Abstract
Cardiovascular disease (CVD) is a major cause of death and morbidity for patients with diabetes, and microvascular disease significantly contributes to the burden of chronic diabetes complications. Patients with type 2 diabetes (T2DM) typically have atherogenic dyslipidemia, characterized by lipid and lipoprotein abnormalities: specifically high levels of triglycerides, low levels of HDL-cholesterol and HDL particles, and significant increases in total and small LDL particle concentration. Statin therapy to lower LDL-cholesterol, a surrogate of LDL particle concentration, is recommended as the first priority of pharmacological therapy for patients with T2DM. However, significant residual CVD risk remains in patients with T2DM treated with statins. Elevated triglycerides and low HDL-cholesterol (triglyceride/HDL axis disorders) represent lipid risk factors that are associated with risk independent of elevated or normal LDL-cholesterol. Several guidelines recognize that combination therapy with statins and other medications including fibrates may be necessary to achieve goals for all lipid risk factors. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was the largest cardiovascular outcomes trial conducted to date in patients with T2DM (N = 9795), and it was the first trial to investigate the long-term effects of fenofibrate on clinical outcomes in this patient population. In FIELD, despite the null primary endpoint (nonsignificant reduction of CHD death and nonfatal MI), fenofibrate provided several significant clinical benefits: 24% reduction in nonfatal myocardial infarctions, 11% reduction in total CVD events, 21% reduction in coronary revascularizations, 18% reduction in hospitalizations for angina pectoris, 38% reduction in vascular and neuropathic amputations, 15% reduction in the rate of progression to albuminuria, and 30% reduction in the need for laser photocoagulation therapy for retinopathy. Furthermore, fenofibrate was well tolerated when used alone or in combination therapy with a statin. FIELD supports an important role for fenofibrate in preventing macrovascular and microvascular complications of diabetes. Adding fenofibrate to statin therapy in high-risk patients with diabetes may significantly reduce the high residual CVD risk that remains after statin monotherapy, as well as reduce the burden of microvascular disease.

Burden of CVD and Microvascular Disease in Patients With Type 2 Diabetes
Patients with T2DM have an increased risk for all forms of CVD, including coronary heart disease (CHD),\(^1\) and CVD is the leading cause of death for patients with diabetes.\(^2\) In response to the compelling epidemiological and pathological data demonstrating a strong association between diabetes and CVD risk, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) has reclassified T2DM from a risk factor to a CHD risk equivalent.\(^7\) A major factor contributing to the increased risk of CVD is atherogenic dyslipidemia, characterized by lipid and lipoprotein abnormalities: specifically high levels of triglycerides, low levels of HDL-cholesterol and HDL particles, and significant increases in total and small LDL particle concentration.\(^8\) There is evidence that each component of this lipid triad is atherogenic; however, the lipid triad as a whole is considered to be a risk factor for CHD.\(^9\) Although an elevated LDL-cholesterol level is a major risk factor for CHD,\(^10\) even those with unremarkable or normal LDL-cholesterol levels have CHD risk. If LDL particles are small, it can take 40-70% more particles to traffic the cholesterol in
plasma, causing a disconnect between LDL-cholesterol and LDL particle concentration (or apolipoprotein B). It is the increased triglyceride level present in very low-density lipoprotein (VLDL) particles that contributes to the small LDL and HDL size typical of atherogenic dyslipidemia. The triglyceride in VLDL particles is exchanged for cholesteryl-ester (CE) in LDL and HDL particles by cholesteryl ester transfer protein (CETP), resulting in triglyceride-rich, CE-poor LDL and HDL particles and triglyceride-poor, CE-rich VLDL particles. Further lipolysis by hepatic and lipoprotein lipase results in small, dense LDL and HDL particles, as well as increased numbers of atherogenic CE-enriched VLDL remnants. Because of their very small size, the HDL particles are subject to renal excretion, thus reducing the HDL particle concentration and HDL-cholesterol. Characteristically, the lipid profile reveals variable LDL-cholesterol, elevated VLDL-cholesterol, reduced HDL-cholesterol, and elevated non–HDL-cholesterol. Aside from lipoprotein abnormalities, elevated triglycerides are associated with increased blood viscosity, decreased flow-mediated dilation, hypercoagulation, and systemic inflammation, which may also adversely affect both LDL particle atherogenicity and HDL functionality. These multiple perturbations help explain why atherogenic dyslipidemia (triglyceride/HDL axis disorders) contributes to risk beyond elevated LDL-cholesterol levels.

Microvascular disease of several tissues significantly contributes to the burden of chronic diabetes complications. During the first 2 decades of the disease, >60% of patients with T2DM develop diabetic retinopathy, estimated to be the most frequent cause of new cases of blindness among adults who are 20-74 years of age. Laser photocoagulation treatment for retinopathy is effective at slowing the progression of retinopathy, but this treatment usually does not restore lost vision. Thus, in order to prevent vision loss, it is imperative to suspect and prevent diabetic retinopathy. Diabetic nephropathy is another microvascular complication of T2DM that occurs in 20% to 40% of such patients and is the single leading cause of end-stage renal disease. Microalbuminuria is the earliest clinical marker of damage to the kidney in patients with type 2 diabetes. Patients with microalbuminuria progress to macroalbuminuria and will ultimately experience a reduction in glomerular filtration rate and progress to end-stage renal failure. Both types of microvascular disease—diabetic retinopathy and nephropathy (initially manifested by microalbuminuria)—have been associated with increased CVD risk and mortality in patients with diabetes. The risk of peripheral amputations is also increased in people who have cardiovascular, retinal, or renal complications of diabetes. Obviously, loss of vision, kidney function, and/or a distal lower limb has significant adverse effects on quality of life and are therapeutic prevention goals for patients with diabetes.

Residual CVD Risk in Patients With Diabetes Treated With Statins

Several statin trials have included patients with T2DM, and the majority of both the prospective or post-hoc data reveal that statins significantly reduce both LDL-cholesterol and CVD events. However, a closer look at CVD event rates in statin trials reveals that in T2DM patients treated with statins, CVD event rates remain higher than those of untreated patients without diabetes (Figure 1). Such data suggest that patients with diabetes have an excess amount of residual CVD risk which is not adequately reduced by lowering LDL-cholesterol levels alone. Since elevated triglycerides and low HDL-cholesterol are independent lipid risk factors for CVD, statin therapy does not eliminate the CVD risk associated with high triglycerides or low HDL-cholesterol. Guidelines have emphasized non–HDL-C, triglycerides, and HDL-cholesterol as additional goals of therapy. The NCEP ATP III guidelines recommend a secondary goal of therapy when triglycerides are elevated (200-499 mg/dL): non–HDL-cholesterol goal is 30 mg/dL above the patient’s LDL-cholesterol goal. The American Diabetes Association (ADA) guidelines recommend reducing triglycerides <150 mg/dL and increasing HDL-cholesterol >40 mg/dL (>50 mg/dL for women) after LDL-cholesterol goals are met. Failure to reach lipid goals for non–HDL-
cholesterol, triglycerides, and HDL-cholesterol may at least in part be responsible for significant residual CVD risk that remains after statin therapy, especially in patients with diabetes. These guidelines recognize that lipid modifying therapies that allow patients to achieve goals for all lipid risk factors may significantly reduce residual CVD risk remaining after statin therapy.

**Reduction of CVD Risk With Fibrates**

Second only to statins, fibrates have been studied in multiple angiographic and large primary and secondary CVD outcome trials, and the accumulated evidence is that fibrates are particularly efficacious in patients with insulin resistance, triglyceride/HDL-cholesterol axis disorders, and/or T2DM. In the primary prevention Helsinki Heart Study (HHS), gemfibrozil provided a 71% reduction in CHD events ($P<.005$) in patients with an LDL-cholesterol to HDL-cholesterol ratio >5 and triglycerides >204 mg/dL, and in the Bezafibrate Infarction Prevention (BIP) study, bezafibrate provided a significant 40% reduction of CHD events in patients with triglycerides $\geq 200$ mg/dL and a 56% reduction of cardiac mortality in patients with 4-5 components of the metabolic syndrome. Patients with T2DM in the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) experienced a 32% reduction in CHD events ($P=.004$), a 41% reduction in CHD death ($P=.02$), and a 40% reduction in stroke ($P=.046$) with gemfibrozil treatment. Further support for the beneficial effect of fenofibrate in patients with T2DM is provided by the Diabetes Atherosclerosis Intervention Study (DAIS). In this trial, fenofibrate reduced the angiographic progression of CHD, as evidenced by a substantial 40% reduction of the progression in minimum lumen diameter ($P=.029$), 25% reduction of the progression in mean segment diameter ($P=.171$), and 42% reduction of the progression in percentage stenosis ($P=.020$). Data from these fibrate trials reveal the clear value of fibrates in reducing CVD risk and the angiographic progression of CHD in patients with atherogenic dyslipidemia and/or T2DM. It is worth noting that in HHS, VA-HIT and DAIS, there was no statin use by placebo or treatment groups.

**Diabetic Patients Have High Residual CVD Risk After Statin Treatment**

<table>
<thead>
<tr>
<th>Event Rate (No Diabetes)</th>
<th>Event Rate (Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On Statin</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>ASCOT-LLA‡</td>
<td>4.9%</td>
</tr>
<tr>
<td>TNT†</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

*CHD death, nonfatal MI, stroke, resuscitated cardiac arrest
†CHD death, nonfatal MI, CABG, PTCA
‡CHD death and nonfatal MI
§CHD death, nonfatal MI, stroke
||CHD death, nonfatal MI, resuscitated cardiac arrest, stroke

**Figure 1. Diabetic patients have high residual CVD risk after statin treatment.**

Residual CVD risk remains in all patients treated with statins; however, residual CVD risk is particularly high in patients with diabetes treated with statins. Statins do not eliminate the increased CVD risk associated with diabetes. Even after patients with diabetes were treated with statins, their CVD event rates (ie, residual CVD risk) were higher than the CVD event rates of those untreated patients without diabetes. HPS, Heart Protection Study (simvastatin); CARE, Cholesterol and Recurrent Events (pravastatin); LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease (pravastatin); PROSPER, Prospective Study of Pravastatin in the Elderly at Risk (pravastatin); ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (atorvastatin); TNT, Treating to New Targets (atorvastatin 10 mg versus 80 mg).
Reduction of CVD and Microvascular Disease With Fenofibrate in FIELD

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was the largest cardiovascular outcomes trial conducted to date in patients with type 2 diabetes (N = 9795), and it was the first trial to investigate the long-term effects of fenofibrate on clinical outcomes in those with normal or near normal lipid profiles. Despite the disproportionate use of nonstudy statins by the end of the trial (statin drop-in was 36% in the placebo group and 19% in the fenofibrate group, P<.0001), the FIELD data suggest an important role for fenofibrate in preventing macrovascular and microvascular complications of diabetes.

Macrovascular Benefits Observed With Fenofibrate in FIELD

Fenofibrate provided a nonsignificant 11% reduction in the primary end point of CHD events (nonfatal myocardial infarction [MI] or CHD death) (P=.16). Further analysis of this end point revealed a significant 24% reduction in nonfatal MI (P=.01) and a nonsignificant (null) effect on CHD death. Fenofibrate provided a significant 11% reduction in the secondary end point of total CVD events (P=.035) and a significant 21% reduction in coronary revascularizations (P=.003) (Figure 2). A significant 18% reduction in hospitalizations for acute coronary syndrome (tertiary end point) was also observed in patients taking fenofibrate (P=.04). Fenofibrate had a particularly beneficial effect in patients who had no prior history of CVD (n = 7664), which comprised 78% of the total population. In these patients, fenofibrate significantly reduced the primary end point of CHD events by 25% (P=.014) and the secondary end point of total CVD events by 19% (P=.004) (Figure 3). There were no significant effects on CHD or total CVD events in patients who had a prior history of CVD. Consistent with other fibrate trials, FIELD patients with HDL-cholesterol <40 mg/dL and patients who met the prespecified definition of dyslipidemia (triglycerides <150 mg/dL and HDL-cholesterol <40 mg/dL for men and <50 mg/dL for women) experienced absolute risk reductions (ARR) in total CVD events of 2.1% and 2.3%. These ARRs are comparable to the 3.2% ARR in major CVD events provided by atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS).
**Microvascular Benefits Observed With Fenofibrate in FIELD**

Tertiary end points in FIELD included the effects of fenofibrate on the microvasculature: the progression of renal disease as indicated by microalbuminuria, vascular and neuropathic amputations, and laser photocoagulation treatment for diabetic retinopathy. The proportion of patients who presented with retinopathy and nephropathy, including microalbuminuria and macroalbuminuria, were well-matched in the treatment arms at baseline. Consistent with observations in DAIS, the rate of progression to albuminuria was significantly reduced by fenofibrate treatment in FIELD. A total of 466 patients in the fenofibrate group progressed from normoalbuminuria to microalbuminuria or from microalbuminuria to macroalbuminuria, compared with 539 patients in the placebo group. Additionally, 462 patients on fenofibrate regressed, compared with 400 patients on placebo. This represented 14% fewer patients progressing and 15% more patients regressing in the fenofibrate group than the placebo group ($P = .002$ for combined effect) (Figure 4). The number of patients with renal disease who required dialysis at any time after randomization was fewer in the fenofibrate group, compared with placebo (16 versus 21 patients, respectively) (Table 1).

There was a significant 38% decrease in vascular and neuropathic amputations observed in the fenofibrate group ($P = .011$). Fenofibrate also significantly reduced the need to undergo laser photocoagulation therapy for progression of diabetic retinopathy. A total of 253 patients on placebo needed 1 or more laser treatments for diabetic retinopathy, compared with 178 patients allocated fenofibrate. This corresponds to a 30% reduction in the number of patients who needed laser treatment for retinopathy with fenofibrate treatment compared with placebo ($P = .0003$) (Figure 5). The effect of fenofibrate occurred at one year and was very similar in reducing laser therapy when confined to the subgroup of patients without retinopathy at baseline.

Although the microvascular benefits of fenofibrate have been demonstrated in DAIS and FIELD, the mechanisms for these beneficial effects have not been elucidated. Hyperglycemia and hypertension are major causes of diabetic microvascular complications, such as retinopathy and nephropathy, and therapeutic agents that control glucose levels and blood pressure significantly reduce these microvascular complications. However, in DAIS, the fenofibrate-induced reduction in the progression of albuminuria was determined...
to be independent of hypertensive status or glycemic control. Similarly, in FIELD, the effect of fenofibrate on the microvasculature could not be explained by differences in baseline or end of study blood pressure, glycosylated hemoglobin (HbA1c) levels, or fasting plasma glucose levels, as these parameters were well-matched at baseline and well-controlled throughout the study. Differences in concomitant cardiovascular medications or glucose-lowering medications also could not explain the beneficial effect of fenofibrate on the microvasculature. One hypothesis is that sorbitol accumulation in cells due to aldose reductase (AR) activity is associated with diabetic microvascular disease. Fenofibrate and other fibrates, via PPAR-alpha agonism, inhibit AR, suggesting a novel attribute of fibrates.

![Figure 4. FIELD: Progression and regression of albuminuria.](image)

Fenofibrate significantly reduced the progression (14%) and increased the regression (15%) of albuminuria. Progression of albuminuria was defined as the number of patients who progressed either from normoalbuminuria to microalbuminuria or from microalbuminuria to macroalbuminuria; regression was defined as the reverse.

![Figure 5. FIELD: Laser treatment for retinopathy.](image)

Fenofibrate significantly reduced the number of patients who needed 1 or more laser treatment for diabetic retinopathy (30% reduction).
**Safety of Fenofibrate in FIELD**

In FIELD, the use of fenofibrate was well tolerated in 9795 patients followed for over 5 years. 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 versus the placebo group; however, these events were rare (Table 1). There were very few clinically significant muscle-related adverse events. Specifically, only 3 patients experienced myositis, and only 4 patients experienced rhabdomyolysis (Table 1). Importantly, each case of rhabdomyolysis fully resolved after discontinuation of study medication, and none of the patients with rhabdomyolysis were on fenofibrate/statin combination therapy. The incidences of alanine aminotransferase (ALT) and creatine phosphokinase (CPK) elevations were not significantly different between treatment groups. There was a nonsignificant reduction in ALT elevations (23 times the upper limit of normal) in the fenofibrate group (22 fenofibrate patients versus 38 placebo patients) (Table 1). Plasma creatinine levels were 14% higher in the fenofibrate group at the end of the study (P<.001; however, this increase was reversible after ceasing fenofibrate therapy, arguing against fenofibrate-related renal toxicity. Fenofibrate-associated changes in creatinine plasma levels have been reported to be due to an increase in the metabolic production rate of creatinine in muscles and not due to accelerated muscular cell lysis, a fall in glomerular filtration rate, or an impairment in renal function. The FIELD trial provides important long-term safety data with fenofibrate in monotherapy and in combination therapy with statins in patients with type 2 diabetes. The 2004 addendum to NCEP ATP III states that unlike gemfibrozil, fenofibrate does not increase the rates of myositis when used with moderate doses of statins.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo n = 4900</th>
<th>Fenofibrate n = 4895</th>
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<tbody>
<tr>
<td>Newly diagnosed cancer</td>
<td>373 (7.6%)</td>
<td>393 (8.0%)</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>48 (1.0%)</td>
<td>67 (1.4%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>32 (0.7%)</td>
<td>53 (1.1%)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>23 (0.5%)</td>
<td>40 (0.8%)</td>
</tr>
<tr>
<td>Myositis</td>
<td>1 (0.02%)</td>
<td>2 (0.04%)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1 (0.02%)</td>
<td>3 (0.06%)</td>
</tr>
<tr>
<td>Renal disease requiring dialysis</td>
<td>21 (0.4%)</td>
<td>16 (0.3%)</td>
</tr>
<tr>
<td>ALT &gt;5x ULN</td>
<td>26 (0.5%)</td>
<td>11 (0.2%)</td>
</tr>
<tr>
<td>CPK &gt;10x ULN</td>
<td>7 (0.1%)</td>
<td>11 (0.2%)</td>
</tr>
<tr>
<td>Creatinine increase &gt;2.3 mg/dL</td>
<td>48 (1.0%)</td>
<td>73 (1.5%)</td>
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Table 1. FIELD: Safety of Fenofibrate.

*None of these patients were taking a statin
†P<.022; ‡P=.031; ULN, upper limit of normal

**Implications for Clinical Practice**

Because of the large numbers of clinical trials supporting their efficacy, the NCEP ATP III and ADA guidelines recommend statins as first line therapy to reduce LDL-cholesterol levels in patients at high risk for CVD who have TG <500 mg/dL. However, residual CVD risk remains in patients treated with statin therapy, and CVD event rates in T2DM patients treated with statins remain higher than CVD event rates of untreated patients without diabetes. The NCEP ATP III and ADA guidelines recognize that non–HDL-cholesterol, high triglycerides, and low HDL-cholesterol are lipid risk factors that are associated with residual CVD risk and that effectively treating these abnormalities may be necessary to reduce that residual CVD risk. The NCEP ATP III guidelines recommend non–HDL-
cholesterol as a secondary target of therapy when triglycerides are elevated (200–499 mg/dL), and the goal for non–HDL-cholesterol is 30 mg/dL above the patient’s LDL-cholesterol goal. Newer epidemiologic data suggest that non–HDL-cholesterol is a superior predictor of risk than LDL-cholesterol, independent of the triglyceride level (Figure 6). The ADA guidelines recommend reducing triglycerides <150 mg/dL and increasing HDL-cholesterol >40 mg/dL (>50 mg/dL for women) after LDL-cholesterol goals are met.

The data from FIELD and DAIS indicate that fenofibrate beneficially impacts both macrovascular and microvascular disease in T2DM patients. In FIELD, fenofibrate provided several significant clinical benefits: 24% reduction in nonfatal MI, 11% reduction in total CVD events, 21% reduction in coronary revascularizations, 18% reduction in hospitalizations for angina pectoris, 38% reduction in vascular and neuropathic amputations, 15% reduction in the rate of progression to albuminuria, and 30% reduction in retinopathy needing laser therapy (Figure 7). Furthermore, fenofibrate was well tolerated when used alone or in combination with a statin.

These data provide compelling evidence that fenofibrate therapy has a relevant place in the comprehensive approach to diabetes management. Both statins and fibrates should have an important role in achieving lipid and lipoprotein goals in T2DM patients to prevent macrovascular disease, and fibrates may play a role in addressing microvascular complications. The ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial will provide additional clinical outcomes data with fenofibrate/statin combination therapy in T2DM. The microvascular benefits revealed in FIELD are a compelling reason alone to consider addition of fenofibrate to statin therapy for patients with T2DM because preventing vision loss, kidney dysfunction, and amputations will significantly improve quality of life for this patient population. Adding fenofibrate to statin therapy in high-risk patients with diabetes is safe and may significantly reduce the high residual CVD risk that remains after statin monotherapy, as well as reduce the burden of microvascular disease.
References


