Treating the Common Dyslipidemia in Patients with Type 2 Diabetes: Insights from FIELD on the Effects of Fenofibrate on CVD Risk

a report by

Sergio Fazio, MD, PhD

Professor of Medicine and Pathology, Atherosclerosis Research Unit, Departments of Medicine and Pathology, Division of Cardiovascular Medicine, Vanderbilt University Medical Center

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Sergio Fazio, MD, PhD, is Professor of Medicine and Pathology in the atherosclerosis research unit in the departments of medicine and pathology in the division of cardiovascular medicine at Vanderbilt University Medical Center in Nashville, Tennessee. He is also the Co-director of the Lipid Clinic an Atherosclerosis Research Unit, and director of the Lipid Laboratory. Dr Fazio has served on review panels with both the National Institutes of Health (NIH) and the American Heart Association (AHA). He also regularly serves as *ad hoc* reviewer for many scientific publications, and is an editorial board member of *Arteriosclerosis, Thrombosis, and Vascular Biology*, and *Journal of Clinical Endocrinology and Metabolism*. Dr Fazio's work has been published in many leading journals, including *Science*, *Journal of Clinical Investigation*, *Circulation*, and *Nature Medicine*. He is an invited presenter at medical and scientific conferences, both nationally and internationally, and holds research grants from the AHA and the NIH. After a clinical fellowship in metabolism at the University of Rome and a research fellowship at the Cardiovascular Research Institute, University of California, San Francisco (UCSF), he was promoted to Instructor in medicine at UCSF before joining the medical faculty at Vanderbilt University. Dr Fazio earned a PhD in molecular biology from the University of Siena, Italy, having graduated from the medical school of the University of Rome, Italy, and completed his internship and residency in internal medicine at this same institution.

Current Indications for Statin and Fibrate Therapy

The evidence of cardiovascular protection afforded by statins has recently extended beyond patients with hypercholesterolemia. With the publication of several trials,[1-7] bold extrapolations of the power of statin therapy in cardiovascular prevention have been offered:

1. Statins equally reduce risk in subjects with or without hypercholesterolemia

2. Statins may be the first choice in patients with diabetes; and

3. The guideline goal for LDL-cholesterol may need to be lowered to 70mg/dL. Thus, it seems that statin therapy may become necessary in high-risk individuals, even in the absence of dyslipidemia and possibly even when LDL-cholesterol levels are <100mg/dL. However, it should be emphasized that the optional goal of LDL-cholesterol levels <70mg/dL applies only to individuals who are very high-risk (i.e. established CVD plus multiple major risk factors), as there are potential side effects of using high statin doses to reduce LDL-cholesterol to very low levels.[8]

Similar momentum has been building for fibrates. These agents were originally indicated for patients with severely high triglyceride levels. However, the benefit of fibrates has recently been extended to treat the atherogenic dyslipidemia that afflicts most patients with type 2 diabetes, which is characterized by high levels of triglycerides, LDL particles that are small and dense, and low levels of HDL-cholesterol.[9-11] The FIELD study, discussed in detail below, provides important data regarding the potential for fenofibrate to reduce cardiovascular risk in patients with type 2 diabetes both with and without dyslipidemia.

Treatment of Atherogenic Dyslipidemia to Reduce Cardiovascular Risk

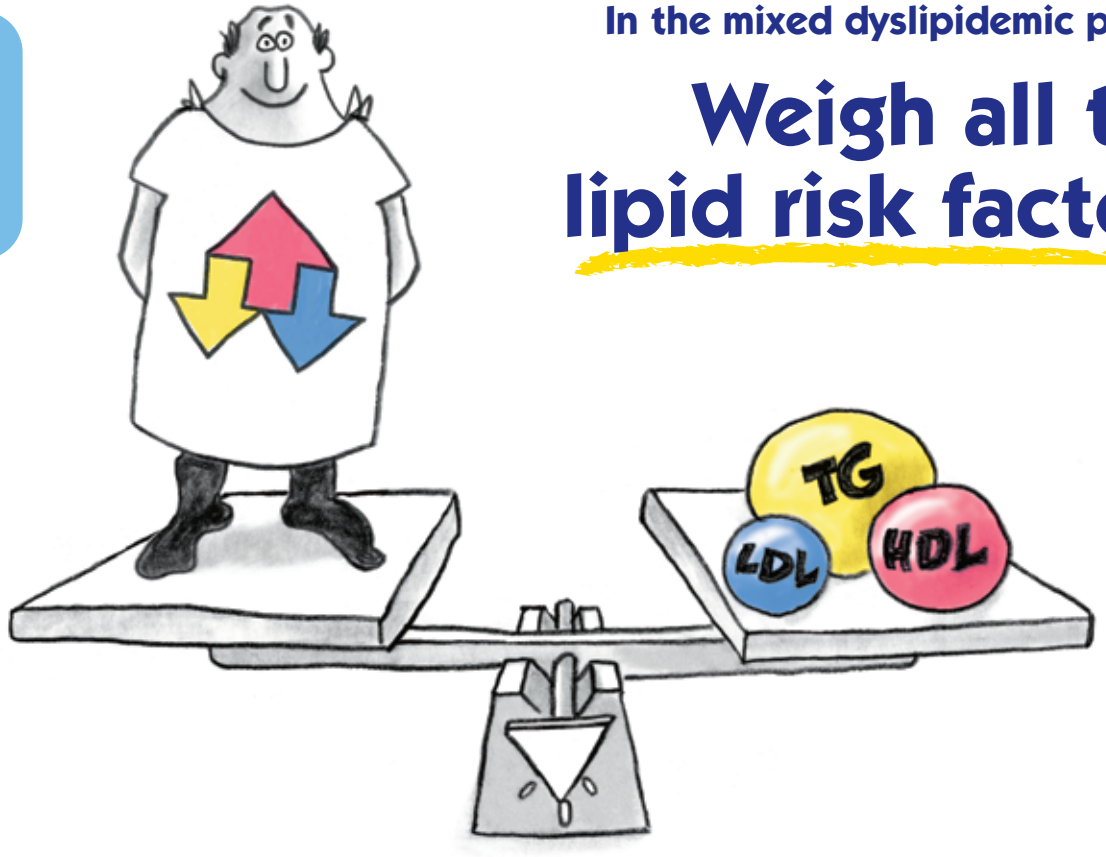
The current guidelines of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[10] and the American Diabetes Association (ADA)[12] highlight the importance of LDL-cholesterol reduction in high risk patients, but at the same time encourage physicians to position all patients with type 2 diabetes and insulin resistance in the high cardiovascular risk category. Because patients with type 2 diabetes and insulin resistance are commonly affected by the atherogenic dyslipidemia, characterized by high triglycerides and low HDL-cholesterol, one could argue that the optimal lipid intervention in these patients should be one targeting these abnormalities. Triglyceride and HDL-cholesterol levels have been shown to predict coronary event rates independently from LDL-cholesterol levels in populations from Europe and the US.[13-15] The knowledge that the ratio of total cholesterol to HDL-cholesterol is the most sensitive index of cardiovascular disease progression highlights the important contribution of atherogenic dyslipidemia to cardiovascular risk, given that this ratio is mostly determined by abnormalities of triglyceride metabolism. This is reflected in the current NCEP ATP III guidelines, which suggest a secondary goal of non-HDL-cholesterol to be only 30mg/dL higher than that for LDL-cholesterol.[10] A subject whose LDL-cholesterol is already at goal but has an inappropriate level of non-HDL cholesterol is a subject affected by hypertriglyceridemia. Thus, current guidelines support aggressive treatment of triglycerides in the high risk patient.[10] Indeed, normalization of the entire lipid profile is becoming the ultimate goal for optimal risk reduction in the high-risk individual.

Clinical Evidence from Statin Trials

The importance of properly treating atherogenic dyslipidemia can be indirectly inferred by the results of the major statin trials. For example, the most impressive statin effects on coronary heart disease (CHD) risk reduction in a high risk population were observed in the Scandinavian Simvastatin Survival Study (4S), where patients had high baseline LDL-cholesterol (188mg/dL) but near normal baseline triglycerides

In the mixed dyslipidemic patient

Weigh all the lipid risk factors



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

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.

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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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(133mg/dL) and HDL-cholesterol (46mg/dL).[16] However, the Cholesterol and Recurrent Events (CARE) study and the Long Term Intervention With Pravastatin in Ischemic Disease (LIPID) trial, where subjects had lower baseline LDL-cholesterol (139mg/dL to 151mg/dL) but higher baseline triglycerides (up to 168mg/dL) and lower baseline HDL-cholesterol (33mg/dL to 39mg/dL), showed more modest cardiovascular outcomes results with pravastatin.[17,18] These data indicate that in a population of patients with mixed dyslipidemia, the exclusive attention to LDL-cholesterol may not be as beneficial as targeting all lipid abnormalities presented. Along these lines, CARE patients with baseline triglycerides above the median value (144mg/dL) did not experience significant cardiovascular risk reduction despite a significant LDL-cholesterol lowering effect.[17]

The Heart Protection Study investigated the cardiovascular risk reduction potential afforded by simvastatin in a population of 20,536 patients who were classified as high-risk (65% had prior CHD and 19% had diabetes), even though the mean baseline LDL-cholesterol was 131mg/dL.[1] Although the subset of HPS patients with low baseline HDL-cholesterol (<35mg/dL) experienced benefits as large as those in patients with high baseline LDL-cholesterol (≥135mg/dL), the residual risk in patients with low baseline HDL-cholesterol was higher than that in any other lipid subcategory after treatment with simvastatin, except in those patients with triglyceride levels ≥354mg/dL. These data suggest that more aggressive control of HDL-cholesterol and triglyceride levels in these patients may optimize risk reduction. Similarly, the CARDS study[3] revealed that patients with type 2 diabetes who were treated with atorvastatin were protected against atherosclerotic complications; however, a lower baseline HDL-cholesterol (<54mg/dL) predicted higher risk in these patients. These data are consistent with the idea that a high residual risk remains after treatment with a statin, especially for those patients with low HDL-cholesterol and/or high triglycerides. Thus, targeting components of the lipid profile beyond LDL-cholesterol may be beneficial in further reducing cardiovascular risk in patients with atherogenic dyslipidemia.

Clinical Evidence from Fibrate Trials

In the Helsinki Heart Study, 4081 men with no prior history of CVD received gemfibrozil or placebo for five years. Gemfibrozil reduced triglycerides by 35% and LDL-cholesterol by 8% and raised HDL-cholesterol by 9%, resulting in a significant 34% reduction in CHD events (P<.02) in the overall population. Interestingly, intervention with gemfibrozil provided a 71% CHD risk reduction in a subset of patients with high triglycerides (>204mg/dL) and low HDL-cholesterol (LDL-cholesterol/HDL-cholesterol ratio >5).19 Furthermore, patients with type 2 diabetes benefited more than the normoglycemic individuals from treatment with gemfibrozil (68% CHD risk reduction).[20] These data support the idea that the patient type most amenable to cardiovascular risk reduction by fibrate therapy is a patient with type 2 diabetes and/or atherogenic dyslipidemia.

The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) evaluated the effect of gemfibrozil in 2531 men with CHD and low HDL-cholesterol.[21] Mean baseline LDL-cholesterol was 111mg/dL, mean baseline HDL-cholesterol was 32mg/dL, and mean baseline triglyceride level was 160mg/dL. Gemfibrozil treatment increased HDL-cholesterol by 6% and reduced triglycerides by 31%. Although there was no significant alteration of LDL-cholesterol with gemfibrozil treatment, there was a significant 22% reduction in the primary end point of CHD events (p=.006) and a significant 29% reduction in the incidence of investigator-designated strokes (p=.04). Gemfibrozil intervention produced a number-needed-to-treat of 23 for coronary events, which compares favorably with the results of the statin trials. In addition, the effect of gemfibrozil therapy on CHD event rates among the 769 diabetic subjects enrolled in VA-HIT was particularly large and apparently superior to the effects of statins in the same patient type.[22] Specifically, patients with type 2 diabetes treated with gemfibrozil experienced a 41% reduction in CHD death (p=.02) and a 40% reduction in stroke (p=.046). These data support the value of fibrate therapy in patients with type 2 diabetes, a prior history of CHD, and atherogenic dyslipidemia. However, the notion that fibrate therapy may represent the intervention of choice for vascular protection in type 2 diabetes requires further investigation in large-scale clinical outcomes trials of patients with type 2 diabetes.

The FIELD Study

The recently published FIELD trial represents a landmark study, as this was the largest cardiovascular outcomes trial conducted with a lipid-lowering medication in patients with type 2 diabetes (N= 9,795).[23] The primary clinical outcome of the study was CHD events, the combined incidence of nonfatal MI and CHD death.[23] Secondary clinical outcomes included total CVD events, which was a composite of CHD events, stroke, CVD death, and coronary and carotid revascularizations. Tertiary clinical outcomes included vascular amputations, the progression of renal disease, and laser treatment for diabetic retinopathy.

Study Population

The FIELD trial tested the hypothesis of fibrate-induced cardiovascular protection in patients with type 2 diabetes who would not have been typically considered eligible for fibrate therapy according to "best practice" standards. Entry criteria included total cholesterol of 116 to 251mg/dL, triglycerides of 89 to 443mg/dL, and total cholesterol to HDL-cholesterol ratio ≥4. The vast majority of subjects enrolled had a fairly normal lipid profile (mean LDL-cholesterol, 119mg/dL; HDL-cholesterol, 43mg/dL; and triglycerides, 154mg/dL), and only 38% of subjects met the prespecified definition of dyslipidemia (triglycerides >150mg/dL and HDL-cholesterol <40mg/dL for men or <50mg/dL for women) at baseline.[24] The fact that lipid-lowering therapy at baseline was an exclusion criterion also indicates that the patients' own doctors did not feel compelled to treat these patients' minor dyslipidemia. However, once enrolled, subjects were free to seek medical advice and to initiate nonstudy lipid-lowering agents without being disqualified from the study. Thus, the results of the FIELD trial are partly confounded by the significant drop-in rates of nonstudy lipid-lowering therapies. At the end of the study, 36% of placebo-assigned patients and 19% of fenofibrate-assigned subjects started non-study lipid-lowering therapy.[24] Importantly, 93% of these nonstudy lipid-lowering agents prescribed were statins.[24]

Lipid Effects

In the overall population, fenofibrate lowered LDL-cholesterol by 6%, triglycerides by 22%, and increased HDL-cholesterol by 1.2% compared to the placebo cohort.[24] In patients who did not start nonstudy lipid-lowering therapy, fenofibrate provided more significant lipid effects (15% decrease in LDL-cholesterol, 27% decrease in triglyceride levels, and 2.1% increase in HDL-cholesterol). However, in those patients who did start nonstudy lipid-lowering therapy (944 fenofibrate patients and 1776 placebo patients), there were no differences between groups except for a small reduction in triglycerides (11%). Of the 944 patients in the fenofibrate group who started nonstudy lipid-lowering therapy, only 581 patients remained on fenofibrate. These lipid data have important implications:

1. The LDL lowering effect of fenofibrate reduced the statin drop-in rate in the treatment group; and

2. Discontinuation of fenofibrate by 38% of patients who added nonstudy lipid-lowering therapy (statin) prevented the evaluation of CVD protection by combination therapy in this subset of patients.

Outcome Results

Overall, the FIELD study revealed a positive effect of fenofibrate, with a trend in benefit for the primary outcome of CHD events (11% risk reduction, p=.16) and significant risk reductions for the secondary outcomes of total CVD events (11% risk reduction, p=.035) and coronary revascularizations (21% risk reduction, p=.003).[24] The primary outcome was a composite of a significant 24% reduction in nonfatal MI (p=0.01), countered by a nonsignificant increase in CHD mortality (p=0.22).[24] Importantly, these cardiovascular outcomes were obtained within the very challenging parameters of a study population predominantly without the dyslipidemia targeted by a fibrate (62% of patients did not meet the definition of dyslipidemia at baseline) and with substantial drop-in rates of nonstudy statin therapy.

The protective effect of fenofibrate was more evident in patients with low baseline HDL-cholesterol (<40mg/dL for men and <50mg/dL for women), high baseline triglycerides (≥151mg/dL), and low LDL-cholesterol (<116mg/dL), patients who were likely to carry the atherogenic dyslipidemia. There was also a significant cardiovascular risk reduction in the 60% of subjects who were younger than 65 years of age (21% risk reduction, P<0.001), and in the 78% of subjects without prior history of CVD (25% reduction, p=0.014).[24]

In the primary prevention cohort (diabetics without CVD), the absolute risk reduction was 1.9%, with a need to treat 53 patients for five years in order to prevent one CVD event. On the other hand, in patients with preexisting CVD, fenofibrate did not reduce CHD or total CVD events. The fact that the drop-in rate of nonstudy lipid-lowering therapy in the secondary prevention placebo group was almost twice the rate in the primary prevention placebo group may help explain why fenofibrate did not appear to have a beneficial effect on cardiovascular outcomes in this cohort. Another way to look at these data is that the higher statin use in the placebo group did not produce the expected benefits of this proven therapy, indirectly providing support to the notion that the protective power of fenofibrate may be in the range of that of statins. Nevertheless, the positive results observed in the patients with type 2 diabetes but without previous CVD indicate that fenofibrate therapy is useful for patients with type 2 diabetes irrespective of baseline lipid values. This is a significant advance in our understanding of fibrate effects on the vessel wall and confirms previous experimental work on vascular protection induced by fenofibrate through nonlipid mechanisms.

Beyond the macrovascular beneficial effects of fenofibrate described above, fenofibrate was also associated with significantly positive effects on the microvasculature. There was significantly less albuminuria progression (14%) and significantly more albuminuria regression (p=0.002) in patients treated with fenofibrate, compared to those treated with placebo.[24] Furthermore, there was a highly significant 30% reduction in the need for laser treatment for diabetic retinopathy (p=0.0003) in the fenofibrate group.[24] These data provide additional evidence that fenofibrate therapy has a relevant place in the comprehensive approach to diabetes management.

no prior history of CVD regardless of the presence of diabetic dyslipidemia. These data also support the use of combination statin and fibrate therapy to accomplish optimal normalization of the lipid profile and achieve synergistic effects on the vascular wall. Based on beneficial effects of fenofibrate on macrovascular and microvascular disease, the FIELD study challenges the notion that statin therapy is the mandatory first choice in diabetic patients without hypercholesterolemia.

This guideline-supported approach, generated as a result of studies showing that lowering LDL-cholesterol will reduce CVD risk in all patients with diabetes and normal lipids, does not consider the likely possibility that triglyceride and HDL-cholesterol level management with fibrates would produce superior benefits in reducing CVD risk in patients with type 2 diabetes and atherogenic dyslipidemia.

The current guidelines encourage aggressive lipid lowering in patients with the type 2 diabetes, but one should keep in mind that these patients present with different forms and degrees of dyslipidemia

Safety

Overall, the use of fenofibrate was well tolerated in patients with type 2 diabetes irrespective of concomitant therapy. Although adverse events were rare, there was a greater risk for pancreatitis (0.5% for placebo and 0.8% for fenofibrate) and pulmonary embolism (0.7% for placebo and 1.1% for fenofibrate) in the fenofibrate group.[24] Out of 9795 patients, only three patients experienced myositis (two patients were on fenofibrate and one was on placebo), and only four patients experienced rhabdomyolysis (three patients were on fenofibrate and one was on placebo). None of the patients with rhabdomyolysis were on combination therapy with a statin.[24]

The ADA recently issued recommendations that give preference to fenofibrate over gemfibrozil in combination with statins[12] as a consequence of previous studies that revealed fenofibrate used in combination with a statin posed less risk for myopathy or rhabdomyolysis than combination therapy with gemfibrozil.[25,26] Additional evidence for this ADA recommendation is provided by the FIELD study, which suggests that combination therapy with fenofibrate and a statin appears to be well tolerated and safe.

Conclusions

In summary, the FIELD trial supports the use of fenofibrate in patients with type 2 diabetes who have

Final Thoughts

Optimal cardiovascular risk reduction will most likely be obtained by carefully matching the diagnosis of a specific lipid abnormality with the therapeutic agent most likely to correct it. The FIELD trial supports this line of reasoning by providing evidence that fenofibrate was most beneficial in reducing CVD risk in patients with type 2 diabetes who had low HDL-cholesterol levels, high triglyceride levels, and low LDL-cholesterol levels, patients who were most likely carriers of the atherogenic dyslipidemia. The current guidelines encourage aggressive lipid lowering in patients with the type 2 diabetes, but one should keep in mind that these patients present with different forms and degrees of dyslipidemia. At a time when guidelines are moving toward endorsement of lower LDL-cholesterol goals, the danger lies in underestimating the risk contributed by atherogenic dyslipidemia and improperly treating this condition in patients with type 2 diabetes. Fibrates, particularly fenofibrate, are safe and effective for the long-term management of patients with high CVD risk, particularly when this increased CVD risk is due to the presence of atherogenic dyslipidemia or type 2 diabetes. ■

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