Fibrates: past history or renaissance?

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Abstract
Fibrates have been in use to modify serum lipids since the 1960s. This review seeks to ascertain their present place in lipid-modifying therapy and prevention of cardiovascular disease, particularly in type 2 diabetes (T2DM).

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Effects on serum lipids, lipoprotein metabolism and inflammatory markers

Fibrates activate the nuclear receptor peroxisome proliferator-activating receptor α (PPARα) which modulates the transcription of genes involved in the synthesis of apoprotein C-III (apo-CIII) and fatty acids. This increases the activity of the enzyme lipoprotein lipase (LPL) and the removal of triglyceride-rich lipoproteins, thereby reducing circulating triglyceride (TG) concentration. Fibrates also increase apoA-I and apoA- II gene expression which, together with increased LPL activity, also result in increased high-density lipoprotein (HDL) formation. Most studies have shown that fibrates reduce plasma TG concentrations by 30-50% and increase HDL cholesterol (HDL-C) by 10-15% although there is considerable variation in the size of these effects.[1] The effects of the fibrates on LDL cholesterol (LDL-C) are variable. LDL-C may be decreased by up to 10%. However, in those individuals who have significantly elevated triglycerides an increase in LDL-C may be observed.

Proprotein convertase subtilisin kexin type 9 (PCSK9) has been shown to be a key regulator of serum LDL-C. Subjects with gain of function mutations in PCSK9 have hypercholesterolaemia whereas those with loss of function mutations have decreased levels of LDL-C. Fenofibrate has been shown to raise circulating PCSK9 protein levels. This action might provide an explanation for the relatively modest LDL-C-lowering effect of fenofibrate.[2]

In a study of 25 insulin-resistant, non-diabetic subjects with the metabolic syndrome, fenofibrate, in addition to its lipid-modifying effects, was found to markedly decrease plasma high-sensitivity C-reactive protein and interleukin-6 (IL-6) though it did not affect adiponectin or tumour necrosis factor-alpha (TNF-α) levels.[3] These actions of fenofibrate might be expected to reduce cardiovascular risk.

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TG and cardiovascular disease (CVD)

An analysis of 17 population-based prospective studies concluded that a 1 mmol/L increase in plasma TG was associated with a 32% increase in risk of incident CVD in men and an 76% increase in women.[4] After adjustment for HDL-C and other risk factors, these risks reduced to 14% in men and 37% in women but they remained statistically significant.

Data from the Copenhagen City Heart Study showed that non-fasting TG levels were strongly associated with increasing risks of myocardial infarction (MI), coronary heart disease (CHD), ischaemic stroke and all-cause mortality in men and women.[5] Data from the Emerging Risk Factors Collaboration, which included 302,430 individuals from 68 long-term studies and 12,785 coronary events, also showed that raised fasting TG and non-fasting TG were associated with increased risk of CHD.[6] This association was, however, attenuated after adjustment for HDL-C and negated after additional adjustment for non-HDL-C. This led to the concept that TG which are not found in the arterial wall do not cause CVD but rather it is caused by the cholesterol content in remnant particles or 'remnant cholesterol'.[7] Using the technique of Mendelian randomisation it was established that remnant cholesterol is associated with risk of ischaemic heart disease independently of HDL-C.[8]

The landmark 4S study,[9] and subsequent statin trials, showed conclusively that statins which lower LDL-C reduced the incidence of CVD and all-cause mortality. The main lipid abnormality in T2DM is the combination of raised TG and low HDL-C. The evidence that correcting these would reduce risk was still controversial.

Early fibrate studies

In the Helsinki Heart Study (HHS) some 4,081 men aged 40-55 years with total cholesterol 7.0 mmol/L, TG 2 mmol/L, HDL < 1.22 mmol/L and who were free of CHD at enrolment were given either the fibrate gemfibrozil or placebo and followed for five years.[10] Statins were not used. The primary endpoints were fatal and non-fatal MI and cardiac death. The results were that HDL-C increased by 11%, and TC, LDL-C and TG reduced by 10,11 and 35%, respectively. The cumulative rate of events was 27.3 per 1,000 in the gemfibrozil group and 41.4 per 1,000 in the placebo group, a 34% relative reduction ($p<0.02$). The main benefit of gemfibrozil in the HHS was found in those who had one or more features of the metabolic syndrome such as a body mass index of ⩾26 kg/m^2, plasma TG ⩾2.3 or HDL-C ⩽1.0 mmol/l. Both the increase in HDL-C and the decrease in LDL-C were predictive of the reduction in CHD events but the decrease in TG was not.

The Veterans Affairs HDL Intervention Trial, VAHIT,[11] was a double-blind placebo-controlled trial of 2,531 men with known CHD aged <74 years with HDL-C <1.0 mmol/l, LDL-C <3.6

mmol/L and TG <3.4 mmo/L. They were given gemfibrozil 1,200 mg daily and followed for 5.1 years. None were taking statins. Their HDL-C increased by 6% and their TG fell by 31%. There was no change in LDL-C. The primary endpoint (non-fatal MI or CHD death) occurred in 275 of the 1,267 (21.7%) patients in the placebo group compared with 219 of 1,264 (17.3%) in the gemfibrozil group. There was a 24% reduction in the combined outcome of death from CHD, non-fatal MI and stroke (p<0.001).

The Bezafibrate Infarction Prevention study (BIP) was a double-blind, placebo- controlled study of 3,090 subjects with CHD (2,825 men and 265 women aged <74 years) with TC 4.7-6.5 mmol/L, TG <3.4 mmol/L and HDL-C <1.16 mmol/L.[12] Bezafibrate 400 mg daily was given and follow-up was 6.2 years. There was no significant effect on the combined incidence of non-fatal MI or death from CHD. In a post hoc analysis, in those with TG >2.25 mmol/L the event rate was 19.7% in the placebo group versus 12.0% in the bezafibrate group, giving a relative reduction of 39% (p=0.02).

Three angiographic studies with fibrates, the Lopid Coronary Angiography Trial (LOCAT),[13] the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT),[14] neither of which reported inclusion of subjects with diabetes, and the Fenofibrate in the Diabetes Atherosclerosis Intervention Study (DAIS) in T2DM subjects,[15] all showed reduced progression of angiographically measured CHD in fibrate-treated subjects compared with those taking placebo.

Type 2 diabetes

In the St Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) study, 164 T2DM subjects aged 35-65 years with no history of CHD received bezafibrate 400 mg daily or placebo and were followed for 3-5 years.[16]

Cardiovascular outcomes were ultrasonic measurements of intima-media thickness (IMT) of the carotid and femoral arteries and CHD as assessed by the WHO cardiovascular questionnaire and Minnesota-coded resting ECGs.

There were no significant differences in the changes in ultrasonic measurements but there was a significantly lower 3-year cumulative incidence in CHD events on Minnesota-coded ECGs.

A post hoc analysis of the landmark 4S study included 202 subjects with T2DM and 4,292 subjects without diabetes.[17] Changes in lipids in T2DM subjects were similar to those in non-diabetic subjects, and there were similar reductions in cardiovascular outcomes and total mortality.

No large-scale clinical endpoint studies of fibrate therapy in T2DM had yet been done. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was set up to assess the effects on coronary morbidity and mortality of long-term treatment with fenofibrate to raise HDL-C and lower TG in people with T2DM.[18] The study enrolled 9,795 T2DM subjects who were not taking statins on entry. They were aged 50-75 years; 2,131 had previous CVD and 7,664 did not. Their measured TC was 3.0-6.5 mmol/L, TG 1.0-5.0 mmol/L and TC / HDL-C ratio was 4 or more. 17% of the placebo group and 8% of the fenofibrate group started statins during the trial.

The primary endpoint of combined incidence of CHD death or non-fatal MI was reduced by a non-significant 11%. Within this population, there was a 25% reduction of the primary endpoint in those without previous CVD but a non-significant 8% increase in CHD events in those with previous CHD. The secondary endpoint of total CVD events was reduced by a significant 11%, with 21% reduction in the need for coronary revascularisation. Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group. There was a non-significant 19% increase in cardiac mortality, largely due to sudden death. The higher rate of statin therapy in the placebo group may have masked a bigger treatment benefit.

Statin/fibrate combination therapy

In the ACCORD study a total of 5,518 T2 DM individuals at high risk of CVD and taking simvastatin were randomly allocated to receive either fenofibrate or placebo in addition, and followed up for 4.7 years.[19] The primary outcome was first occurrence of non-fatal MI, non-fatal stroke or death from cardiovascular causes. Secondary outcomes were the combination of the primary outcome plus various other cardiovascular outcomes. The combination of fenofibrate and simvastatin did not reduce the event rate compared with simvastatin alone for either primary or secondary outcomes. These results did not support the use of combination therapy with simvastatin and fenofibrate in high-risk T2DM subjects. However, in a subgroup analysis there was some benefit in those with high serum TG and low HDL-C which had persisted despite statin therapy.

Since there was uncertainty about the effects of fibrates on cardiovascular outcomes, a meta-analysis of their effects on major clinical outcomes was undertaken. [20] Data from 18 trials including 45,058 subjects, 2,870 major cardiovascular events, 4,552 coronary events and 3,880 deaths were analysed. Five of the trials were on subjects with T2DM (16,656 subjects). Fibrate therapy produced a 10% risk reduction for major cardiovascular events and a 13% risk reduction for coronary events. There was no benefit for stroke, all-cause or cardiovascular mortality, sudden death or non-vascular mortality. It was concluded that in high-risk individuals and in those with combined hyperlipidaemia a meaningful reduction in risk could be achieved.

Despite the plethora of trials, and although plasma TG are associated with increased cardiovascular risk, it remained uncertain whether lowering TG by fibrates would reduce the incidence of cardiovascular events in T2DM.

The Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial was set up to ascertain whether reduction of plasma TG in people with T2DM with mild to moderately elevated plasma TG and low HDL-C using pemafibrate, a new and potent fibrate, would improve cardiovascular outcomes.[21] It was a multinational double-blind randomised placebo-controlled event-driven trial. In all, 10,497 T2DM subjects (66.9% with previous CVD) were included, with fasting TG 2.2-5.6 mmol/L and HDL-C ⩽1.0 mmol/L. Ninety-six percent of all subjects were on statins. They

were randomised to receive 0.2 mg pemafibrate bd or placebo. Follow-up was 3.4 years. Primary endpoints were non-fatal MI, ischaemic stroke, hospitalisation for unstable angina, unplanned coronary revascularisation or death from cardiovascular causes. Secondary endpoints included hospitalisation for heart failure, death from any cause and new or worsening peripheral vascular disease.

Pemafibrate reduced TG by 26% and raised HDL-C by 5.1% and remnant cholesterol by 25.6%.

Compared with placebo, pemafibrate did not reduce the incidence of primary or secondary endpoints.

Thus, the PROMINENT study failed to show clinical benefit in those with raised TG and low HDL-C, the very group in which post-hoc analyses of previous studies had shown benefit.

The question remains: what is now the role of fibrate drugs? The logical expectation that these agents which lower plasma TG and raise HDL-C should improve cardiovascular outcomes in those with raised TG and low HDL-C, the typical dyslipidaemia of T2DM, has not been fulfilled.

Fibrates do not have a primary role in cardiovascular risk reduction. They may perhaps still be used in those at high cardiovascular risk on statins who still have raised TG and low HDL-C, especially those with T2 DM, and in those with statin intolerance.

Non-lipid effects of fibrates: possible new roles in diabetic microangiopathy

Albuminuria

In the FIELD study the rate of progression to albuminuria was significantly reduced in the fenofibrate-treated group.[18] 539 (11%) of placebo-treated subjects progressed from normoalbuminuria to microalbuminuria compared with 466 (10%) in the active treatment group. In addition, 2.6% more subjects allocated to fenofibrate showed regression or non-progression of micro-albuminuria. During the study 21 subjects in the placebo group needed dialysis compared with 16 in the fenofibrate group. These results confirmed those of the Diabetes Atherosclerosis Intervention Study (DAIS), [15] an angiographic study that also used fenofibrate. The effect could not be explained by changes in HbA_{1c}, concomitant medications or in blood pressure. During the study, plasma creatinine remained 10-12 µmol/L higher than in the placebo group. In the subset of patients who were studied 8 weeks after stopping study medication, plasma creatinine had returned to pre-treatment levels. The mechanism by which fenofibrate affects microalbuminuria is not clear. In animal studies fenofibrate can reduce the expansion of mesangial matrix and glomerular hypertrophy as well as collagen deposition and the expression of transforming factor-1 in renal tissue, thus reducing proteinuria and glomerular fibrosis.[22]

Diabetic retinopathy

As part of the FIELD study,[18,20] information was obtained regarding the use of laser treatment for diabetic retinopathy at each clinic visit. In a substudy of 1,012 patients standardised retinal photography was carried out to determine the cumulative incidence of diabetic retinopathy and its component lesions. A pre-specified endpoint of the FIELD study was the requirement for laser treatment for retinopathy. The requirement for first laser treatment for all retinopathy was significantly lower in the fenofibrate-treated group (3.4%) than in the placebo group (4.9%), an absolute risk reduction of 1.5%. In the ophthalmology substudy in patients with pre-existing retinopathy, significantly fewer patients on fenofibrate (3.1%) had a 2-step progression compared with patients on placebo (14.6%) (p=0.004). Treatment with fenofibrate reduced the need for laser treatment for retinopathy; this was not related to serum lipid concentrations.

In the ACCORD study,[19,24] a subgroup of 2,856 subjects randomised to receive either fenofibrate or placebo in addition to simvastatin were evaluated for the rate of progression of diabetic retinopathy. At 4 years, 6.5% in the fenofibrate group showed progression compared with 10.2% in the placebo group.

A systematic review and meta-analysis of randomised placebo-controlled trials investigating the effects of fenofibrate therapy included 19,504 subjects with 80,000 years of follow up.[25] It was concluded that fenofibrate treatment reduced the need for retinal laser treatment by more than 20%.

Studies are underway to examine the effects of fenofibrate on retinopathy progression. These include the LENS (Lowering Events in Non-proliferative retinopathy in Scotland) trial to ascertain whether fenofibrate over 3 years will slow the progression of observable retinopathy compared to placebo in more than 1,000 patients with T1DM and T2DM across Scotland. The mechanism by which fenofibrate could influence the progress of diabetic retinopathy is currently unknown.

Lower limb amputations

As part of the FIELD study,[18] information about non-traumatic amputation was routinely gathered. This was a pre-specified tertiary endpoint.[26] Amputations were classified as minor (below ankle) and major (above ankle) and were also classified on the basis of whether or not large vessel disease was present in the limb in order to distinguish those amputations related to large artery atherosclerosis from those predominantly related to microvascular disease. The risks of first amputation (45 vs 70 events, p=0.02) and minor amputation events without known large vessel disease (18 vs 32 events, p=0.027) were lower for those in the fenofibrate group than in the group on placebo but there was no difference between the groups in the risk of major amputations. This effect was independent of HbA_{1c} or serum lipids.

A possible mechanism is that experimental activation of PPARα in the epidermis stimulates differentiation and inhibits proliferation. This results in accelerated barrier formation after trauma, which may be clinically beneficial. [27]

Conclusion

Numerous prospective studies have not shown that fibrates consistently improve cardiovascular outcomes in contrast to statins. Fibrates do not have a primary role in cardiovascular disease prevention. However, fenofibrate in particular has been

Key message

- Fibrates do not now have a primary role in cardiovascular disease prevention
- Fibrates, in particular, fenofibrate may provide a safe and inexpensive means of reducing the progression of microvascular disease in T2 DM

shown to reduce progression of albuminuria, retinopathy and the risk of amputations in T2DM. This treatment might provide a simple and inexpensive way of slowing progression of microvascular disease in T2DM and possibly T1DM. Further studies are needed to verify this observation before fibrates can be incorporated into routine care.

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