Treatment of Hypertriglyceridemia With Fibric Acid Derivatives: Impact on Lipid Subfractions and Translation Into a Reduction in Cardiovascular Events

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This review investigates how the treatment of hypertriglyceridemia with fibric acid derivatives impacts lipid concentrations, lipid particle size, and the rate of cardiovascular events: expressly, to decide whether the use of fibric acid derivatives is an effective treatment option in the reduction of cardiovascular endpoints for patients with specific lipid parameters at baseline. Fibric acid derivatives reduce fasting triglyceride (TG) values by 15% to 50% (depending on baseline level) and low-density lipoprotein cholesterol (LDL-C) by 8%, and raise high-density lipoprotein cholesterol (HDL-C) by 9%. In conjunction with a statin, the amount of TG lowering is approximately doubled with the addition of the fibrate. When measured, fibrates decrease the TG concentration of very low-density lipoprotein cholesterol particles while increasing the TG content of LDL particles. The mean size of LDL particles increases and there is a substantial reduction in the number and proportion of small, dense LDL. In randomized trials in primary and secondary prevention populations, fibrates were associated with a significant reduction in nonfatal myocardial infarction in most studies. In the subgroup with elevated TG and/or depressed HDL-C at baseline, all trials have found statistically significant relative risk reductions of 27% to 65% in the primary cardiovascular endpoint of myocardial infarction and cardiovascular death.

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Key words: Fibrates • Dyslipidemia • Hypertriglyceridemia • Cardiovascular events

The prevalence of hypertriglyceridemia, a condition in which serum triglyceride (TG) levels are elevated, is increasing in the United States. Mounting evidence indicates that hypertriglyceridemia increases a patient's risk for adverse cardiovascular (CV) events. Various factors can promote CV risk, including increased serum TG levels, atherogenic lipid profile (elevated small, dense low-density lipoprotein cholesterol [LDL-C] levels, and low high-density lipoprotein cholesterol [HDL-C] levels), insulin resistance, and a prothrombotic propensity. Hypertriglyceridemia is a CV risk marker because it represents this complicated cluster of lipid abnormalities and is associated with several other independent CV risk factors, including obesity and diabetes.

Hypertriglyceridemia is a disorder of lipid metabolism, which is characterized by an elevation in fasting TG > 150 mg/dL or nonfasting TG > 180 mg/dL, and can be due to familial or acquired disease that can lead to other disorders (eg, atherosclerosis and pancreatitis). The Fredrickson classification (Table 1), which originally aided in the delineation of dyslipidemic disorders, defines the six types of hyperlipidemia. According to this classification, hypertriglyceridemia is common in all categories except type IIa.

Hypertriglyceridemia can be classified as primary or secondary. Primary (or endogenous) hypertriglyceridemia is the result of various genetic defects that lead to disorders of TG metabolism. Genetic mutations of lipoprotein lipase, particularly the CG and GG genotypes of the *Sst*I gene, which codes for apolipoprotein (apo) C-III, are associated with hypertriglyceridemia.[1,2] When hypertriglyceridemia is the result of an unhealthy lifestyle, obesity, or another medical condition, the condition is termed *secondary hypertriglyceridemia*; many factors are implicated, including poor diet, lack of exercise, obesity, diabetes mellitus (DM), advanced hepatic or renal disease, hypothyroidism, and excessive daily or binge alcohol consumption. Because of the intricacy of the interactions between environmental and genetic factors, a distinction between primary and secondary hypertriglyceridemia cannot be made from the fasting lipid profile alone.

The National Cholesterol Education Program Adult Treatment Panel III defined elevated fasting TGs as ≥150 mg/dL. Using that criterion, the Third National Health and Nutrition Examination Survey found that the prevalence of hypertriglyceridemia in US adults aged 20 years and older was approximately 35% in men and 25% in women. Elevated triglyceride levels in African American men and women were 21% and 14%, respectively; 40% and 35% in Mexican American men and women, respectively; and 37% and 25% in white American men and women, respectively.[3] The rate of severe hypertriglyceridemia (TG > 500 mg/dL) is 1.7% in the general population.[4]

The treatment of hypertriglyceridemia involves dietary and lifestyle changes. Importantly, substantial weight loss can result in the greatest and most sustained reduction of TG levels.[5] Reducing sugar, starch, and saturated fat in the diet, abstinence from alcohol, increasing exercise, and glycemic control of DM all can lead to improvements in TG values by reducing the fatty acid substrate and by activating lipoprotein lipase.[6] The mainstays of pharmacotherapy have been nicotinic acid, ω-3 fatty acids, and fibric acid derivatives. The preponderance

Table 1
The Fredrickson Classification of Hyperlipidemia

	Lipoprotein Affected	Elevated Serum Lipid	Cause	Risk
Type I	Chylomicrons	TG	Homozygous ApoC-II or LPL deficiency	Pancreatitis
Type IIa	LDL	TC	Multifactorial: genetic + environmental factors	CVD
Type IIb	VLDL, LDL	TG, TC, LDL-C	Multifactorial: genetic + environmental factors	CVD
Type III	IDL, VLDL	TG, TC	Homozygous ApoE2 + environmental factors	CVD
Type IV	VLDL	TG, TC*	Multifactorial: genetic + environmental factors	Pancreatitis, CVD, gallstone disease
Type V	VLDL, chylomicrons	TG	Unknown	Pancreatitis

*Unchanged.

Apo, apolipoprotein; CVD, cardiovascular disease; IDL, intermediate density lipoprotein; LDL-C, low-density lipoprotein-cholesterol; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein; TG, triglycerides; TC, total cholesterol.

of randomized trial data with measures of atherogenic dyslipidemia and CV outcomes has been generated in the study of fibric acid derivatives. In conducting this review, our goal was to investigate how the treatment of hypertriglyceridemia with fibric acid derivatives impacts lipid fractions, LDL-C particle size and number, and the rate of subsequent CV events. Furthermore, we endeavored to distill the clinical evidence currently available to determine the utility of fibric acid derivatives as an evidenced-based treatment option for patients with elevated TG levels (> 200 mg/dL) and/or low HDL-C (≤ 40 mg/dL in men and ≤ 50 mg/dL in women) for the primary or secondary prevention of ischemic heart disease.

Clinical Pharmacology of Fibric Acid Derivatives

Fibric acid derivatives (or fibrates) are a class of drugs that demonstrate lipid-modulating abilities. Commercially available fibric acid derivatives (fenofibric acid, fenofibrate, bezafibrate, and gemfibrozil) perform similar actions in treating lipid concentrations in plasma. Fibrates induce lipoprotein lipolysis by behaving as a ligand to the peroxisome proliferator-activated receptor (PPAR) α subunit, activating the transcription of multiple genes, including those that upregulate lipoprotein lipase, a catabolic enzyme (Figure 1).[7] Increased lipoprotein lipase enhances the metabolism of TG-rich particles, such as chylomicrons and very low-density lipoprotein (VLDL) (Figure 2).[8,9] In addition, PPARα stimulation influences multiple pathways in reverse cholesterol transport (Figure 2).[7] When treating hypertriglyceridemia, fibrates are generally preferred before other drugs to regulate plasma TG

Figure 1. *PPARα activation by fenofibric acid. The PPAR/RXR and PGC-1 as a coactivator work to activate transcription. The heterodimer binds cognate NRRE within the promoter region of the target gene. PPAR facilitates interactions with other coactivators with enzymatic activity such as the ability to modify chromatin and the process of gene transcription. CBP, cAMP responsive element binding protein; DRIP, vitamin D receptor interacting protein; NRRE, nuclear receptor response elements; POL II, polymerase II; PPARαperoxisome proliferator-activated receptor-α; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; RXR, retinoid X receptor; SRC, steroid receptor coactivator; TRAP, thyroid hormone receptor-associated protein. Reprinted with permission from Finck and Kelly. Peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) regulatory cascade in cardiac physiology and disease.* Circulation. *2007;115:2540-2548.*[7]

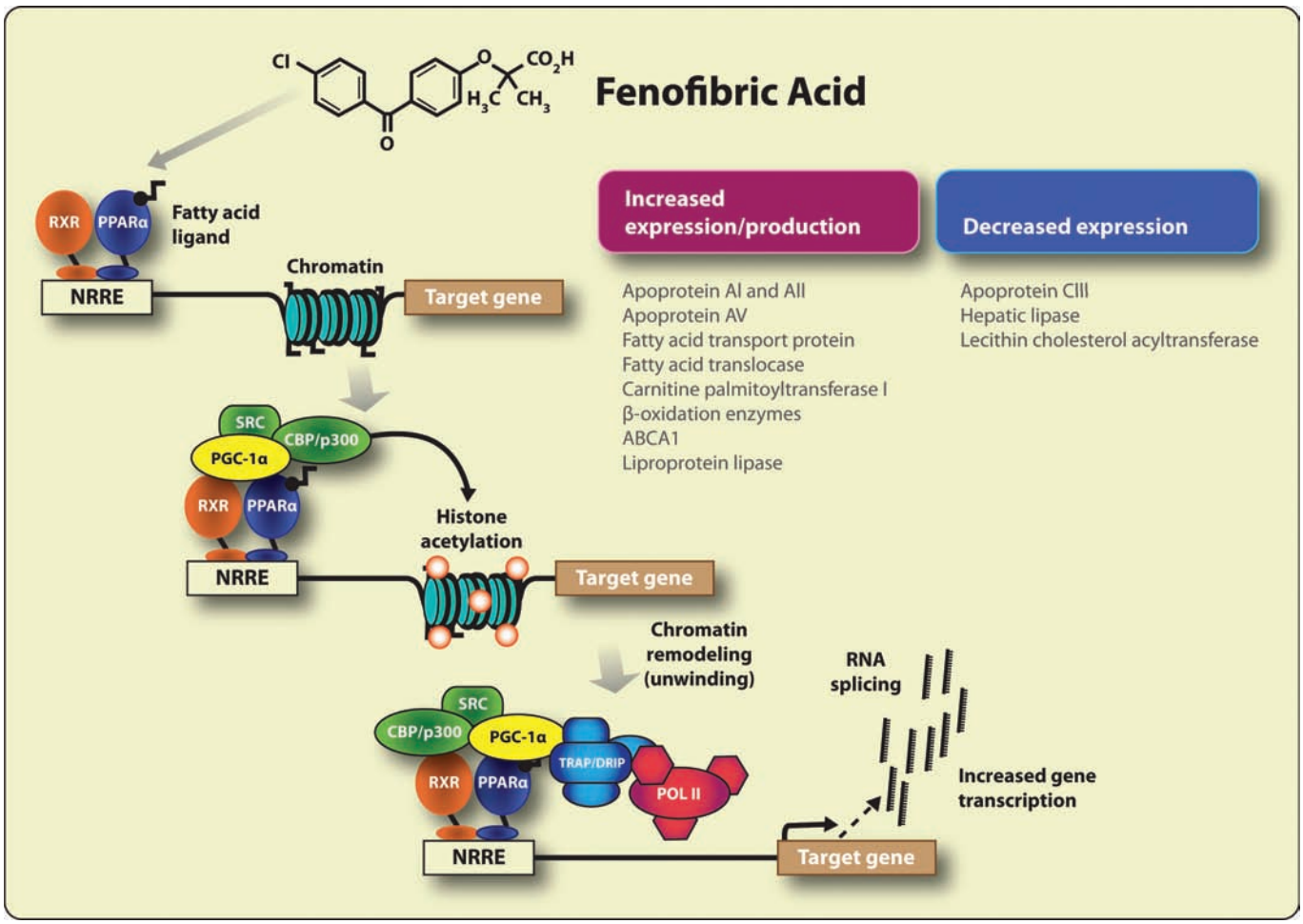
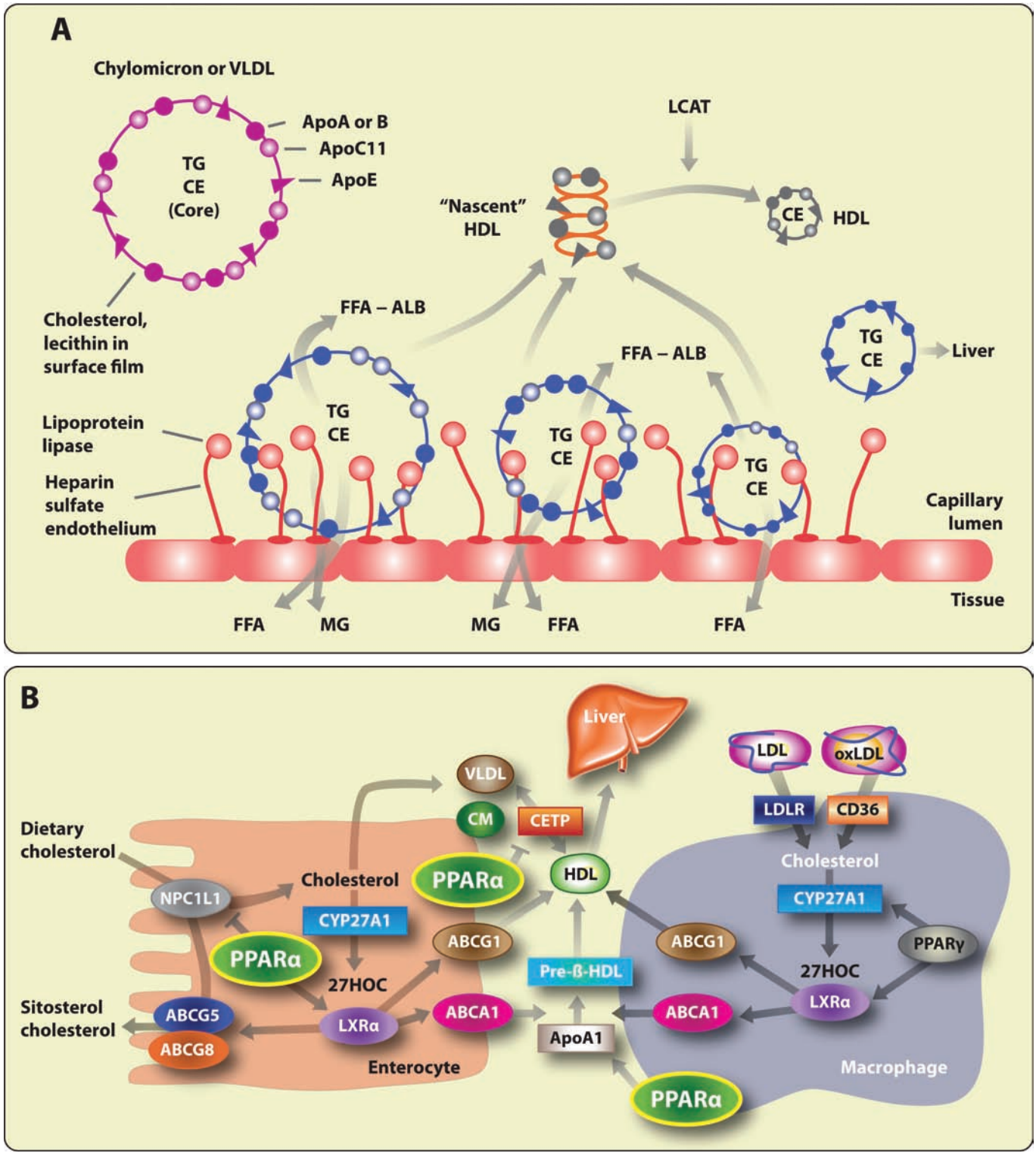


Figure 2. *Major actions of fibric acid derivates on lipid metabolism include activation of lipoprotein lipase* **(A)** *and influences on multiple steps in reverse cholesterol transport* **(B)**, *including reduction of NPC1L1 and fractional cholesterol absorption, and may promote cholesterol secretion into the gastrointestinal lumen by stimulating CYP27A1 and LXR activation of ABCA1 and ABCG1. PPARα induces apo A-I and inhibits CETP, and thus increases circulating HDL cholesterol levels. 27HOC, 27-hydroxy cholesterol; ALB, albumin; Apo, apolipoprotein; CE, cholesteryl ester; CM, chylomicron; FFA, free fatty acid; HDL, high-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LXR, liver X receptor; MG, monoglyceride; PPAR, peroxisome proliferator-activated receptor; TG, triglyceride; VLDL, very low-density lipoprotein; Panel B reprinted with permission from Li and Chiang. Regulation of bile acid and cholesterol metabolism by PPARs.* PPAR Res. *2009;2009:501739.*[9]



levels effectively and reduce the risk of autolytic pancreatitis.[10] Fibrates are indicated for the treatment of types IIa, IIb, III, IV and V dyslipidemias (Table 1). Fibrates influence fatty acid uptake and reduce hepatic TG, increasing production of HDL by increasing production of apo A-I and apo A-II in the liver, and stimulating removal of LDL-C components.[7-11] By these mechanisms, fibrates aid dyslipidemic patients in improving plasma TG and overall cholesterol levels.

Galimberti and Defranceschi,[12] in 1947, and Thorp and Waring, in 1962,[13] described the observations of a fibric acid derivative, ethyl-α-4-chlorophenoxyisobutyrate, as a compound that effectively lowered lipids in animal models with minimal toxicity. In human trials, the compound (later named clofibrate) demonstrated an ability to decrease levels of lipids as a monotherapy. Additionally, it reduced VLDL and LDL fractions in combinations with androsterone in hypercholesterolemic patients. The United States approved the use of clofibrate in 1967 for the treatment of hyperlipidemia. Thorp and Waring[13] attempted to change the chemical structure of clofibrate when studies revealed that murine species developed clofibrate-induced hepatomegaly. The World Health Organization Cooperative Trial on Primary Prevention of Ischaemic Heart Disease using clofibrate found that there was excess mortality in the clofibrate-treated group despite favorable lipid effects, with 47% more deaths occurring during the treatment period with clofibrate, compared with 5% after treatment, clofibrate had been discontinued. These deaths were due to a wide variety of causes other than heart disease, and remain "unexplained."[14] Clofibrate modifications failed to meet safety and effectiveness standards[15]; subsequent development efforts yielded beclobrate, bezafibrate, gemfibrozil, fenofibrate, and fenofibric acid.

It has been reported that up to 10% of individuals on fibric acid therapy will experience significant dose-dependent elevations in their liver transaminase levels. These elevations may follow a number of separate hepatic pathologies, including benign induction of the production of transaminases, cholestatic hepatitis, hepatocellular hepatitis, and chronic active hepatitis. Fatal hepatitis was reported during the clinical development of beclobrate.[16] For these reasons, regular screening of liver function is recommended in all patients on fibrates. Patients also report abdominal pain, nausea, constipation, and diarrhea. Myositis has also been reported, specifically in patients using gemfibrozil, those with concomitant statin therapy and/or decreased renal function, the elderly, patients with diabetes, and those with hypothyroidism. Gemfibrozil specifically impairs glucuronidation, one of the clearance steps for statins; therefore, individuals who have impaired clearance of statins due to other factors have an increased risk of rhabdomyolysis when fibrates are added to the regimen.[17] This does not appear to be a class effect and there is no evidence of impaired glucuronidation with fenofibrate or fenofibric acid. Fibrates also elevate levels of homocysteine[18] and have been shown to be associated with an increased risk of venous thromboembolism.[19]

Fibrates may increase the muscular production of creatine and its metabolic product, creatinine, and at the same time reduce renal blood flow in a reversible manner.[20] Thus, a small increase in serum creatinine and a reduction in estimated glomerular filtration rate can be expected with this class of drugs.[21] These effects are modest and are only of significance in very advanced chronic kidney disease (creatinine clearance < 30 mL/min), particularly in those who are taking concomitant statins. In this case, there can be accumulation of both the fibrate and the statin or statin alcohol, which may pose a risk for muscle toxicity. More than a 30% increase in serum creatinine should prompt the discontinuation of the fibrate.[22]

Fibrates are contraindicated in patients with any significant history of hypersensitivity to fibrates, and those with hepatic, renal, gallbladder dysfunction or disease. Fibrates should be discontinued in patients found to have gallstones because they may increase lithogenesis by increasing the saturation of cholesterol in bile.[23] Patients with risk factors for venous thromboembolism and pulmonary embolism may show increased incidence of these adverse events while on fibrates.[19,24] Finally, patients on warfarin and concomitant fibrate therapy should be monitored and have their anticoagulant doses adjusted accordingly because of the ability of fibrates to inhibit multiple cytochrome P450 isoenzymes.

Fibrates induce lipoprotein lipolysis by behaving as a ligand to the peroxisome proliferator-activated receptor (PPAR) α subunit, activating the transcription of multiple genes, including those that upregulate lipoprotein lipase, a catabolic enzyme. Increased lipoprotein lipase enhances the metabolism of TG-rich particles, such as chylomicrons and very low-density lipoprotein (VLDL). In addition, PPAR α stimulation influences multiple pathways in reverse cholesterol transport.

Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Thrombocytopenias and agranulocytosis are extremely uncommon. Other infrequent adverse events include headaches, anxiety, vertigo, sleep disorders, loss of libido, and alopecia. All fibrates are considered Class C in pregnancy and should therefore not be used in women who are pregnant or nursing.

Methods

A systematic review of the literature available through PubMed and the National Library of Medicine was performed to compare the treatment of hypertriglyceridemia with fibric acid derivatives (Figure 3). We searched for only English language, human, prospective, randomized, double-blind, placebo-controlled trials with relevant text words and medical subject headings that included all spellings of *fenofibrate*, *bezafibrate*, *gemfibrozil*, *fibrate*, *fibric acid*, and *fenofibric acid*. Our literature search identified 544 potentially relevant studies. We eliminated 433 of these studies on the basis of their abstracts. We narrowed our search results for the remaining 112 studies, 86 of which were subsequently excluded because they were either not randomized, were retrospective subgroup analyses from prospective trials, or were reviews or editorials. Thus, our systematic review included 26 relevant articles that reported data from prospective randomized trials where the treatment allocation included a fibric acid derivative. For each product we provide a brief description of the agent and summarize the most relevant trials.

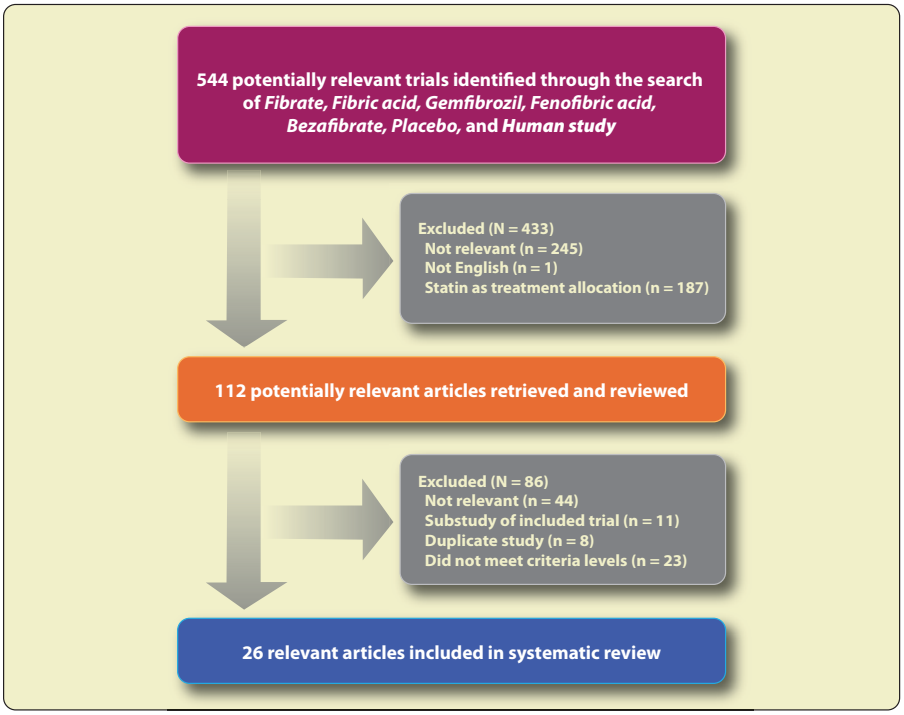
Gemfibrozil

Gemfibrozil was introduced to the US market in 1976.[25] The chemical name of gemfibrozil is 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid, with an empirical formula of $C_{15}H_{22}O_3$.[26] In humans, oral gemfibrozil undergoes metabolism by oxidation of ring methyl group, producing hydroxymethyl and carboxyl metabolites. The major metabolites are 1-*O*-gemfibrozil-β-D-glucuronide and 5′-carboxyl gemfibrozil. Approximately 94% of gemfibrozil is secreted in urine as glucuronide conjugate, and < 6% is excreted in feces. Gemfibrozil is one of many pharmaceutical products consistently detected in aquatic environments, such as surface water or wastewater.[27] Gemfibrozil is one fibrate that adversely reacts with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), resulting in higher rates of rhabdomyolysis than other fibrate derivatives, as indicated above.[28]

We identified 10 trials that used gemfibrozil as the primary treatment of hypertriglyceridemia. Of these 10 trials, only two studies included data on LDL particle size and number after the treatment was administered to patients. Otvos and colleagues[29] demonstrated that 1200 mg/d of gemfibrozil for 28 weeks increased LDL particle size by 0.5 nm (average LDL particle size is ~ 22 nm), lowered the particle number by 5%, and decreased the number of small dense LDL particles by 20%. O'Neal and colleagues[30] demonstrated that the same dose of gemfibrozil for 24 weeks in patients with DM resulted in an LDL particle size increase of 0.5 nm ($P < .02$).

The use of gemfibrozil to improve patient lipid profiles and evaluate CV events has been studied extensively over the years. The Helsinki Heart Study (HHS)[31] randomized 4081 middle-aged men (aged 40-55 years) with non-HDL levels > 200 mg/dL to 1200 mg gemfibrozil or placebo. In the gemfibrozil treatment group, TGs were lowered by 35% from a baseline of 175 mg/dL, LDL-C dropped by 8% from a baseline of 189 mg/dL, and

Figure 3. *Flow diagram for principal trials included in systematic review.*



HDL-C rose by 9% from a baseline of 47 mg/dL. A primary event occurred in 21.7% and 17.3% in the placebo and gemfibrozil groups, respectively (relative risk reduction [RRR] 22%; $P = .006$). With gemfibrozil there was a 24% RRR in the combined outcome of death from coronary heart disease (CHD), nonfatal myocardial infarction (MI), and stroke ($P < .001$). After the trial was completed in 5 years, 64% of those randomized to gemfibrozil and 65% of those randomized to placebo chose to receive long-term open-label gemfibrozil. Gemfibrozil confirmed a 24% adjusted RRR in CV events. There was a 70% reduction in CV events in those with a body mass index > 27.5 kg/m^2 and a baseline TG ≥ 184 mg/dL.[31] An important observation is that the HHS was conducted before the widespread use of statins or other LDL-C–lowering treatment, and as a result the mean LDL-C over the course of the trial exceeded 170 mg/dL; thus, patients could have been considered relatively untreated for this factor.

The Veterans Affairs HDL Intervention Trial (VA-HIT) was conducted at 20 Veterans Affairs Hospitals in 2351 men with established CV disease and low baseline HDL-C ($\leq$ 40 mg/dL), and randomized subjects to gemfibrozil, 1200 mg/d, versus placebo.[32] As compared with those on placebo, patients assigned gemfibrozil had a 31% reduction in TG (baseline 160 mg/dL), no change in LDL-C (113 mg/dL) during the study, and a 6% increase in HDL-C (baseline 33 mg/dL). For the primary outcome of CHD death and nonfatal MI, gemfibrozil resulted in a 22% RRR ($P = .006$). Strokes, transient ischemic attacks, carotid endarterectomy, and hospitalization for congestive heart failure were significantly reduced in those assigned gemfibrozil (RRR of 29%, 59%, 65%, and 22%, respectively). There were also fewer coronary revascularizations and peripheral vascular procedures, although these differences were not statistically significant.

Bezafibrate

Bezafibrate, introduced in 1977, is not commercially available in the United States. The chemical name of bezafibrate is 2-(4-{2-[(4-chlorobenzoyl)amino]ethyl}phenoxy)-2-methylpropanoic acid, with an empirical formula of $C_{19}H_{20}ClNO_4$. Bezafibrate circulates in plasma in its original form, and 50% of bezafibrate is secreted in urine; the hydroxylation and glucuronidation processes occur to 20% of bezafibrate, which is secreted through urine. Bezafibrate increases cyclic guanosine monophosphate in the plasma, which in turn regulates glycogenolysis. Bezafibrate reduces the blood vessel constricting peptide endothelin-1, and, thus, is associated with lower measured blood pressure.[1]

We identified five trials that used bezafibrate as the primary treatment of hypertriglyceridemia. Of these five trials, only the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) included data on LDL-C particle size after treatment was administered to patients.[33] This small study included 42 patients treated with bezafibrate and 39 treated with placebo, and observed a 46% reduction in TG contained in VLDL, a 14% increase in the TG contained in LDL particles, a 12% overall reduction in LDL-C, a 3% reduction in apo B, and a 1% increase in HDL-C. There was a 23% reduction in the number of small, dense LDL particles and the mean particle size increased by 0.32 ± 0.43 nm, or 1%. This trial attempted to evaluate changes in coronary angiographic appearance but was too small to have meaningful results.

The Bezafibrate Infarction Prevention (BIP) study was conducted at 18 centers in Israel and included patients aged 45 to 74 years with coronary artery disease.[34] In this study, 3090 patients with moderately elevated total cholesterol (TC, 180-250 mg/dL) and low HDL-C ($<$ 45 mg/dL) were randomized to receive 400 mg of bezafibrate daily or placebo for 6.2 years. Subjects randomized to bezafibrate demonstrated a 21% reduction in TG from a baseline of 145 mg/dL, a 4% reduction in LDL-C from a baseline of 148 mg/dL, and an 18% increase in HDL-C from a baseline of 35 mg/dL. There was a reduction in the primary endpoint of MI or sudden death from 15.0% to 13.6% (RRR 9.4%) but this was not statistically significant ($P = .26$).

Fenofibrate

Fenofibrate is a modified form of clofibrate. The chemical name is 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, with an empirical formula of $C_{20}H_{21}O_4Cl$. Oral administration of fenofibrate is absorbed by the gastrointestinal tract and rapidly hydrolyzed by esterases to form the active metabolite, fenofibric acid. About 60% of fenofibrate is secreted in urine as fenofibric acid and conjugates of glucuronic acid, and 25% of excretion is in feces. A small amount of fenofibric acid is reduced to benzhydrol metabolites, conjugated with glucuronic acid, and secreted in urine.[35]

We identified 11 trials that used fenofibrate as the primary treatment of hypertriglyceridemia. Of these 11 trials, only two included data on LDL particle size after the treatment was administered to the patients. Vakkilainen and associates[36] observed an average 6% increase in LDL particle size, which was associated with an increase in lipoprotein lipase activity. Davidson and colleagues[37] found that subjects with TG $>$ 200 mg/dL

after treatment with fenofibrate have smaller increases in the LDL particle size compared with those with lower on-treatment TG concentrations.

In addition to increased LDL particle size, other fenofibrate studies measured the effect of the drug on TC, LDL-C, HDL-C, and TG concentration. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial randomized 9795 patients with DM to 200 mg of micronized fenofibrate daily or placebo, and the primary endpoint was a composite of CHD death or nonfatal MI.[38] In the FIELD study there was a 15% reduction in TG from a baseline of 153 mg/dL, a 21% reduction in LDL-C from a baseline of 119 mg/dL, and a 3% rise in HDL-C from a baseline of 43 mg/dL. Fenofibrate did not reduce the primary endpoint of coronary events (relative reduction [RR] of 11%; $P = .16$). However, there was a significant 24% reduction in nonfatal MI ($P = .010$). Total CV disease events were significantly reduced from 13.9% to 12.5% (RRR 11%; $P = .035$). This finding included a 21% reduction in coronary revascularization (RR = 0.79; $P = .003$).

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial[39] randomized 5518 patients with type 2 DM who were being treated with open-label simvastatin to receive either fenofibrate or placebo in a prospective, blinded allocation. The primary outcome was the first occurrence of nonfatal MI, nonfatal stroke, or death from CV causes. The mean follow-up was 4.7 years. With fenofibrate, there was a 26% reduction in TG from a baseline of 164 mg/dL, a 19.1% reduction in LDL-C from a baseline of 100 mg/dL, and an elevation in HDL-C of 8% from a baseline of 38 mg/dL. The primary outcome rate was 2.2%/year in the fenofibrate group and 2.4%/year in the placebo group (RRR 8%; $P = .32$). There were also no significant differences between the two study groups with respect to death or any secondary outcome. Prespecified subgroup analyses suggested heterogeneity in treatment effect according to sex, with a benefit for men and possible harm for women ($P = .01$ for interaction), and a possible interaction with benefit for patients with both a high baseline TG level and a low baseline HDL-C ($P = .057$ for interaction).[39]

Fenofibric Acid

Fenofibric acid is the active metabolite of fenofibrate. There have been multiple individual randomized trials and pooled analyses from these trials evaluating the individual and combination impact of oral fenofibric acid, 135 mg/d, on conventional lipid parameters.[11,40-46] A randomized trial (n = 760, TG $\geq$ 150 mg/dL, HDL-C $<$ 40 mg/dL [men], $<$ 50 mg/dL [women], LDL-C $\geq$ 130 mg/dL) of 135 mg/d of fenofibric acid in addition to rosuvastatin, 5 mg/d, for 24 weeks resulted in a 40% reduction in TG and was well tolerated.[47] Jones and colleagues[42] randomized 1445 subjects with the same entry criteria to fenofibric acid, 135 mg alone, rosuvastatin alone at three doses (10, 20, or 40 mg), and the combination of fenofibric acid, 135 mg, with the 10- and 20-mg doses of rosuvastatin. From a baseline TG of approximately 280 mg/dL and an LDL-C of approximately 154 mg/dL, combination therapy with fenofibric acid and rosuvastatin, 10 mg, reduced TG (-47.1% vs -24.4%) and LDL-C (-37.2% vs -6.5%) (both $P < .001$). Similarly, significant improvements were observed with fenofibric acid plus rosuvastatin, 20 mg, in TG (-42.9% vs -25.6%) and LDL-C (-38.8% vs -6.5%). Mohiuddin and colleagues[43] performed a similarly structured trial (n = 657) of fenofibric acid, 135 mg, alone and in combination with simvastatin, 20 and 40 mg, and reported concordant results. Goldberg and colleagues,[44] using the same entry criteria, randomized 613 patients to 135 mg/d of fenofibric acid, atorvastatin (20, 40, or 80 mg), or combination therapy (fenofibric acid + atorvastatin 20 or 40 mg) for 12 weeks. As expected, fenofibric acid with atorvastatin, 20 mg, resulted in significantly greater improvements in TG (–45.6% vs –16.5%) and HDL-C (14.0% vs 6.3%). The reduction in LDL-C was –33.7% with atorvastatin, 20 mg, versus –3.4% with fenofibric acid alone. Greater improvements were observed with the combination of fenofibric acid and atorvastatin, 40 mg, in TG (–42.1% vs –23.2%) and HDL-C (12.6% vs 5.3%). Goldberg and colleagues[48] went on to recently report on a total of 1393 women pooled from three latter trials in patients with mixed dyslipidemia (LDL-C $\geq$ 130 mg/dL, TG $\geq$ 150 mg/dL, and HDL $<$ 50 mg/dL). With low-dose combination treatment, TG decreased 46% and HDL-C level increased 20% compared with a 20% decrease in TG and an 8% increase in HDL with low-dose statins alone. With the moderate-dose combination, the TG decreased 44% and HDL-C increased 21%, compared with a 26% reduction in TG and an 8% increase in HDL-C with moderate-dose statins alone. In terms of triple therapy (statin, fibrate, and ezetimibe), Jones and associates[45] have concluded a 543 patient trial with TG $\geq$ 150 mg/dL and $<$ 400 mg/dL, randomized to fenofibric acid, 135 mg, or placebo for 12 weeks, each coadministered with atorvastatin, 40 mg, plus ezetimibe, 10 mg. Both treatment regimens lowered LDL-C by $>$ 50%; however, the addition of fenofibrate resulted in significantly greater reductions in TG (-57.3% vs -39.7%), non–HDL-C (-55.6% vs -51.0%), improvements in HDL-C (13.0% vs 4.2%; $P < .001$), and

modest lowering of apo B (−49.1% vs −44.7). A pooled analysis of two randomized trials of fenofibric acid in addition to rosuvastatin found similar additional reductions in TG with the combination compared with statins alone in the elderly.[46,49] Thus, the addition of fenofibric acid more than doubled the TG reduction seen with a statin alone. There has been an analysis in 2453 patients pooled from three randomized trials demonstrating that the proportion of patients with large, more buoyant particles (pattern A) rose from 9.8% to 17.0% with statin monotherapy, whereas it increased from 11.0% to 49.3% with the combination of a statin plus fenofibric acid.[50] There were no CV event outcomes trials of fenofibric acid found in our search; however, the Atorvastatin plus Fenofibric acid in the Reduction of Intermediate Coronary Atherosclerosis (AFRICA) study is measuring the impact of fenofibric acid on coronary atheroma volume measured by coronary computed tomographic angiography.[51] The Safety and Efficacy Study Using ABT-335 in Combination With Atorvastatin, to Study the Effects on Thickening of the Blood Vessel Wall in Patients With Abnormal Lipid (Fat) Levels in the Blood (FIRST) Study is evaluating the independent and combination effects of fenofibric acid and atorvastatin on carotid intima medial thickness.[52]

Discussion

CV Risk Reflected by Hypertriglyceridemia

The traditional risk factors for CV disease include age, male sex, genetics, smoking, hypertension, DM, obesity, and hyperlipidemia. Increased levels of fasting serum TGs are commonly seen in obese patients with hypertension, elevated fasting blood sugar, and insulin resistance, and are associated with low levels of HDL-C and increased numbers of small, dense LDL particles.[43] Thus, although the epidemiology of TG and the translation of lowering TG with treatment is not as strong as it is for LDL-C, hypertriglyceridemia is a readily identifiable risk marker that indicates an underlying pathogenic dyslipidemia. Furthermore, the correlation of high serum TG levels and multiple health ailments makes it a highly visible and modifiable parameter for the management of CV risk.

A meta-analysis by Hokanson and Austin[53] examined the RR for the incidence of CVD per 89 mg/dL increase in TG levels and found a summary RR of 1.32 (95% confidence interval [CI], 1.07-1.98) for men and 1.76 (95% CI, 1.69-2.05) for women. However, the adjusted RR estimates controlled for HDL-C levels and markedly attenuated the measures of association. For men, the multivariate RRs for TG were 0.98-1.39, with a summary RR of 1.14. For women, the summary RR was 1.37.[53] Even with the adjustment for HDL-C, a significant increase of CV risk was observed in both men and women. These multivariate RR estimates were associated with a 14% and 37% increase in risk for men and women, respectively. Faergeman and coworkers[54] demonstrated that, in patients treated with statins in the setting of randomized trials, the baseline TG level was associated with the risk of CV events. Thus, this summary of many prior epidemiologic studies suggests that TG levels alone have a modest relationship with incident CVD, likely because the TG concentration is not tightly linked to atherogenicity (except when levels are sufficiently elevated and/or HDL-C is reduced), indicating that there is a higher fraction of small, dense LDL particles in the bloodstream.[55] Beyond small dense LDL, elevated TG may identify a more atherogenic dyslipidemia by reflecting more TG-rich lipoprotein remnant particles and an impaired fibrinolytic system; however, these pathophysiologic mechanisms are far more speculative.[56]

The traditional risk factors for CV disease include age, male sex, genetics, smoking, hypertension, DM, obesity, and hyperlipidemia.

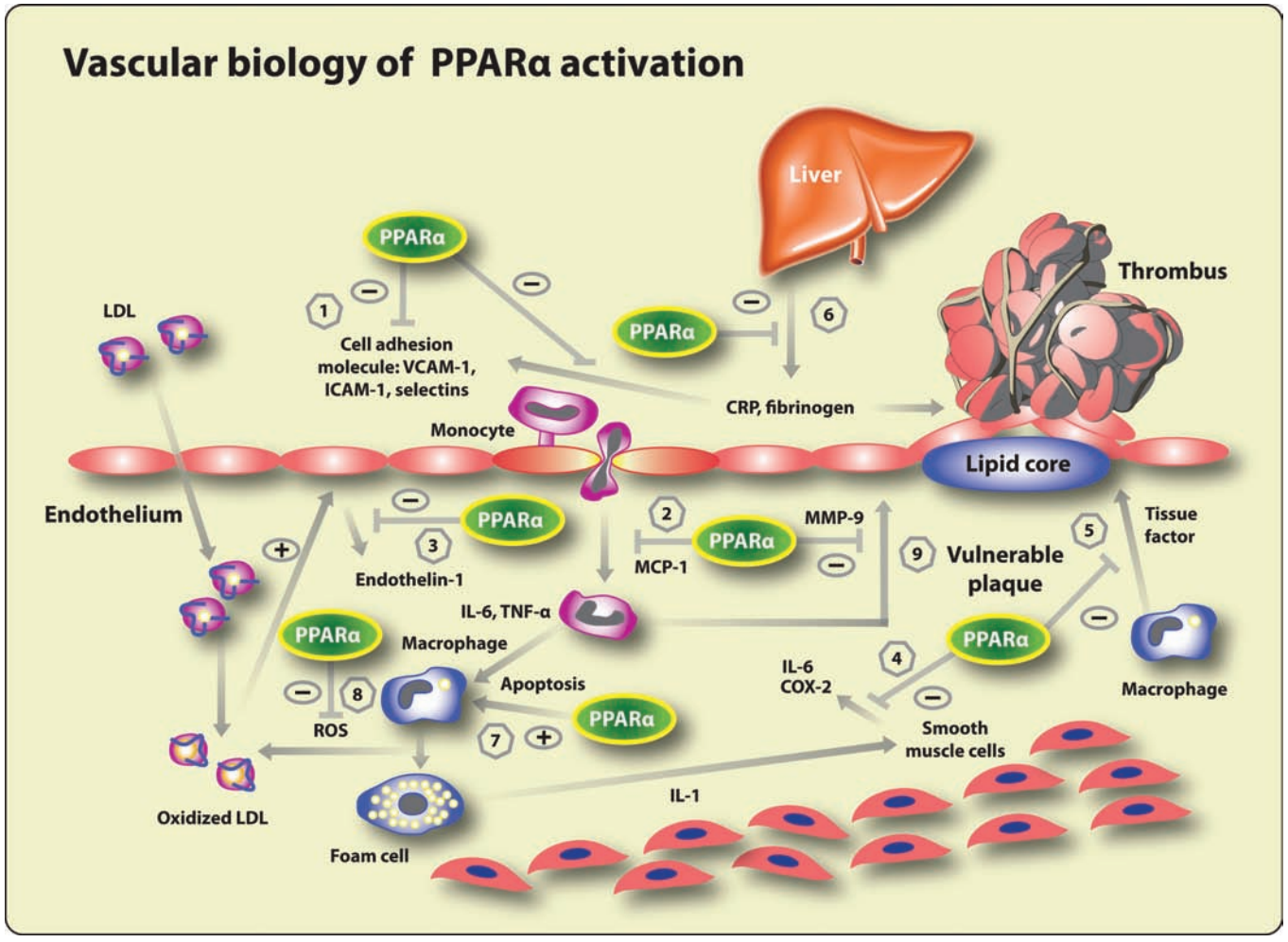
Small, Dense LDL-C and Atherosclerosis

Atherosclerosis is the accumulation of esterified cholesterol that forms atheromatous plaque in the arteries. Various factors, such as smoking, high blood pressure, DM, and elevated cytokines and cell signaling proteins promote and accelerate the development of atherosclerosis by facilitating either cholesterol deposition or its modification once in the artery wall. However, the major ongoing influence in atherosclerosis is lipid accumulation that forms a plaque in the intima and media, the middle and innermost layers of the artery wall.[57] An atheroma can become a massive amount of cholesteryl ester within the interstitial space surrounding the smooth muscle cells and in the smooth muscle cells themselves if deposition exceeds the rate of efflux.[58] This is a strong signal for the smooth muscle cell to undergo transformation into an osteoblastic-like cell and begin to secrete extracellular calcium into the interstitial mass of the atheroma.[59] The single greatest determinant of cholesterol deposition is the LDL-C concentration, and more specifically, the number of small, dense particles.[60] Small, dense particles not only have a greater potential for ingress of free and esterified cholesterol, but are also less likely to be cleared by LDL receptors, and therefore have a longer circulatory time. Our results indicate that although fibric acid derivatives result in relatively large reductions in TG and modest changes in LDL-C and

HDL-C, likely their most antiatherogenic effects include reducing the number of small, dense LDL particles and raising the overall mean size of the entire population of particles. By this action, there is less deposition of cholesterol, perhaps lower degrees of oxidation, and, with slightly improved HDL-C concentrations, there may be improved efflux of cholesterol from macrophages and hence more efficient reverse cholesterol transport. This paradigm may not be dissimilar to that of statins; however, considerable translational research is needed to solidify these concepts.[61] Beyond changes in lipid fractions, fibrates may influence vascular disease at a more fundamental cellular level.

The PPARs are ligand-activated transcription factors that control both lipid and glucose metabolism. They regulate gene expression by binding with the retinoid X receptor as a heterodimeric partner to specific DNA sequences, termed *PPAR response elements*. In addition, PPARs may also modulate gene transcription by directly interfering with other transcription factor pathways in a DNA-binding independent manner. The activation of PPARα by pharmacologic agents has at least seven mechanisms of action outside of their effects on lipid metabolism that may play a role in favorably altering the pathogenesis of atherosclerosis, as shown in Figure 4.[62] Thus, either by translational clinical

Figure 4. *Activation of PPARα by its ligands inhibits several steps in the development and progression of atherosclerosis, plaque rupture, and thrombus formation, including 1) expression of adhesion molecules (VACM-1, ICAM-1, and selectins) on the endothelial cells, reducing the attachment of inflammatory cells to endothelium; 2) migration of monocytes into the subendothelial space by downregulation of MCP-1; 3) release of endothelin-1 in response to oxidized LDL particles and thrombin, inhibiting proliferation of smooth muscle cells; 4) release of inflammatory cytokines such as IL-6 and prostaglandin-generating enzyme COX 2 from smooth muscle cells and macrophages; 5) thrombogenesis at the site of plaque rupture by suppression of release of tissue factor from activated macrophages in response to inflammatory cytokines; and 6) expression and release of fibrinogen and CRP from liver in response to inflammatory cytokines. Activation of PPARα also leads to 7) apoptosis of cytokine-activated macrophages; 8) increased destruction of ROS generated by macrophages; and 9) maintenance of plaque stability by induction of macrophage apoptosis and suppression of MMP-9 release. COX, cyclooxygenase; CRP, C-reactive protein; ICAM, intercellular adhesion molecule; HDL-C, high-density lipoprotein cholesterol; IL, interleukin; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; MCP, monocyte chemotactic protein; MMP, matrix metalloproteinase; PPAR, peroxisome proliferator-activated receptor; RS, reactive oxygen species; TG, triglycerides; TNF, tumor necrosis factor; VACM, vascular cell adhesion molecule. Reprinted with permission from Israelian-Konaraki Z and Reaven. Peroxisome proliferator-activated receptor-alpha and atherosclerosis: from basic mechanisms to clinical implications.* Cardiol Rev. *2005;13:240-246.*[62]



epidemiology or a variety of cellular changes occurring in the cells that participate in atherosclerosis, there is considerable biologic rationale for a salutary effect of PPARα activation.

Synthesis of Trials and Meta-Analyses

In a pooled analysis, Loomba and Arora[63] found that fibrates across many trials, on average, lower TGs by 30%, lower TC by 8%, and raise HDL-C by 9%. Accordingly, we found that, in all trials, fibrates substantially reduced TG levels, and in the presence of statins, roughly doubled the TG-lowering effect of a statin alone. When examined, fibrates reduced the TG content of VLDL, and increased the TG of LDL, rendering the overall LDL particle size slightly larger, and markedly reducing the fraction of LDL particles that are small and dense. Fibrates modestly lowered LDL-C and raised HDL-C; however, these effects are more variable, dependent on baseline TG levels, and were not consistently related to clinical outcomes. The overall results of the outcomes trials are mixed due to the variation in the baseline populations, concomitant treatments, and the choice of primary endpoints. This taken into consideration, fibrates as a class tend to reduce composite CV events without an impact on mortality. If the baseline hypertriglyceridemic group (with low HDL-C in some trials) is considered alone, there is a consistent reduction in the composite endpoint inclusive of CV death seen in all large trials of fibric acid derivatives, as shown in Figure 5.

Our results are consistent with the recent meta-analyses that have sequentially over time monitored the clinical impact of fibrates in CV trials. In 2007, Saha and colleagues[64] reported on 36,489 patients from 10 published, randomized, placebo-controlled trials. After excluding trials of clofibrate, they found fibric acid derivatives did not significantly reduce CV mortality, fatal MI, or stroke. However, they did significantly reduce the odds of nonfatal MI by approximately 22% ($P < .00001$). This analysis held when performed in the subgroup with DM (11,590 patients from 6 trials).[65] A meta-analysis by Abourbih and coworkers[66] largely confirmed these findings. In 2010, Jun and colleagues[67] identified 18 trials providing data for 45,058 participants and found that fibrate therapy was associated with a 10% RRR for major CV events ($P = .048$) and a 13% RRR for coronary events ($P < .0001$), but had no benefit on stroke, cardiac death, sudden death, or all-cause mortality. Recently, Goldfine and associates[68] have summarized the RRR for fibrate trials in the subgroup with either an elevated TG and/or depressed HDL at baseline, and demonstrated a 27% to 65% reduction in the primary CV endpoint of MI and cardiac or sudden death.[68] Figure 5 demonstrates these RRRs with the subgroup population proportions in the trials of 14%, 100%, 11%, 21%, and 17% for HHS, VA-HIT, BIP, FIELD, and ACCORD, respectively.

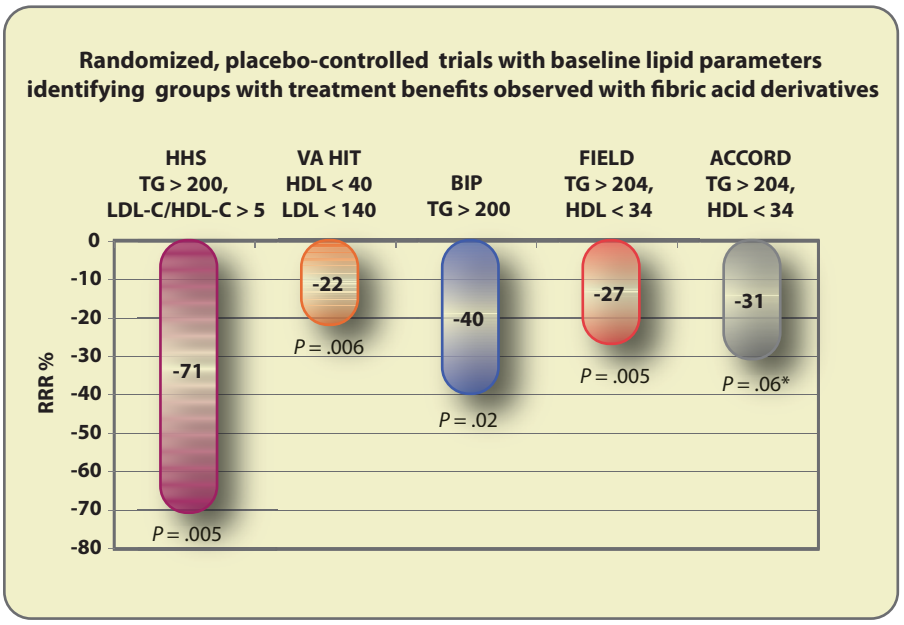


Figure 5. *Large, randomized prospective, placebo-controlled trials of fibrates and the baseline lipid characteristics identifying the population who experienced a treatment benefit. All concentrations are in mg/dL.* *P *value as reported from an interaction term. ACCORD, Action to Control Cardiovascular Risk in Diabetes; BIP, Bezafibrate Infarction Prevention; CV, cardiovascular; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; RRR, relative risk reduction; HDL-C, high-density lipoprotein cholesterol; HHS, Helsinki Heart Study; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; VA-HIT, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Data from Goldfine AB et al.[68]*

Conclusions

Fibrates consistently demonstrate advantageous effects by substantially lowering TG, modestly lowering LDL-C, elevating HDL-C, increasing mean LDL particle size, and reducing the fraction of small, dense LDL particles. Overall, and particularly in the subgroup with fasting hypertriglyceridemia and or depressed HDL-C at baseline, fibrates lower the rate of CV events as defined as primary endpoints in large randomized trials. Although not proven, the data suggest that, in patients with hypertriglyceridemia currently receiving a statin,

fibrates will not only further reduce TG levels, but possibly result in additional CV protection. ■

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Main Points

- Hypertriglyceridemia suggests the presence of small, dense low-density lipoprotein cholesterol (LDL-C).
- Fibrates are peroxisome proliferator-activated receptor-α agonists that reduce triglyceride (TG) levels and decrease the amount of small, dense LDL-C.
- In aggregate, when TGs are elevated > 200 mg/dL, clinical trials suggest that rates of cardiovascular events are reduced with fibrates, in addition to other forms of lipid-lowering therapy.
- Fenofibric acid is the latest generation of fibrates that has been found to be both safe and effective for lowering TGs in patients treated with concomitant statins.

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