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Review

Fibrates and coronary risk reduction

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Abstract

Many medications are currently available to correct lipoprotein abnormalities when lifestyle measures alone are not sufficient. No single agent or class of agents is able to correct all of the lipoprotein abnormalities. This paper reviews the role of one class, the fibrates, in the management of lipid disorders and summarizes the clinical trial information relating to their impact on coronary artery disease.

Keywords: Fibrates; Coronary heart disease; Clinical trials; Triglyceride; Cholesterol; Diabetes; Metabolic syndrome

Contents

1. Introduction

There still seems to be an almost competitive debate as to which class of lipid lowering drugs should be used either initially or exclusively to treat lipid disorders. As in the case of diabetes, where there are several hypoglycemic medications and the physician's choice of a particular drug depends on the nature of the patient's diabetes, so in hyperlipidemia, the choice of a lipid modifying drug should be determined by the nature of a person's major lipoprotein abnormality. In other words, if the predominant problem is

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an elevation of LDL-cholesterol then initial therapy should be directed to correcting it. On the other hand, if it is hypertriglyceridemia and a low HDL-cholesterol, then initial therapy should be aimed to correct these. In this second situation the drug chosen would most often be a member of the fibrate family. This review is intended to summarize the effects of the fibrate class of medications and to highlight their clinical relevance in reducing the coronary risk in the general dyslipidemic population and in particular subgroups in which a particular treatment benefit has been observed.

2. Overview of the fibrates

This class of medications has been available since the 1970s. The first member of the group was ethylchlorphenoxyisobutyrate, clofibrate. Clofibrate, as well as others that followed, was chemically related to fibric acid and hence this group of drugs has been called fibric acid derivatives, or "fibrates" (Fig. 1). The next fibrate was the widely used drug gemfibrozil. More recently, the two in widespread use are bezafibrate and fenofibrate. Two others have seen limited clinical use, etofibrate and ciprofibrate.

In general, the major lipoprotein effects of fibrates are to reduce levels of plasma triglycerides by 30 to 50% and to increase levels of HDL-cholesterol by 6 to 5%. The magnitude of their effect is directly related to the severity of those lipoprotein abnormalities at baseline [1–3]. Fibrates may also

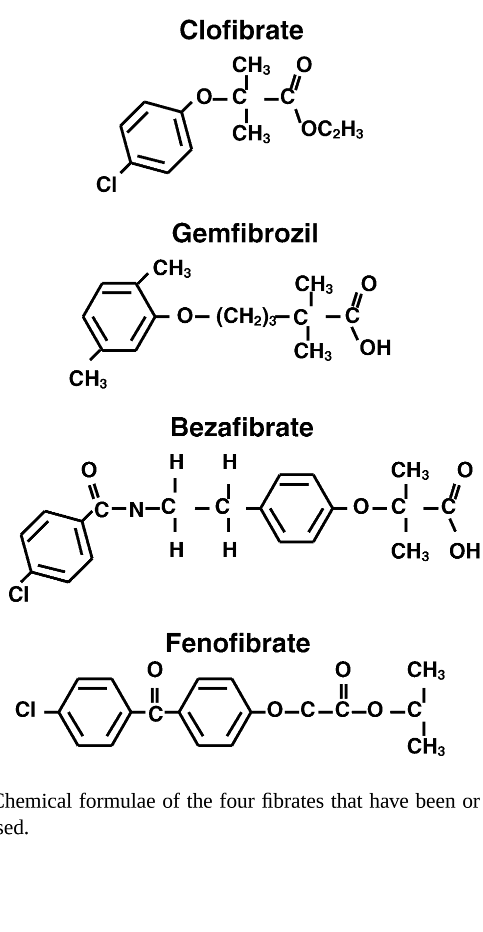

Fig. 1. Chemical formulae of the four fibrates that have been or are commonly used.

reduce LDL-cholesterol, but the extent of its effect is variable. While gemfibrozil does not reduce LDL-C levels, bezafibrate or fenofibrate can do so in a range of 10–20% depending on the lipoprotein abnormality. In fact, in people who have very high triglyceride-rich lipoproteins, treatment with gemfibrozil may result in an increase in LDL-cholesterol. Even though the quantitative effect of fibrates on LDL-C may be variable, they do make LDL less atherogenic by shifting the population of LDL particles to those of larger size.

The fibrates' primary mode of action is to activate one of a group of nuclear receptors peroxisome proliferator-activated receptors (PPARs), specifically PPAR-alpha. This paper is not intended to be a review of the PPARs and their activators. For such reviews, the reader is referred to references [4]. Activation of PPAR-alpha modulates the expression of several genes involved in lipoprotein metabolism. The activity of lipoprotein lipase is increased and results in an increase in the clearance of circulating triglyceride-rich lipoproteins [5]. The synthesis of apoC-III is decreased [5]. ApoC-III inhibits lipoprotein lipase [6]. Hence, low apoC-III levels will further enhance the clearance of triglyceride-rich lipoproteins. ApoC-III synthesis is also increased in hypertriglyceridemic individuals [7,8]. Thus reducing apoC-III gene expression by PPAR-alpha agonists may enhance both the clearance of the triglyceride-rich lipoproteins and the decrease in their production. PPAR-alpha agonists also increase hepatic fatty acid oxidation thereby reducing the esterification of free fatty acids and leading to a further decrease in VLDL-triglyceride production. Recently, PPAR-alpha agonists have also been found to increase apoA-V gene expression, the overexpression of which results in triglyceride reduction [6,9]. The fibrates increase HDL production by transcriptional induction of the synthesis of the major HDL apolipoproteins, apoA-I and apoA-II [4,5], and also enhance reverse cholesterol transport through an increase in the adenosine triphosphate-binding cassette-1 (ABC-A1) cholesterol transporter and in the scavenger receptor SR-BI/CLA-1 [4,10,11].

3. Prevention trials

This review will examine the effects of fibrate treatment on coronary artery disease. In doing so, it will address angiographic and clinical event studies. Both will be considered as the results of clinical trials show a good relationship between angiographic changes and clinical event changes. In some cases this relationship has even been seen within the same trial [12–14]. These have been described and the use of angiographic information as a surrogate for clinical information has been reviewed by Waters [15].

4. Prevention trials in the general population

The first issue to be addressed in this review will be whether treatment with fibrates reduces clinical coronary events in the general population. For the purposes of this

Table 1
Summary of clinical coronary event studies with fibrates in the general population

Trial (primary 1°/secondary 2° intervention)	Agent (n, gender)	End point	Change in active group (⇓ decrease, ⇔ none)	p
WHO (1°)	Clofibrate (7194, M)	Non-fatal MI	⇓	<0.05
Newcastle (2°)	Clofibrate (497, M & F)	Sudden death and fatal MI	⇓ In those with prior angina	≤0.02
Scottish (2°)	Clofibrate (717, M & F)	Sudden death and fatal MI	⇓ In those with prior angina	<0.02
CDP (2°)	Clofibrate (3892, M)	Fatal and non-fatal MI	⇔	ns
Stockholm IHD Secondary Prevention Study (2°)	Clofibrate + NA (544, M & F)	Total mortality, IHD mortality	⇓	<0.05, <0.01
Helsinki Heart Study (1°)	Gemfibrozil (4081, M)	Sudden death and fatal plus non-fatal MI	⇓	<0.02
BECAIT (2°)	Bezafibrate (92, M)	PCI or CABG	⇓	0.019
BIP (2°)	Bezafibrate (3090, >90% M)	Sudden death and fatal plus non-fatal MI	⇔ Overall, ⇓ if TG high	ns, <0.02
VA-HIT (2°)	Gemfibrozil (2531, M)	Non-fatal MI and CHD death	⇓	0.006

review, the term "general population" will be used to indicate people with lipid abnormalities irrespective whether they also have diabetes and/or the metabolic syndrome. To date, such studies have been reported with clofibrate, bezafibrate, and gemfibrozil. They will be briefly reviewed. A summary description of these studies is reported in Table 1.

4.1. Studies with clofibrate

The 1970s saw the first of the multicenter clinical event lipid intervention trials. Among 1103 clofibrate-treated participants in the Coronary Drug Project, the 5-year cardiovascular event rate was not different from that observed in the 2789 placebo-treated people [16].

The largest of this group of studies was the World Health Organization Clofibrate Study [17]. It examined 15,745 men who did not have coronary artery disease. They were divided into tertiles according to their cholesterol level. The lowest tertile was given placebo and the highest tertile was randomized either to placebo or clofibrate. It is noteworthy that although the major lipid effects of the fibrates is to reduce triglyceride levels and to increase those of HDL-cholesterol, levels of plasma triglyceride were only measured in the Edinburgh cohort at 5, 6 and 7 years after clofibrate treatment had been started. Also, in the initial analyses, the intention to treat approach was not used. In spite of these limitations, those treated with clofibrate had 20% fewer first major coronary events and 25% fewer non-fatal myocardial infarctions (MI). This beneficial conclusion was, however, overshadowed by the reported increase in mortality from non-cardiovascular diseases, and particularly in cancer that occurred in those treated with clofibrate [17]. This initial report was incomplete in its follow up. When more complete follow-ups were published 2 and 4 years later [18,19], the difference in cancer incidence was smaller. Furthermore, it is intriguing to speculate on the implications of the observation that the incidence of cancer in the clofibrate group was greater than that of the placebo group in the highest tertile of cholesterol, but was not higher than that in the placebo treated people in the lowest cholesterol tertile. Moreover, two other clofibrate coronary endpoint studies, the Scottish Physicians Study [20] and the Newcastle Study [21], conducted with a total of 1214 people at about the same time and subsequent studies conducted with other fibrates did not observe similar increases in cancer.

The Scottish Physicians Study [20] examined 717 and the Newcastle Study [21] 497 individuals. Each study included men and women who had previous ischemic heart disease. In both combined, there were significantly fewer deaths among those who had prior angina and were treated with clofibrate [22]. There was, interestingly, no difference among those who had previously had a myocardial infarction. Another study that used clofibrate was the Stockholm Ischemic Heart Disease Secondary Prevention Study [23]. This study compared myocardial infarct survivors, 279 of whom were treated with an open label combination of nicotinic acid and clofibrate and 276 of whom were controls. Total mortality was reduced by 26% and ischemic heart disease mortality by 36% in the active treatment compared to the control group. These benefits were related to the reduction of serum triglyceride levels. Although this study was analyzed by the intention-to-treat approach, its interpretation is limited by its open label design and by the fact that combination lipid treatment was used.

4.2. Studies with bezafibrate

There have been three studies that examined clinical events associated with bezafibrate treatment. As noted earlier, the first of these, the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) Study was initially designed to be an angiographic examination of the effects of treatment with bezafibrate in 92 young male myocardial infarct survivors [12]. Even though the investigators had not anticipated a significant difference in clinical events, they did observe that those treated with bezafibrate had less coronary events than those treated with placebo (3 versus11, respectively, $p = 0.02$.

A larger clinical trial, the Bezafibrate Infarction Prevention (BIP) Study, a secondary intervention study, looked into the effects of bezafibrate on fatal and non-fatal myocardial infarctions and sudden death [24]. In its overall population of 2825 men and 265 women, it failed to demonstrate a statistically significant reduction of events. This may have had several reasons. Because the results of the 4S study became known while BIP was still in progress, a large number of BIP participants were also given a statin. This could have reduced both the overall event rate and the difference between the likelihood of observing a difference between the placebo and the active drug groups. The nature of the population studied probably also had a major impact on the outcome. This will be considered in greater detail later.

Recently, 783 men with lower extremity arterial disease were treated with bezafibrate versus 785 men with placebo, the Lower Extremity Arterial Disease Event Reduction (LEADER) trial. There was no significant reduction in the incidence of coronary heart disease and stroke combined, but there was a significant reduction in non-fatal events, particularly in those men under age 65 years [25].

4.3. *Studies with gemfibrozil*

The Helsinki Heart Study, a primary intervention study conducted in 4081 Finnish men with hypercholesterolemia, was a landmark fibrate lipid intervention study utilizing gemfibrozil [1]. Treatment with gemfibrozil resulted in a 10% reduction in total cholesterol, an 11% reduction in LDL-cholesterol, a 35% reduction in triglyceride and an 11% increase in HDL-cholesterol levels. In comparison to the placebo group, over 5 years, those randomized to gemfibrozil had 34% fewer total coronary events ($p < 0.05$) and 37% fewer non-fatal myocardial infarctions ($p < 0.02$). No significant difference in the overall mortality was observed between the two groups. The gemfibrozil-associated reduction in CHD incidence reflected both the reduction in LDL-cholesterol, the increase in HDL-cholesterol and the increased ratio of HDL-cholesterol/total cholesterol [26]. The benefit observed in the subgroup that had the characteristics of the metabolic syndrome will be considered later.

More recently a major secondary intervention study using gemfibrozil, the Veterans' Administration HDL Intervention Trial (VA-HIT), has been published [2]. It selected men with known coronary artery disease, LDL-cholesterol levels that were not elevated and low HDL-cholesterol levels. Treatment with gemfibrozil reduced not only the risk of major cardiovascular event by 22% ($p = 0.006$), but also reduced the combined outcome of death from coronary heart disease, non-fatal MI and stroke by 24% ($p < 0.001$).

4.4. *Do the fibrates reduce angiographic disease?*

While atherosclerosis underlies myocardial infarction, not all who have coronary atherosclerosis will have a myocardial infarct. The actual clinical event may involve other processes such as arrhythmias. Hence, in order to determine whether these drugs have an effect on the coronary arteries themselves, it is necessary to study their architecture. Until very recently, the best way to do this on a large scale was to conduct an angiographic trial. Even though coronary angiograms only show the lumen of the arteries, they have allowed information about coronary architecture to be obtained. Two angiographic trials have been conducted in general populations utilizing fibrates as the active treatment modality (Table 2). One trial, conducted in patients with type 2 diabetes, will be considered later.

The BECAIT Study described above [12] observed that participants treated with bezafibrate had significantly less progression of their angiographically determined focal coronary atherosclerosis. The second study, the Lopid Coronary Angiography Trial (LOCAT) [27] examined 395 men with low HDL-cholesterol levels ($\leq$1.1 mmol/L) and LDL-cholesterol $\leq$4.5 mmol/L, who had undergone coronary artery bypass grafting and who were randomized to receive either gemfibrozil or placebo. The angiographic disease progression in the native coronary segments (i.e. those not affected by the graft) was significantly less in men receiving gemfibrozil. Gemfibrozil treatment resulted in less ($p = 0.009$) progression of coronary artery disease in the native coronary segments. This benefit was primarily related to the decline in IDL and LDL triglyceride and cholesterol and the increase in HDL_3 cholesterol [28]. Thus these angiographic trials mirrored the benefits seen in the clinical event studies. This suggested that, at least some of the clinical event benefit was a reflection of decreased progression of coronary atherogenesis.

Table 2
Summary of coronary angiographic studies with fibrates

Trial (primary 1°/secondary 2° intervention)	Population (*n*, gender)	Agent (*n*, gender)	Progression in active group (⇓ less, ⇔ no difference, ⇑ more)	*p*
LOCAT (2°) native coronary segments	Post-CABG (395, M)	Gemfibrozil	⇓ Average diameter progression	0.009
			⇓ Minimum lumen diameter progression	0.002
BECAIT (2°)	Post-MI (92, M)	Bezafibrate	⇓ Minimum lumen diameter progression	0.049
			⇓ Percent stenosis progression	ns trend
			⇓ Mean segment diameter progression	ns trend
DAIS (1° & 2°)	Type 2 diabetes (418, M & F)	Fenofibrate	⇓ Minimum lumen diameter progression	0.02
			⇓ Percent stenosis progression	0.02
			⇓ Mean segment diameter progression	ns trend

5. Particular subgroups within the general population who benefited from lipid intervention with fibrates

5.1. Fibrates and coronary artery disease in the metabolic syndrome

For many years there have been suggestions that insulin resistance or hyperinsulinemia are accompanied by an increased coronary risk. The Quebec Heart Study provided epidemiologic data indicating that a high triglyceride level and an increased waist circumference marked an individual at high coronary risk [29]. These two features are a part of the group of clinical and biochemical characteristics that have been called the metabolic syndrome. The National Cholesterol Education Program Adult Treatment Panel III [30] indicated that the presence of three of the following five factors marked an individual as having a high probability of having the metabolic syndrome. The five factors are the following: abdominal obesity (defined as a waist circumference in men >102 cm and in women >88 cm); high plasma triglycerides (≥150 mg/dL, 1.7 mmol/L); low HDL-cholesterol (in men <40 mg/dL, 1.0 mmol/L and in women <50 mg/dL, 1.3 mmol/L); high blood pressure (≥130/85 mmHg); and impaired fasting glucose (≥110 mg/dL, 6.1 mmol/L). The World Health Organization has taken a more pathophysiologic approach to the definition, feeling that a common underlying feature is insulin resistance [31,32]. The metabolic syndrome is defined as requiring one of the following two factors: (1) impaired glucose regulation — impaired glucose tolerance or impaired fasting glucose or diabetes; (2) insulin resistance; together with two or more of the following four factors: (1) increased arterial pressure (≥140/90 mmHg); (2) elevated plasma triglycerides (≥1.7 mmol/L; 150 mg/dL) and/or reduced HDL-cholesterol (in men <0.9 mmol/L, 35 mg/dL and in women <1.0 mmol/L, 39 mg/dL); (3) central obesity (a waist to hip ratio in men >0.90 and in women >0.85) and/or BMI >30 kg/m^2); (4) microalbuminuria (urinary albumin excretion rate ≥20 (g/min).

A closer examination of the populations studied in the trials described above shows that some people had more benefit from fibrate treatment than did others. The participants in the WHO Clofibrate Trial were divided into tertiles according to their body mass index (BMI = weight (kg)/height (m)^2). Those who showed the greatest benefit were in the highest BMI tertile in the clofibrate group (BMI > 29) [17]. Similarly, in the Helsinki Heart Study, the greatest benefit from gemfibrozil treatment in reducing coronary risk was observed in those with a BMI >30 kg/m^2 [67]. The VA-HIT found a strong correlation between BMI and waist circumference (r = 0.995), and between fasting plasma insulin levels and waist circumference (r = 0.968) [33,34]. This suggested that although BMI is not one of the ATP III characteristics used to define the metabolic syndrome, it does correlate well with waist circumference and with insulin resistance. Hence, these two earlier studies suggest that the effects of the fibrates are strongest in those individuals who have a high probability of having the metabolic syndrome.

The Helsinki Heart Study also ranked its participants by their baseline levels of triglyceride and HDL-cholesterol. Those whose coronary risk showed the greatest benefit from treatment with gemfibrozil were those in the highest tertile for triglyceride and lowest tertile for HDL-cholesterol [67] As the group in whom the Helsinki Heart Study in which the greatest coronary benefit of gemfibrozil was found was that with people who had the combination of a high BMI (which imply a high waist circumference and insulin resistance), a low HDL and a high level triglyceride, there is a strong suggestion that most of the benefits of the fibrate treatment were in those with the metabolic syndrome. A similar conclusion was suggested in the BIP Study. In it, a preplanned analysis of the study subgroup with baseline plasma triglyceride levels above 200 mg/dL, one of the characteristics of the metabolic syndrome, found that in this group bezafibrate treatment was associated with a highly significant reduction (−39.5%, p = 0.02) in clinical coronary events [24]. It was these suggestions that led the BIP investigators to conduct a post hoc analysis of their subpopulation that fit the ATP III characteristics of the metabolic syndrome. That analysis indicated a highly significant coronary benefit in those study participants who had the metabolic syndrome (personal communication from Prof. S. Behar and presented to the European Association for the Study of Diabetes, 2004).

Recognizing the importance of insulin resistance as either as a feature of the metabolic syndrome or fundamental to it, makes one of the subgroup analyses of the VA-HIT interesting. That study subdivided its population into quartiles according to their fasting insulin levels. Fasting insulin levels in the general population correlate reasonably well with insulin resistance. The gemfibrozil-induced reduction in coronary events was greater the higher the fasting insulin level (i.e. the more insulin resistant the person) and was significant in the top quartile (fasting plasma insulin >39 μU/mL) [33]. Hence, all of these studies point to the coronary benefits of the fibrates being greatest in people with the metabolic syndrome and least in those without.

5.2. Fibrates and coronary artery disease in diabetes

People with the metabolic syndrome are recognized to be particularly likely to develop diabetes mellitus [34]. Therefore it is reasonable to examine whether the beneficial effects of the fibrates are also seen in those with diabetes. This discussion will be confined to type 2 diabetes as the data to date have all come from type 2 diabetes. Furthermore, this is the most common form of diabetes and poses the largest problem in terms of coronary artery disease.

The first hint of a beneficial effect came from the Helsinki Heart Study. A few of its participants had diabetes (76 on placebo and 59 on gemfibrozil) and there was a suggestion of coronary benefit in those who received gemfibrozil [35].

There were too few with diabetes for this to be able to be more than a suggestion that would give rise to subsequent studies. The St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study was designed to examine the effects of bezafibrate on carotid intimal medial thickness (recently used as a surrogate marker for coronary artery disease) in participant with type 2 diabetes [36]. No differences in intima media thickness were observed between the placebo and bezafibrate-treated groups. The investigators then re-examined the population to see whether bezafibrate treatment had any effect on ischemic heart disease. This was defined as clinical events or as ischemic changes on electrocardiograms, the latter being a rather broad and at times nonspecific definition. With the limitations of post hoc analysis and of the definition of ischemic heart disease, the investigators did find that bezafibrate treatment was accompanied by significantly less ischemic heart disease in diabetes [36]. The primary report of the VA-HIT included a pre-planned analysis to examine the effects of gemfibrozil treatment in the subgroup of its population known to have diabetes. Gemfibrozil treatment had a beneficial effect on coronary clinical events in that subgroup [2]. Subsequently the subgroup was expanded to include also those discovered to have diabetes. Gemfibrozil reduced coronary mortality in this expanded population [33]. The Diabetes Atherosclerosis Intervention Study (DAIS) was the first study specifically confined to those with type 2 diabetes and designed to determine whether correcting the lipoprotein abnormalities typically seen in type 2 diabetes would alter the progression of coronary artery disease [37]. The investigators chose to do this as a double-blind placebo controlled study using fenofibrate in the actively treated participants. It assessed coronary artery disease angiographically and was neither designed nor powered to be a clinical event study.

The fenofibrate treated group had significantly less progression of the two parameters reflecting focal coronary artery disease, i.e. minimum lumen diameter and percent stenosis. There was also a trend to less progression of the parameter reflecting diffuse disease, i.e. mean segment diameter, the parameter chosen for sample size calculations [3]. The previously mentioned parallelism between angiographic findings and clinical events was also seen in DAIS. There was a 23% reduction in clinical events in the fenofibrate treated group. However, as the study was not powered to be a clinical event study, no statistical conclusions could be drawn from this result. They have, however, formed the basis of a large study examining the effects of fenofibrate on clinical events in type 2 diabetes, the Fenofibrate Intervention Event Lowering in Diabetes (FIELD) Study.

These studies indicate that the benefits seen among people with the metabolic syndrome are also seen among people with diabetes. About 15% of people with type 2 diabetes do not have insulin resistance [38]. The increased coronary risk associated with diabetes appears to be either confined to, or greatest in that approximately 80–90% who do have insulin resistance [38,39]. Recently, a post hoc analysis of the BIP study shows that the bezafibrate treatment reduced secondary endpoints (hospitalization for unstable angina, PTCA, CABG) only in patients with normal fasting glucose ($p = 0.04$) [40]. It will be worthwhile to determine whether the beneficial effects of the fibrates in diabetes are confined to those who are resistant to insulin.

6. The pharmacological basis of the coronary benefit of fibrates

In general, the primary lipid effect of the fibrates is to reduce plasma levels of triglyceride and to increase HDL-cholesterol level. The fibrates may also produce a small reduction of LDL-cholesterol, depending on the fibrate, the baseline levels of plasma triglyceride and LDL-cholesterol. However, their much more striking effect on LDL is to shift the LDL population toward a higher proportion of large-buoyant particles and a lower proportion of small-dense ones. This would be expected to account for the beneficial coronary effects of the fibrates despite of lack of consistency between studies. Neither the Newcastle [21] nor the Scottish study [20] with clofibrate found a relationship between the degree of lipid reduction and the observed coronary benefit. However, the WHO Clofibrate Trial did find a relationship between reduction of high plasma cholesterol and reduction of the incidence of non-fatal infarction [17]. Examining the VA-HIT indicated that the gemfibrozil-induced lipid changes accounted at most one-quarter of the reduction in coronary events [41]. Similarly, in DAIS, approximately 10% of the angiographic benefit was explained by the fenofibrate-produced in the size of the LDL population, and in the concentrations of plasma cholesterol, plasma triglyceride, apoB, LDL-cholesterol and HDL-cholesterol [42]. This raises the possibility that non-lipid effects (i.e. pleotropic effects) of these drugs could, at least in theory, account for the reduction in coronary risk. These pleiotropic effects include an anti-inflammatory action as evidenced by a reduction in acute phase reactant such as C-reactive protein as well as a number of cytokines, IL-6, TNF-alpha and interferon-gamma [43–45]. They also decrease procoagulant factors such as fibrinogen (which is also an acute phase reactant) and plasminogen activator inhibitor-1 [46,47]. Cellular adhesion molecules and monocyte chemoattractant protein-1 [48] are also reduced by the fibrates. The presence of microalbuminuria increases coronary risk. Fenofibrate was found to reduce the progression of microalbuminuria in the people with diabetes studied in DAIS [49]. The fibrates can also alter endothelial function as evidenced by an increase flow-mediated vasodilation [50,51]. Although there is some contrary evidence [52], there are studies suggesting that the fibrates can also reverse another coronary risk factor, insulin resistance [53,54]. Which if any of these or other pleotropic effects will be found to account for the clinical trial observations remains to be determined.

7. Relationship to statins

This article reviews the role of fibrates, one class of drugs with particular benefits for people with the metabolic syndrome or with diabetes. Other lipid lowering drugs such as statins have also demonstrated benefit in such patients [55–59]. Each class of drugs should be used in relation to the predominant lipoprotein abnormality.

It is interesting to note that the beneficial effects of the statins may also be greatest in those with the metabolic syndrome. A re-examination of the 4S study [60] noted that the benefits of simvastatin in this secondary intervention study were observed in those who fell into the highest quartile for plasma triglyceride and lowest quartile for HDL-cholesterol. No benefits were noted in those who were in the lowest quartile for triglyceride and the highest quartile for HDL-cholesterol. The former group had, at least, the lipid characteristics of the metabolic syndrome. This observation and those noted earlier with the fibrates raise one intriguing suggestion, that lipid intervention may be beneficial mainly in those with the metabolic syndrome. On the other hand, it is also possible that the event rates are greatest in those who are at the highest risk, such as people with the metabolic syndrome, and that they will therefore be the ones most likely to show a treatment effect.

There may be situations, if neither a fibrate nor a statin alone achieves the desired goal, in which the two may need to be used together. In some, but not all countries this is an “off-label” use of the drugs. The main concern in using such combination therapy has been the possibility of myopathy. The development of myopathy appears to be related to the blood levels of the statins. The reported cases are most common with gemfibrozil. When gemfibrozil is coadministered with a variety of statins such as simvastatin, lovastatin, atorvastatin, or cerivastatin the statin blood levels achieved are higher than when these statins are administered alone or in combination with a placebo [61]. However, when these statins are coadministered with fenofibrate, the statin blood levels are not increased [61]. Initially, it was thought that the problems arose because of a drug interaction on their cytochrome mediated oxidation. However, these particular three statins are oxidized by cytochrome P450 3A4 [62] and this isoform of cytochrome P450 is not inhibited by gemifbrozil [63]. Recently, it has been recognized that glucuronidation of the fibrates and of the hydroxy acids of the statins also plays a role in their metabolism and that may be the site for the drug interaction problems. The glucuronidation of the statins involves two of the six uridinediphosphoglucuronyl transferase (UGT) isozymes, 1A1 and 1A3. These two isozymes are also among those involved in the glucuronidation of gemfibrozil, but play very minor roles in the glucuronidation of fenofibrate [64]. Hence, if gemfibrozil were to be coadministered with a statin, they may compete with each other for glucuronidation. Thus, less statin might be eliminated and its blood levels would be higher than if the statin were to be administered alone. On the other hand, because 1A1 and 1A3 play very little role in the glucuronidation of fenofibrate, if the statin were to be coadministered with fenofibrate the blood levels would not be greater than those attained if the statin were administered alone.

To date there are no objective large and long-term clinical trial data relating to the interaction of the different fibrates and the statins. A recent summary of the events of myopathy reported to the U.S. Food and Drug Administration pointed out that there were very many more such events in those receiving statins plus gemfibrozil than in those receiving statins plus fenofibrate [65]. This indicates that fibrates are not all the same and would be consistent with the biochemical data summarized above.

Thus, it appears that, with appropriate caution, combination therapy may be used where needed. Such caution includes not using combination therapy if the fibrate used is gemfibrozil, if the patient is elderly or hypothyroid or has renal failure, and it includes appropriate monitoring for muscular side effects. However, clinical trials such as the ACCORD trial [66], are still needed to determine whether the use of fibrate/statin combination therapy produces greater coronary benefit than does treatment with either alone.

8. Conclusions

It is now clear from many studies that “lipid lowering” drugs can reduce coronary risk. Most studies conducted with fibrates indicate that they have a definite, albeit not exclusive, role in this pharmacologic treatment. While the various fibrates appear to differ from each other in their potential for side effects, they appear to share in their ability to lessen the development of coronary artery disease. Their effects are partly mediated through their impact on lipoprotein abnormalities. In addition, they have non-lipid pleotropic effects which, at least theoretically, may also play a role in their cardiac benefits. The benefits of the fibrates, and possibly also of the statins appear to be greatest among those individuals who have features of the metabolic syndrome or of diabetes. With appropriate caution and recognition that this is “off-label” in many countries, fenofibrate or bezafibrate may be useful in combination with a statin to treat lipoprotein abnormalities that are not corrected with monotherapy alone.

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