



REVIEW OF FIBRIC ACID DERIVATIVES IN PRIMARY AND SECONDARY PREVENTION OF CORONARY HEART DISEASE

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The fibric acid derivatives, also known as fibrates, are well established as effective agents for managing dyslipidemia, in particular elevated concentrations of triglyceride-rich very-low-density lipoprotein (VLDL) and VLDL remnants and low levels of high-density lipoprotein cholesterol (HDL-C) that are typically associated with the dyslipidemia characteristic of type 2 diabetes and the metabolic syndrome. There are currently two fibrates available in the United States: gemfibrozil (Lopid®) and fenofibrate (Antara®, Lofibra®, TriCor®, Triglid®). Clofibrate has been discontinued in the United States since it has been associated with cholangiocarcinoma and other gastrointestinal cancers.¹ Other fibrates that are available worldwide include bezafibrate and ciprofibrate.

Fibrates are indicated for the treatment of hypercholesterolemia, hypertriglyceridemia, and as adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and apolipoprotein-B (apo-B), and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia.² The use of fibric acid derivatives has decreased over the years because of unimpressive results in major clinical trials, safety concerns, and the emergence of HMG-CoA reductase inhibitors, more commonly known as statins. While statins are considered first-

line therapy for dyslipidemia based on their efficacy in reducing levels of LDL-C, they exhibit only modest effects by decreasing triglycerides about 15-35% and increasing HDL up to 15%.³

The safety and efficacy of fibrates have been reviewed in six major clinical trials during the past 30 years. The results have generated mixed findings when evaluating overall mortality, cardiovascular events, and adverse effects. The inconsistent outcomes may be a result of differences among individual fibrates and highly varied study populations. In this article, the pharmacology of the fibrates is discussed along with evaluating their role in the primary and secondary prevention of coronary heart disease (CHD).

Mechanism of Action

Fibrates have a complex mechanism of action, involving several steps in the metabolism of lipoproteins. Primarily, fibrates affect the peroxisome proliferator activated receptor (PPAR)- α (Table 1).⁴ The PPARs are a group of nuclear receptors predominantly expressed in tissues, such as the liver, kidney, heart and muscle, that metabolize fatty acids.⁵ On activation by binding of the fibrate, PPAR- α binds as heterodimers with a retinoid X receptor (RXR), which then recognizes and binds to

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specific PPAR- α response elements leading to expression modulation of the target genes.⁵ In particular, the activity of lipoprotein lipase is increased and synthesis of apoC-III is decreased, which both enhance the clearance of circulating triglyceride-rich lipoproteins.⁶ PPAR- α activation regulates gene expression involved in metabolic pathways including lipid metabolism, thereby reducing triglyceride concentrations and increasing HDL concentrations. Fatty acid oxidation in the liver is also increased resulting in decreased synthesis of VLDL.⁷ In addition, fibrates promote a shift towards producing larger, more buoyant LDL particles that are less susceptible to oxidation and have higher affinity for the LDL receptor.⁸ Fibrates also appear to stimulate reverse cholesterol transport by modulating macrophage cholesterol efflux, cholesterol transport, and bile acid synthesis, thereby enhancing HDL concentrations.⁹

The described mechanisms of action generate significant decreases in plasma triglyceride concentrations ranging from 20–50% and elevations in HDL concentrations ranging from 10–35%.⁸ Fibrates have varying effects on LDL concentrations. Among patients with increased LDL concentrations, modest reductions of 5–20% have been observed; however, fibrates can increase LDL concentrations if accompanied by hypertriglyceridemia, secondary to the enhanced lypolysis of VLDL by lipoprotein lipase.⁵ Therefore, fibrates are primarily used for the treatment of hypertriglyceridemia and atherogenic dyslipidemia (i.e. elevated plasma triglyceride concentrations, small dense LDL particles, low HDL concentrations).

Table 1: Effects of PPAR- α stimulation by fibrates¹⁰

ApoAI mRNA transcription stabilization
↑ apoAI and apoAII → ↑ HDL particle size number
↓ apoCIII → ↓ TG → ↑ LDL size
↑ LPL → ↓ TG → ↑ HDL cholesterol
↑ LPL → improved post-prandial lipidemia
↑ hepatic VLDL and apoB degradation
↓ VLDL and apoB production

Apo = apolipoprotein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LPL = lipoprotein lipase; mRNA = messenger RNA; TG = triglycerides; VLDL = very-low-density lipoprotein

Major Trials of Fibrate Therapy

The safety and efficacy of fibrates have been assessed in six major outcome studies during the past 30 years (**Table 2**).

Coronary Drug Project

The Coronary Drug Project (CDP) was one of the earliest lipid trials published in 1975.¹² It was designed to determine safety and efficacy of several antihyperlipidemic drugs in preventing a recurrent CHD event among men with a history of myocardial infarction. One of the treatment groups, in which patients were randomly assigned to receive clofibrate, continued until the end of this approximately 5-year study. The rate of CHD events was reduced 9% in the clofibrate group, but the difference between groups was not statistically significant. The study brought up concern regarding clofibrate because of a lack of effectiveness on overall mortality and a significantly higher rate of cholelithiasis compared with placebo. The authors concluded that the CDP results provided no evidence with which to suggest the use of clofibrate among men with CHD.

World Health Organization Study

In 1978, the results from the World Health Organization (WHO) cooperative trial in the primary prevention of ischemic heart disease using clofibrate generated more doubt regarding the use of fibrates.¹³ Men, ages ranged from 30–59 years with hypercholesterolemia without cardiovascular disease, were randomly assigned to take clofibrate or placebo and were followed for an average of 5.3 years. The clofibrate group had a 25% reduction ($p < 0.05$) in nonfatal myocardial infarction compared to placebo; however, overall mortality and the rate of cholelithiasis and cholecystectomy were significantly higher with clofibrate than placebo. Patients receiving clofibrate had a 9% decrease in total cholesterol concentrations, which was less than the expected 15% reduction. The higher mortality rates associated with clofibrate were partly due to a higher rate of malignant neoplasms of the liver, gallbladder, and intestines; however, mortality rates among the clofibrate group for cancer were similar to the official mortality statistics for individuals from the same area. The authors believed the increased mortality may have been exaggerated because of unexpectedly low death rates among subjects in the control group. Patients gaining

Table 2: Key Findings from Major Trials of Fibrate Therapy¹¹

Trial	Duration (yrs)	N	Population	Drug and daily dose	Lipid changes (%)	Outcomes
CDP	5	3892	Men, 2° prevention	Clofibrate 1.6g	TC: ↓ 8% TGs: ↓ 25%	CHD: ↓ 9% (p = 0.12) Total mortality: no change ↑ cholelithiasis and cholecystectomy
WHO	5.3	10,627	Men, 1° prevention	Clofibrate 1.6g	TC: ↓ 9%	Nonfatal MI: ↓ 25% (p < 0.05) Total mortality: ↑ with clofibrate ↑ cholelithiasis and cholecystectomy with clofibrate
HHS	5	4081	Men, 1° prevention	Gemfibrozil 1200mg	TC: ↓ 11% LDL: ↓ 10% TGs: ↓ 43% HDL: ↑ 10%	CHD: ↓ 34% Nonfatal MI: ↓ 37% Total mortality: no change
VA-HIT	5.1	2531	Men, 2° prevention	Gemfibrozil 1200mg	TC: ↓ 4% LDL: 0% TGs: ↓ 31% HDL: ↑ 6%	CHD death and nonfatal MI: ↓ 22% Total mortality: ↓ 11% (NS)
BIP	6.2	3090	Men and women, 2° prevention	Bezafibrate 400mg	TC: ↓ 4.5% LDL: ↓ 6.5% TGs: ↓ 21% HDL: ↑ 18%	Fatal and nonfatal MI and sudden death: ↓ 9% (NS) Total mortality: no change
FIELD	5	9795	Men and women with DM	Fenofibrate 200mg	TC: ↓ 11% LDL: ↓ 12% TGs: ↓ 29% HDL: ↑ 5%	CHD death and nonfatal MI: ↓ 11% (NS) Total mortality: ↑ 19% with fenofibrate (NS) Total cardiovascular events: ↓ 11%

↓ = decrease; ↑ = increase; N = number of patients; 1° = primary; 2° = secondary; DM = diabetes mellitus; CDP = Coronary Drug Project; CHD = coronary heart disease, NS = not statistically significant; WHO = World Health Organization; MI = myocardial infarction; HHS = Helsinki Heart Study; TC = total cholesterol; TGs = triglycerides; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol; VA-HIT = Veterans Affairs HDL Intervention Trial; BIP = Bezafibrate Infarction Prevention; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes

the most benefit from clofibrate had higher baseline cholesterol concentrations and greater reductions in total cholesterol, or experienced a substantial reduction in serum cholesterol levels with co-morbid cardiovascular risk factors. Nevertheless, the results of the WHO trial and CDP produced substantial doubt concerning clofibrate, and subsequent prescribing of the agent decreased dramatically.

Helsinki Heart Study

The Helsinki Heart Study (HHS),¹⁴ a double-blind, placebo-controlled study including more than 4,000 men at moderate risk of CHD treated with gemfibrozil (1,200 mg/day), was published in 1987. It showed an 11% decrease in LDL-C, a 35% decrease in triglycerides, and an 11% increase in HDL-C compared with placebo. These changes were associated with a 34% reduction (95% CI, 8.2-52.6%; p<0.02) in major coronary events at five years, as well as a 37% reduction (p<0.05) in non-fatal myocardial infarction in men free of CHD. There was no

significant difference in overall mortality between the two groups. The HHS also provided data regarding the safety of fibrates, as cases of newly diagnosed cancer and the rates of cholecystectomy were not different between the groups.

Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) was another randomized, placebo-controlled trial using gemfibrozil.¹⁵ Men with a history of CHD and low HDL levels were assigned randomly to receive gemfibrozil or placebo for 5 years. Gemfibrozil generated significant changes in HDL and plasma triglyceride concentrations compared to placebo, whereas LDL concentrations showed no significant difference. Patients in the treatment group were 22% (95% CI, 7-35%; p=0.006) less likely to experience CHD death or a nonfatal myocardial infarction compared to those in the control group. Though not designed to

assess overall mortality, the investigators reviewed the number of deaths and reported an 11% (95% CI, -8 to 27%; $p = 0.23$) reduction in mortality with gemfibrozil compared with placebo. Further analyses of VA-HIT data proposed that the major reason for clinical events being reduced was increased HDL levels from gemfibrozil.¹⁶ Like the HHS, VA-HIT generated favorable results regarding long-term safety of fibrates because the incidence of newly diagnosed cancer and gallbladder disease between treatment and control groups was no different.

Bezafibrate Infarction Prevention Study

The Bezafibrate Infarction Prevention (BIP) study was another randomized, placebo-controlled trial studying the effects of bezafibrate, a fibrate not available in the United States, among men and women with CHD.¹⁷ Bezafibrate therapy demonstrated significant reductions in triglyceride and LDL concentrations and fibrinogen while elevating HDL levels. When the study was completed, bezafibrate was associated with a 9% reduction ($p=0.26$) in fatal and nonfatal myocardial infarction and sudden death. Overall mortality rates and frequency of newly diagnosed cancer were similar among the groups, showing bezafibrate to be safe agent among adults with CHD, but it had no significant effect on the frequency of major coronary events.

Fenofibrate Intervention and Event Lowering in Diabetes Study

Published recently, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study intended to offer additional information on the use and safety of fibrates in diabetic patients.¹⁸ Men and women not receiving statin therapy at the beginning of the trial were assigned randomly to fenofibrate or placebo for 5 years. All participants had type 2 diabetes mellitus, and 37% of patients experienced a cardiovascular event in the past. Treatment with fenofibrate resulted in significant reductions in total cholesterol levels, triglyceride concentrations, and LDL levels compared with the control group. Fenofibrate produced a 5% increase in HDL early in the study; however, this decreased to only 2% by the end of the study. Patients taking fenofibrate had an 11% reduction (95% CI, -5 to 25%; $p=0.16$) in coronary events (CHD death and nonfatal myocardial infarction), but also a nonsignificant increase in overall mortality (11%, 95% CI, -5 to 29%; $p = 0.18$), com-

pared with the control group. The lower rate of coronary events was due primarily to the decrease in nonfatal myocardial infarction. Also, a reduction in total cardiovascular events was observed with the fenofibrate group. Compared with the placebo group, those in the treatment group were more likely to experience pancreatitis and pulmonary embolism.¹⁸ The results of the FIELD study were much anticipated in hopes of determining the role fibrates play in the treatment of cardiovascular disease, but unfortunately they did not live up to that expectation. With only modest reductions in cardiovascular events and no significant changes in overall mortality, the FIELD study hardly helped define the role of fibrates.

Discussion Regarding Mixed Results

Although fibrates do not provide significant LDL reductions, they do increase HDL levels and reduce triglyceride concentrations.¹⁹ In addition, the fibrates generate improvements in many of the emerging risk factors, including CRP level, fibrinogen level, and small dense LDL particles.²⁰ The general metabolic effects of fibrates would suggest that they are the best agents for individuals with type 2 diabetes mellitus or metabolic syndrome. The following key points address the primary reasons why the major fibrate studies have provided varied results.

Firstly, a major possibility for mixed results may be due to the diverse study populations in fibrate trials.¹¹ Although data from fibrate trials are not identical, two groups that appear to receive the most benefit from fibrates are patients with mixed dyslipidemia (low HDL levels and elevated plasma triglyceride concentrations) and/or impaired glucose homeostasis (i.e., type 2 diabetes mellitus, prediabetes or metabolic syndrome).²¹⁻²² When reviewing baseline lipid levels of study participants, it is apparent that a fibrate was not the best selection as a lipid lowering agent.¹⁷ The most common lipid abnormalities of the study subjects were elevated LDL and total cholesterol levels, but at the time of the earlier studies, drug therapy for lowering LDL levels was limited primarily to bile acid resins and niacin. Also, most of the studies had limited numbers of patients with diabetes mellitus. Recruiting more patients with mixed dyslipidemia and glucose impairment would provide more positive findings since fibrates seem to be more effective in that patient population. Lastly,

fibric acid derivatives have shown to reduce some of the newer cardiovascular risk factors that are strongly associated with mixed dyslipidemia and metabolic syndrome.²³ This may help explain why fibrates have generally provided greater efficacy at reducing cardiovascular events among these populations in post hoc analyses.

Although post hoc data from fibrate trials suggest greater reductions in clinical events among patients with metabolic syndrome or type 2 diabetes mellitus, results from the FIELD study did not completely support these findings as the reductions in cardiovascular events were modest compared with post hoc results of previous fibrate studies.¹¹ Several reasons may explain why the patients did not experience greater benefit with fenofibrate. First, a significantly greater number of patients in the control group began other lipid-modifying agents (primarily statins) potentially masking the effects of fibrate therapy. Second, baseline lipid levels were not the most advantageous for using fibrate therapy because individuals appear to have a more favorable clinical response when baseline plasma triglyceride concentrations exceed 200 mg/dl and the HDL concentration is less than 40 mg/dl. Subgroup analysis of the FIELD study showed patients with low HDL levels (< 40 mg/dl for men and < 50 mg/dl for women) or plasma triglyceride concentrations of 150 mg/dl or greater experienced a decreased rate of cardiovascular events; however, subjects meeting the criteria for metabolic syndrome experienced more clinical events compared with those without metabolic syndrome.¹¹ Further analyses of these subpopulations are needed to clarify the inconsistent results.

Slight differences among individual fibric acid derivatives may have also added to inconsistency in safety and efficacy reported in clinical trials.¹¹ Gemfibrozil has provided the most impressive data at decreasing clinical events. However, drug interactions, especially with concomitant statin use, and potential for higher rates of myopathies may limit use in clinical practice. Fenofibrate seems to be more effective than gemfibrozil at positively altering lipid parameters and does not significantly affect statin metabolism; however, the FIELD study did not provide the robust evidence required to indicate exclusive use of this agent.²⁴ In addition, safety concerns regarding slight, but significant increases in pancreatitis and pulmonary embolism in recent trials suggest a need for health professionals to be aware of

these possible adverse effects. A class effect cannot be ruled out since the rates of pulmonary embolism and pancreatitis were not reported in most other major fibrate trials.

Conclusion

The exact role of fibric acid derivatives in lipid lowering therapy and prevention of CHD is still unclear. Early studies involving clofibrate were disappointing because of only modest reductions in CHD events and considerable safety concerns. The HHS, which used gemfibrozil, provided reassurance in terms of long-term safety of fibrates and demonstrated reductions in CHD events, but did not reduce overall mortality. Further analyses of fibrate trials evaluated patients with lipid profiles more conducive to the effects of fibric acid derivatives. The positive results of these studies suggest a potential value of fibrates when used in appropriate populations. With the publication of the FIELD study came expectations of solidifying a larger market for fibrates in treatment of cardiovascular disease; however, due to mixed results, further research is needed to better determine the best targeted usage of these agents. Results of recent ongoing trials, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, may determine if this class will once again play a greater role in the management of dyslipidemia and the prevention of coronary heart disease.

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