The role of fenofibrate in clinical practice

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Abstract
Clinical guidelines highlight the importance of dyslipidaemia management for reducing the risk of cardiovascular disease in patients with type 2 diabetes and metabolic syndrome. While statins represent the main focus of therapy, there is increasing evidence that the addition of a fibrate such as fenofibrate provides further reduction in risk. Fenofibrate also offers a number of benefits beyond lipid modification; these are mediated by peroxisome proliferator-activated receptor-alpha (PPARα) activation and appear to be independent of effects of glucose and lipid metabolism. Furthermore, as shown by the Fenofibrate Intervention for Event Lowering in Diabetes (FIELD) study, fenofibrate treatment has promising effects in preventing progression of diabetes-related microvascular complications.

PPARα is critical to lipid metabolism in the liver. Recent findings which showed that pioglitazone, a PPARγ agonist with weak PPARα activity, improved fatty liver disease in patients with non-alcoholic steatohepatitis (NASH) and metabolic syndrome or type 2 diabetes have prompted interest in whether more potent PPARα agonists, such as fenofibrate, may have a role in the management of non-alcoholic fatty liver disease (NAFLD). The combination of fenofibrate and a statin is well tolerated, with no apparent increase in the risk of myopathy, unlike gemfibrozil-statin combination therapy.

In overview, the available evidence indicates that the combination of fenofibrate with a statin is a useful approach for optimising reduction in the risk of cardiovascular disease in patients with type 2 diabetes and metabolic syndrome, as well as delaying the progression of diabetes-related microvascular complications. Data are awaited from the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) study to evaluate the outcome benefits of this approach.


doi:10.3132/dvdr.2007.053

Key words: cardiovascular disease, combination therapy, dyslipidaemia, fenofibrate, metabolic syndrome, microvascular disease, type 2 diabetes.

Introduction
Type 2 diabetes and metabolic syndrome are individually associated with an increased risk of macrovascular and microvascular disease. There is clear evidence that intensive control of glucose and blood pressure reduces microvascular outcomes but neither intervention is sufficient to reduce the risk of macrovascular atherosclerotic disease. Thus, therapeutic approaches require multifactorial intervention to address the metabolic, inflammatory and vascular abnormalities associated with these insulin-resistant states.

An atherogenic dyslipidaemic profile characterised by elevated triglycerides (TG), a low level of high-density lipoprotein cholesterol (HDL-C) and a preponderance of small, dense low-density lipoprotein (LDL) particles is typically associated with both the metabolic syndrome and type 2 diabetes. Notably, levels of LDL cholesterol (LDL-C) may be normal or only modestly elevated. In the United Kingdom Prospective Diabetes Study, abnormal lipids (elevated LDL-C and low HDL-C) were identified as the two main risk factors for coronary heart disease (CHD) in type 2 diabetes. These data emphasise the importance of dyslipidaemia management for reducing coronary risk in these insulin-resistant states.

Reduction of cardiovascular risk beyond statin therapy
Lowering LDL-C with a statin is the primary recommended therapeutic strategy for dyslipidaemia management in these patients, and is supported by an extensive evidence base.

In the Heart Protection Study, which included a cohort of 5,963 patients with type 1 or 2 diabetes (29% of the total study group), treatment with simvastatin 40 mg daily for five years was associated with a significant relative reduction by 22% (p<0.0001) in the first occurrence of major vascular events (non-fatal myocardial infarction [MI] or CHD death, stroke and revascularisation) in diabetes patients compared with placebo. Additionally, the Collaborative Atorvastatin Diabetes Study (CARDS), which included 2,838 patients with diabetes and retinopathy, albuminuria, current smoking or hypertension, showed that treatment with atorvastatin 10 mg daily was associated with a significant (p=0.001) 37% relative risk reduction in the primary end point (a composite of acute CHD events, coronary revascularisation and stroke). As a result of this finding, CARDS was terminated two years earlier than expected (after a median duration of follow-up of 3.9 years).

It should be noted, however, that other trials, notably the Antihypertensive and Lipid-Lowering to Prevent
Heart Attack Trial (ALLHAT), the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and the Atoavastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN), failed to show a significant benefit of statin therapy on outcome in diabetes patients.

A substantial proportion of patients fail to achieve recommended lipid targets with statin monotherapy. Data from the Third National Health and Nutrition Examination Survey (NHANES III 1988–1994) show that of 15.3 million individuals with the metabolic syndrome and elevated TG (>2.26 mmol/L), more than 75% have non-HDL-C (i.e. total cholesterol – HDL-C) above targets recommended by clinical guidelines.

Together, these data suggest that reduction in this excess coronary risk requires additional therapeutic intervention. Data from a recent meta-analysis reinforce this viewpoint. Despite optimal statin therapy, coronary event rates remained substantially higher in patients with diabetes than in those without diabetes, in both primary and secondary prevention settings (coronary event rates over 10 years of 17–18% and 55–58%, respectively) (figure 1). This excess risk may be in part attributable to low plasma levels of HDL-C, as well as elevated levels of TG.

The potential of fibrate therapy for reducing cardiovascular risk

Fibrates are effective in addressing all three components of the atherogenic dyslipidaemia that typically characterises type 2 diabetes and metabolic syndrome, with effects mediated by peroxisome proliferator-activated receptor-alpha (PPARα activation). Clinical data from subgroup analyses in patients with diabetes and/or features of the metabolic syndrome included in the Helsinki Heart Study, a primary prevention trial, and the Veterans Affairs HDL Intervention Trial (VA-HIT), a secondary prevention trial, show the benefit of fibrate monotherapy in these settings (table 1).

Notably, data from VA-HIT, which enrolled a total of 2,531 men with established CHD, mildly elevated LDL-C (>3.63 mmol/L) and low plasma levels of HDL-C (<1.04 mmol/L), provided clear evidence of the efficacy of fibrates in reducing coronary risk in patients with diabetes or impaired fasting glucose. Treatment with gemfibrozil (1,200 mg/day) was associated with a significant 32% relative risk reduction in the composite end point of CHD death, MI and stroke in this subgroup (p=0.004), compared with an 18% relative risk reduction in patients with normal fasting glucose. Furthermore, gemfibrozil treatment led to significantly greater reductions in the relative risk for CHD death (by 41%, p=0.02 vs. 3% in patients with normal fasting glucose) and stroke (by 40%, p=0.046, vs. 10%). In addition, treatment with bezafibrate in the Bezafibrate Infarction Prevention (BIP) study in a subgroup of patients with elevated triglycerides (>2.26 mmol/L), a feature of the metabolic syndrome, significantly reduced coronary risk by 39.5% (p=0.002), supporting the value of fibrate therapy in this patient group.

More recently, the FIELD study in 9,795 patients with type 2 diabetes and at moderate cardiovascular risk (estimated 10-year risk of about 12%), demonstrated clinical benefit with fenofibrate 200 mg daily. The FIELD study population was typical of early-stage type 2 diabetes patients, with a low prevalence of established cardiovascular disease (78% of patients had no prior cardiovascular disease), good glycaemic control (HbA1C 6.9%, which was maintained over the course of the study), and a relatively low incidence of microvascular disease (21%). Only 38% of patients would have qualified for lipid-lowering therapy in clinical practice, based on their lipid profile. While fenofibrate treatment was associated with a non-significant 11% relative reduction in...
the primary end point of non-fatal MI and CHD death (a reduction in absolute event rates from 11.7% to 10.4%, p=0.36), there was a significant 11% relative reduction in total cardiovascular events (from 29.0% to 25.8%, p=0.035) (table 1). An excess of drop-in use of lipid-modifying agents (predominantly statins) in the placebo arm may have contributed to masking the effect of fenofibrate therapy on the primary end point. Subgroup analyses also indicated a stronger effect with fenofibrate in patients without prior cardiovascular disease (showing a relative reduction in the primary end point by 25%, p=0.014, in patients without prior cardiovascular disease).24

Are the benefits of fenofibrate attributable to effects beyond lipid lowering?

In addition to lipid-modifying effects, treatment with fenofibrate offers additional benefits that may contribute to cardiovascular risk reduction. Obese insulin-resistant individuals have excess levels of plasma free fatty acids from adipose tissue. In lean individuals, insulin secretion can be impaired if plasma free fatty acids are increased to levels seen in obesity with a low-dose lipid infusion, indicative of a poor adaptive response to increased flux of free fatty acids.25,26 These findings are of relevance when considering the effects of lipid-modifying therapy on glucose metabolism. Nicotinic acid, an alternative agent suggested for addition to statin therapy for management of combined dyslipidaemia, appears to decrease insulin sensitivity by about 15–20%.26,27 Clinical studies show that whereas acute treatment with nicotinic acid inhibits hormone-sensitive lipase, prolonged administration (for at least three months) resulted in a rebound deleterious increase in free fatty acid levels.29 There was no rebound increase in free fatty acid levels in another study in individuals with metabolic syndrome who were treated with fenofibrate for three months. Fenofibrate also improved markers of systemic inflammation, independent of effects on hepatic or muscle insulin sensitivity, and beyond marked improvements in lipoprotein subclasses and particle size.29 It has been suggested that these effects may have contributed to cardiovascular risk reduction observed with fenofibrate treatment, as in the FIELD study.24

Microvascular complications

Microvascular complications associated with type 2 diabetes, specifically retinopathy, nephropathy and neuropathy, are associated with significant morbidity and they substantially impair the quality of life of patients and their caregivers.30–32 There is evidence from the FIELD study that treatment with fenofibrate has promising effects in attenuating the progression of microvascular complications of diabetes, the first time that this has been demonstrated for any lipid-modifying therapy (figure 2). In this study, fenofibrate treatment led to statistically significant relative reductions in the rate of retinal laser treatment (by 30%, p=0.0003), with treatment benefit observed within the first year. There was also significant improvement in the evolution of albuminuria (with a relative increase in regression by 15% and decrease in progression by 14%, p=0.002);24 the latter finding corroborates preliminary evidence from the Diabetes Atherosclerosis Intervention Study (DAIS).33 Furthermore, a significant rela-

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Table 1. Summary of the efficacy of fibrates in patients with diabetes or features of the metabolic syndrome

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>End point</th>
<th>Absolute event rate (%)</th>
<th>Relative risk reduction (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HHS</strong>18,19</td>
<td>4,081 men, no prior cardiovascular disease (per 1,000 person-years)</td>
<td>Non-fatal MI + CHD death</td>
<td>41.4</td>
<td>27.3</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17.5</td>
<td>3.9</td>
</tr>
<tr>
<td><strong>VA-HIT</strong>20,21</td>
<td>2,531 men with CHD</td>
<td>Non-fatal MI, CHD death + stroke</td>
<td>26.0</td>
<td>20.4</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>29.4</td>
<td>21.2</td>
</tr>
<tr>
<td><strong>BIP</strong>22,23</td>
<td>3,090 men and women with previous MI</td>
<td>Non-fatal MI + CHD death</td>
<td>15.0</td>
<td>13.6</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.4</td>
<td>14.1</td>
</tr>
<tr>
<td><strong>FIELD</strong>24</td>
<td>9,795 (100%) men and women with type 2 diabetes; 2,131 (22%) had a history of cardiovascular disease</td>
<td>- Non-fatal MI + CHD death</td>
<td>11.7</td>
<td>10.4</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Total CVD events</td>
<td>29.0</td>
<td>25.8</td>
<td>11</td>
</tr>
</tbody>
</table>

Notes:
- Unless specified otherwise; b Triglycerides ≥ 2.3 mmol/L and LDL/HDL > 5; c Baseline HDL-C 0.80 mmol/L, triglycerides 1.85 mmol/L;
- d Baseline HDL-C 0.85 mmol/L, triglycerides T.92 mmol/L.

Key: HHS = Helsinki Heart Study; VA-HIT = Veterans Affairs HDL Intervention Trial; BIP = Bezafibrate Infarction Prevention study; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes study; MI = myocardial infarction; CHD = coronary heart disease; CVD = cardiovascular disease; NS = not statistically significant; HDL-C = high-density lipoprotein cholesterol.
tive reduction in the number of non-traumatic amputations was observed with fenofibrate (by 38%, p=0.011), indicative of both microvascular and macrovascular benefit.\textsuperscript{34} These effects of fenofibrate on microvascular disease appeared to be independent of the degree of glycaemic and blood pressure control, as well as concomitant medication.\textsuperscript{24} Thus, these data suggest a potential advantage of early intervention with fenofibrate in a primary prevention setting.

Effects on the liver
Because PPAR\(\alpha\) activity is critical to liver fat metabolism, there has been increasing interest in its role in the development of non-alcoholic fatty liver disease (NAFLD). Recent evidence suggests that PPAR\(\alpha\) agonists may prevent NAFLD and non-alcoholic steatohepatitis (NASH), complications that are commonly associated with obesity (figure 3). In a recent study, pioglitazone, a PPAR\(\gamma\) agonist with weak PPAR\(\alpha\) activity, was shown to improve fatty liver disease and glucose and lipid homeostasis in patients with NASH and metabolic syndrome or type 2 diabetes.\textsuperscript{35} These data have led to the suggestion that more potent PPAR\(\alpha\) agonists such as fenofibrate may have a role in this indication. The potential clinical implications may be considerable given that NAFLD is thought to affect about one in three adults in the US (and about two in three adults who are overweight).\textsuperscript{36}

Combination therapy
In overview, the available evidence suggests that the combination of fenofibrate and a statin is a useful approach for optimising reduction in the risk of premature cardiovascular disease in patients with type 2 diabetes and metabolic syndrome, as well as delaying progression of diabetes-related microvascular complications.

Short-term studies have demonstrated superior lipid-modifying efficacy in patients with type 2 diabetes treated with the combination of atorvastatin plus fenofibrate, compared with either monotherapy.\textsuperscript{37} Outcome data are awaited from the lipid arm of the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) study in about 5,500 patients with type 2 diabetes who either have a history of cardiovascular disease or are at high risk for it, to

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**Figure 2. Fenofibrate significantly improved microvascular complications associated with type 2 diabetes**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative (%)</th>
</tr>
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<tbody>
<tr>
<td>Retinopathy needing laser therapy</td>
<td>10%</td>
</tr>
<tr>
<td>Albumin excretion rate</td>
<td>15% increase in repress 14% decrease in progression</td>
</tr>
<tr>
<td>Non-traumatic amputation</td>
<td>18%</td>
</tr>
</tbody>
</table>

Data from Keech et al.\textsuperscript{24}

**Figure 3. Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are complications associated with increased free fatty acid levels characteristic of the metabolic syndrome**

Key: FFA = free fatty acids; FPG = fasting plasma glucose; VLDL = very low-density lipoprotein

**Figure 4. Pharmacokinetic interaction with co-administration of gemfibrozil and simvastatin but not fenofibrate and simvastatin**

Data from Backman et al.\textsuperscript{43}, Bergman et al.\textsuperscript{46}
evaluate whether adding fenofibrate to simvastatin reduces cardiovascular risk beyond the reduction achieved with simvastatin alone.48

While efficacy considerations suggest that the combination of a statin and fibrate could prove useful for management of dyslipidaemia in type 2 diabetes and metabolic syndrome, there are tolerability issues. Both statin and fibrate monotherapy are associated with a risk of myopathy,23,49 and this risk appears to be enhanced when these agents are co-administered. However, there do appear to be differences in the potential for myopathy between fibrates. Recent review of the Food and Drug Administration’s Adverse Events Reporting System (AERS) database showed that the risk of myopathy was 15-fold higher with gemfibrozil plus a statin (other than cerivastatin) compared with fenofibrate plus statin.49 This is corroborated by evidence from the FIELD study. While there were very few cases of muscle toxicity reported (three patients in the fenofibrate group and one in the placebo group developed rhabdomyolysis; two patients and one patient, respectively, developed myositis), none of these cases occurred in patients on a combination of fenofibrate plus a statin.50

Differences in the potential for pharmacokinetic interaction when fibrates are co-administered with a statin can explain these findings. Gemfibrozil interacts with the same family of glucuronidation enzymes involved in statin bio-transformation.42 As a result, co-administration of gemfibrozil and a statin can cause a two- to six-fold increase in the statin area under the curve (AUC) and hence exposure to the drug (figure 4).43-45 By contrast, co-administration of fenofibrate and a range of commonly prescribed statins does not appear to influence the pharmacokinetics of the statin significantly (figure 4).46-49 These data indicate that fenofibrate would be the preferred fibrate for combination with a statin, a view confirmed by a recent consensus review of fibrate safety.50

Conclusion
Multifactorial intervention is essential in reducing the risk of both microvascular and macrovascular outcomes in type 2 diabetes. While statins remain the cornerstone of dyslipidaemia management, the addition of a fibrate such as fenofibrate may offer further reduction in cardiovascular risk. Fenofibrate may also offer a number of effects beyond lipid modification, mediated by PPARα activation. Treatment with fenofibrate appears to improve systemic inflammation, independently of effects of glucose and lipid metabolism. Data from the FIELD study also indicate promising effects with fenofibrate in preventing progression of diabetes-related microvascular complications.48 Although further investigation is warranted, these effects of fenofibrate are likely to impact substantially on disease morbidity and patient quality of life in type 2 diabetes. Additionally, data showing that pioglitazone, a weak PPARα agonist, has efficacy in NAFLD50 suggest the possibility of benefit with fenofibrate. The available evidence indicates that the combination of fenofibrate and a statin is an effective and well-tolerated option for management of dyslipidaemia in patients with type 2 diabetes and metabolic syndrome, with beneficial effects on both macrovascular and microvascular disease. Data are awaited from the ongoing ACCORD study to evaluate the outcome benefits and safety of this therapeutic approach.

Conflicts of interest statement
AZ has received honoraria for lectures from Astra-Zeneca, Sanofi-Aventis and Solvay. KC has received honoraria for lectures from Abbott, Merck & Co., Pfizer, Sanofi-Aventis and Solvay.

References
18. Frick MH, Elo O, Haapa K et al. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipid-