Do fibrates offer special benefits in treating diabetic dyslipidaemia? Lessons from FIELD

HUGH F MCINTYRE

Abstract

Although levels of total cholesterol are similar between populations with and without diabetes, there are important differences in lipid sub-fractions, with diabetic dyslipidaemia characterised by reduced levels of high-density lipoprotein (HDL) cholesterol and elevated triglycerides. In addition, small, dense, low-density lipoprotein (LDL) particles may increase atherogenicity. These differences may account for the increased vascular risk reported in diabetic populations. The benefit of HMG Co-A reductase inhibitors, primarily through LDL cholesterol reduction, has been demonstrated in populations with ischaemic heart disease. Fibrates are synthetic activators of the α subclass of the peroxisome proliferator-activated receptor (PPAR), and are reported to raise HDL cholesterol and lower triglyceride levels preferentially. The FIELD study was designed to assess whether the theoretical benefit offered by fibrates in diabetic dyslipidaemia was reflected in improved cardiovascular outcomes.

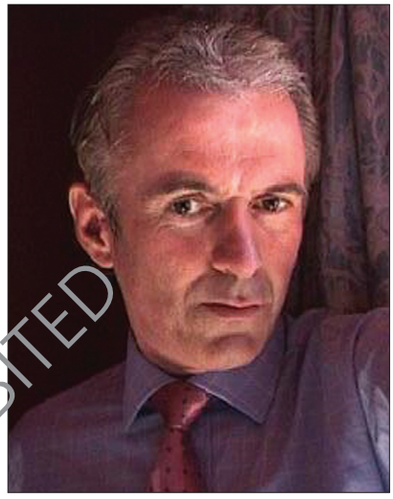
Key words: FIELD, fibrates, dyslipidaemia, diabetes, statins.

Br J Cardiol 2006;**13**:205–08

Introduction

Whilst total cholesterol levels are not substantially different between patients with type 2 diabetes and those without diabetes who are of similar age and sex, people with diabetes frequently have below average high-density lipoprotein (HDL) cholesterol levels and elevated triglyceride (TG) levels, which independently increase risk of coronary heart disease.[1,2] In addition, although low-density lipoprotein (LDL) cholesterol levels may not be raised in patients with diabetes, the LDL particles are thought to be more atherogenic, being smaller and denser. This diabetic pattern of dyslipidaemia can, in theory, be corrected by fibrates, which have been shown to raise HDL cholesterol and lower triglyceride levels. This paper addresses whether this translates into clinical benefit.

The Conquest Hospital, The Ridge, St Leonards-on-Sea, East Sussex, TN37 7RD.
Hugh McIntyre, Consultant Physician, and Honorary Consultant Cardiologist (Royal Brompton Hospital, London)
Correspondence to: Dr Hugh F McIntyre
(email: hugh.mcintyre@esht.nhs.uk)



Hugh McIntyre

Fibrates and diabetic dyslipidaemia

The fibrate hypolipidaemic drugs are synthetic activators of the α subclass of peroxisome proliferator-activated receptors (PPARs). PPARs have extensive physiological functions, including control of glucose and lipid metabolism, regulation of cholesterol levels, oxidation of fatty acid and adipogenesis. They may also modulate vascular inflammation. Potentially favourable metabolic effects of fibrates include increased cholesterol efflux from macrophages, increased levels of HDL cholesterol and decreased plasma TG and very low-density lipoprotein (VLDL) cholesterol.[3] In addition to alteration of lipid profile, fenofibrate has been shown to reduce progression of coronary artery stenosis in patients with type 2 diabetes.[4] A reduction in triglyceride-rich LDL cholesterol particles and an increase in overall LDL cholesterol particle size may underlie this potentially anti-atherogenic effect.

Lipid lowering and cardiovascular outcome in diabetic dyslipidaemia

The benefit – primarily through LDL cholesterol reduction – of HMG Co-A reductase inhibitors (statins) has been demonstrated in many studies which, until recently, concentrated on ischaemic heart disease and included small diabetic subgroups. The Heart Protection Study (HPS),[5] was the first to provide sufficient numbers of patients to demonstrate the benefit of statin therapy in a diabetic subgroup. More recently, CARDS (the Collaborative Atorvastatin Diabetes Study)[6] found a 37% reduction in major

Table 1. Plasma concentrations of lipids at baseline and study close

	Baseline concentrations		Final concentrations		Absolute and relative difference at close*
Full cohort (fenofibrate n = 4,895; placebo n = 4,900)	**Fenofibrate**	**Placebo**	**Fenofibrate**	**Placebo**	
TC (mmol/L)	5.04	5.03	4.23	4.56	-0.33 (-6.9%)
LDL-C (mmol/L)	3.07	3.07	2.42	2.60	-0.17 (-5.8%)
HDL-C (mmol/L)	1.10	1.10	1.13	1.12	+0.01 (+1.2%)
TG (mmol/L)	1.73	1.73	1.47	1.87	-0.41 (-21.9%)
Started on other lipid-lowering medication (fenofibrate n = 944; placebo n = 1,776)					
TC (mmol/L)	5.25	5.20	3.98	4.12	-0.08 (-1.6%)
LDL-C (mmol/L)	3.23	3.31	2.13	2.18	-0.02 (-0.7%)
HDL-C (mmol/L)	1.03	1.08	1.05	1.12	-0.01 (0.5%)
TG (mmol/L)	2.22	2.08	1.74	1.84	-0.24 (-10.9%)
Not started on other lipid-lowering medication (fenofibrate n = 3,951; placebo n = 3,124)					
TC (mmol/L)	4.99	4.87	4.29	4.82	-0.66 (-13.1%)
LDL-C (mmol/L)	3.03	2.93	2.50	2.84	-0.46 (-14.7%)
HDL-C (mmol/L)	1.11	1.11	1.15	1.13	+0.02 (+2.1%)
TG (mmol/L)	1.89	1.85	1.41	1.88	-0.51 (-27.3%)

* Fenofibrate difference (baseline to close) minus placebo difference (baseline to close).

Key: TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides

cardiovascular events in patients with type 2 diabetes and at least one additional risk factor.

Fibrates had been studied several years before statins were introduced. Two large primary prevention studies found a reduction in vascular events but with conflicting impact upon mortality.[7,8] Very small numbers of patients with diabetes were included. Concerns with trial design and side effects in these studies, and the subsequent introduction of statins, drew attention away from fibrates. Only two large-scale trials of fibrate therapy for secondary prevention have since been completed.[9,10] Discrepancy between results has been attributed to their differing populations. Despite theoretical promise, it remained unclear whether fibrates, alone or in combination with a statin, offered specific benefit in diabetic dyslipidaemia. There have also been concerns about the combination.[11]

The FIELD study

The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study[12] included patients with type 2 diabetes for whom, at the time of randomisation, lipid-modifying therapy was not mandated by local protocol. Following a dietary run-in phase, patients were eligible if they had a total cholesterol (TC) of between 3.0 and 6.5 mmol/L plus either a TC:HDL ratio of 4.0 or more, or plasma TG concentration of between 1.0 and 5.0 mmol/L. Thereafter, patients completed six weeks of single-blind placebo and six weeks of single-blind fenofibrate therapy. Baseline demographic characteristics were well matched between treatment groups. After five years, 954 of those allocated fenofibrate (20%) and 950 of the patients allocated placebo (19%) had discontinued study medication.

Decisions about changes in therapy for diabetes or co-morbid conditions, including lipid lowering, were left at the discretion of the patients' primary care doctor or specialist physician. The results of emerging findings from the lipid-lowering trials (e.g. the Heart Protection Study) were communicated to the treating doctors. The FIELD study specifically allowed for introduction of statins; 19% of the fenofibrate group and 36% of the placebo group commenced statin therapy during the trial period. Statin usage was greater in patients with previous cardiovascular disease (19% *vs.* 11% with no prior cardiac disease), in younger compared with older subgroups and in those with higher baseline total cholesterol and LDL cholesterol levels.

HbA_{1C} did not differ significantly between treatment and placebo groups; fasting glucose fell from 8.5 mmol/L to 7.5 mmol/L and 8.5 mmol/L to 7.9 mmol/L, respectively. Median blood pressure also fell from 140/82 mmHg to 136/77 mmHg in the fenofibrate group compared with 140/82 mmHg to 138/78 mmHg in the control group.

Cholesterol reduction

Table 1 shows plasma concentrations of lipids at baseline and study close. On completion of the study, for the total cohort, allocation to fenofibrate resulted in a 7% reduction in total cholesterol, 6% reduction in LDL cholesterol, 22% decrease in triglycerides and a 1.2% increase in HDL cholesterol compared to placebo. The table also indicates that for patients not started on other lipid-lowering therapy (fenofibrate n=3,951; placebo n=3,124), allocation to fenofibrate reduced total cholesterol by 13%, LDL cholesterol by 15% and triglycerides by 27%, while HDL cholesterol increased by 2%. Initial differences in HDL cholesterol declined over the study period even in those patients not started on other lipid-lowering therapy.

Outcomes

After a mean follow-up of five years, fenofibrate was associated

Table 2. Effect of treatment on primary and secondary outcomes

	Fenofibrate (n=4,895) n (%)	Rate*	Placebo (n=4,900) n (%)	Rate*	HR	p value
Primary outcomes						
Coronary events	256 (5%)	10.4	288 (6%)	11.7	0.89	0.16
Non-fatal MI	158 (3%)	6.4	207 (4%)	8.4	0.76	0.01
CHD mortality	110 (2%)	4.4	93 (2%)	3.7	1.19	0.22
Secondary outcomes						
Total CVD** events	612 (13%)	25.8	683 (14%)	29.0	0.89	0.035
All revascularisation	380 (10%)	15.8	471 (10%)	19.7	0.80	0.001
Coronary revascularisation	290 (7%)	11.9	364 (7%)	15.0	0.79	0.003
Total mortality	356 (7%)	14.2	323 (7%)	12.9	1.11	0.18
Total stroke	158 (4%)	6.4	175 (4%)	7.1	0.90	0.36
CVD** mortality	140 (3%)	5.6	127 (3%)	5.1	1.11	0.41

* Rate per 1,000 person-years at risk ** Cardiovascular disease

Key: HR = hazard ratio; MI = myocardial infarction; CHD = coronary heart disease; CVD = cardiovascular disease

with a non-significant 11% relative reduction in the primary outcome of coronary events, comprising coronary heart disease (CHD) death and non-fatal myocardial infarction (MI). There were significant reductions in non-fatal MI (24%), total cardiovascular disease events (11%), coronary revascularisation (21%) and all revascularisation (20%), with a non-significant reduction in total stroke. In contrast, there were non-significant increases in CHD mortality (19%), total mortality (11%), and cardiovascular disease mortality (11%) (table 2). Treatment effects appeared after approximately two years, with five-year event rates for total cardiovascular disease of 12.5% and 13.9% for the fenofibrate and placebo groups, respectively. For the primary outcome, benefit was significantly larger for patients with no previous cardiovascular disease (19% reduction, p=0.004), and in younger (< 65 years) rather than older patients (20% reduction, p=0.003).

Benefit was seen for microvascular outcomes. The rate of progression of proteinuria (from normo- to microalbuminuria or from micro- to macroalbuminuria) occurred in significantly fewer patients taking fenofibrate (466 patients [10%], compared to 539 [11%] in the placebo group). Regression of albuminuria occurred in 462 patients on fenofibrate compared to 400 on placebo (a 2.6% difference for regression or no progression, p=0.002). Of those patients taking placebo, 253 required laser treatment compared to 178 taking fenofibrate (a 1.6% difference, p=0.0003).

Additional lipid-lowering treatment

After adjustment for new lipid-lowering therapy, fenofibrate reduced the risk of CHD events by 19% (p=0.01) and of total cardiovascular disease events by 15% (p=0.004). The corresponding estimated risk reduction associated with starting statin therapy was 49% (p<0.001) and 26% (p<0.001) for CHD events and total cardiovascular disease events, respectively.

Tolerability

Fenofibrate was generally well tolerated irrespective of concomitant therapy. One patient on placebo and three allocated fenofibrate had rhabdomyolysis (all cases fully resolved). None of these patients was taking a statin therapy. The incidence of pancreatitis was low, with 40 cases in the fenofibrate group and 23 in the placebo group (p=0.031). Results showed a small increased risk of pulmonary embolism (p=0.022) and deep vein thrombosis (p=0.074) associated with fenofibrate. There were no differences in incidence of newly diagnosed cancers. There were no significant changes in diabetic parameters, blood pressure or bodyweight during the study. Abnormalities of liver function were uncommon.

The FIELD study in context

Design

The trial involved a large number of patients over a clinically relevant timeframe. The observed event rate was less than expected and left the trail underpowered, although placebo event rates for death from CHD or non-fatal MI were similar to those in the recent CARDS study.

The rise in HDL cholesterol was smaller than expected despite the persistence of changes in LDL cholesterol and triglycerides. This is not clearly explained. Early differences in HDL cholesterol were observed in all groups but diminished by two-thirds over the trial period irrespective of added lipid-lowering medication. The lipid changes across all groups suggests that this is not a 'failing' of the fibrate. Overall triglyceride levels fell by 22%, whilst LDL cholesterol reduction was also less than expected at 6%. The latter finding may be explained by added therapies.

The addition of other lipid-lowering medication was inevitable; anticipated and pre-specified analysis was performed. This was a necessary compromise to allow the primary hypothesis to be tested. However, the more frequent addition of statin therapy in higher-risk groups makes the results difficult to interpret and seems likely to have reduced the observed benefit of fenofibrate. In effect, what the study ended up comparing was

Key messages

- Diabetic populations are at increased vascular risk over their non-diabetic comparators although their total cholesterol levels may be similar
- Diabetic dyslipidaemia describes typical abnormalities of lipid subfractions, with reduced HDL cholesterol levels and increased triglyceride levels seen in diabetes. In addition, LDL particles are reported to be smaller and denser
- HMG Co-A reductase inhibitors (statins) produce vascular benefit predominantly through reducing LDL cholesterol
- Fibrate hypolipidaemic agents, by preferentially increasing HDL cholesterol level and reducing triglyceride levels, may offer added benefit in patients with diabetic dyslipidaemia

treatment with fenofibrate (alone in 3,951 and with statin in 944 patients) against placebo alone (3,124 patients) and statin alone (1,776 patients).

Outcomes

The reason for the non-significant increases in total mortality, CHD mortality and cardiovascular mortality is unclear. The last is paradoxical considering the significant reduction in total cardiovascular disease events. The significantly increased number of thrombotic events in the fenofibrate group had not previously been reported, and there were no significant differences in rates of malignancy. Speculative explanations would include the play of chance, an unforeseen characteristic of the fibrate, or possibly the greater propensity for statin usage in the placebo group, which may have preferentially reduced mortality in that group. Whilst there are similarities with earlier fibrate trials, in this study there remained a net 11% benefit (with confidence intervals consistent with an event rate in excess of 5% or a reduction of 25%). For the first time lipid lowering has been shown to improve microvascular disease significantly in diabetic patients, with progression of proteinuria reduced and 75 fewer episodes of laser treatment for retinopathy required. These findings are notable given the relatively small differences in lipid profile between groups at study completion. In addition, fenofibrate was well tolerated and appeared safe to use.

Unanswered questions

Do fibrates offer specific benefit in diabetic dyslipidaemia? The answer is a qualified yes. Fenofibrate afforded significant benefit in both macrovascular and microvascular disease despite smaller changes in lipids than expected. It is important to know whether the trend for increased mortality observed is a true effect or due to concomitant therapy. Whilst information in specific populations within the study would be helpful, it is uncertain whether the study can fully provide this; in particular, comparison of mortality rates in the 'monotherapy groups' may be hindered by confounding baseline characteristics.

Does the combination of fibrate and statin offer increased benefit? This study suggests that the combination is safe, and further information is awaited. As for clinical practice, the current emphasis placed on use of statins in the management of diabetic hyperlipidaemia remains appropriate. Where lipids remain elevated, particularly triglycerides, fenofibrate may offer additive value in selected populations. Perhaps inevitably, the necessary compromise of added medication may have prevented the primary hypothesis from being clearly tested. The field was never level. Fibrates should not be abandoned – hopefully further data from the study will guide their wisest use.

Conflict of interest

HM has no direct conflict of interest to declare. He has received fees and honoraria for travel, conference, lectures and consultancy from the pharmaceutical industry.

References

1. Fontbonne A, Eschwege E, Cambien F *et al.* Hypertriglyceridemia as a risk factor for coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes. *Diabetologia* 1989;**32**:300-04.
2. Assmann G, Schulte H. Triglycerides and atherosclerosis; results from the Prospective Cardiovascular Munster Study. *Arterioscler Rev* 1991;**22**:51-7.
3. Lewis GF, Uffelman KD, Szeto LW *et al.* Interaction between free fatty acids and insulin in the acute control of very low density lipoprotein production in humans. *J Clin Invest* 1995;**95**:158-66.
4. Kwiterovich PO. Clinical relevance of the biochemical, metabolic and genetic factors that influence low-density lipoprotein heterogeneity. *Am J Cardiol* 2002;**90**:30i-47i.
5. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7-22.
6. Colhoun HM, Betteridge DJ, Durrington PN *et al.* on behalf of the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;**364**:685-96.
7. Committee of Principal Investigators. Report on a cooperative trial in the primary prevention of ischaemic heart disease using clofibrate. *Br Heart J* 1978;**40**:1069-118.
8. Frick MH, Elo O, Haapa K *et al.* Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;**317**:1237-45.
9. Rubins HB, Robins SJ, Collins D *et al.* Gemfibrozil for secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-density lipoprotein cholesterol Intervention Trial study group. *N Engl J Med* 1999;**341**:410-18.
10. The BIP Study Group: Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. The Bezafibrate Infarction Prevention (BIP) Study. *Circulation* 2000;**102**:21-7.
11. Chang JT, Staffa JA, Parks M, Green L. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepedemiol Drug Saf* 2004;**13**:417-26.
12. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised control trial. *Lancet* 2005;**366**:1849-61.