Is There a Role for Fibrates in the Management of Dyslipidemia in the Metabolic Syndrome?

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Abstract—The outcomes of fibrate trials have varied: positive with gemfibrozil in the primary prevention Helsinki Heart Study and the secondary prevention VA-HIT trial; positive with reservations in the primary prevention WHO trial (clofibrate); and mixed with bezafibrate in the secondary prevention BIP study and with fenofibrate in the combined primary and secondary prevention FIELD study. Overall, the mixed results, combined with potential for adverse effects when given in combination with statins, have limited the use of these fibrates as cardioprotective agents. However, post hoc analyses of several of the fibrate studies have shown that people with features of the metabolic syndrome, particularly overweight people with high plasma triglyceride levels and low levels of HDL cholesterol, derive a disproportionately large reduction in cardiovascular events when treated with these agents. Thus, there is a strong case for the use of a fibrate to reduce the cardiovascular risk in overweight people with high triglyceride and low HDL-C. However, it should be noted that such people also have their cardiovascular risk reduced by statin therapy. It remains to be determined whether the combination of a fibrate plus statin reduces the risk beyond that achieved with a statin alone. (Arterioscler Thromb Vasc Biol. 2008;28:39-46.)

Key Words: fibrates ■ metabolic syndrome ■ triglyceride ■ HDL ■ cardiovascular events

Fibrates have been used for many years and have been widely investigated in terms of their tolerability and safety, their effects on plasma lipids, and their ability to inhibit the development of atherosclerosis. These compounds include clofibrate, ciprofibrate, bezafibrate, fenofibrate, and gemfibrozil. Their place in the management of cardiovascular disease was given a substantial boost by the consistency of the results of post-hoc analyses from the Helsinki Heart Study (HHS), and the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), both of which used gemfibrozil as the active agent, as well as the Bezafibrate Infarction Prevention (BIP) study. In all of these studies, treatment with a fibrate was associated with a disproportionately large reduction in cardiovascular events in people with features of the metabolic syndrome or type 2 diabetes.

It was most surprising, therefore, that the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study yielded a nonsignificant primary end point and less than expected benefits in several secondary end points. These results raise a number of questions that have major implications in terms of the future of fibrates and PPARα activators for managing cardiovascular disease.

There are several possible explanations for the unexpected and disappointing results in FIELD. It is possible that the previous post-hoc subgroup analyses of the HHS, VA-HIT, and BIP trials were chance findings and that fibrates do not,
in fact, have beneficial effects in people with the metabolic syndrome and type 2 diabetes. It is also possible, however, that fibrates are markedly cardioprotective in people with the metabolic syndrome and type 2 diabetes and that there were other reasons for the outcome in FIELD. For example, an excess drop-in to statin therapy in the placebo group may have hidden what could otherwise have been a greater beneficial effect of fenofibrate. But it is also possible that fenofibrate had adverse effects that masked its potential cardiovascular benefits.

Mechanism of Action of Fibrates

Fibrates belong to a class of drugs that exert their effects by activating the hormone-activated nuclear receptors, peroxisome proliferator-activated receptor α (PPARα) and, to a lesser extent, PPARβ/δ and PPARγ.6,7 PPARs regulate gene expression by forming heterodimers with activated retinoid-X-receptor (RXR) and binding to specific peroxisome proliferator response elements (PPREs) in the promoter region of the target gene.6,7 Three subtypes of PPARs have been described: α, β/δ, and γ. Each subtype is encoded by a specific gene. Expression of the different subtypes varies in different tissues, with PPARα being highly expressed in liver, heart, kidney, muscle, brown adipose tissue, and vascular cells.7–10

PPARα is activated by endogenous molecules, such as fatty acids11 and also by synthetic compounds such as fibrates. As far as can be judged, all fibrates have a similar mode of action, although reports of variations in their clinical effects indicate that there must be some differences in the mechanism of action between the individual members of the class.

Activation of PPARα by fibrates stimulates the oxidation of free fatty acids in the liver,12 diverting them away from triglyceride synthesis and thus reducing the hepatic synthesis of triglyceride-rich lipoproteins.9 The activation of PPARα also induces expression of the gene for lipoprotein lipase (LPL), the enzyme responsible for hydrolyzing triglyceride in triglyceride-rich lipoproteins in plasma.13 Thus, activators of PPARα lower the concentration of plasma triglyceride by reducing its rate of synthesis and increasing its rate of hydrolysis. An additional effect of activating PPARα is the inhibition of synthesis of apolipoprotein (apo) C-III.14 Because apoC-III delays the catabolism of triglyceride-rich lipoproteins, its inhibition provides a further mechanism by which PPARα-activators such as fibrates lower the concentration of plasma triglyceride.

Fibrates also impact on the concentration of high-density lipoprotein cholesterol (HDL-C) in humans, although the precise mechanisms are not known. Fibrates increase expression of the genes for both apo A-I and apo A-II, the 2 main apolipoproteins of HDL.15,16 although the magnitude of the increases in the plasma concentrations of these proteins tends to be small. Generally, the increase in plasma apoA-II is greater than that of apoA-I.16–18 This results in an increase in the concentration of HDL particles containing both apoA-I and apoA-II but a decrease in those containing apoA-I without apoA-II.18,19 Other potential mechanisms by which fibrates increase the level of HDL-C include an enhancement of cell cholesterol efflux secondary to an induction of cell ABCA1 expression.20 although others have not been able to confirm this.21 Fenofibrate has been reported to decrease SR-B1 in the liver,22 an action that would contribute to an elevation of HDL-C but which may not necessarily translate into a reduction in atherosclerosis.

The effect of fibrates on the concentration of plasma lipids is influenced to a considerable degree by the baseline lipid levels. Analysis of the effect of baseline lipid levels on the response to gemfibrozil in 1028 participants with good compliance in the HHS23 indicated that the absolute (mg/dL) increment in HDL-C was independent of the baseline HDL level. Consequently, the percentage increase in HDL-C is greater when the baseline level is low.23 The ability of gemfibrozil to decrease the plasma triglyceride level and to increase the concentration of HDL-C is most pronounced in subjects with higher fasting plasma triglyceride levels.24 Similar results have been reported with fenofibrate, with the greatest percentage increase in HDL-C being observed in people with low baseline HDL-C levels.25,26

There have been many studies comparing the lipid modifying effects of different fibrates.27–31 Most studies have concluded that there are only minor differences in the effects of different fibrates on triglyceride levels, with reductions of 30% to 50% being reported for most members of the class. In contrast, the HDL-C raising effect of fibrates varies widely between different studies, ranging from as little as 2% to as much as 25%. Some reports have suggested that the HDL-C raising effect of fenofibrate is superior to the others members of the class.32 However, this was not apparent in the FIELD study in which fenofibrate increased HDL-C by only about 2%4 and did not raise the level of apoA-I at all.18 In fact, the HDL-C raising effects of fibrates in most of the long term, large-scale trials have been relatively small,2,4 especially in people with diabetes.4,33 However, as outlined below, the cardioprotective properties of fibrates may be largely independent of their effects on plasma lipid levels, especially in people with features of the metabolic syndrome.

Fibrates also lower LDL-C levels, although the magnitude is variable and very much less than observed with statins. The LDL-C lowering achieved with fibrates tends to be greater in people with elevated levels of LDL-C.34 On the other hand fibrates have little LDL-C lowering activity when levels of plasma triglyceride are high.35 Fibrates also increase LDL particle size36,37 and decrease the concentration of triglyceride-rich lipoprotein remnants.36 These latter effects are potentially antiatherogenic and appear to be mediated equally well by all fibrates.

Safety and Tolerability of Fibrates

As with statins, fibrates are well tolerated by most people. The most common reported adverse effects of fibrates have been gastrointestinal in nature. These are mostly mild and generally transient. Other reported adverse effects include headache, anxiety, vertigo, dizziness, sleep disorders, arthralgia, rash, pruritus, urticaria, and blurred vision. Fibrates are well tolerated in people with diabetes. As fibrates are metabolized in the kidney and excreted via the renal route, they are not recommended for use in patients with renal problems.
Very few life-threatening effects have been reported when fibrates are used as monotherapy, although the coadministration of fibrates with statins is associated with a small but significant increase in death from rhabdomyolysis. This problem is more pronounced with gemfibrozil than with other fibrates and was identified as a serious problem when gemfibrozil was used in combination with cerivastatin. Another potential adverse effect of fibrates is that they increase plasma levels of homocysteine and creatinine.

Elevations of homocysteine have been observed with most fibrates, although the magnitude varies with different members of the class. Fenofibrate has been reported to increase homocysteine by 36% to 55%, gemfibrozil by 0% to 18%, and bezafibrate by 18% to 19%. The mechanism by which fibrates increase homocysteine is not known. Nor is it known whether the elevated creatinine is of clinical importance. The FIELD study included patients with and without manifest cardiovascular disease at entry. A subgroup analysis of HHS addressed the effect of BMI on the response to gemfibrozil, an observation that has led many to argue against the continued use of this drug class. It is relevant to note that there was no significant excess of noncoronary deaths in any of the subsequent trials with gemfibrozil (HHS and VA-HIT), bezafibrate (BIP) or fenofibrate (FIELD).

Human Intervention Studies With Fibrates
The place of fibrates as therapeutic agents depends on their ability to impact favorably on clinical outcomes. The efficacy of these agents in correcting abnormal lipid profiles is irrelevant unless it translates into a reduction in clinical events. For this reason, the importance of fibrates as lipid-modifying agents rests on the results of the end point intervention trials. Five large-scale, prospective, double-blind end point trials using fibrates as the active agent have now been completed. The World Health Organization (WHO) Clofibrate Study and HHS1 were primary prevention trials, whereas the VA-HIT2 and BIP3 studies were secondary prevention trials conducted in people with manifest CHD. The FIELD study4 included patients with and without manifest cardiovascular disease at entry.

The World Health Organization Clofibrate Study
The World Health Organization (WHO) Clofibrate Study5 included 10,627 men who were predominantly hypercholesterolemic. Triglyceride and HDL-C levels were not reported. Coronary heart disease events in the WHO trial were reduced from 7.4% in the placebo group to 5.9% in the clofibrate group, a relative risk reduction of 20% (P<0.05). However, there was also a small but significant excess of non-coronary deaths in the group receiving clofibrate, an observation that has led many to argue against the continued use of this drug class. The effectiveness of treatment with gemfibrozil increased in creatinine and homocysteine.

Another potential adverse effect of fibrates is that they increase plasma levels of homocysteine and creatinine. The strongest evidence base relate to studies of fenofibrate that increases creatinine levels by 8% to 27%. Similar results have been obtained in very small studies with bezafibrate and ciprofibrate. Small increases in creatinine have also been observed in people treated with gemfibrozil. The mechanism by which fibrates increase creatinine is not known. Nor is it known whether the elevated creatinine is of clinical relevance. The fact that the creatinine elevation associated with fenofibrate treatment is fully reversible within a few weeks of ceasing therapy suggests that it does not reflect permanent renal damage. The relationship between fibrate-induced increases in creatinine and homocysteine is not known.

The Helsinki Heart Study
The Helsinki Heart Study: Influence of BMI. The bars indicate the rate of total cardiac end points (nonfatal MI, fatal MI, sudden cardiac death, unwitnessed death) at 5 years in the gemfibrozil group compared with placebo. P indicates placebo group; G, gemfibrozil group.

Figure 1. Reduction of CHD events by gemfibrozil in Helsinki Heart Study: Influence of BMI. The bars indicate the rate of total cardiac end points (nonfatal MI, fatal MI, sudden cardiac death, unwitnessed death) at 5 years in the gemfibrozil group compared with placebo. P indicates placebo group; G, gemfibrozil group.
of subjects with a BMI >26 kg/m², the net difference in cardiac end points between the gemfibrozil and placebo groups was 21 events (25 of 1119 versus 46 of 1081, respectively). This represented a risk reduction in the overweight subjects of 47.5%. In marked contrast, in the group of people whose BMI was ≤26 kg/m², the difference in cardiac end points between the gemfibrozil and placebo groups was 7 events (31 of 927 subjects versus 38 of 954 subjects), representing a risk reduction of only 16% in this leaner subgroup.

The results of the HHS have also been analyzed in terms of the ability of baseline lipid levels to predict CHD events in the placebo group and also the benefits of treatment with gemfibrozil.34 The concentration of LDL-C was a poor predictor of risk in this population. The levels of HDL-C and serum triglyceride, on the other hand, were strong predictors. A concentration of HDL-C <1.08 mmol/L (<42 mg/dL) was associated with a relative risk 1.73 times greater than that in subjects whose HDL-C level was ≥1.08 mmol/L (≥42 mg/dL). Likewise, subjects whose serum triglyceride was >2.3 mmol/L (>204 mg/dL) had a relative risk 1.81 times greater than that in subjects with a serum triglyceride level ≤2.3 mmol/L (≤204 mg/dL). The excess risk associated with lower HDL-C and higher serum triglyceride (Figure 2A) was essentially abolished by treatment with gemfibrozil.

The Veterans Affairs High-Density Lipoprotein Intervention Trial

VA-HIT was a double-blind placebo-controlled trial that included 2531 men with known clinical CHD and aged <74 years.2 To be eligible for inclusion, subjects had to have a low level of both HDL-C (<1.0 mmol/L, <40 mg/dL) and LDL-C (<3.6 mmol/L, <140 mg/dL) and a plasma triglyceride <3.4 mmol/L (<300 mg/dL). The mean baseline concentrations of HDL-C and LDL-C were 0.83 mmol/L (32 mg/dL) and 2.88 mmol/L (111 mg/dL), respectively. The active treatment was gemfibrozil 1200 mg per day and the mean follow-up was 5.1 years. One year after randomization the concentration of HDL-C was increased by 6% (P<0.001) and the plasma triglyceride was decreased by 31% (P<0.001). These changes were sustained for the duration of the study. There was a nonsignificant 4% reduction in plasma total cholesterol but no change in the concentration of LDL-C.

The primary end point (nonfatal MI or death attributable to CHD) was reduced by 22% in the gemfibrozil group (P=0.006), with a benefit of therapy becoming apparent during the third year of follow-up.2

There were 220 (17.4%) deaths from all causes in the placebo group compared with 198 (15.7%) in the gemfibrozil group, although this difference did not reach statistical significance. There were 51 cancer deaths in the placebo group and 45 in the gemfibrozil group, a difference that was not statistically different. There was no significant difference between the 2 groups in the rate of death from any specific cause.

Overall, the study medication was well tolerated, with dyspepsia being the only symptom that occurred more frequently in the active group than in the placebo group. The numbers of subjects with elevations of either creatine kinase or liver enzymes in the 2 groups were not statistically different.

The relationship between lipid levels and coronary events in the VA-HIT study was reported in a subsequent paper.57 Several conclusions were drawn. The baseline concentrations of HDL-C, plasma triglyceride, apo B, apo A-I, and HDL₃-C (although not LDL-C or HDL₂-C) were all significant predictors of CHD events during the trial. As in the HHS, the baseline level of plasma triglyceride was also predictive of the magnitude of the benefit derived from treatment with gemfibrozil. However, in terms of lipid levels during the trial, it was only the achieved concentration of HDL-C that predicted event rates. On-trial levels of LDL-C and plasma triglyceride were not predictive. When the data were subjected to multivariable Cox proportional hazards analysis, it was found that CHD events during treatment with gemfibrozil were reduced by 11% for every 0.13-mmol/L (5 mg/dL) increment in the achieved level of HDL-C (P=0.02). But it was also noted that the level of HDL-C achieved could...
account for only about one quarter of the observed benefit of the drug. This finding raised the possibility that gemfibrozil may have cardioprotective properties beyond those explained by its effects on plasma lipid concentrations.

The Bezafibrate Infarction Prevention Study
The BIP study was a double-blind, placebo-controlled trial that included 3090 subjects with clinically manifest CHD (2825 men, 265 women) aged <74 years. The concentration of plasma total cholesterol ranged from 4.7 to 6.5 mmol/L (180 to 250 mg/dL), the plasma triglyceride concentration was <3.4 mmol/L (<300 mg/dL), and the concentration of HDL-C was <1.16 mmol/L (<45 mg/dL). The active treatment was bezafibrate 400 mg per day and the mean follow-up was 6.2 years. There was no significant effect of bezafibrate on the combined incidence of nonfatal MI or death from CHD (the primary end point of the study).

A post-hoc subgroup analysis indicated the possibility of a substantially greater benefit of bezafibrate in the subset of patients in whom the entry concentration of plasma triglyceride was >2.25 mmol/L (>200 mg/dL, Figure 2B). In this subgroup, the event rate was 19.7% in the placebo group and 12.0% in the bezafibrate group, indicating a relative reduction of 39% (P=0.02). A further post hoc, subgroup analysis of the BIP study found that in 1470 patients with the metabolic syndrome (as defined by ATP-III), bezafibrate was associated with reduced risks of any MI (hazard ratio 0.71, P=0.02) and nonfatal MI (hazard ratio 0.67 (P<0.009). Moreover, in the 575 patients who had 4 to 5 components of the metabolic syndrome, bezafibrate was associated with a 56% reduction in the risk of cardiac death (hazard ratio 0.44, P=0.005).

These findings added to the observations from both the HHS and the VA-HIT studies that a higher baseline triglyceride level, such as in patients with the metabolic syndrome, identifies a group of people who derive a substantial additional cardiovascular benefit from treatment with a fibrate.

The Fenofibrate Intervention and Event Lowering in Diabetes Study
The FIELD study was a randomized, double-blind, placebo-controlled parallel-group trial among 9795 middle-aged to elderly people with type 2 diabetes. After a placebo run-in phase followed by a fenofibrate run-in phase, patients with a total cholesterol of 3.0 to 6.5 mmol/L (116 to 252 mg/dL) and total/HDL cholesterol ratio ≥4.0 or plasma triglyceride >1.0 to 5.0 mmol/L (87 to 435 mg/dL) were randomized to micronised fenofibrate 200 mg/d or matching placebo. All other treatments, including introduction of statin therapy after randomization, were at the discretion of the patient’s usual doctor. The primary outcome was CHD events (CHD death or nonfatal MI); for prespecified subgroup analyses the outcome was total CVD events (the composite of CVD death, MI, stroke, and coronary and carotid revascularization). Follow up was a median of 5.0 years. Averaged over the study period, similar proportions had discontinued study medication (placebo group, 9.7% versus fenofibrate group, 10.5%), whereas significantly more patients allocated placebo (17.4%) had commenced other lipid-lowering drugs, predominantly statins, than those allocated fenofibrate (8.4%).

Treatment with fenofibrate reduced the plasma triglyceride by 29% and LDL-C by 12%; these effects were apparent for the duration of the trial. Fenofibrate increased the level of HDL-C by 5% at 4 months but this was reduced to an increase over placebo of about 2% at the conclusion of the study. The explanation for such an attenuation in the effect of fenofibrate on HDL-C is not known.

CHD events occurred in 5.9% of the placebo group and 5.2% of the fenofibrate group, a relative reduction of 11% (P=0.16). This reflected a significant 24% reduction in nonfatal MI (P=0.010) and a nonsignificant 19% increase in CHD mortality (P=0.22). Total CVD events were reduced by 11% from 13.9% to 12.5% (P=0.035); this included a significant 21% reduction in coronary revascularization (P=0.003) and a nonsignificant 10% reduction in stroke (P=0.36). Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group (P=0.18). Among patients with no prior CVD, total CVD events were reduced by 19% (P=0.004) but this was not the case in patients with prior CVD in whom there was a nonsignificant 2% increase in events (P=0.85). Patients allocated to the fenofibrate group had less progression of albuminuria (P<0.002) and a significantly lower rate of laser treatment for retinopathy (5.2% versus 3.6%, P<0.001); the mechanism underlying these renal and retinal effects is not known. Fenofibrate was associated with a slightly increased risk of pancreatitis (0.5% versus 0.8%) and pulmonary embolism (0.7% versus 1.1%), but no other significant adverse effects were observed.

Treatment with fenofibrate in the FIELD study increased the plasma homocysteine level by 35% from a median of 11.2 μmol/L in the placebo group to 15.1 μmol/L in the treated group. On the basis of the results from epidemiological studies, an increase in homocysteine of this magnitude could theoretically translate into a 10% to 20% increase in cardiovascular events. It is noteworthy that the fenofibrate-induced increase in HDL cholesterol in the FIELD study (less than 2% at study end) and the reduction in cardiovascular events (11%) were both much less than predicted from the results of trials using other fibrates that have a smaller effect on levels of homocysteine. Recent studies demonstrating that homocysteine inhibits the synthesis of apo-I in the liver suggest that the less than expected cardiovascular benefits of treatment with fenofibrate in the FIELD study may well have been the consequence of a sustained increase in the plasma concentration of homocysteine inhibiting the synthesis of apoA-I and thus opposing the expected increase in concentration of HDL cholesterol.

In line with the earlier trials there was a trend toward greater event reduction with fenofibrate in FIELD participants who had lower baseline levels of HDL-C.

Effects of Fibrates on Cardiovascular Risk in the Metabolic Syndrome
An elevated baseline level of plasma triglyceride identifies patients in whom treatment with a fibrate produces a reduction in CHD events that is substantially greater than in the study population as a whole. This was apparent with gemfi-
Possible anti-atherogenic mechanisms of fibrates

- Reduced level of plasma triglyceride
- Reduced chylomicron and VLDL remnants
- Increased reverse cholesterol transport
- Increased LDL size
- Increased level of HDL-C

Figure 3. Effects of fibrates with the potential to protect against cardiovascular disease.

Fibrates have been shown to reduce cardiovascular risk in people with the metabolic syndrome. Given that statins have been shown to reduce cardiovascular risk in all groups in whom they have been studied (including people with the metabolic syndrome), it is apparent that fibrates have a therapeutic role only if they have additional benefits in people already on statins. Because statins reduce risk in everyone, although the benefits of fibrates are largely confined to people with features of the metabolic syndrome, it is likely that the mechanisms by which stains and fibrates protect are distinct. If this is the case, it is possible that fibrates will reduce the residual risk in patients with diabetes or the metabolic syndrome who are already well treated with statins. This proposition is currently being investigated in the ACCORD Study in which diabetic subjects on a statin have been randomized to receive fenofibrate or placebo. In the meantime, the balance of (circumstantial) evidence favors treatment with the combination of a fibrate and a statin in high risk overweight people who also have an elevated plasma triglyceride and low level of HDL-C.

The Question Then Arises: Which Fibrate?

On the basis of available evidence, the answer should be gemfibrozil. The HHS and VA-HIT studies have shown that gemfibrozil is extremely effective in reducing cardiovascular risk in people with features of the metabolic syndrome such as overweight, hypertriglyceridemia, and low HDL-C. However, concerns about muscle problems associated with the addition of gemfibrozil to a statin tend to limit the use of this combination. Evidence supporting the use of bezafibrate is less robust, although the subgroup analysis of those with the metabolic syndrome in the BIP study provided results remarkably similar to those with gemfibrozil in the HHS and VA-HIT studies. The observation that muscle problems appear to be less of an issue when fenofibrate is combined with a statin has led to suggestions that fenofibrate is the agent of choice if a fibrate is to be added to a statin. However, the evidence in support of the cardioprotective benefits of
fenofibrate is less robust than has been reported for gemfibrozil. The true place of fenofibrate may emerge after the results of the ACCORD study are reported. In the meantime, practicing physicians will have to make their decisions about whether to use the combination of fibrates and statins on the basis of circumstantial evidence. The choice of which fibrate then becomes an assessment of the relative efficacies of the different agents in the clinical trials against which must be balanced factors such as the muscle problems associated with gemfibrozil and the greater increase in homocysteine and creatinine associated with the use of fenofibrate.

The ideal will be to develop a PPARα agonist that has the cardioprotective properties of gemfibrozil, the safety of coadministration with statins of fenofibrate, and no other potentially adverse effects such as an elevation of homocysteine and creatinine.

Disclosures
P.J.B. has received honoraria from Abbott, AstraZeneca, Fournier, LifeCycle Parma, Merck, Pfizer, and SanofiAventis; has served on the advisory boards of Abbott AstraZeneca, Fournier, LifeCycle Parma, Merck, Pfizer, and SanofiAventis; and has received research support from Pfizer. K.-A.R. reports no potential conflicts of interest.

References


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