

Use of fibrates in the metabolic syndrome: A review

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Abstract

The use of fibrates in the treatment of dyslipidaemia has changed significantly over recent years. Their role appeared clear at the start of this century. The Helsinki Heart Study and Veterans Affairs High-Density Cholesterol Intervention Trial suggested significant benefit, especially in patients with atherogenic dyslipidaemia. However, this clarity disintegrated following the negative outcomes reported by the Bezafibrate Infarction Prevention, Fenofibrate Intervention and Event Lowering in Diabetes and Action to Control Cardiovascular Risk in Diabetes randomised controlled trials. In this review we discuss these and other relevant trials and consider patient subgroups such as those with the metabolic syndrome and those needing treatment to prevent the microvascular complications associated with diabetes in whom fibrates may be useful. We also discuss observations from our group that may provide some explanation for the varying outcomes reported in large trials. The actions of fibrates in patients who are also on statins are interesting and appear to differ from those in patients not on statins. Understanding this is key as statins are the primary lipid lowering agents and likely to occupy that position for the foreseeable future. We also present other features of fibrate treatment we have observed in our clinical practice; changes in creatinine, liver function tests and the paradoxical high density lipoprotein reduction. Our purpose is to provide enough data for the reader to make objective decisions in their own clinical practice regarding fibrate use.

Key words: Fibrates; Metabolic syndrome; Paradoxical high density lipoprotein cholesterol decrease; High density lipoprotein cholesterol; Cardiovascular disease; Peroxisome proliferator-activated receptor; Randomised control trial; Triglycerides

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Core tip: Atherogenic dyslipidaemia is characterised by low high density lipoprotein cholesterol (HDL-C) and raised triglycerides, this pattern being associated with adverse cardiovascular risk. The fibrate class of drugs has been shown to both elevate HDL-C and reduce triglyceride concentrations. Despite several randomised control trials the data remain conflicting in regards to the use of fibrates in cardiovascular disease management. Our objective is to consolidate and summarise the literature to clarify the current evidence base.

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INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of death worldwide^[1] and in the United Kingdom in 2012, accounted for 28% of deaths^[2]. Treatment is based on reducing modifiable risk factors with lowering of serum lipid levels one of the major targets^[3]. Despite overwhelming evidence showing that statin-induced reduction of serum low density lipoprotein cholesterol (LDL-C) is associated with a marked reduction in CVD risk^[4] there appears to be a high residual risk^[5] perhaps due to other lipoprotein particles associated with cardiovascular risk^[6-8]. Therefore, additional therapies may be useful to target these atherogenic lipoprotein particles and it is in this context that fibrates could have a useful clinical role. The evidence for this claim will be reviewed.

ATHEROGENIC DYSLIPIDAEMIA, THE METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE

Statins competitively inhibit HMG CoA reductase and thereby effect a decrease in hepatic cholesterol synthesis. This results in the up-regulation of LDL receptors consequently increasing LDL uptake which in turn lowers plasma cholesterol^[9]. Following the 4S secondary prevention randomised control trial (RCT) in 1994^[10], statins have formed the cornerstone of lipid reduction strategy in CVD prevention guidelines^[3,11]. The "lower is better" hypothesis regarding cholesterol and LDL-C levels^[4] has been supported by trials including treating to new targets^[12], The Reversal of Atherosclerosis with Aggressive Lipid Lowering^[13] and Pravastatin or Atorvastatin Evaluation and Infection

Therapy^[14]. Importantly, studies such as A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound Derived Coronary Atheroma Burden (ASTEROID)^[15] and Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin vs Atorvastatin (SATURN)^[16] suggest even regression of atheromatous plaque is possible if LDL-C levels are lowered sufficiently.

However, despite optimal reduction of LDL-C with statins and, correction of other modifiable risk factors, CVD risk is not eliminated^[6]. The source of this residual risk may be due to other atherogenic lipid species such as reduced high density lipoprotein cholesterol (HDL-C) and/or raised triglycerides (TG) which are only modestly affected by statin therapy. The association between CVD and low HDL-C was first reported by Barr *et al.*^[17] nearly 60 years ago and confirmed in prospective studies such as the Framingham Heart Study^[18] and the Munster Heart Study^[19,20]. This association appears to be independent of LDL-C^[18]. Cardiovascular event rates in statin trials also reflect this; when the study cohort is stratified by HDL-C, HDL-C levels remain associated with CVD even following LDL-C reduction^[6]. Elevated TG levels have also been linked with CVD in studies such as multiple risk factor intervention trial and the Copenhagen City Heart Study^[7,8].

The lipid profile characterised by low HDL-C and high TG is termed atherogenic dyslipidaemia or the atherogenic lipoprotein phenotype (Table 1). This forms one of the characteristic features of the metabolic syndrome. This syndrome gained global recognition following the Banting Lecture delivered by Reaven^[21] in 1988 to the American Diabetes Association. He termed the combination of hypertension, dyslipidaemia and glucose intolerance as syndrome X and suggested that affected individuals were at higher risk of atherosclerosis^[21]. The International Classification of Disease code now terms syndrome X, the metabolic syndrome^[22]. Various groups have provided classification systems for the metabolic syndrome (Table 1)^[23]. These include the World Health Organisation (WHO)^[24], European Group for the Study of Insulin Resistance^[25], American College of Endocrinology^[26], National Cholesterol Education Program - Adult Treatment Panel III^[27] and, more recently, the international diabetes federation (IDF)^[28]. Although the classifying characteristics are the same in these classifications, the thresholds for inclusion differ. A consensus was reached in 2009 with the IDF, National Heart, Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis and the International Association for the Study of Obesity agreeing on threshold levels that mirrored those of the IDF^[29].

There is debate as to the clinical usefulness of making a diagnosis of metabolic syndrome. While the syndrome is associated with a doubling of CVD risk^[30], much of this increase is the sum of the individual classifying components^[31]. Bayturan *et al.*^[32] reviewed 3459 patients

Table 1 The thresholds defining the metabolic syndrome issued by individual organisations (reproduced from: Strange *et al*^[23])

Group	WHO ^[24]	EGIR ^[25]	NCEP/ATP III ^[27]	AACE ^[26]	IDF consensus ^[28]	IDF consensus (10 to < 16 yr) ^[112]
Definition	IGT, IFG, T2DM or lowered insulin sensitivity plus 2 of the following	Plasma insulin > 75 th percentile plus 2 of the following	3 of the following	IGT or IFG plus any of the following based on clinical judgement	See below	
Europoid waist circumference (cm)	W:H > 0.90 M, W:H > 0.85 F or BMI > 30 kg/m ²	≥ 94 M, ≥ 80 F	≥ 102 M, ≥ 88 F	BMI ≥ 25 kg/m ²	≥ 94 M, ≥ 80 F or BMI > 30 kg/m ² plus 2 of the following	> 90 th percentile plus 2 of the following
Triglyceride (mmol/L)	> 1.7	> 1.7	≥ 1.7	> 1.7	> 1.7	≥ 1.7
HDL (mmol/L)	< 0.91 M, < 1.01 F	< 0.91	< 1.03 M, < 1.29 F	< 1.03 M, < 1.29 F	< 1.03 M, < 1.29 F	< 1.03
BP (mmHg)	≥ 140/90	≥ 140/90 or on treatment	≥ 130/85	≥ 130/85	SBP ≥ 130 or DBP ≥ 85 or on treatment	SBP ≥ 130 and/or DBP ≥ 85
Glucose (mmol/L)	IGT, IFG or T2DM	IGT or IFG (but not diabetes)	≥ 5.6 ^[113] or diabetes	IGT or IFG (but not diabetes)	≥ 5.6	≥ 5.6 or known T2DM
Others	Microalbuminuria ACR > 30 mg/g			Other features of IR ¹		

¹Includes polycystic ovary syndrome, family history or ethnic group susceptible to type 2 diabetes, sedentary lifestyle and advancing age. ACR: Albumin creatinine ratio; BMI: Body mass index; DBP: Diastolic blood pressure; F: Female; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; IR: Insulin resistance; SBP: Systolic blood pressure; M: Male; T2DM: Type 2 diabetes mellitus; W:H: Waist to hip ratio; HDL: High density lipoprotein; WHO: World Health Organisation; NCEP: National cholesterol education program; EGIR: European group for the study of insulin resistance; IDF: International diabetes federation; AACE: American Association of Clinical Endocrinologists.

included in 7 trials using plaque progression measured by intravascular ultrasonography as outcome. Although the metabolic syndrome was significantly associated with increased plaque, the relationship lost significance when adjusted for serum TG, body mass index (BMI), HDL-C, blood pressure value/treatment of hypertension. In the multiple regression model just serum TG concentrations > 1.70 mmol/L remained significantly associated with plaque progression, this perhaps making a further case for fibrate therapy as potent triglyceride reducing agents in hypertriglyceridaemia^[32].

Although evidence indicates that the metabolic syndrome does not add prognostic risk in an individual patient, we and others^[33] argue that it has practical merit. Awareness of the metabolic syndrome makes it easier to adopt a holistic approach to care rather than focussing on individual risk factors. It may be even more useful in a research setting. The characteristics of the syndrome are associated with each other, but also individually increase CVD risk. Thus, the entire network of risk factors must be considered. Indeed, the various phenotypes of the syndrome prompt the use of specific therapies. For example, the syndrome is characterised by weight gain that may be ameliorated by nutritional advice resulting in weight loss and reduced hypertriglyceridaemia and increased HDL. Such advice and intervention should be first line treatment which is continued throughout treatment even if initial efforts are unsuccessful. Insulin resistance and hypertension may also be improved by this approach. Fibrates, by causing elevation of HDL-C and reduction of TG, may be ideally suited to treating people with this condition. The discovery and action of fibrates will now be described.

DISCOVERY AND DEVELOPMENT OF FIBRATES

Chemically fibrates are based on phenylethyl acetic acid, a derivative of dehydrocholic acid. The compounds were developed as insecticides by imperial chemical industries (ICI) Laboratories in England (the pharmaceutical division is now part of Astra Zeneca) and accidental exposure by farm workers in France in 1953 provided the first observation that they could cause reduction of lipids in serum^[34]. This finding was confirmed in rats though the mechanism of cholesterol reduction was unknown^[35]. Subsequently, work at ICI identified several oxyisobutyric acid derivatives with similar effects, an observation that led in 1962 to the development of clofibrate (ethyl- α -4-chlorophenoxyisobutyrate), the first therapeutically useful fibrate^[36].

Fenofibrate, which is a benzoyl derivative of clofibrate with higher efficacy, was produced in 1974^[37]. In the late 1970's and early 1980's gemfibrozil^[38], bezafibrate^[39] and ciprofibrate^[40] were added to the structurally diverse fibrate family^[41]. Clofibrate and fenofibrate are pro-drugs that are hydrolysed to their active metabolites clofibric acid and fenofibric acid respectively, while gemfibrozil and bezafibrate are active compounds. Development of fibrates as a class was hindered by concerns of murine hepatic carcinogenicity thought to be associated with peroxisomal proliferation^[42,43]. However, Blümcke *et al*^[44], in 1983 demonstrated that humans were not at increased risk of hepatic tumour formation. Clofibrate became non-viable as a therapeutic agent when the WHO cooperative trial, a primary prevention trial, showed a 47% increase in mortality, mainly non-cardiac,

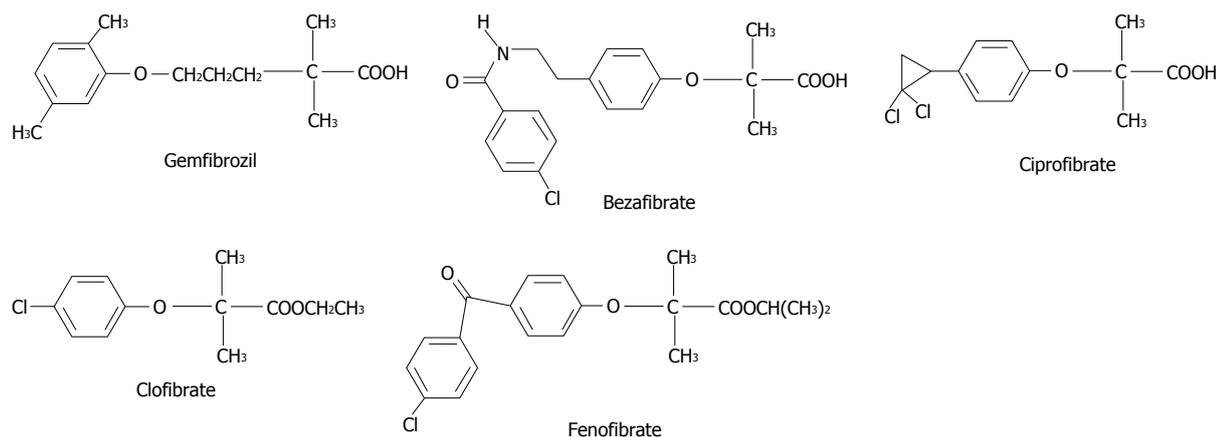


Figure 1 Chemical structures of fibrates that have been used clinically.

in the treatment arm^[45]. The other fibrates remain clinically available though their role is under review following variable outcomes in RCTs (see below).

METABOLISM OF FIBRATES

With the exception of gemfibrozil, the role of individual members of the phase 1 detoxifying cytochrome p450 supergene family in the metabolism of fibrates is unclear. Significantly, gemfibrozil inhibits CYP2C8 which is involved in the metabolism of the statin cerivastatin, thereby potentially causing an increase in the plasma concentration of the statin and an increased risk of rhabdomyolysis. Subsequently in 2001, cerivastatin was withdrawn^[46]. It is recommended that when treating patients with both a fibrate and statin that gemfibrozil be avoided^[47]. Other fibrates in clinical use have not shown a similar interaction with statins. Fibrates also cause reversible elevations in creatinine levels and, though this is not usually a contraindication for use, fibrate dose should be reduced or the drug withheld in those with renal impairment as recommended by the manufacturer^[47]. Doses of fibrates should be reduced or withheld in those with renal impairment as per manufacturer's advice. The chemical structures of fibrates in clinical use are shown in Figure 1.

FIBRATE PHARMACOLOGY

Initially, fibrates were thought to work *via* an androsterone-like effect^[36] though later it was realised that their therapeutic target was the nuclear peroxisome proliferator-activated receptor (PPAR). Nuclear receptors are one type of receptor capable of recognising external stimuli and effecting internal changes *via* mediation of expression of key genes and hence, protein synthesis. In the 1980's it was recognised that fibrates affect transcription of various proteins associated with lipid metabolism^[48,49] and it is now known that PPAR receptors are one of the cell's mechanisms for regulation of energy homeostasis.

PPAR α was first cloned in the mouse^[50], and this was followed 2 years later by work from Dreyer *et al.*^[51] who cloned 3 types of PPAR (PPAR α , PPAR γ and PPAR β/δ) in *Xenopus*. PPAR α has subsequently been identified in other species (*e.g.*, humans, amphibians, teleosts and cyclostomes)^[52]. There are structural similarities between the 3 PPAR subtypes. LDL and very LDL (VLDL) activate PPAR α in the presence of lipoprotein lipase which suggests that esterified triacylglycerols and fatty acids may be the natural ligands^[53].

The PPAR-retinoid X receptor (RXR) heterodimer exists in active and inactive states. When inactive it is bound to co-repressors such as the nuclear receptor co-repressor or the silencing mediator for retinoid and thyroid hormone receptors. When a ligand binds to either PPAR or RXR a conformational change in the heterodimer takes place and the co-repressor dissociates in order for the complex to bind and activate co-activators such as the steroid receptor co-activator 1. When the PPAR-RXR complex is activated it binds to the peroxisome proliferator response element found in the upstream region of target genes^[54] and induces transcription.

Fibrates bind and activate PPAR α and regulate gene expression, thereby influencing fatty acid and lipoprotein metabolism in liver, muscle, both skeletal and cardiac, and kidney^[55]. Synthesis of apoprotein (Apo)-A I, Apo-A II, ApoC-III, lipoprotein lipase, ATP-binding cassette transporter A1, cholesterol ester transfer protein, scavenger receptor class B-type 1 and ApoA5^[56-58], factors mainly controlling HDL and VLDL metabolism, are altered by activated PPAR α . Thus, fibrate therapy leads to increased HDL-C concentrations, a greater reduction in TG levels and a modest decrease in LDL-C concentrations^[59]. Fibrates also have a role in preventing the hypertriglyceridaemia associated with pancreatitis. Guidelines do suggest fibrates as first-line TG lowering treatment to reduce the risk of pancreatitis, with nicotinic acid, omega 3 supplements and statins also considered^[60].

The clinical efficacy of fibrates in CVD risk management will now be examined.

Table 2 Details of the large fibrate outcome trials in the total cohort are provided in this table

Trial	HHS	VA-HIT	BIP	FIELD	ACCORD
Drug	Gemfibrozil	Gemfibrozil	Bezafibrate	Fenofibrate	Fenofibrate
Dose	1200 mg/d	1200 mg/d	400 mg/d	200 mg/d	200 mg/d
Primary endpoint	MI (fatal and non-fatal), cardiac death	Combined incidence of nonfatal MI and death from CAD	MI (fatal and non-fatal), sudden death	CHD death, non-fatal MI	Non-fatal MI, non-fatal stroke, or CVD death
Mean follow-up (yr)	5	5	6	5	5
Patients (total)	Fibrate = 2051; placebo = 2030	Fibrate = 1264; placebo = 1267	Fibrate = 1548; placebo = 1542	Fibrate = 4895; placebo = 4900	Fibrate = 2765; placebo = 2753
Effect on Lipids (%) change from baseline)	LDL-C: -10; TC: -11; TG: -43; HDL-C: +10	LDL-C: 0; TC: -4; TG: -31; HDL-C: +6	LDL-C: -6.5; TC: -4.5; TG: -21; HDL-C: +18	LDL-C: -12; TC: -11; TG: -29; HDL-C: +5	LDL-C: -19; TC: -14; TG: -22; HDL-C: +8.4
Outcomes	CHD: ↓ 34%; non-fatal MI: ↓ 37%; total mortality: No change	CHD and non-fatal MI: ↓ 22%; total mortality: ↓ 11% (NS)	Fatal and nonfatal MI and sudden death: ↓ 9% (NS); total mortality: No change	CHD and non-fatal MI: ↓ 11% (NS); total mortality: ↑ 19% (NS)	Nonfatal MI nonfatal stroke CVD death: ↓ 8% (NS); total mortality: ↓ 9% (NS)

HHS: Helsinki Heart Study; VA-HIT: Veterans Affairs High-Density Cholesterol Intervention Trial; BIP: Bezafibrate Infarction Prevention; FIELD: Fenofibrate Intervention and Event Lowering in Diabetes; ACCORD: Action to Control Cardiovascular Risk in Diabetes; CVD: Cardiovascular disease; NS: Not significant; LDL-C: Low density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglycerides; HDL-C: High density lipoprotein cholesterol; MI: Myocardial infarction; CAD: Coronary artery disease; CHD: Coronary heart disease.

FIBRATE INTERVENTION TRIALS: GEMFIBROZIL

There is a theoretical basis behind the hypothesis that fibrates would be a useful adjunct in CVD risk management; epidemiological studies indicate their value in the treatment of the atherogenic dyslipidaemia associated with CVD risk. However, published data are conflicting. RCTs with gemfibrozil^[61,62] have shown overall benefit while those using fenofibrate^[63,64] and bezafibrate^[65] have been negative in terms of the primary end point. Details of these trials including the primary end points are presented in Table 2. Clearly, these data are very different to those obtained from trials using statins; all members of that drug group demonstrate CVD risk-lowering effects. The larger fibrate RCTs will be described and reasons suggested for these discrepancies.

Considering the positive gemfibrozil studies first, the helsinki heart study (HHS) lasted for 5 years and studied a large cohort of men comparing 600 mg gemfibrozil twice daily against placebo (2051 and 2030 men respectively). Inclusion criteria included adult men aged 40-55 years with a non-HDL-C > 5.2 mmol/L^[61]. The mean LDL-C of the study group was 4.88 mmol/L^[66]. The comparison of relative risk in cardiovascular outcomes demonstrated a 34% statistically significant reduction with fibrate therapy; 27.3 events in the gemfibrozil and 41.4 events in the placebo group per 1000 individuals^[61]. Prior to the widespread use of statins this was a simple comparison of fibrates against no other lipid lowering therapy. Subgroup analysis demonstrated that those with an elevated TG and reduced HDL-C level had greater relative risk reduction providing the first evidence that fibrates may be most useful in those with atherogenic dyslipidaemia^[67].

The second large, gemfibrozil study (2531 participants), the Veterans Affairs High-Density Cholesterol Intervention Trial (VA-HIT), selected patients with

established coronary disease^[62]. Completed over 10 years after the HHS this again compared gemfibrozil (1200 mg/d) vs placebo and only in men. Inclusion age was higher, selecting those aged < 74 years, and low HDL-C < 1.0 mmol/L. LDL-C was not affected by treatment, but HDL-C was elevated by 6% and TGs decreased by 31% and total cholesterol (TC) by 4% when compared to placebo. The primary outcome in this secondary prevention RCT was myocardial infarction or cardiovascular death. It is also worth noting that the LDL-C of the cohort was below 3.6 mmol/L, in an attempt to negate LDL-C related CVD risk. The median follow-up was 5.1 years and during this period the relative risk was significantly reduced by 22% in the treatment group (absolute event rate was 17.3% in the treatment vs 21.7% in the placebo control arms), and even more so in individuals with features of insulin resistance when a sub group analysis was carried out^[62].

FIBRATE INTERVENTION TRIALS: FENOFIBRATE

The clinical usefulness of Fenofibrate has been assessed in 2 large RCTs; the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD-LIPID) trials^[63,64]. The FIELD trial was the larger and selected only patients with type 2 diabetes mellitus. In total, 9795 participants (4895 given fenofibrate and 4900 placebo) aged between 50-75 years were enrolled and followed up for a mean of 5 years; 2131 participants had a previous history of CVD. Unlike VA-HIT, which used low HDL-C as an inclusion criterion^[62], TG were the primary lipid type with either the TG/HDL-C ratio (≥ 4.0) or TG (1.0-5.9 mmol/L) level defining inclusion. In addition TC had to be between 3.9-6.5 mmol/L and those with plasma creatinine > 130 μ mol/L were excluded. A non-significant difference in coronary events, the primary outcome was observed; 5.2% participants in

the fenofibrate arm and 5.9% in the control arm^[63].

Interpretation of these data are complicated by the addition of statin therapy during the follow-up to any individual not satisfying the TC and LDL-C targets due to the evidence based change in practice at the time (2002 - publication of the heart protection study)^[68]. This resulted in different rates of statin treatment; 17% in the placebo and 8% in the fenofibrate arms. This discrepancy could have masked any benefits gained from fenofibrate therapy and, effected changes in the lipid profile. In the fenofibrate treatment group reductions of TC by 11%, LDL-C by 12%, and TG by 29%, with an increase in HDL-C of 5% after 4 mo, were observed (the improvement in HDL-C dropped from 5% to 2% at the end of the 5 years, the reasons for this are unclear)^[63].

In a *post hoc* examination of the FIELD study data, 80% of the cohort met the criteria for metabolic syndrome^[27,69]. CVD events were significantly reduced in those with low HDL-C, hypertension and most of all in those with marked atherogenic dyslipidemia (27% relative risk reduction, number needed to treat to prevent one coronary event was 23)^[69].

Similar to the FIELD study, the ACCORD-LIPID also examined the effects of fenofibrate in those with type 2 diabetes mellitus and an HbA1c $\geq 7.5\%$ (58 mmol/mol). Published 5 years (2010) after the FIELD study, statin therapy based on LDL-C targets was now well established and therefore, the study was designed to examine whether additional benefit could be gained from adding fenofibrate to simvastatin therapy. With fewer patients than FIELD, 5518 patients, on open-label simvastatin with or without established CVD, were randomised to fenofibrate (2765) or placebo (2753). Age criteria was 40-79 years for those with CVD and increased to 55-79 years for those with 2 additional CVD risk factors followed up for a mean of 4.7 years. When glycated haemoglobin was ≥ 58 mmol/mol together with established CVD the age at entry was restricted to 40-79 years^[64].

The range of LDL-C was 1.55-4.65 mmol/L and HDL-C was < 1.42 mmol/L for women and < 1.29 mmol/L for men; TGs were < 8.5 mmol/L for those in the treatment arm and < 4.5 mmol/L for those on placebo. LDL-C reduction was similar in the treatment and placebo arms but HDL-C was significantly increased, albeit only to a small degree (0.09 mmol/L vs 0.06 mmol/L), and TGs significantly lower (0.47 mmol/L vs 0.18 mmol/L) in the treatment arm. First occurrence of the primary outcome, non-fatal myocardial infarction or stroke or death from cardiovascular causes, was not significantly different being 2.2% in the treatment arm compared with 2.4% in the placebo. Secondary outcomes, individual components of the primary outcomes and a composite of the primary outcomes including total mortality, revascularisation and admission to hospital for heart failure, were also not significantly different^[64].

The diabetes atherosclerosis intervention study (DAIS), non-clinical endpoint trial, coronary artery athero-

sclerosis progression on angiogram, with fenofibrate looked at 418 men and women (207 and 211 subjects in the fenofibrate group and placebo groups respectively) with type 2 diabetes (mean HbA1c: 48 mmol/mol) with at least one demonstrable coronary lesion. This small trial did show a significantly slower rate of atherosclerosis progression but was not powered towards clinical outcomes^[70]. Davidson *et al*^[71], in the Fenofibrate Reducing Residual Risk on Statin Therapy trial, also examined a non-clinical endpoint, carotid intimal thickening, in participants on atorvastatin with 342 randomised to placebo and 340 patients to fenofibrate. Inclusion criteria included a dyslipidaemia and history of vascular disease. Unlike DAIS, no significant difference was found in endpoint between the treatment groups^[71].

FIBRATE INTERVENTION TRIALS:

BEZAFIBRATE

A large bezafibrate RCT, the Bezafibrate Infarction Prevention (BIP) study, studied a secondary prevention population, previous myocardial infarction or angina, over 6.2 years. A total of 3090 men and women aged 45-74 years were randomised to bezafibrate 400 mg vs placebo with starting TC 4.7-6.5 mmol/L and HDL-C ≤ 1.17 mmol/L, TG ≤ 3.4 mmol/L, and LDL-C ≤ 4.65 mmol/L. Non-significant reductions in myocardial infarctions (both fatal and non-fatal) and sudden death occurred in the treatment arm (13.6%) vs placebo (15%). Treatment did however, increase HDL-C by 18% and reduce TG by 21%^[65].

Subgroup analysis of the BIP study data demonstrated a significant and large reduction (almost 40%) in the primary end point, reduction of fatal or non-fatal myocardial infarction or sudden death, in those with TG ≥ 2.26 mmol/L^[65]. When longer term data and subgroup analysis used in a *post hoc* analysis focused on those with 3 of the 5 risk factors classifying the metabolic syndrome (HDL-C, TG, glucose, BMI and blood pressure), the myocardial infarction and non-fatal myocardial infarction rates were significantly lower as was cardiac mortality^[72].

In contrast, a smaller double blinded placebo control trial, Bezafibrate Coronary Atherosclerosis Intervention Trial, besides showing significant increases in HDL-C and decreases in TC, TG, VLDL and fibrinogen, did show significant reduction in coronary event rate. This was mirrored by angiographic improvements assessed by mean minimum lumen diameter. This study selected only males under 45 years of age with dyslipidaemia who had survived a myocardial infarction^[73].

Meade *et al*^[74] in 2002 recruited 1568 patients with lower extremity arterial disease; 783 of these patients were randomised to bezafibrate. The primary outcome measures (coronary heart disease and stroke), as in the BIP trial, did not show a significant change. The secondary outcomes, such as non-fatal coronary events, were significantly reduced. Further, there was

possible reduction in the severity of claudication. The median value of HDL-C of the study group was relatively high (> 1.1 mmol/L), with median TC of 5.6 mmol/L and median TG between 2.1-2.2 mmol/L in placebo and treatment arms. It may be thought that patients with such values would be better treated with statins, even at the point of recruitment into the study. We do concur with this view. Interestingly significantly more participants in the placebo group dropped out due to being started on a statin than those in the treatment arm^[74]. This open label nature of the study design leading to unequal treatment with statins between the treatment and control groups, like in the FIELD study, could have influenced the outcome.

Thus, we have several large non-gemfibrozil trials that did not show benefit. Many authors have noted discrepancy between study outcomes, procedures and populations. The open label regarding statin addition (proportions of patients on statins were different between the arms) in the FIELD study and the complicated inclusion criteria seen in the ACCORD-LIPID trial make it difficult to draw conclusions with certainty. The crucial question as to whether fibrates have any role in CVD management remains unanswered except, perhaps in those with marked hypertriglyceridaemia. Sub-group analysis suggests a role for fibrates, but is complicated by lack of study power to detect multiplicity and heterogeneity of treatment effects therefore must be cautiously weighed against^[75].

META-ANALYSIS OF FIBRATE TRIALS

Subgroup analysis suggests a benefit from using fibrates in those with the metabolic syndrome^[67,69,72,76]. It will, however, need another RCT with narrower inclusion criteria to confirm this benefit. Could this benefit be confirmed by meta-analysis of the existing data? One such study of 5 large trials saw a significant reduction of 28% in cardiovascular risk in those with atherogenic dyslipidaemia, compared with 6% (non-significant) in the comparator group. The study selected only those with HDL-C < 0.91 mmol/L and TG > 2.2 mmol/L, approximately 11%-33% of the trial participants in the 5 trials^[77].

A larger meta-analysis, published following the ACCORD-LIPID study^[64], summarised 40 years of fibrate outcome data^[78]. Major cardiovascular events (myocardial infarction and cerebrovascular events), coronary events, coronary revascularisation, stroke, heart failure, cardiovascular deaths and new-onset albuminuria were the outcomes together with side effects. Studies were identified from Medline, Embase and the Cochrane Library database and filtered down to 18 trials comprising 45058 individuals. Mortality from any cause was not significantly reduced but major cardiovascular events were, the greatest effect occurring in trials with higher mean TG levels. There did not appear to be any difference between trials with regards to baseline HDL-C concentrations, type of fibrate or dose used in the

trials^[78].

Other potential factors effecting fibrate efficacy

Interestingly there was concern about excess risk in women for the primary outcome (first occurrence of non-fatal myocardial infarction, stroke or death from cardiovascular causes) raised by the ACCORD-LIPID study^[64]. Sub-group analysis, of the FIELD data however, did not confirm excess risk in women given fenofibrate, instead it suggested that the fibrate may be more efficacious in women compared to men^[79].

There is also conflict with regard to which patients gain most benefit from fibrate use: Patients treated for primary or secondary prevention, specific age groups and co morbidities (*e.g.*, diabetes). In sub-group analysis of the HHS data, the 628 participants with suspected coronary heart disease who were excluded from the original study^[61], showed no benefit from gemfibrozil, this finding at odds with that from the main study group^[80]. However this finding was compatible with the findings of the BIP trial of bezafibrate^[65]. Using ECG data in the FIELD cohort, sub-group analysis revealed that those who had had a silent myocardial infarct gained substantially more benefit from fenofibrate than those who had not with regards future cardiovascular events^[81]. In a study of individuals with peripheral vascular disease (LEADER study), sub-group analysis suggested that the younger the patient (< 65 years) the more benefit (reduced coronary events) from bezafibrate^[74]. Those with diabetes appear to have more favourable outcomes from fibrate treatment^[61-63,70]. However, other studies have not confirmed these findings^[64,71] though LDL-C levels varied between the studies.

It has also been suggested that those with a higher baseline LDL-C may benefit from HDL elevating therapies, such as fibrates, more than those with a lower starting level^[82]. In a meta-analysis of therapies (including fibrates) that reduced non-HDL-C and raised HDL-C, non-fatal myocardial infarction occurrence was reduced significantly by treatment, but, when studies that included those with low LDL-C were examined, the reduction was only significant in those with high LDL-C at baseline. Kuhnast *et al*^[82] went on to demonstrate that the reduction in non-fatal myocardial infarction appeared to be associated with reduction in LDL-C and was not associated with any elevation in HDL-C^[82]. This raises the question, if LDL-C levels are reduced sufficiently is there a requirement for additional lipid lowering therapy? However, as we have stated previously, residual risk following LDL-C reduction appears high in patients with low HDL-C. The ACCORD-LIPID trial suggests that this risk may not be reduced by fibrates^[64]. An understanding of the effect on lipids, of statin/fibrate combination therapy is essential before reaching conclusions. Our work described later will suggest some interesting patterns that need further study.

Effects of fibrates on microvascular complications

The sequelae of atherosclerotic disease include both

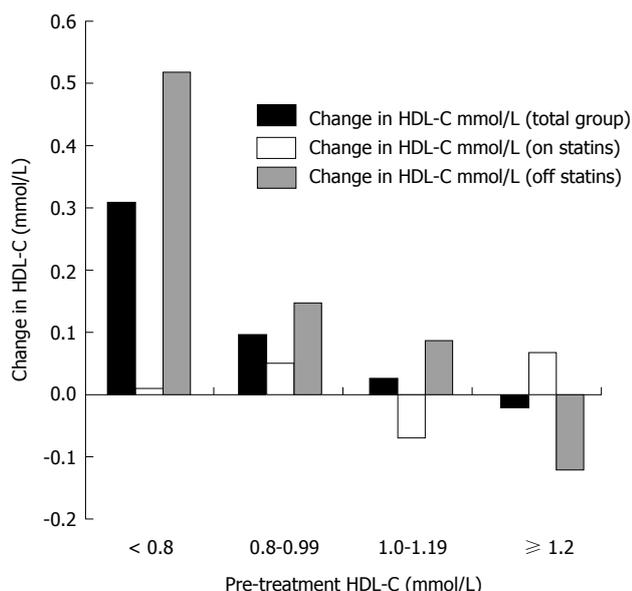


Figure 2 Change in high-density lipoprotein cholesterol following fibrate treatment stratified by pre-treatment high-density lipoprotein cholesterol concentrations in 248 patients (adapted from Ramachandran *et al*^[86]) - permission received *via* Rightslink. HDL-C: High density lipoprotein cholesterol.

macrovascular and microvascular damage. So far, we have considered the evidence for macrovascular effects though there are data to suggest that fibrates may affect microvascular outcomes. The first study that demonstrated microvascular benefit was the FIELD study which demonstrated a significant reduction in the rate of progression of albuminuria. In those on fenofibrate, the albuminuria improved^[63]. Creatinine levels were also lower in the original treatment group, when off treatment in a wash-out study 5 years later. The microvascular benefit was maintained with less deterioration and progression of albuminuria with improvement continuing in some^[63]. Microalbuminuria and macroalbuminuria development were also significantly reduced by fenofibrate in ACCORD-LIPID trial in line with the FIELD study data^[64].

Microvascular eye complications have also been studied; in the FIELD study the number of participants requiring laser application for proliferative retinopathy or macular oedema was recorded. There was a significant decrease in laser therapy for retinopathy in those treated with fenofibrate^[84]. The ACCORD-Eye study looked at secondary outcome data to study factors that might reduce the progression of diabetic retinopathy^[85]. This analysis demonstrated that fenofibrate in addition to simvastatin and intensive glycaemic control, but not intensive blood pressure control, were significantly effective^[85]. Therefore, there are data indicating microvascular benefit from fibrates though studies designed to examine microvascular complications as primary endpoints would be beneficial in helping characterise the patient groups to whom benefit would apply.

Thus far we have seen no clear and irrefutable evidence for fibrate use, particular for CVD. There is

however, a tantalising suggestion that treatment of patient subgroups such as those with atherogenic dyslipidaemia and other vascular disease complications including nephropathy and retinopathy, may benefit from treatment with fibrates. The role of fibrates in a post-statin world with a plethora of other CVD drugs is unclear. Though lacking the clarity of double-blinded RCTs there is a wealth of experience of fibrate use and such data can add weight to current theories and identify areas that should be studied in the future. We now describe some observations made by our group that may help explain the current confusion. We will also identify potential roles for fibrates and also highlight suggested work that is required in the future.

OBSERVATIONS MADE BY OUR RESEARCH GROUP

By 2006, with the publication of the BIP and FIELD studies it became clear that fibrate treatment was associated with inconsistent results. Hence, we established a programme to investigate the metabolic effects of fibrates in an out-patient setting (with about 7000 clinic visits per annum) at the Heart of England Foundation NHS Trust. In addition to changes in lipids we collected data on liver and renal function. We also have collected data on the rare paradoxical change in HDL-C that is seen following fibrates and thiazolidinedione (PPAR γ agonists) treatment.

As shown above, analysis of the large RCTs has suggested possible subgroup benefit from fibrate use in those with low pre-treatment HDL-C levels and elevated TG. Our work would support this with HDL-C increase and TG reduction associated independently with lower HDL-C level and higher TG pre-treatment levels respectively^[86,87]. A significantly greater increase was seen in HDL in this cohort when comparing participants with entry HDL-C < 1.0 mmol/L vs \geq 1.0 mmol/L, but not in those also on statins. The association between HDL-C change and baseline HDL-C (stratified) following fibrates in 257 patients is seen in Figure 2. It is clear that the association is evident only in patients not on statin treatment. These data could support a recommendation that fibrates be reserved for those with low HDL-C^[86]. Similarly HDL-C levels, after 6 mo of fenofibrate treatment, were also described in 1994 as being greatest in patients with lower pre-treatment HDL-C, although the nature of the association was not well characterised. Mean increase, in 1334 patients, of HDL-C was significant in the total cohort but larger in those with a baseline HDL-C \leq 0.91 mmol/L; 15.2% vs 37.9%^[88]. Our data suggest that those with high TG may also gain most benefit in TG reduction. This relationship between baseline TG and TG change was not affected by statin treatment. Our series also suggested that TG reduction, while associated with baseline TG levels, was independent of the baseline HDL-C^[87].

Both the above findings support the subgroup

analyses from the RCTs; maximum CVD risk reduction being observed in patients with low HDL-C and or elevated TG levels. However, our data indicates that concurrent statin treatment may lead to a more complex pattern. Our results suggest that the specific benefit from fibrates in patients also treated with statins may lie with TG reduction and not an increase in HDL-C as both changes appear to be independent^[87]. Our finding is complemented by a recent retrospective study by Scholz *et al*^[89] which highlighted the risk posed by elevated TG levels in the metabolic syndrome and pointed to TG lowering by fibrates and omega 3 fatty acids being potentially an important mechanism of cardiovascular event reduction.

The loss of the above association between baseline HDL-C and HDL-C increase (no significant change in HDL-C was observed following fibrates in patients also on statins) in the statin treatment group may be significant in explaining the outcome of the FIELD^[86]. As we have mentioned previously in the FIELD study more individuals in the placebo group were on statins^[63]. It is interesting to speculate whether the actions of fibrates are altered by statins. This could also have a bearing on the outcome seen in the ACCORD-LIPID trial^[64]. Over the past 20 years statins have been the principal lipid lowering agent for CVD risk reduction^[3,11]. It is extremely unlikely therefore, that fibrates would form the first line intervention in any future CVD guidance. Thus, it is worth further investigating the effects of fibrates on lipids when combined with a statin. The ACCORD-LIPID^[64] trial did this, but we suggest that the group of patients with the atherogenic lipoprotein pattern be further investigated regards lipid and lipoprotein changes.

A measure of HDL function/cholesterol efflux as opposed to HDL-C change in various patient subgroups including those also on statins would also be useful in view of the findings of Rohatgi *et al*^[90]. When they analysed the data from the Dallas Heart Study it was seen that the relationship between baseline HDL-C and atherosclerotic CVD was not significant [hazard ratio (HR) = 1.08, 95%CI: 0.59-1.99] when adjusted for other traditional risk factors (age, gender, race, diabetes, hypertension, smoking status, BMI, TC, TG and statin use) and HDL particle concentration after a median follow-up of 0.4 years. However, in a similar model, adjusted for the same variables and HDL-C the highest quartile of cholesterol efflux capacity was significantly associated with CVD in comparison with the lowest quartile (HR = 0.33, 95%CI: 0.19-0.55)^[91]. Thus, we suggest that another dimension has to be added when fibrates are investigated in the future, HDL function should also be looked at in addition to concentration.

Our work examining the role of fibrates in those with conditions related to the atherogenic dyslipidaemia or metabolic syndrome, such as in the treatment of non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD), is suggestive of benefit. Not only have liver function tests (LFTs) been improved by fibrate use in those with probable NAFLD/NASH but the

improvements were related to baseline LFTs; greatest benefit gained by those with highest baseline LFTs. It is possible that this reduction was due to treatment of NAFLD/NASH by the fibrate^[92] which would be in keeping with current theories on NAFLD/NASH aetiology. A two or three hit hypothesis for NAFLD/NASH was initially proposed with accumulation of hepatic fat being the "first hit"^[93,94]. Oxidative stress, mitochondrial abnormalities and hormonal imbalance (*e.g.*, adiponectin and leptin levels) impairing hepatocyte regeneration and proliferation were considered as possible candidates for the second and third hit^[95,96]. Fibrates may have a beneficial effect on fatty acid oxidation (reducing hepatic fat accumulation) and inflammation^[95,96]. Thus, improvement in LFTs associated with fibrates may be due to improving these risk factors.

Our work has also confirmed that increases in creatinine concentration is often seen following fibrate use, in line with that described in the FIELD study^[63,83], this increase appears to be reversible on discontinuing treatment. We have described the frequency distribution in estimated glomerular filtration rate (eGFR) that may be seen^[97]. Clinically this is important as a lower eGFR could lead to withdrawal of other drugs such as metformin, incretins and sodium glucose transporter 2 inhibitors in patients with type 2 diabetes. We also identified the patient group where hypercreatininaemia was more likely: Male gender, lower baseline creatinine concentrations, non-diabetics and greater decrease in TG levels^[98].

PARADOXICAL EFFECTS OF FIBRATES

Despite the evidence clearly demonstrating increases in HDL-C caused by statins there have been "paradoxical HDL-C decreases" described. This rare phenomenon also appears to occur in some treated with either a fibrate or a thiazolidinedione (PPAR γ agonists). The paradoxical HDL-C decrease was initially reported by Chandler *et al*^[99] in 1994; HDL-C was seen to decrease from 0.9 to 0.18 mmol/L following ciprofibrate treatment. A similar paradoxical response in 2 patients was noted when rosiglitazone was added to fenofibrate^[100]. In a case series of this phenomenon in 5 patients, we suggested heterogeneity in response following fibrate and rosiglitazone treatment^[101]. We also showed that pioglitazone also demonstrated this phenomenon, until then only rosiglitazone had been implicated^[102]. Fibrates and glitazones combined with fibrates have been estimated to reduce HDL-C by 0.02% and 1.39% respectively^[103]. The pathophysiology of this is unknown but theories include that this is *via* a PPAR α based mechanism as HDL-C metabolism is affected by PPAR γ activators *via* the PPAR α receptor^[104].

We investigated this rare phenomenon in 25 patients attending our metabolic clinic; the paradoxical HDL-C decrease was defined by us as a reduction in HDL-C of greater than 50%. This relatively large group of patients with this rare phenomenon enabled us to investigate the

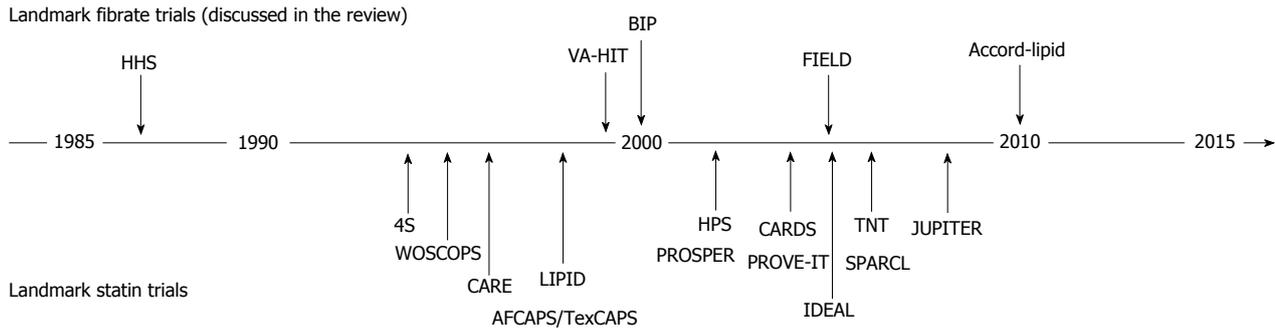


Figure 3 A time line with landmark statin and fibrate randomised control trials (arrows indicate the year of main publication). The fibrate trials are discussed in the review, while the statin trials are only mentioned when relevant. All the statin trials showed that lowering of LDL-C significantly reduced the cardiovascular event chosen as study outcome. 4S: The scandinavian simvastatin survival study; WOSCOPS: West of scotland coronary prevention study; CARE: Cholesterol and recurrent events trial; LIPID: Long-term intervention with pravastatin in ischaemic disease trial; AFCAPS/TexCAPS: Air force/Texas coronary prevention study; HPS: Heart protection study; PROSPER: The prospective study of pravastatin in the elderly at risk; CARDS: Collaborative atorvastatin diabetes study; PROVE-IT: The pravastatin or atorvastatin evaluation and infection therapy trial; IDEAL: The incremental decrease in events through aggressive lipid lowering study; TNT: Treating to new targets trial; SPARCL: The stroke prevention by aggressive reduction in cholesterol levels trial; JUPITER: Justification for the use of stains in primary prevention: An intervention trial evaluating rosuvastatin trial.

differing presentation patterns^[101,102]. These included: (1) the phenomenon observed with all fibrates; (2) effect observed with one fibrate, but not other fibrates; (3) when rosiglitazone (but not pioglitazone) was added to a fibrate; (4) when either rosiglitazone or pioglitazone were added to a fibrate; (5) effect only seen when the dose of fibrates and/or glitazones was increased; and (6) decrease in Apo-A1 - seen in all, except in one patient.

Many questions remain about this interesting group of patients. Most of these, such as whether the CVD risk of these patients is different to those not showing this phenomenon, may remain unanswered due to small numbers. Understanding the mechanisms is problematic as clinical heterogeneity is evident even within this rare group. At this stage we would recommend withdrawal of the offending fibrate, although it is worth trying another fibrate, if fibrate treatment is indicated, albeit with regular measures of HDL-C.

FIBRATES AND CVD: GUIDELINES

The National Institute for Health and Care Excellence (NICE) lipid modification guidelines (CG181) issued in the United Kingdom in 2014 do not recommend routine use of fibrates for primary or secondary prevention, in those with chronic kidney disease or type 1 diabetes^[3]. Fibrates may be considered in the context of mixed dyslipidaemia and hypertriglyceridaemia though guidance is not particularly specific, particularly for those with TG between 4.5-9.9 mmol/L. For hypertriglyceridaemia urgent specialist referral, for those with TG > 20 mmol/L in the absence of poorly controlled diabetes and alcohol excess, is recommended. Intermediate TG levels (10-20 mmol/L) should trigger a repeat for confirmation and if patients demonstrate a fasting TG > 10 mmol/L they should also be referred to a specialist. The complexity and variety of various dyslipidaemias is not catered for in this guidance and therefore, we urge clinicians to consider individualised care or specialist

referral to make a decision based on the available evidence, pathophysiology and clinical context, which is acknowledged by NICE and recommended in European guidance^[3,11]. Therefore fibrates are not currently a main feature of CVD risk management. However we urge clinicians to consider them, particularly in those who may gain the most benefit, *e.g.*, atherogenic dyslipidaemia.

FIBRATES AND CVD: A PERSONAL VIEW

We have well over 20 years of experience in secondary care clinics using all available lipid lowering agents. Our approach to CVD risk reduction is to critically evaluate current evidence and apply it in patient management together with an understanding of the physiology and pathology of atherogenesis. This may be at odds with the current trend which may have led to the NICE guidelines of 2014^[3]. At present RCTs dominate the landscape. However, RCTs are selective and real world experience should also play a significant part. We do concur that in most cases of dyslipidaemia statins are the front-line agents. Figure 3 shows a time line with landmark statin and fibrate studies highlighted. The statin trials have all showed significant reductions in the cardiovascular events chosen as outcomes in the respective studies. Each successive trial has added another layer of knowledge to the point that further large scale trials may not be of use. As we have seen previously the understanding of fibrates has travelled in the opposite direction. However, after having considered the overall evidence, our view is that fibrates neatly complement statins (and other LDL-C reducing agents). Their action is on VLDL and HDL, particles which are not significantly affected by statins. Fibrates are very complex compounds with a myriad of actions. At times paradoxical effects are seen which add to the complexity.

We have to reiterate that guidelines are for guidance and education. As practitioners of medicine we have

to combine them with knowledge and understanding of the underlying disorder(s). This is the approach we have adopted and we do use fibrates in patients with hypertriglyceridaemia, the decision reached on a case by case basis. Thus, it was reassuring that the subgroup (metabolic syndrome) outcomes and meta-analyses support our viewpoint. Regarding HDL-C we are not certain as to the role of fibrates. This is mainly as HDL metabolism/cholesterol efflux is not measured as opposed to HDL-C. Our approach will change in the future with further study.

FUTURE DEVELOPMENTS

Other existing TG medications such as omega-3 fatty acids have a less clear evidence base than fibrates in regards to CVD risk reduction. This may be due to lack of specific efficacy or that the benefit is not mediated directly by TG reduction but by other unidentified mechanisms. Further, research is required to answer these questions and also the effects in combination with fibrates.

Development of novel agents that treat hypertriglyceridaemia (including genetic hypertriglyceridaemic states) with greater efficacy may clarify the role of TG reduction in CVD risk management. For example gene therapy with lipoprotein lipase replacement may well reduce pancreatitis in those with familial lipoprotein lipase deficiency, however, long term data and larger patient numbers are required to establish their role regards CVD outcomes^[105].

Further elucidation, of the role of TG and CVD, may also occur with the introduction of non-HDL in the recent NICE guidance on lipid guidance and CVD risk assessment^[3]. This will lead to postprandial hypertriglyceridaemia being represented in CVD risk assessment^[3]. Data suggest that postprandial hypertriglyceridaemia is an independent CVD risk factor and that it is non-fasting TG, rather than fasting TG, that provide the main risk^[106]. There is evidence that fibrates are useful in ameliorating vascular damage caused by postprandial elevations in TG level by targeting TG metabolism, although the evidence is not conclusive at the current time with robust outcome data lacking^[107-109].

CONCLUSION

Clearly the evidence for fibrate use in CVD remains controversial with subgroup and *post hoc* analysis suggesting that PPAR α agonism by fibrates in those with low HDL-C and elevated TG levels, the atherogenic dyslipidaemia, could provide additional benefit. However, the blanket use of statins, suggested by guidelines, may contribute to the underlying dyslipidaemia and metabolic derangement being ignored and additional therapies not being offered. Statins should be the front-line agent in our view, except in patients with significantly elevated TG. However, there exists data that suggests that in patients with the atherogenic

dyslipidaemia, the dyslipidaemia seen in the metabolic syndrome, fibrates may have a role. This evidence is perhaps submerged by the data collected from statin RCTs. In the United States the prevalence of metabolic syndrome is about 40%^[110], therefore, small benefits in this group may have a large impact on the global CVD burden.

Besides CVD, other macrovascular and microvascular complications may be ameliorated by fibrates and therefore a holistic and individualised treatment plan is encouraged. What are required are trials looking at fibrates and statins in relevant groups designed to detect CVD benefits. Work may be aided by the development of high potency PPAR α agonists, the assumption being that greater efficacy at lipid reduction and increased cholesterol efflux may translate to greater and therefore universally detectable CVD benefit which would put the current controversy to rest^[111].

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