Fibrate Therapy in Patients with Metabolic Syndrome and Diabetes Mellitus

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Patients with metabolic syndrome and type 2 diabetes mellitus are usually in moderately high-risk, high-risk, or very high-risk cardiovascular categories and present major therapeutic challenges. The dyslipidemia in such patients is typically a disorder of the triglyceride/high-density lipoprotein axis (TG/HDL axis) characterized by an excess of triglyceride-rich lipoproteins and a reduction of HDL. Very often, lifestyle therapy and statin monotherapy fail to achieve guideline goals, necessitating combination therapies. Fibric acids (or fibrates), are agonists of peroxisome proliferator–activated receptor α, which have amassed significant lipid-surrogate and clinical outcome trial data, especially in insulin-resistant patients, typical of those with metabolic syndrome or type 2 diabetes mellitus. Current guidelines advocate fibrate use as an add-on to statin therapy when TG/HDL abnormalities exist in such patients. In this paper, we review pertinent and recent trial data, mechanisms of action, and the safety of fibrate therapy.

Introduction

The lipid profile in metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM) patients with insulin resistance often manifests as a triglyceride/high-density lipoprotein (TG/HDL) axis disorder, with elevations of TG and reductions of HDL cholesterol [1]. Increased total cholesterol (TC)/HDL cholesterol ratios or non-HDL cholesterol levels are typical. There is both an overproduction and delayed catabolism of apolipoprotein (apo) B-containing triglyceride-rich lipoprotein (TRLP), which often have increased amounts of apoCI [2], apoCIII, apoAII [3], and decreased apoAV [4], all of which delay particle catabolism, leading to rheologic abnormalities such as increased blood viscosity, endothelial dysfunction (manifested as decreased flow-mediated dilation), and hypercoagulation (manifested as elevated plasminogen activated receptor-1 and fibrinogenemia) [5]. Cholesteryl ester transfer protein (CETP) mediates an exchange of TG for cholesteryl ester (CE) between very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) and HDL. Subsequent interactions with lipoprotein (LP) and hepatic lipase generate smaller, denser LDL and HDL particles, the latter of which become vulnerable to renal excretion because of their very small size. Because it requires 40% to 70% more small LDL particles than large LDL particles to transport a given level of cholesterol, there is a significant disconnect between LDL cholesterol and LDL particle concentration or apoB. Advanced lipoprotein analysis using nuclear magnetic resonance spectroscopy most often demonstrates increased large VLDL, smaller VLDL remnants, small LDL, and a lack of large HDL particles in MS and T2DM patients [6].

Trial Data

Epidemiologic data from multiple studies have established the increased cardiovascular risk associated with T2DM, and the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) considers T2DM a coronary risk equivalent [7]. Though the clinical utility of the designation of MS has been called into question recently [8], most studies also show such patients to be at increased cardiovascular (CV) risk. The American Heart Association has issued a scientific statement on recognizing and treating patients with MS [9].

3-Hydroxy-3-methylglutary coenzyme A reductase inhibitors (ie, statins) have considerable prospective and post hoc outcome trial data on T2DM patients, with relative risk reduction (RRR) averaging 25% to 40%, which is similar to that seen in patients without diabetes. With the recent publication of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial [10•], fibrates also now have considerable post hoc or prospective data from outcome trials, including T2DM patients, with RRR in the range of 11% to 30% [11–14].

Significant residual risk remains in patients treated with statin or fibrate monotherapy. In part this may be due to failure to reach NCEP lipid goals of therapy, namely LDL cholesterol and non-HDL cholesterol. In such instances, NCEP recommends using combination

therapy [15]. It is reasonable to speculate that therapies with synergistic or additive mechanisms of action may offer increased event reductions, especially in higher-risk patients. Multiple other clinical guidelines, including that of the American Diabetes Association, also call for addressing this residual risk by increasing the use of lipid-modifying combination therapies [16].

Review of clinical outcome data from fibrate trials has shown significantly better efficacy for CV event reduction in insulin-resistant patients. The Helsinki Heart Trial [11] was a primary prevention study of 4081 asymptomatic middle-aged men (40–55 years of age) with elevated non-HDL cholesterol randomized to placebo or gemfibrozil. The primary endpoint of coronary heart disease (CHD) risk, defined as definite fatal and nonfatal myocardial infarctions (MI) and cardiac death, was reduced by 34% ($P < 0.02$) [11]. Post hoc analysis of a subset of 292 likely insulin-resistant patients with TG greater than 204 mg/dL and LDL/HDL ratio greater than 5 showed a 71% reduction ($P < 0.005$) of CHD risk, which was substantially greater than the CHD risk reduction for the entire trial population. There was a 78% reduction in major CV events if TG were greater than 200 mg/dL, HDL less than 40 mg/dL, and body mass index greater than 26 [17]. A small subset ($n = 59$) with T2DM showed a nonsignificant RRR of 68% compared with placebo [18].

The Diabetes Atherosclerosis Intervention Study (DAIS) trial [12] was the first and only angiographic trial enrolling exclusively T2DM patients ($n = 418$) randomized to fenofibrate or placebo. The fenofibrate group showed a significant improvement in three angiographic markers of atherosclerosis and a nonstatistically significant RRR of 23% of combined cardiac endpoints in a trial not empowered to test outcomes [12]. Interestingly, the fenofibrate-induced lipid changes explained only a minority of the angiographic benefits. A post hoc analysis revealed significant slowing of progression to and regression from microalbuminuria [19].

The Veterans Administration–HDL Intervention Trial (VA-HIT) [14], a secondary prevention trial of 2531 men, was the first to demonstrate that a non-LDL cholesterol–reducing drug (gemfibrozil) reduced events in high-risk patients with low HDL cholesterol, elevated TG, and unremarkable LDL cholesterol levels. Post hoc analysis of the 769 patients with T2DM (average TG of 164 mg/dL, HDL cholesterol of 31 mg/dL, and LDL cholesterol of 108 mg/dL) demonstrated a 32% ($P < 0.004$) reduction in major CV events. In this subset, despite only a modest 2 mg/dL increase in HDL cholesterol and no change in LDL cholesterol, there were event reductions superior to that in the VA-HIT study as a whole, with a 32% RRR of the combined endpoint, a 41% decrease of the CHD death rate ($P < 0.02$) and a nonsignificant 40% decrease in stroke ($P < 0.046$) [20]. In another post hoc analysis, fasting insulin level was the best predictor of fibrate-associated risk reduction in the nondiabetic subjects (ie, those with MS) [21].

In both the DAIS and VA-HIT studies, the relationship between fibrate-induced lipid changes was not strongly related to angiographic changes or the RRR. However, LP changes in HDL and LDL particle counts had significantly better correlation with event reduction in VA-HIT and were independent of particle cholesterol concentrations [22•]. In patients with insulin resistance, defined by the Homeostasis Model Assessment equation, RRR had no relationship to baseline or on-treatment TG or HDL cholesterol level [21].

The Bezafibrate Infarction Prevention (BIP) trial [13], a secondary prevention trial enrolling 3090 men with a baseline LDL cholesterol level of 148 mg/dL randomized to bezafibrate, did not demonstrate a statistically significant RRR in the overall group. However, in a preplanned analysis of the high-TG group (> 200 mg/dL), risk reduction started in the first year and reached 40% reduction in major arteriosclerotic clinical events (defined as fatal MI, nonfatal MI, or sudden death) at 5 years [13]. Post hoc analysis showed that in the 1470 patients with MS there was a significant 28% decrease in MI ($P < 0.02$). CV event reduction was also related to the severity of MS, as those with four or more of the five NCEP-ATP III MS parameters had a significant 35% decrease in MI ($P < 0.05$) and 56% decrease in CHD death ($P < 0.005$) [23]. Long-term follow-up showed that cardiac mortality decreased significantly with increasing tertiles of on-treatment change in HDL cholesterol [24]. In this analysis, bezafibrate had a significant favorable effect on secondary endpoints only in patients with normal fasting glucose [25].

The multinational FIELD trial was the largest placebo-controlled clinical outcome study ever conducted with a cholesterol-modifying medication, enrolling men ($n = 6138$) and women ($n = 3657$) aged 50 to 75 years with T2DM who had no clear indication for lipid-lowering therapy. There were 7664 (of 9795) patients who were without prior CV disease. Patients had no clear indication for lipid-lowering therapy, but entry criteria required a TC of 115 to 250 mg/dL plus TC/HDL cholesterol ratio greater than 4.0 or TG greater than 90 mg/dL. Glycemic control was excellent, with an average HgbA1C of 6.9%. At the end of the trial, 78% of the participants were on oral hypoglycemic agents and 30% were on insulin. Mean baseline lipids were 196 mg/dL for TC, 152 mg/dL for TG, 42 mg/dL for HDL cholesterol, and 117 mg/dL for LDL cholesterol. Patients were randomized to 200 mg of micronized fenofibrate versus placebo. After randomization, decisions concerning lipid treatment were left to the primary care physician, who was notified of new guideline updates and breaking trial results (Heart Protection Study) by newsletter. The original primary outcome was coronary heart death, but 2 years into the study it was expanded CHD events, which were the combined total of death or nonfatal MI. There were several specified secondary endpoints, including

Table 1. Outcomes of the FIELD study

	Placebo, *n (%)**	Fenofibrate, *n* (%)†	Hazard ratio (95% CI)	Log rank, *P*
Primary outcomes				
CHD events	288 (6%)	256 (5%)	0.89 (0.75–1.05)	0.16
CHD mortality	93 (2%)	110 (2%)	1.19 (0.90–1.57)	0.22
Nonfatal myocardial infarction	207 (4%)	158 (3%)	0.76 (0.62–0.94)	0.01
CHD events: primary prevention			0.75 (0.59–0.94)	0.014
CHD events: secondary prevention			1.08 (0.84–1.38)	0.55
Secondary outcomes				
Total cardiovascular events	682 (14%)	612 (13%)	0.89 (0.80–0.99)	0.035
Cardiovascular disease mortality	127 (3%)	140 (3%)	1.11 (0.87–1.41)	0.41
Total mortality	323 (7%)	356 (7%)	1.11 (0.95–1.29)	0.18
Total stroke	175 (4%)	158 (3%)	0.90 (0.73–1.12)	0.36
Nonhemorrhagic stroke	158 (3%)	144 (3%)	0.91 (0.73–1.14)	0.43
Coronary revascularization	363 (7%)	290 (6%)	0.79 (0.68–0.93)	0.003
All revascularization	471 (10%)	380 (8%)	0.80 (0.70–0.92)	0.001
Tertiary outcomes				
Vascular and neuropathic amputations‡	74 (2%)	51 (1%)	0.69 (0.49–0.99)	0.04
Laser treatment for retinopathy	253 (6%)	178 (4%)	0.70 (0.58–0.85)	0.000
Hospitalizations for angina‡	252 (6%)	209 (5%)	0.82 (0.69–1.00)	0.04
Need for dialysis	21 (1%)	16 1%)		

*There were 4900 patients in the placebo group.
†There were 4985 patients in the fenofibrate group.
‡Keech, Unpublished data.
CHD—coronary heart disease; FIELD—Fenofibrate Intervention and Event Lowering in Diabetes.
(*Adapted from* FIELD Study Investigators [10•].)

total cardiovascular events, coronary revascularizations, all revascularizations, stroke, and both coronary vascular and total mortality. There were multiple tertiary prespecified endpoints, including progression of renal disease, laser treatment for diabetic retinopathy, nonfatal cancers, vascular and neuropathic amputations, hospitalizations for angina pectoris, and hospital admissions. The use of interim analyses required the final *P* value to be less than 0.047 for statistical significance [10•].

The results of the FIELD trial were mixed (Table 1). The overall major event rate in the trial was only 1.1% per year, making FIELD among the lowest-risk trials to date with any lipid-lowering agent. Only 5.9% of the patients on placebo and 5.2% of the patients on fenofibrate had a coronary event (relative event reduction of 11%; hazard ratio of 0.89; 95% CI, 0.75–10.5; $P = 0.16$). This corresponded to a significant 24% decrease in nonfatal MI (0.76; 95% CI, 0.62–0.94; $P = 0.010$) and a nonsignificant increase in CV mortality (1.19; 95% CI, 0.90–1.57; $P = 0.22$). The secondary outcome of total CV events was significantly reduced by fenofibrate from 13.9% to 12.5% (0.89; 95% CI, 0.80–0.99; $P = 0.035$), including a significant 21% reduction in coronary revascularization (0.79; 95% CI, 0.68–0.93; $P = 0.003$) and a nonsignificant total mortality increase of 11% (1.11; 95% CI, 0.95–1.29; $P = 0.18$). The effect of fenofibrate was particularly beneficial in the patients without prior CVD (78% of the total population), reducing the incidence of the primary endpoint of coronary events by 25% ($P = 0.014$) and the secondary outcome of total CV events by 19% ($P = 0.004$) in this population. On the tertiary outcomes, the fenofibrate group had a 30% reduction in laser treatment for retinopathy ($P < 0.001$), an effect that persisted with or without retinopathy at baseline. There was also a 31% decrease in amputations ($P = 0.04$) and an 18% reduction in hospitalizations for angina ($P = 0.04$) (Keech, Unpublished data). In other analyses there was an 11% reduction in the progression of albuminuria ($P = 0.002$) in the fenofibrate group, and FIELD also makes a significant contribution to the existing database for CV event reduction in women, who are traditionally under-represented in such trials, demonstrating the benefit of fenofibrate in reducing total CV events ($P = 0.04$) [10•].

The results from FIELD must be interpreted in light of the substantial use of both multiple CV medications, including statin drugs, throughout the trial. The authors conclude that the higher proportion of statin use in the placebo group may have obscured some of the beneficial effects of fenofibrate therapy. The HR for the statin

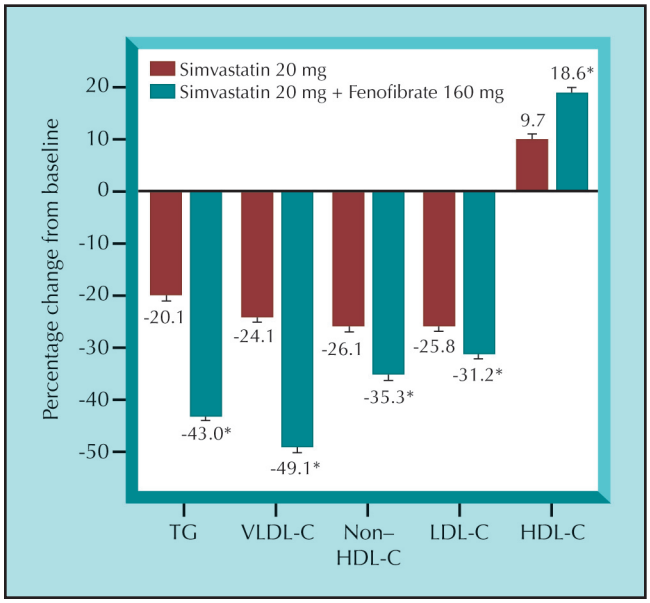

Figure 1. Change from baseline in lipid parameters. *Asterisk* indicates $P < 0.001$. C—cholesterol; HDL—high-density lipoprotein; LDL—low-density lipoprotein; TG—triglyceride; VLDL—very low-density lipoprotein. (*Adapted from* Grundy et al. [28•]; with permission.)

drop-in rate was 0.47 (95% CI, 0.44–0.51; $P < 0.001$), indicative of twice as much statin use in the placebo group compared with fenofibrate groups. There was a greater statin drop-in rate in the secondary versus the primary prevention patients, and of course multiple previous trials have established the benefit of statin therapy in T2DM patients [26]. Interestingly, of those in the placebo group who received lipid-lowering medication ($n = 1318$), 74% remained on placebo, whereas in the fenofibrate group only 62% remained on fenofibrate ($P = 0.0001$). The trial design accounted for a 10% drop-in rate for other lipid-lowering therapies (> 90% of these were statins), but by the end of the trial, statin drop-in was 36% in the placebo group and 19% in the fenofibrate group, resulting in a 34% reduction in LDL cholesterol in the group of 2720 patients started on other lipid-lowering therapy. Cox regression analysis of the predefined assumption of other lipid-lowering therapy or drop-in suggests a significant 19% reduction of the primary outcome of CV events ($P = 0.01$) by fenofibrate and a significant 15% reduction of the secondary outcome of total CV events ($P = 0.004$). Estimated risk reductions in patients starting with other lipid-lowering therapies on a fenofibrate background in these analyses were 49% ($P < 0.001$) for CHD events and 26% ($P < 0.001$) for total cardiovascular disease events, respectively, although the authors speculate that these regression analyses may be significant overestimates [10•]. Reasonable conclusions from FIELD are that in T2DM patients without existing clinical events (primary prevention patients), fenofibrate can reduce several important clinical outcomes, including nonfatal MI and revascularizations, and may well have microvascular benefits. This is the first time that a lipid-lowering agent has been shown to impact the risk of both macrovascular and microvascular events in a large-scale clinical study. No prospective outcome data with fenofibrate/statin combination therapy will exist until publication of the ongoing Action to Control Cardiovascular Risk in Diabetes trial (ACCORD) [27], which in one arm prospectively addresses the issue of combined simvastatin/fenofibrate therapy in approximately 5000 T2DM patients.

There are many trials of lipid, lipoprotein, and nonlipid surrogates in largely insulin-resistant patients that have demonstrated benefits from fibrate monotherapy or increased benefits with the combination of fibrates with other lipid agents. The simvastatin and fenofibrate for combined dyslipidemia (SAFARI) trial [28•] looked at 618 patients (> 70% insulin resistant) with mixed dyslipidemia and showed an additive effect of fenofibrate to 20 mg of simvastatin in all lipid and lipoprotein parameters studied, including LDL particle size (Fig. 1). Trials with fenofibrate/atorvastatin demonstrated the complementary effects of these two agents on lipoprotein parameters and markers of endothelial function [29,30]. Fenofibrate combined with ezetimibe in 625 patients (approximately 75% with insulin resistance) was well tolerated and showed the complementary effects of these two agents in reducing LDL cholesterol, non-HDL cholesterol, and apoB, as well as causing a favorable shift in LDL particle size [31]. The combination of niacin and gemfibrozil produced marked and significant changes in lipid levels in a study of patients with TG/HDL cholesterol axis abnormalities: LDL cholesterol decreased by 14%, HDL cholesterol increased by 24%, the ratio of TC to HDL cholesterol decreased by 30%, and TG decreased by 52% [32]. In a small angiographic trial with composite endpoints of clinical events that included hospitalization for angina, MI, transient ischemic attack and stroke, death, and cardiovascular procedures, triple therapy with gemfibrozil, niacin, and a resin was successful [33].

Fibrates: Mechanism of Action

As previously noted, insulin-resistant patients often have overproduction of large, apoB-containing TRLPs. Peroxisome proliferator–activated receptor α (PPARα) is a ligand-activated nuclear receptor that regulates multiple genes involved with glucose and fatty acid metabolism, lipoprotein synthesis and catabolism, and vascular inflammation. Natural ligands include several fatty acids (saturated and unsaturated) and their derivatives, including eicosanoids. The PPARα/ligand complex requires heterodimerization with the retinoid X receptor/retinoic acid complex. After interaction with tissue-specific protein co-repressors or activators, the dimer attaches to distinct gene response elements, causing transcription of messenger RNA. Fibrates, at concentrations much higher than natural ligands, also agonize PPARα (Fig. 2) [34,35••].

Fibrates enhance widespread fatty acid metabolic processes, including beta oxidation and omega hydroxylation of fatty acids, effects on fatty acid transport protein (fatty acid uptake) and fatty acid activation, induction of both carnitine palmitoyltransferase I (which translocates fatty acids into mitochondria), and acyl coenzyme A dehydrogenases. These enhanced fatty acid catabolic processes reduce TG synthesis, which may improve insulin sensitivity [36,37].

Fibrates noncompetitively inhibit acyl-CoA:diacylglycerol acyltransferase (DGAT2), an enzyme that enhances TG formation by catalyzing the addition of fatty acids to monocylglycerol and diacylglycerol. With less TG formation there is post-translational degradation of apoB, with the ultimate result being reduced formation of TRLPs [38]. In the presence of reduced numbers of TRLPs, CETP activity will be diminished, thereby reducing the TG/CE exchange between VLDL and LDL and HDL, resulting in increased LDL and HDL particle sizes [39]. Large LDLs are more readily cleared by hepatic LDL receptors, and larger HDLs are less vulnerable to renal excretion, which increases HDL particle (apoAI) levels. By inducing increased production of LP lipase and apoAV and inhibiting production of apoCIII, PPARα agonists enhance efficient catabolism of TRLPs [40–42]. The combination of decreased TG synthesis, VLDL production, and TRLPs reduces postprandial lipemia, improves flow-mediated dilation, lessens blood viscosity, and is associated with reduced levels of prothrombotic markers like fibrinogen [43,44].

Fibrates have multiple effects on HDL (apoA-I mediated) cholesterol transport. There is increased production of HDL's major apolipoproteins, apoA-I and apoAII. Through a PPARα interaction with liver X receptor (LXR), there is upregulation of ATP binding cassette A1 (ABCA1), resulting in lipidation on pre-β HDL (the first step in enhanced HDL cholesterol transport) [45]. With diminished CETP activity, the more mature, larger α2 and α1 HDLs (HDL2) can deliver the cholesterol to steroidogenic tissue (forward cholesterol transport) or return to the liver (direct reverse cholesterol transport). At both sites PPARα-upregulated scavenge receptor-B1 (SR-B1) delipidation of the HDL occurs, generating increased numbers of smaller, delipidated α3-HDL (HDL3) [46••]. The increased hepatic cholesterol can be excreted into the biliary system and ultimately the small intestine via hepatic ABCG5 and ABCG8 transporters. There is also a PPARα effect on both decreased bile acid synthesis and alkaline phosphatase [47,48]. A potential major benefit of fibrates is their ability to delipidate cholesterol-laden macrophages by upregulating macrophage sterol efflux transporters ABCA1, ABCG1, ABCG4, and SR-B1, in a process termed macrophage reverse cholesterol transport (Fig. 3) [49,50,51•].

The effects on lipoprotein synthesis and catabolism explain how fibrates reduce TG and apoB, and increase apoA-I, HDL particles, and HDL cholesterol but have variable effects on LDL cholesterol. Paradoxically, when fibrates are given to patients with very high TG levels, there may be an increase in LDL cholesterol. Several factors are at play. By significantly enhancing lipolysis of TRLPs, there will be a more rapid formation of LDL particles. The reduced-particle TG lessens CETP-mediated CE/TG exchange between TRLPs and LDL, shifting LDL particle size. Enhanced LDL production and increased LDL size results in increased LDL cholesterol. The simple therapeutic solution to this perceived dilemma is to facilitate hepatic clearance of LDL by upregulating LDL receptors with lifestyle adjustments or statin or statin/ezetimibe use [52,53]. Such combinations as previously discussed dramatically improve lipid and LP concentrations.

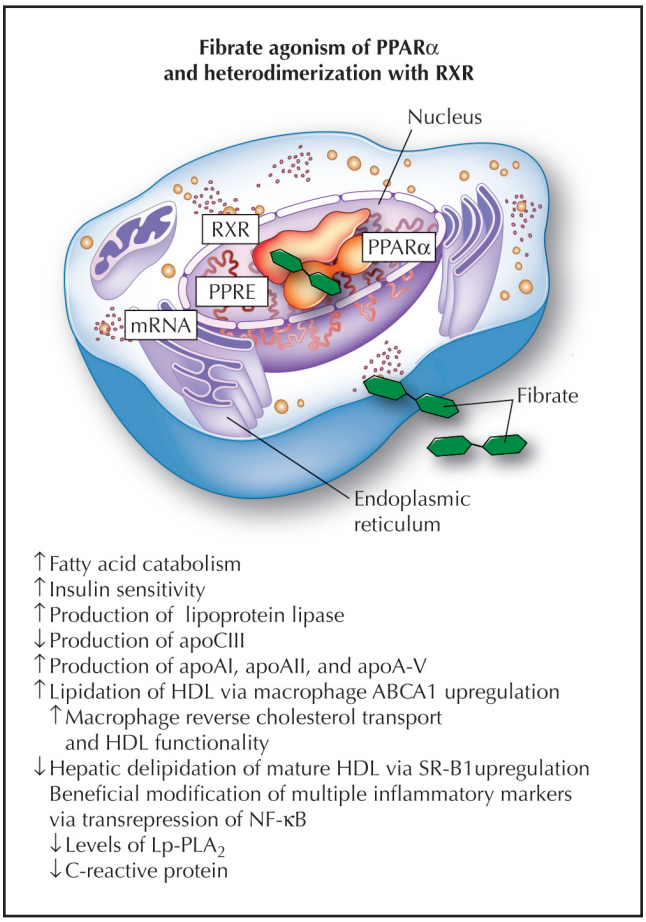

Figure 2. Peroxisome proliferator–activated receptor α (PPARα) is a nuclear receptor that, when agonized by endogenous ligands (numerous fatty acids) or therapeutic agents like fibrates, forms a heterodimer with a retinoid X receptor (RXR)/retinoic acid complex. After being influenced by co-activator or co-repressor proteins, the complex attaches to various PPAR response elements (PPRE) on genes. Transcription of messenger RNA (mRNA) regulates protein synthesis and ultimately many cellular actions. ABCA1—adenosine triphosphate binding cassette A1; apo—apolipoprotein; HDL—high-density lipoprotein; Lp-PLA_2—lipoprotein-associated phospholipase A_2; NF-κB—nuclear factor-κB; SR-B1—scavenger receptor-B1.

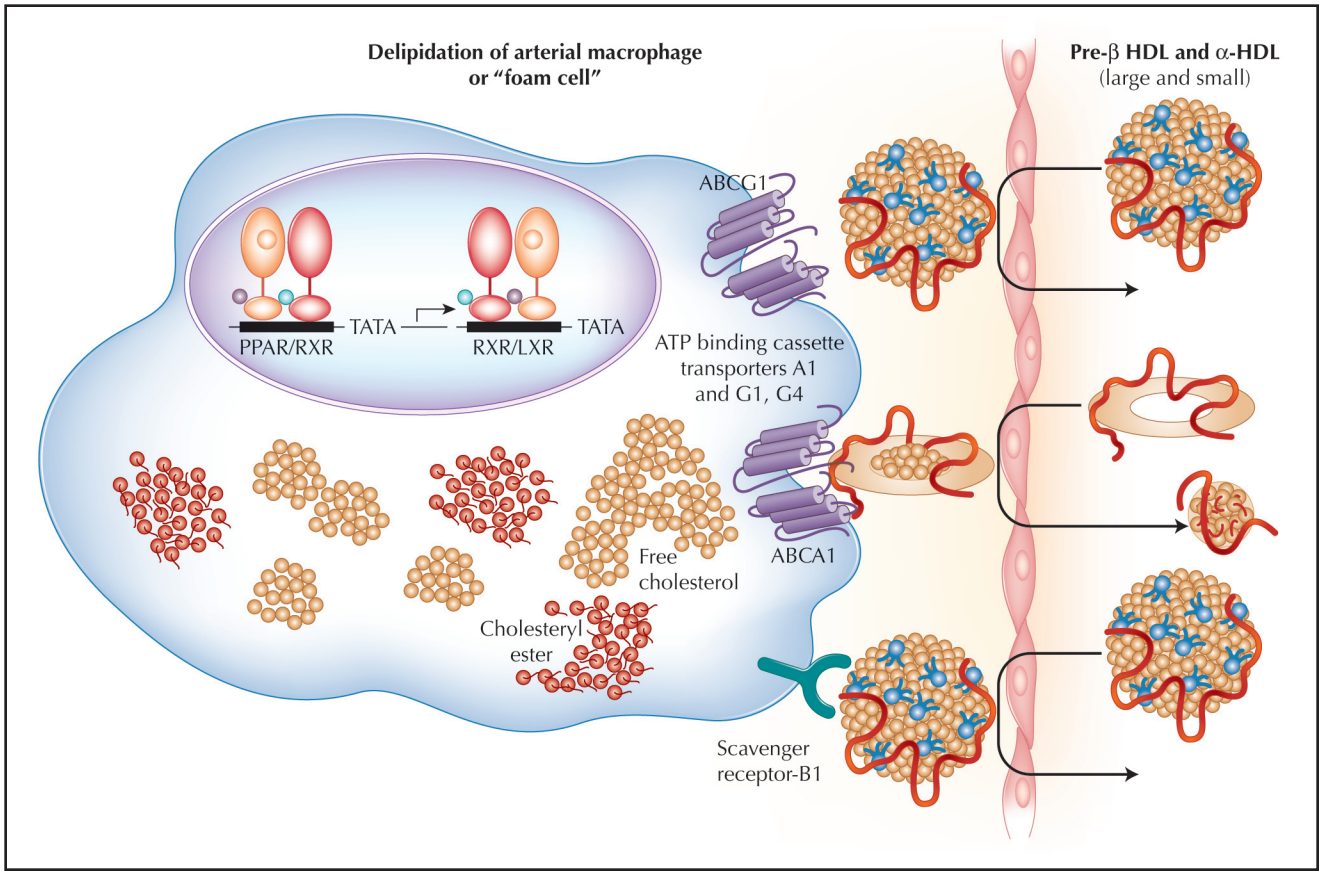

Figure 3. Fenofibrate increases apolipoprotein AI-induced cholesterol efflux from normal macrophages. Both increased concentrations of cellular sterols as well as crosstalk from peroxisome proliferator–activated receptor α (PPARα) agonism enhance expression of liver X receptor (LXR), which upregulates production and translocation of several sterol efflux proteins. Macrophage reverse cholesterol transport does not affect plasma high-density lipoprotein (HDL) cholesterol level. ABC—adenosine triphosphate binding cassette.

In the BIP trial, bezafibrate demonstrated an ability to improve glycemic status and delay the onset of impaired fasting glucose and T2DM. Whether these effects are due to enhanced fibrate-induced free fatty acid catabolism or a possible PPARα effect is unknown [54]. Fenofibrate use has also been associated with increased adiponectin concentration [30,55], decreased insulin levels, and improved insulin sensitivity [56], which may help explain the reduction in microvascular endpoints seen in FIELD [10•] and DAIS [19].

Of likely clinical importance are the many "pleiotropic" (ie, nonlipid) effects seen in multiple fibrate studies. Through a PPARα transrepression of nuclear factor-κB, fibrates have beneficial effects on numerous chemokines, cytokines, and inflammatory markers associated with atherogenesis. Studies show fenofibrate can have beneficial effects on C-reactive protein, lipoprotein-associated phospholipase A_2, metalloproteinase, selectins, cellular adhesion molecules, tissue factor, thromboxanes, monocyte chemotactic protein, tumor necrosis factor-α, and endothelin [57–60]. Such effects may lead to decreased inflammatory cell recruitment and activation, decreased thrombosis and vasoconstriction, and increased plaque stability.

Fibrates: Safety and Concerns

In multiple clinical trials, modern fibrates (bezafibrate, fenofibrate, and gemfibrozil) have been well tolerated [11–13]. In the FIELD study, fenofibrate was associated with slight increases in pancreatitis (0.5% vs 0.8%; $P = 0.031$), deep venous thrombosis ($P = 0.074$), and pulmonary embolism (0.7% vs 1.1%; $P = 0.022$) [10•]. There was no significant increase in newly diagnosed cancers, liver function abnormalities, or creatinine kinase levels [10•]. There was a nonsignificant reduction in incidence of elevated alanine aminotransferase, with 26 cases (0.6%) in placebo versus 11 cases (0.3%) in fenofibrate group, which suggests fibrates could be of benefit in steatohepatitis. Although not proven, the pancreatitis risk is believed related to the combination of increased biliary secretion of lithogenic cholesterol and alteration of bile acid synthesis.

Unlike gemfibrozil, fenofibrate is known to raise serum creatinine concentration, which is related to increased muscular production of creatinine, not increased renal toxicity (impaired renal blood flow or glomerular filtration) [61]. However, in one study cystatin levels increased and the author suggested pos-

sible PPARα impairment of vasodilatory prostaglandins [62]. In FIELD, serum creatinine remained an average of 10 to 12 μmol/L (0.11–0.13 mg/dL) higher in the fenofibrate group at the end of the study. At the conclusion of the trial, creatinine levels rapidly returned to normal upon drug cessation, arguing against fenofibrate-related renal toxicity. Hyperhomocysteinemia, a known effect associated with fibrate therapy, averaged 3.7 μmol/L higher in the fenofibrate group in FIELD, with a rapid return to normal after trial conclusion and drug cessation. The explanation for the increase is not well understood. An effect on PPARα response elements involved with transsulphuration and remethylation pathways has been hypothesized [63]. Interestingly, in the DAIS study, fenofibrate-associated homocysteine levels were not associated with angiographic worsening [64]. One might conjecture that the homocysteine elevation may help explain the nonsignificant increase in venous thrombosis seen in FIELD and lack of total mortality benefit in this and other fibrate trials. The hyperhomocysteinemia can be reduced by supplementation with folic acid and B vitamins, and some recommend their use when prescribing fibrates [65,66].

In FIELD, fenofibrate was generally well tolerated on a statin background (2000 patient-years of statin/fenofibrate data), adding confidence to the combination use of these two agents. There were no cases of rhabdomyolysis in the patients using the fenofibrate/statin combination. The NCEP-ATP III 2004 addendum noted that unlike gemfibrozil, fenofibrate does not seem to increase the risk of myositis when combined with moderate doses of statins [15]. This is due to the lack of an interaction between fenofibrate and glucuronidation enzymes necessary for metabolism of lipophilic statins [67]. Jones and Davidson [68] and Corsini et al. [69•], in a careful analysis of prescription records and US Food and Drug Administration safety reports, conclude fenofibrate is significantly less likely to be associated with myopathy than are statin/gemfibrozil combinations.

Since the World Health Organization trial using clofibrate there have been questions about increases in total mortality seen in that study and lack of total mortality reductions in others. In FIELD, there was a nonsignificant increase in CHD death, which in reality is a null or chance finding. Reducing total mortality is a very problematic endpoint in today's clinical trials where both placebo and therapeutic groups receive aggressive cardiovascular risk reduction treatments with other drugs [70]. There was heavy use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and aspirin in FIELD, with significantly more patients in the placebo group receiving β-blockers ($P = 0.011$) and angiotensin-converting enzyme inhibitors ($P = 0.003$). NCEP-ATP III specifically addressed the mortality issue of fibrates by stating "the worldwide experience with fibrates is vast. No evidence of specific toxicity that enhances non-CHD mortality has emerged. Such experience, taken in the light of all the clinical trials provides little support for the concern that fibrates carry significant short term toxicity that precludes their use for appropriately selected patients." [7].

Conclusions

Second only to statins, fibrates have been studied in multiple angiographic and large primary and secondary CV outcome trials. Next to statins, no class of drugs has been so extensively studied in diabetic patients as have fibrates. The accumulated evidence is that fibrates are most efficacious in insulin-resistant patients and best used in the moderately high-risk, high-risk, or very high-risk categories of patients, in combination therapy (fenofibrate) with statins, or perhaps in combination with statin/ezetimibe to achieve NCEP-ATP III non-HDL cholesterol goals or American Diabetes Association goals for TG and HDL cholesterol. Clinicians must always keep in mind that many of the event-lowering benefits of fibrate therapy may not be discernible in the lipid profile and that one must rely on clinical trial data to appreciate their benefits.

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