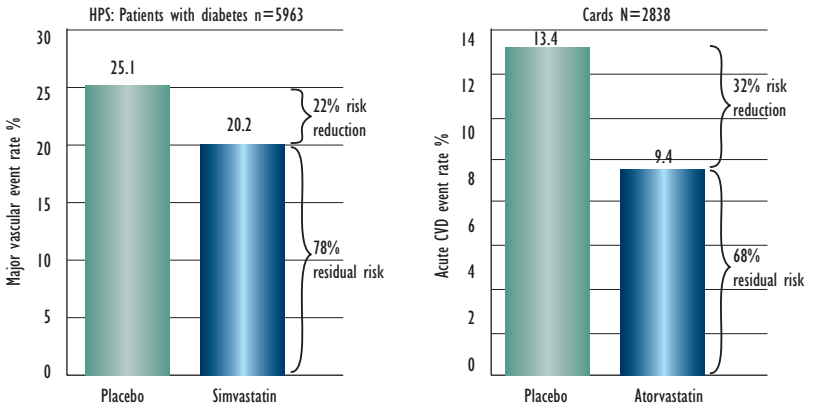
FIELD Trial Results and Clinical Implications

FIELD—Study Design and Study Population

All patients in FIELD had no clear indication for lipid-modifying treatment at study entry.[14] The median duration of the diagnosis of diabetes was five years, and patients' blood glucose levels were well controlled both at baseline and throughout the study.[14] Baseline lipid parameters were mean total cholesterol, 195mg/dl; LDL-cholesterol, 119mg/dl; HDL-cholesterol, 43mg/dl; and median triglyceride, 154mg/dl. Only 38% of patients met the trial definition of dyslipidemia (triglycerides >150mg/dl and HDL <40mg/dl for men or <50mg/dl for women) at baseline.[14] Furthermore, 78% of patients had no history of CVD. Thus, the majority of patients in FIELD were in the early stage of diabetes, with optimally controlled glucose levels, 'average' lipid levels, and no history of CVD.

Unforeseen at the start of the study, FIELD was a trial

Figure 1: Residual CVD Risk in Diabetic Patients Treated with Statins



Simvastatin therapy reduced CVD risk by 22% in the Heart Protection Study (HPS),[7] and atorvastatin therapy reduced CVD risk by 32% in the Collaborative Atorvastatin Diabetes Study (CARDS).[8] Nevertheless, significant residual cardiovascular risk remained in diabetic patients treated with statins in HPS and CARDS (78% and 68%, respectively).

Figure 2: Residual CVD Risk Remaining after Statin Treatment in Patients with and without Diabetes

	Event rate (no diabetes)		Event rate (diabetes)	
	On statin	On placebo	On statin	On placebo
HBS*(CHD patients)	19.8%	25.7%	33.4%	37.8%
CARE†	19.4%	24.6%	28.7%	36.8%
LIPID‡	11.7%	15.2%	19.2%	22.8%
PROSPER§	13.1%	16.0%	23.1%	18.4%
ASCOTT-LLA‡	4.9%	8.7%	9.6%	11.4%
TNT	7.8%	9.7%	13.8%	17.9%

Residual CVD risk remains in all patients treated with statins; however, residual CVD risk is particularly high in patients with diabetes treated with statins. Even after patients with diabetes were treated with statins, their CVD event rates (i.e. residual CVD risk) in large-scale clinical trials were higher than the CVD event rates of those patients without diabetes on placebo. Thus, statins reduce but do not eliminate the increased CVD risk associated with diabetes. HPS = Heart Protection Study (simvastatin),[7] CARE = Cholesterol and Recurrent Events (pravastatin),[24] LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease (pravastatin),[25] PROSPER = Prospective Study of Pravastatin in the Elderly at Risk (pravastatin),[6] ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (atorvastatin),[26] TNT = Treating to New Targets (atorvastatin 10 mg versus 80 mg).[27]

**CHD death, non fatal MI, stroke, revascularizations*

†CHD death, non fatal MI, CABG, PTCA

‡CHD death and non fatal MI

§CHD death, non fatal MI, stroke

CHD death, non fatal MI, resuscitated cardiac arrest, stroke

that was designed and enrolled in one era of risk assessment and lipid-lowering therapy (1990s) and finished in another era (2000s). The FIELD study design did allow for lipid-lowering therapy to be added by the patients' healthcare providers if clinically indicated after randomization (1998–2000). By the end of the study, 36% of placebo and 19% of fenofibrate patients ($p < 0.0001$) were taking non-study lipid-lowering therapy (>93% were statins).[14] The substantial statin drop-in rates in FIELD were most likely a result of the 2001 publication of the NCEP ATPIII guidelines,[1,15] which reclassified diabetes from a risk factor to a CHD risk equivalent, and the 2002 publication of the HPS results,[5] which suggested all high-risk patients should be taking a statin regardless of baseline LDL-cholesterol. The advances in treatment guidelines likely contributed to the increased statin use in the FIELD study population, even though their lipid levels at baseline did not make them obvious candidates for lipid-lowering therapy.

FIELD—Cardiovascular Disease Outcomes

Fenofibrate reduced the primary end-point of CHD events by 11% ($p = 0.16$). An analysis of the individual components of the primary end-point indicated that fenofibrate significantly reduced non-fatal myocardial infarctions (MIs) by 21% ($p = 0.01$) but did not have a significant effect on CHD death (see *Figure 3*). Fenofibrate significantly reduced the secondary end-point of total CVD events by 11% ($p = 0.035$) and coronary revascularizations by 21% ($p = 0.003$) (see *Figure 3*).[14] The absolute risk reduction of CVD events was highest in patients with dyslipidemia (2.3%), consistent with results of other fibrate trials.[9,16]

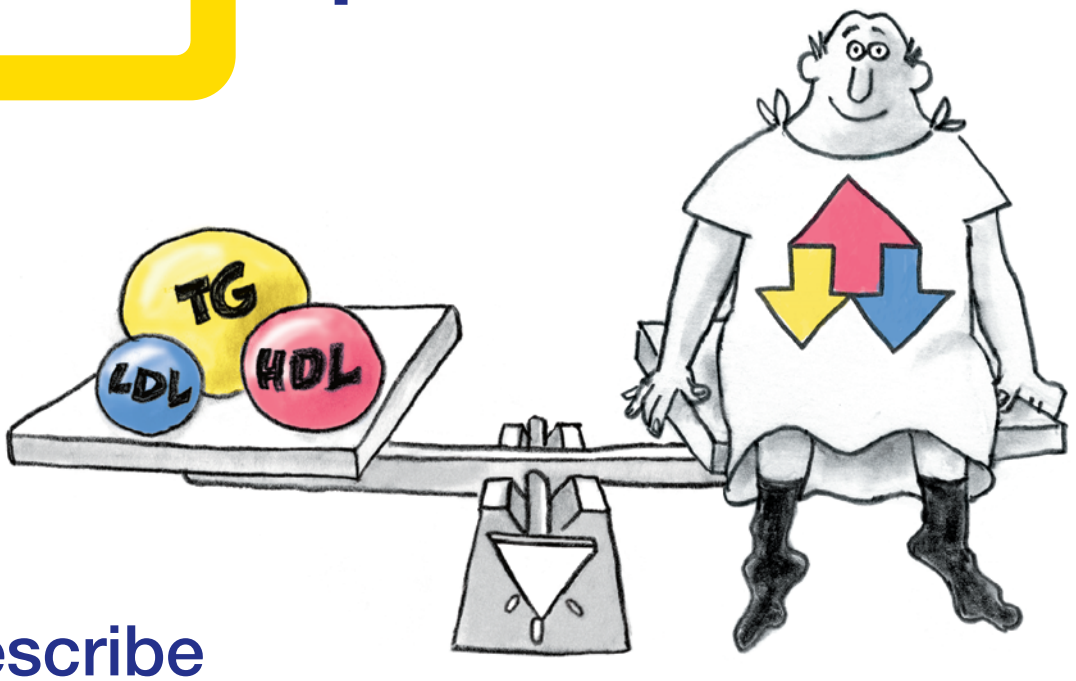
Fenofibrate treatment had a particularly beneficial effect in 78% of the population who had no prior CVD. In these patients, fenofibrate significantly reduced both the incidence of the primary end-point (CHD events) by 25% ($p = 0.014$) and the incidence of the secondary end-point (total CVD events) by 19% ($p = 0.004$) (see *Figure 4*). In contrast, fenofibrate did not have a significant effect on CHD or CVD events in 22% of the population who had prior CVD. As may be expected, the proportion of statin drop-ins was higher in patients who had prior CVD,[14] making the on-treatment LDL-cholesterol levels in the treated and placebo groups nearly identical, and this may explain why the use of fenofibrate did not appear to reduce the incidence of CHD events in these patients.

The placebo group five-year CHD event rate of 5.9% is remarkably low for patients with T2DM. The low rate of CHD events in the 'high-risk' placebo group in FIELD raises the question of whether CHD events alone are a meaningful clinical trial end-point given the continuing improvement of background usual care. It has been suggested that a broader composite of total CVD events may be a more appropriate end-point than CHD events both in prevention trials and risk prediction in clinical practice.[17]

The relatively low CHD risk of the FIELD patient population as well as the disproportionate placebo drop-in use of statins may have masked some of the benefit of fenofibrate on cardiovascular outcomes. A similar argument can be made for two recent trials that failed to show a benefit of atorvastatin in

In the mixed dyslipidemic patient

Weigh all three lipid risk factors



Prescribe

TriCor® 145 mg
fenofibrate tablets & **48 mg**

- Significant improvement across key lipid parameters vs placebo[1]
  —Increased HDL-C —Reduced TG —Reduced LDL-C
- Established safety profile[1]

Type IIa/IIb Indications[1]: •TriCor is indicated as adjunctive therapy to diet in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson types IIa and IIb) to: increase high-density lipoprotein cholesterol (HDL-C), reduce triglycerides (TG), reduce low-density lipoprotein cholesterol (LDL-C), reduce total cholesterol (Total-C), reduce apolipoprotein B (Apo B). •Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and nonpharmacological interventions alone has been inadequate.

Important Safety Information[1]: •TriCor is contraindicated in patients with: hypersensitivity to fenofibrate; hepatic or severe renal dysfunction including primary biliary cirrhosis; unexplained persistent liver function abnormality; and preexisting gallbladder disease. •Fenofibrate has been associated with increases in serum transaminases. Regular liver function monitoring should be performed, and therapy discontinued if enzyme levels persist >3 times the normal limit. •Fenofibrate may lead to cholelithiasis. If cholelithiasis is confirmed, TriCor should be discontinued. •TriCor may increase the effects of coumarin-type anticoagulants. Dosage adjustment based on frequent prothrombin time/INR determinations is advisable. •The combined use of TriCor and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk. This combination has been associated with rhabdomyolysis, markedly elevated creatine kinase levels and myoglobinuria, leading to acute renal failure. •TriCor may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Muscle pain, tenderness, or weakness should have prompt medical evaluation. Discontinue TriCor if markedly elevated CPK levels occur or myopathy/myositis is suspected or diagnosed. •The effect of TriCor on coronary heart disease morbidity and mortality and noncardiovascular mortality has not been established. •Other precautions include pancreatitis, hypersensitivity reactions, and hematologic changes. •Adverse events most frequently observed in clinical trials: abnormal liver function tests; respiratory disorder; abdominal pain; back pain; and headache.

Reference: 1. TriCor tablets package insert, Abbott Laboratories.

www.tricortablets.com

Please see adjacent brief summary of Full Prescribing Information

Solvay Pharmaceuticals

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A Promise for Life

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

TRICOR® 48 mg and 145 mg
(fenofibrate tablets)

℞ only

CONTRAINDICATIONS
TRICOR is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

TRICOR is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

TRICOR is contraindicated in patients with preexisting gallbladder disease (see **WARNINGS**).

WARNINGS
Liver Function: Fenofibrate at doses equivalent to 96 mg to 145 mg TRICOR per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 96 mg to 145 mg TRICOR per day and was 0% in those receiving dosages equivalent to 48 mg or less TRICOR per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with TRICOR , and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. TRICOR therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with TRICOR because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA Reductase Inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) and pravastatin (40 mg) once daily for 10 days increased the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3α-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively.

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRICOR and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRICOR therapy should be stopped.

Mortality: The effect of TRICOR on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Other Considerations: In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between TRICOR (fenofibrate tablets), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to TRICOR .

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

PRECAUTIONS
Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting TRICOR therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of TRICOR. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 145 mg per day.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs. 0%, and rash in 1.4 vs. 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of TRICOR administration.

Skeletal muscle: The use of fibrates alone, including TRICOR, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions

Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.

HMG-CoA reductase inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take TRICOR at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including TRICOR (fenofibrate tablets), there is a risk that an interaction will lead to deterioration. The benefits and risks of using TRICOR with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD) of 145 mg/day, based on mg/meter^2 of surface area). At a dose of 200 mg/kg/day (at 6 times the MRHD), the incidence of liver carcinomas was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24-month study in a different strain of rats, doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD based on mg/meter^2 surface area) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD (200 mg/kg/day).

A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg/day; 2 times the human dose), and Gemfibrozil (250 mg/kg/day; 2 times the human dose) (multiples based on mg/meter^2 surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21-month study in mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 0.7, and 3 times the MRHD on the basis of mg/meter^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18-month study at the same doses, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD. Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

Pregnancy Category C: Safety in pregnant women has not been established. Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose (MRHD) and embryocidal in rabbits when given at 9 times the MRHD (on the basis of mg/meter^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of approximately 9 times the MRHD of 145mg/day of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of approximately 10 times the MRHD to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of approximately 7 times the MRHD to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of fenofibrate at 9 to 18 times the MRHD to female rabbits caused abortions in 10% to 25% of dams and death in 7% of fetuses at 18 times the MRHD.

Nursing mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS
CLINICAL: Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4% **	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 145 mg TRICOR

** Significantly different from Placebo

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

BODY AS A WHOLE: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.

CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.

DIGESTIVE SYSTEM: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.

ENDOCRINE SYSTEM: Diabetes mellitus.

HEMIC AND LYMPHATIC SYSTEM: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.

METABOLIC AND NUTRITIONAL DISORDERS: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.

MUSCULOSKELETAL SYSTEM: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.

NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.

RESPIRATORY SYSTEM: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, allergic pulmonary alveolitis, pneumonia, laryngitis, and sinusitis.

SKIN AND APPENDAGES: Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.

SPECIAL SENSES: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.

UROGENITAL SYSTEM: Urinary frequency, prostatic disorder, dysuria, abnormal kidney function, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

OVERDOSAGE
There is no specific treatment for overdose with TRICOR . General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

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reducing CHD events in patients with diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN)[18] and the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA).[19] All patients in ASPEN (n = 2,410) and a subgroup of ASCOT-LLA patients (n = 2,532) had T2DM, and the majority of patients had no history of CVD, 'average' lipid parameters, and low placebo CHD event rates (ASPEN, 5.5%;[18] ASCOT-LLA, 3.6%[19]). Furthermore, all three trials spanned the same time period in which advances were made in the treatment guidelines for diabetic patients, and this probably contributed to the high end-of-study statin drop-in rates in the trials (FIELD, 36%;[14] ASPEN, 27%;[18] ASCOT-LLA, 14%[19]).

The ASPEN trial did not meet any of its cardiovascular end-points in the overall population or in the subgroups of patients with or without a history of CVD. Although ASCOT-LLA did not meet its primary end point of CHD events, atorvastatin significantly reduced total CVD events by 23%.[19] These three trials indicate that the types of patients recruited, the trial design, changing treatment guidelines (statin drop-ins), and continued improvement in usual care may obscure the beneficial effect of the study drug.

FIELD—Microvascular Disease Outcomes

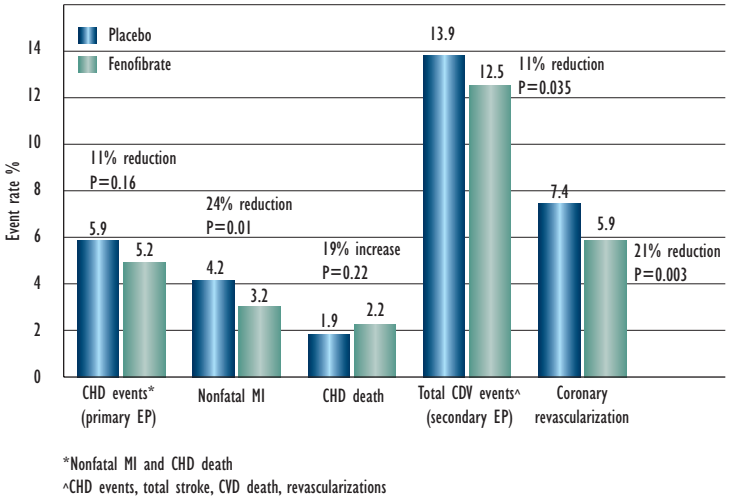
Fenofibrate significantly improved microvascular disease. The need for laser treatment for retinopathy was reduced by a highly significant 30% (p = 0.0003) and the rate of progression to albuminuria was reduced by 14%, while 15% of patients regressed (p = 0.002 for combined effect) (see *Figure 5*).[14] These results were consistent with findings from the quantitative angiography trial, Diabetes Atherosclerosis Intervention Study (DAIS), which revealed that fenofibrate was associated with reduced progression from normal albumin excretion to microalbuminuria.[20] Fenofibrate's beneficial effects on retinopathy and renal protein excretion need further confirmation in clinical trials since these are important clinical outcomes in the overall management and quality of life of patients with diabetes.

FIELD—Safety Outcomes

Fenofibrate treatment was well tolerated, with patients taking placebo experiencing similar adverse events. Pancreatitis and pulmonary embolism, although of low incidence, occurred at a significantly higher rate in fenofibrate patients.[14] Median plasma creatinine levels were 14% higher in the fenofibrate group at study end, compared with placebo (p <0.001); however, these fenofibrate-associated increases in creatinine were not associated with acute renal insufficiency and were reversible in a subgroup of patients eight weeks after ceasing therapy.[14]

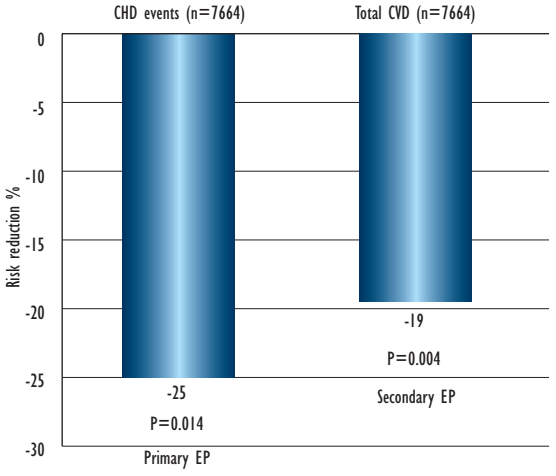
Plasma levels of homocysteine were 35% higher in fenofibrate patients at study end; this elevation has been observed previously and was also reversible in a subgroup of patients eight weeks after ceasing therapy.[14] Whether elevated serum homocysteine is a risk factor for CVD is not clear, but recent clinical trials of folate treatment to reduce homocysteine levels has not reduced CVD events.[21,22] Analysis of the

Figure 3: FIELD—Cardiovascular End-points in Overall Population



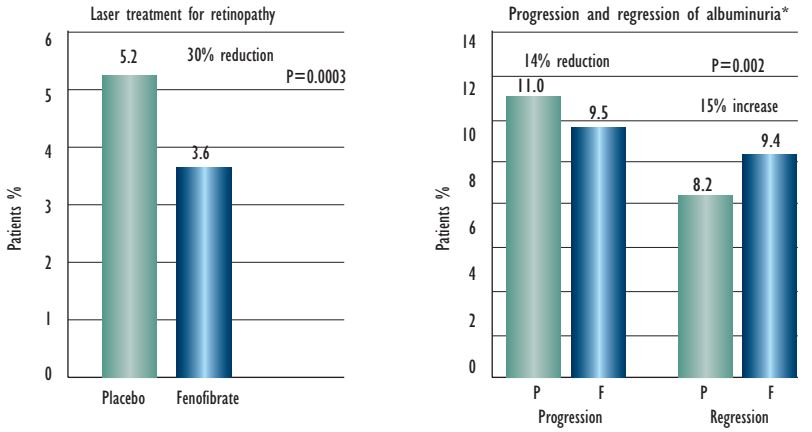
Fenofibrate significantly reduced the incidence of non-fatal myocardial infarctions (MI), total CVD events (secondary end-point (EP)), and coronary revascularizations. The incidence of CHD events (primary EP) was reduced by 11% (p = 0.16).[14]

Figure 4: FIELD—Cardiovascular End-points in Patients With No Prior CVD



In FIELD, 78% of the study population had no prior history of CVD (n = 7,664). In this primary prevention population, fenofibrate significantly reduced the incidence of the primary end-point (CHD events) by 25% (p = 0.014) and significantly reduced the incidence of the secondary end-point (total CVD events) by 19% (p = 0.004).[14]

Figure 5: FIELD—Microvascular Disease End-points



**Progression of albuminuria was defined as the proportion of patients who progressed either from normoalbuminuria to microalbuminuria or from microalbuminuria to macroalbuminuria.*
Fenofibrate significantly improved at least two indicators of microvascular disease. Patients treated with fenofibrate (F) experienced a significantly lower incidence of laser treatment for retinopathy (p = 0.0003) and a significantly reduced progression and increased regression of albuminuria (p = 0.002), compared with those patients treated with placebo (P).[14]

DAIS results revealed that the fenofibrate-mediated increase in homocysteine did not correlate with any adverse clinical events and did not attenuate the beneficial effects of fenofibrate on coronary atherosclerosis progression.[23]

Although a significant proportion of patients were taking fenofibrate plus a statin (as many as 19% in the fenofibrate arm by study end), there were few clinically significant muscle-related adverse events in either group.[14] Only three out of the 9,795 patients experienced myositis (two fenofibrate and one placebo), and four patients experienced rhabdomyolysis (three fenofibrate and one placebo).[14] Each case of rhabdomyolysis fully resolved after discontinuation of therapy, and none of the patients with rhabdomyolysis were on combination therapy with a statin. Furthermore, the incidence of alanine aminotransferase (ALT) and creatine phosphokinase (CPK) elevations was not significantly different between treatment groups. This trial may provide important corroborating evidence that fenofibrate therapy is safe when combined with statins, and further analysis of this subgroup is anticipated.

Conclusions

Lipid management guidelines emphasize the high-risk status of patients with T2DM and the importance of intensive LDL-cholesterol lowering. However, residual CVD risk remains in patients with T2DM on statin therapy compared with non-diabetic patients who are untreated (see *Figure 2*). This excess risk may be due to components of atherogenic dyslipidemia other than LDL-cholesterol (i.e., high triglycerides and low HDL-cholesterol).[4–6]

Fibrates are particularly effective at reducing CVD risk in patients with atherogenic dyslipidemia and/or diabetes, and the FIELD trial confirms and extends data from previous fibrate trials on CVD event reduction in patients with diabetes.[10-11] Fenofibrate significantly reduced the incidence of non-fatal MI by 24%, total cardiovascular events by 11%, and coronary revascularizations by 21% in the overall population.[14] In patients with no prior CVD, fenofibrate significantly reduced both the primary end-point of CHD events by 25% and the secondary end-point of total CVD events by 19%.[14]

Other important findings from FIELD suggest improvement in diabetic microvascular disease, such as reduced laser therapy for retinopathy and less progression to and more regression of albuminuria. The majority of patients in FIELD had low CHD risk (ie, early stage of diabetes, optimally controlled glucose levels, 'average' lipid levels, and no history of CVD), and there was a two-fold greater number of placebo compared with fenofibrate patients receiving statin therapy; these factors undoubtedly had a blunting effect on the trial outcomes, yet there were significant benefits with fenofibrate.

Future subanalyses of cardiovascular event rates in placebo-treated patients with add-on statins versus fenofibrate patients with add-on statins should yield important information about fenofibrate's safety and its incremental benefit on residual CVD risk.

In summary, the FIELD results increase the evidence for use of fenofibrate as a monotherapy option for patients without CVD who have diabetes and an atherogenic dyslipidemia with an average LDL-cholesterol level. The concomitant use of fenofibrate with statins may significantly reduce residual CVD risk in these patients, and we await the results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial to provide the answer. ■

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