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. 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. The NCEP ATPIII guidelines indicate that lowering LDL-cholesterol is the first priority of lipid-lowering therapy. Elevated triglycerides and low HDL-cholesterol are independent risk factors for CVD, and statin therapy does not eliminate the residual CVD risk associated with high triglycerides or low HDL-cholesterol.

Recent statin trials such as the Heart Protection Study (HPS), which included a subgroup of 5,963 diabetic patients, and the Collaborative Atorvastatin Diabetes Study (CARDS), which enrolled 2,838 T2DM patients, 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. In HHS patients with diabetes, gemfibrozil reduced CHD events by 68% (p = 0.19). 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. 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) 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. 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. 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. 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...
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). The substantial statin drop-ins in FIELD were most likely a result of the 2001 publication of the NCEP ATPIII guidelines,14,15 which reclassified diabetes from a risk factor to a CHD risk equivalent, and the 2002 publication of the HPS results,1 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 nonfatal 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 fibrates trials.14,16

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

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),5 CARE = Cholesterol and Recurrent Events (pravastatin),24 LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease (pravastatin),8 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

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

<table>
<thead>
<tr>
<th>Event rate (no diabetes)</th>
<th>Event rate (diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On statin</td>
<td>On placebo</td>
</tr>
<tr>
<td>HPS† (CHD patients)</td>
<td>19.8%</td>
</tr>
<tr>
<td>CARE‡</td>
<td>19.4%</td>
</tr>
<tr>
<td>LIPID†</td>
<td>11.7%</td>
</tr>
<tr>
<td>PROSPER§</td>
<td>13.1%</td>
</tr>
<tr>
<td>ASCOTT-LLA‡</td>
<td>4.9%</td>
</tr>
<tr>
<td>TNT</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

Residual CVD risk is defined as the difference between event rates on placebo and on statin in patients with diabetes. HPS = Heart Protection Study (simvastatin),5 CARE = Cholesterol and Recurrent Events (pravastatin),24 LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease (pravastatin),8 PROSPER = Prospective Study of Pravastatin in the Elderly at Risk (pravastatin),6 ASCOTT-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, CABG, PTCA

CHD death, non fatal MI, stroke, revascularizations

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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.

Please see adjacent brief summary of Full Prescribing Information.
Precautions

Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently elevated above the desirable range before initiating fenofibrate therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, management of other medical problems such as diabetes mellitus and hyperphosphatemia that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, orthostatic hypotension) should be changed or discontinued prior to consideration of high-dose lovastatin-lowering drug therapy.

Continued therapy: Liver function tests should be followed for at least the first year of therapy and thereafter yearly. Changes in liver enzyme levels should be evaluated by the clinician. If liver enzyme abnormalities are seen, the drug should be discontinued.

Adverse Reactions

Adverse Reactions Reported During Clinical Trials

The most common adverse reactions include increase in liver enzymes, elevation of creatine phosphokinase levels, and diarrhea.

The adverse events reported in about 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 6% of patients treated with fenofibrate and in 3% with placebo.

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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)\textsuperscript{18} and the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA).\textsuperscript{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%; ASCOT-LLA, 3.6\%\textsuperscript{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\%;\textsuperscript{14} ASPEN, 27\%;\textsuperscript{18} ASCOT-LLA, 14\%\textsuperscript{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\%.\textsuperscript{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).\textsuperscript{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.\textsuperscript{19} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 have not reduced CVD events.\textsuperscript{21,22} Analysis of the
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).14

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.

**References**

Optimizing Cardiovascular Outcomes in Patients with Type 2 Diabetes


