Fibrates have a long history in cardiovascular disease. These drugs raise high-density lipoprotein (HDL)-cholesterol, reduce triglycerides and improve small dense low-density lipoprotein (LDL) so would be expected to have large effects in type 2 diabetes, where this is the typical lipid profile. The general trial results with these agents have been confusing, with varying cardiovascular benefits. The Fenofibrate Intervention and Endpoint Lowering in Diabetes (FIELD) study recruited a low-risk population with a lipid profile that would be more usually treated with a statin. FIELD showed a non-significant 11% reduction (p=0.16) in the primary end point of coronary events and a significant 11% benefit on the secondary end point of cardiovascular events and procedures (p=0.04). Most of the benefits were seen in primary prevention and non-fatal myocardial events. Fenofibrate had little effect on HDL-C; the effects of the trial are consistent with the LDL-C reducing potential of this drug.

FIELD, because of unequal statin drop-in, gives little evidence on statin-fibrate combination therapy but does reinforce the available data on the safety of fenofibrate-statin combination therapy. In addition, fenofibrate showed possible benefits on microvascular disease end points, including albuminuria and retinopathy.

On current data fenofibrate and gemfibrozil seem to be reasonable second-line agents in type 2 diabetes or secondary prevention with low HDL-C, respectively, based on outcome evidence. In combination therapy, drug-specific safety considerations will affect the exact choice of agent, especially in combination with statins, but the efficacy of combination therapy still requires validation in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.

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Key words: diabetes, fibrates, FIELD study.

Introduction
The early trials
Fibrates have a long history in cardiovascular disease. The first fibrate trials in coronary heart disease were conducted in 1971. The Edinburgh and Newcastle studies showed benefits on event reduction and led to the first large-scale end point studies.1,2 The Coronary Drug Project compared nicotinic acid (niacin), clofibrate, D-thyroxine and equine oestrogen in men. The thyroxine and oestrogen arms were discontinued due to lack of benefit. Thus, of these prototypal lipid-lowering compounds, only clofibrate and nicotinic acid continued over five years. When the results were presented, a moderate non-significant effect was seen with clofibrate while larger cardiovascular benefits were seen with nicotinic acid (table 1).2 No mortality benefit was seen with either agent but an excess of venous thrombosis was noted with clofibrate. After 15 years a mortality benefit was observed with nicotinic acid, even after many patients had discontinued the original therapy.

Fibrates went into eclipse following subsequent trials. The large-scale World Health Organization clofibrate trial showed benefit at the cost of excess non-cardiovascular mortality.3–4 Other later fibrate studies have proved confusing – the Lower Extremity Arterial Disease study7 and the Beazafibrate Infarction Prevention (BIP) study8 were negative whereas the Veterans Affairs HDL Intervention Trial (VA-HIT)9 and the Helsinki Heart Study10 were positive. None of these studies included enough patients with diabetes for results to be definitive.

Fibrates and atherosclerosis
The introduction of statins changed the focus of lipid lowering to low-density lipoprotein cholesterol (LDL-C) reduction; stunning success followed success with these agents. A meta-analysis of the major statin trials has shown that these agents reduce coronary mortality by 11% in secondary prevention and 22% in primary prevention, and that they average a 20–25% event reduction/mmol/L LDL-C reduction.11 Early data from the 200 patients with diabetes in the Scandinavian Simvastatin Survival Study (4S)12 and an analysis of patients with diabetes and low LDL-C from the Cholesterol And Recurrent Events (CARE)13 and Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID)14 studies showed that statins were likely to be effective in patients with diabetes. This was subsequently confirmed in the diabetes subgroup recruited to the Heart Protection Study15 and in the Collaborative Atorvastatin Diabetes Study (CARDs),16 where event reductions of 25–35% paralleling changes in LDL-C were observed (table 1).

Cardiovascular risk in diabetes
In the meantime fibrates had become the focus of renewed interest as the dyslipidaemia of type 2 diabetes was charac-
terised as comprising a lipid triad of low high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and the presence of small dense LDL. Fibrates were shown to increase HDL-C, reduce triglycerides and increase particle sizes of both LDL and HDL particles. A similar lipid profile is seen in patients with the metabolic syndrome, and one secondary prevention trial (VA-HIT) in patients with low HDL-C (0.85 mmol/L) and low LDL-C (2.85 mmol/L) showed that gemfibrozil reduced cardiovascular events by 22%, with similar benefits in both the patients with and without diabetes.9 This counteracted the negative results of the BIP study, which showed only non-significant benefits except in a post-hoc analysis of a high triglyceride (> 2.3 mmol/L) subgroup, in whom larger effects were seen.8 A re-analysis of earlier data from the primary prevention Helsinki Heart Study also suggested dramatic benefits, with a 78% event reduction in a subgroup with obesity, high triglycerides and low HDL-C, analogous to features later defined as the metabolic syndrome.17

Type 2 diabetes is the end result of the metabolic syndrome. Multiple studies have shown that the prevalence of diabetes increases dramatically with the number of metabolic syndrome-associated risk factors.18 The most recent International Diabetes Federation definition of the metabolic syndrome specifically includes diabetes (hyperglycaemia) as a qualifying characteristic.19 Thus, given the increased cardiovascular risk in diabetes and that associated with the metabolic syndrome and the benefits of fibrates on increasing HDL-C, reducing triglycerides, increasing lipoprotein particle size, improving transaminases and reducing

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Definitions of coronary heart disease (CHD) and cardiovascular disease (CVD) end points vary between trials with respect to the contribution of coronary or vascular interventions, and defined acute coronary syndromes. Primary end points are highlighted in bold.

Abbreviations: B = bezafibrate; C = clofibrate; CHD = coronary heart disease; CVD = cardiovascular disease; F = fenofibrate; HDL-C = high-density lipoprotein cholesterol; G = gemfibrozil; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides
progression to type 2 diabetes, there was a need for a trial of fibrates in diabetes.

The FIELD study

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was designed to investigate this hypothesis. The FIELD study recruited 9,795 patients with type 2 diabetes in Australia and Finland.20-22 The patients had low rates of smoking, good glycaemic (6.9% HbA1C) and moderate blood pressure (144/82 mmHg) control, average lipid levels and a five-year history of diabetes.22 The population was mixed, including 22% with established atherosclerosis (5% with myocardial infarcts, 12% with stable angina, 7% with strokes and 4% with a percutaneous coronary intervention). Many patients had early diabetes as 24% were controlled by diet and 60% required only diet or hypoglycaemic monotherapy and showed good glycaemic control (HbA1C = 6.9 [6.1–7.8] %). Only 19% had micro-albuminuria and 3% macroalbuminuria. During the study the overall placebo group event rate for the cohort was low and similar to CARDS at only 1% per year.22 This is lower than that seen in the West of Scotland Coronary Prevention Study in normoglycaemic men with hypercholesterolaemia (1.8%).23

Patients were randomised to fenofibrate 200 mg or placebo and co-prescription of other lipid-lowering agents (94% statins) was allowed. As might be expected given the publication of data from CARDS and Heart Protection Study (HPS), substantial drop-in to statin therapy occurred in FIELD, with 17% receiving statins in the placebo group and 8% in the fenofibrate group. This discrepancy reflects the fact that fenofibrate reduces LDL-C by 6%, in contrast to gemfibrozil which had no effect on LDL-C in VA-HIT. Overall drop-out from trial medication, at 14% during the course of the trial, was comparable to statin trials.

FIELD: primary results

The original study end point for FIELD was cardiovascular mortality but since event rates were so low this was changed to fatal and non-fatal coronary heart disease and summed changes in apolipoprotein A-I and B levels. Data from the FIELD study are shown both as presented and after correction for statin therapy (FIELDc).
p=0.07)\textsuperscript{4} and the PROspective pioglitAzone Clinical Trial in macroVascular Events (PRO ACTIVE) study (10%; \(p=0.10\)).\textsuperscript{5} As in these studies, the secondary cardiovascular disease end points in FIELD, which may be more relevant to clinical practice,\textsuperscript{6} including stroke and also interventional procedures, were positive with reductions of 11% (\(p=0.09\); NNT=100) and 11% (\(p=0.04\); NNT= 70), respectively. As guidelines focus prevention strategies on total cardiovascular disease, including interventional procedures, the secondary end points may be more clinically relevant.\textsuperscript{7,8}

FIELD: secondary and tertiary end points

A greater reduction was seen in non-fatal (24%; \(p=0.01\)) than fatal (19% increase; \(p=0.22\)) myocardial infarction (MI) in FIELD. This pattern is consistently seen in fibrate trials.\textsuperscript{9,10,13} No benefit was seen in the secondary prevention subgroup (\(p=0.85\)), compared with a 24% reduction in the pure monotherapy group (\(p=0.001\)). However, the secondary prevention population is small (1,500 patients) and thus probably underpowered for subgroup analysis. Yet the lesser reduction in benefit in secondary prevention is also a feature of statin trials: meta-analysis of most of the statin trials shows a reduction of 11% vs. 22% in mortality in secondary as opposed to primary prevention.\textsuperscript{11}

The concomitant therapy problem

The FIELD study is complicated by concomitant therapies. It is noticeable that the benefits of fenofibrate on HDL-C (3.5–5.0%) attenuate after two years and become minimal (1.2%); they also differ from the results seen in the active run-in phase (+6%). A number of factors could explain this including desensitisation to fibrate therapy. However, simpler explanations exist: considerable drop in occurred to agents that affect HDL-C. Data from the VA-HIT study suggest that fibrates may have a smaller HDL-C raising effect in diabetes.\textsuperscript{12} Statins raise HDL-C by 3–6% at lower doses and drop-in occurred in 36% ± 2% in placebo and fibrate groups, at rates predicted by the difference in LDL-C between the groups. In addition, insulin therapy, which started at 8% and rose to 30% in both groups, would raise HDL-C levels dramatically.

The changes in lipids seen in the ‘combination therapy’ group were not consistent with combination therapy as seen in the run-in phase for fenofibrate monotherapy,\textsuperscript{14} meta-analyses of fibrate-statin studies\textsuperscript{15} or in the SAFARI trial. The latter, a placebo-controlled trial of the efficacy of fenofibrate 200 mg and 20 mg simvastatin, suggested that a 31% reduction in LDL-C, a 43% reduction in triglycerides and a 19% increase in HDL-C ought to be achieved.\textsuperscript{16} A pre-specified correction was performed for the effects of statin therapy and this implied a 49% reduction in coronary heart disease (CHD) and 26% for cardiovascular disease (CVD) events due to statin therapy - greater than results seen in any previous statin trial in diabetes. Alternatively, correcting statistically for statin therapy, fenofibrate reduced events by 19% and 15%, respectively, for CHD and CVD.

In the primary prevention group, the lipid changes were consistent with the actions of fenofibrate, showing a 15% reduction in LDL-C, 27% in triglycerides and a 2% increase in HDL-C. These changes differed significantly from the secondary prevention cohort and gave a cleaner 11% reduction in events. This implies that all the benefits of fenofibrate therapy could be explained by its LDL-C reducing effects, in line with the 1% rule for reduction in coronary events and in LDL-C. The basis of the LDL-reducing effect of fenofibrate may relate to a peroxisomal proliferating activator receptor (PPAR) alpha inhibitory action on proprotein convertase subtilisin kexin 9 (PCSK-9) to increase LDL receptor expression.\textsuperscript{17} The lack of clear significant effect of fenofibrate on HDL-C means that the 1% effect on CHD events expected for every 1% in rise in HDL-C was not really tested.\textsuperscript{18}

FIELD and the metabolic syndrome

Fibrates have been suggested to have more benefits in patients with low HDL-C; this effect was seen in FIELD (univariable \(p=0.02\)) and indeed fibrates seemed to be beneficial in the low LDL-C group (<3 mmol/L) (\(p=0.03\)), implying that the results of VA-HIT might be reproduced in a FIELD subgroup. However, formal testing for heterogeneity found no difference in these subgroups. Bezafibrate has previously been shown to reduce the incidence of myocardial infarction by 27% (15.2% to 11.1%) in 1,470 patients with metabolic syndrome in the BIP study.\textsuperscript{19} However, no benefit was seen in the overall study in the large subgroup (84%) in FIELD with NCEP-ATP III defined metabolic syndrome (\(p=0.07\)), those with higher triglycerides (>1.7 mmol/L) (\(p=0.07\)), larger waist circumference (\(p=0.1\)) or among patients with raised triglyceride and low HDL-C (\(p=0.06\)).

FIELD: safety characteristics

Fenofibrate was generally safe in FIELD, though a few potentially disturbing features were noted. Reversible rises in homocysteine (4 μmol/L) and in creatinine (11 μmol/L) were also seen, as is the case with fibrates. Excess rates of events with fenofibrate were seen in both secondary prevention and in those receiving combination therapy, and concern has been raised about the increase in sudden cardiac death (70 vs. 54; \(p=0.12\)). None of these were statistically significant. However, other side-effects were significantly increased. Venous thrombotic events were increased by fenofibrate therapy (120 vs. 80; \(p=0.02\)). A similar 50% rise in venous thrombolic events had previously been seen with clofibrate in the Coronary Drug Project (CDP) trial (5.2% vs. 3.3%; \(p=0.004\)).\textsuperscript{1} Excess pancreatitis was seen in FIELD (40 vs. 23; \(p=0.03\)), and may reflect the lithogenic potential of fibrates that was noted previously in the WHO study (59 vs. 24 cholecystectomies; \(p<0.001\)).\textsuperscript{1}

Fenofibrate: unexpected benefits

Unexpected benefits of fibrate therapy were noted in FIELD. Although fenofibrate raised creatinine, this was associated with a 2 mmHg reduction in systolic blood pressure and a 2.6% reduction in grade of albuminuria (\(p=0.002\)) and also a 1.6% reduction in laser eye therapy for retinopathy. Previously, fenofibrate had been shown to reduce microalbuminuria in the Diabetes Atherosclerosis Intervention
More definitive analyses are awaited to confirm these findings, including detailed data on microalbuminuria and a formal retinopathy sub-study. They will have to be interpreted with care given the changes in glycaemic therapy in the cohort over the course of the study. It is possible that fibrate therapy, in contrast to statin therapy, may have benefits on diabetic microvascular disease.

FIELD: an overview
FIELD is a confusing and somewhat disappointing trial. It recruited a low-risk population with type 2 diabetes, who had a lipid profile more usually treated with a statin. FIELD showed benefits on a secondary end point of cardiovascular events but only a trend to reduction of coronary events. Most of the benefits were seen in primary prevention and non-fatal myocardial events. As fenofibrate had little effect on HDL-C, the effects of the trial are consistent with the potential of this drug to reduce LDL-C. FIELD gives little evidence on statin-fibrate combination therapy, given the discrepancy in efficacy, but does reinforce the available data on the safety of fenofibrate-statin combination therapy. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, in which fenofibrate is added to baseline 20–40 mg simvastatin, may answer this question.

In choosing a fibrate (in contrast to statins), the identity of the individual compound may have significant effects on both outcomes and safety profiles. This has already complicated attempts at meta-analysis of fibrate trials which did not rely on primary data. It is entirely possible that, in contrast to statins, the utility of fibrates will never be fully proven in terms of all-cause mortality: clinicians will have to rely on interpreting their benefits on cardiovascular events. On current data, fenofibrate and gemfibrozil seem to be reasonable second-line agents in type 2 diabetes and/or low HDL-C, based on outcome evidence. Drug-specific safety considerations will affect the exact choice of agent, especially in combination with statins.

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References
Clinical guide for the healthcare professional

High Density Cholesterol: The New Target

Authors: Philip Barter, Kerry-Anne Rye

Intervention trials using statins to lower LDL cholesterol (LDL-C) have consistently shown impressive reductions in major cardiovascular events. However, despite the effective lowering of LDL-C in these trials, there is an unacceptably high residual risk of having a major cardiovascular event. One reason for this relates to the presence of a low level of HDL cholesterol (HDL-C). The combined results of population studies and clinical trials support the now accepted view that raising the level of HDL-C should be considered as a therapeutic target of importance comparable to that of lowering LDL-C. The time of HDL-C as a therapeutic target has arrived.

This handbook for clinicians is written by two internationally recognised authorities in this critically important field; Philip Barter and Kerry-Anne Rye of The Heart Research Institute, Sydney, Australia. It provides a clear understanding comparable to that of lowering LDL-C. The combined results of population studies and clinical trials support the now accepted view that raising the level of HDL-C should be considered as a therapeutic target of importance comparable to that of lowering LDL-C. The time of HDL-C as a therapeutic target has arrived.

So, what are HDLs? Where are they formed? How are they regulated? What is their function? How do they protect against atherosclerosis? Why is the optimal level of HDL-C low in some people and how can it be raised? These, and many other questions, are addressed in this book.

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