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

a report by

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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, 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.

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. 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) and the American Diabetes Association (ADA) 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 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. The knowledge of the role 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. 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. 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...
Type IIa/IIb Indications: TriCor® (fenofibrate) tablets are 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:

• 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

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TRICOR® 48 mg and 145 mg (fenofibrate tablets)  


definitive diagnosis.

CONTRAINdications

TRICOR is contraindicated in patients who exhibit hypersensitivity to fenofibrate tablets. TRICOR is contraindicated in patients with hepatic or severe renal impairment. TRICOR is contraindicated in patients with preexisting gallbladder disease (domed head/hunched shoulders/rounded body/abnormal chest, dysplastic, cystic, or polycystic changes). Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of TRICOR.

PANCREATitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with acute pancreatitis due to direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the biliary tract.

Hyperpotassemia: Reaction: Acute hyperpotassemia reactions including rhabdomyolysis with or without renal dysfunction have occurred rarely during treatment with gemfibrozil. The benefits of treating hypertriglyceridemia may outweigh the increased risk for this drug reaction. It is advisable to discontinue TRICOR if acute renal dysfunction occurs.

Renal Function Tests Abnormal 7.5%** 1.4%

TRICOR therapy should be stopped.

Anemia, leukopenia, ecchymosis, purpura, ecchymosis, ecchymosis. Therapy should be discontinued if a persistent leukopenia is noted.

Liver Function Tests Abnormal 7.5%** 1.4%

Diabetes mellitus.

PACIentS with a history of pancreatitis, hepatic insufficiency, severe renal impairment or vomiting should be carefully considered, and the lowest effective dose employed.

Angina pectoris, hypertension, vasodilatation, anemia, leukopenia, ecchymosis, ecchymosis, ecchymosis.

Diabetes mellitus.

GASTROINTESTINAL SYSTEM: Anemia, leukopenia, ecchymosis, purpura, ecchymosis. Therapy should be discontinued if a persistent leukopenia is noted.

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

NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paraesthesia, dry mouth, hyperventilation, neurasthenia, malaise, and somnolence.

SKIN AND ALLEVIATIONS: Rash, pruritus, cysts, herpes zoster, urticaria, angioedema, angioedema, angioedema, angioedema. Therapy should be discontinued if a persistent rash is noted.

URINARY SYSTEM: Proteinuria, albuminuria, leukocyturia, pyuria, hematuria, dysuria, cystitis, pollenuria, eosinophiluria.

Gastrointestinal System: Myositis, myalgia, arthrosis, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myalgia.

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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. Although the subset of HPS patients with low baseline LDL-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 LDL-cholesterol was higher than that in any other lipid subclass 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 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). Furthermore, patients with type 2 diabetes benefited more than the normoglycemic individuals from treatment with gemfibrozil (68% CHD risk reduction). 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. 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. 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). The primary clinical outcome of the study was CHD events, the combined incidence of nonfatal MI and CHD death. 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 251 mg/dL, triglycerides of 89 to 443 mg/dL, and total cholesterol to HDL-cholesterol ratio ≥4. The vast majority of subjects enrolled had a fairly normal lipid profile (mean LDL-cholesterol, 119 mg/dL; HDL-cholesterol, 43 mg/dL; and triglycerides, 154 mg/dL), and only 38% of subjects met the prespecified definition of dyslipidemia (triglycerides >150 mg/dL and HDL-cholesterol <40 mg/dL for men or <50 mg/dL for women) at baseline. 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. Importantly, 93% of these nonstudy lipid-lowering agents prescribed were statins.

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. 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 381 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=0.16) and significant risk reductions for the secondary outcomes of total CVD events (11% risk reduction, p=0.035) and coronary revascularizations (21% risk reduction, p=0.003). 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). 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 (<40 mg/dL for men and <50 mg/dL for women), high baseline triglycerides (≥151 mg/dL), and low LDL-cholesterol (<116 mg/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). 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. Furthermore, there was a highly significant 30% reduction in the need for laser treatment for diabetic retinopathy (p=0.0003) in the fenofibrate group. These data provide additional evidence that fenofibrate therapy has a relevant place in the comprehensive approach to diabetes management.

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. 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.

The ADA recently issued recommendations that give preference to fenofibrate over gemfibrozil in combination with statins 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. 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 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.

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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