

FIELD GAZETTE

Dates for Your Diary

- International Diabetes Federation Western Pacific Congress - Bangkok 22-26 October <http://www.idfwpr2005.org/>
- American Heart Association Scientific Session 2005 - Dallas 13-16 November <http://scientificsessions.americanheart.org/portal/scientificsessions/ss/>

View from the FIELD



The FIELD trial is impressively broad in its scope. Which element of the data in particular, do you believe will be most eagerly awaited by healthcare professionals?

Clearly the result that will be of greatest interest will be whether treatment with fenofibrate will reduce cardiovascular events in people with type 2 diabetes and whether it will be possible to define which subgroups will benefit most. The possibility that fenofibrate might have a positive effect on the microvascular complications of type 2 diabetes is also an outcome of interest. As well as the results of the fenofibrate treatment, we expect that Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) will provide us with a lot of information on prognostic factors for heart disease and stroke in type 2 diabetes, based on the large number of people participating.

In your opinion, what will be the most significant changes to clinical practice if the FIELD results are positive?

FIELD should lead to clearly defined guidelines for the use of fenofibrate in the management of people with type 2 diabetes. Positive results from FIELD will also create greater awareness of the importance of diabetic dyslipidaemia as a risk factor for cardiovascular disease.

How important do you think it is that FIELD includes such a wide range of 'typical' type 2 diabetes patient types?

Most patients who joined the FIELD trial were receiving community based care from their local doctors and we did not require them to have other cardiovascular risk factors. For these reasons we consider the FIELD trial patients to be more representative of people with type 2 diabetes in the community than those included in previous large studies.

What contribution do you think studies like FIELD will make to generating greater understanding of the growing burden of type 2 diabetes?

Studies like FIELD, which focus on patients with type 2 diabetes, do highlight the importance of type 2 diabetes as a risk factor for heart disease and stroke. Other data gathered during the study will highlight the 'burden of disease' associated with having type 2 diabetes.

Compounds within the fibrate class have markedly different profiles. What particular features of fenofibrate make it so appropriate for the FIELD study?

The factors that make fenofibrate appropriate for a large-scale intervention study in people with type 2 diabetes are its effectiveness in lowering triglyceride and raising HDL-cholesterol, with some reduction of LDL-cholesterol, and its ability to reduce fibrinogen. In addition, its once daily dosing and its lack of interference with statin metabolism make it the ideal fibrate for the FIELD study.

Professor James Best – Chair of Medicine and Head of Department, Department of Medicine, St. Vincent's Hospital

Introduction

Welcome to the third edition of the FIELD Gazette. In this edition we will be keeping you up to date with the landmark FIELD study which is scheduled to launch on 14 November in Dallas. We will also be providing you with more information on FIELD and how it differs from other trials. Once again we hope you enjoy this newsletter and of course welcome any feedback that you may have.

Exploring FIELD



Over the past decades, considerable trial data has been generated demonstrating the cardiovascular benefits of lowering low-density lipoprotein cholesterol (LDL-C) with statins in a wide range of patient groups, including those with diabetes.¹

Patients with type 2 diabetes, particularly those with features of the metabolic syndrome, typically have lipoprotein profiles of population average LDL levels, low high-density lipoprotein (HDL) levels and raised triglycerides (TG). Additionally, although LDL-C is quantitatively normal in diabetic subjects, the LDL-C particles are considered more atherosclerotic because they tend to be smaller and denser than in non-diabetic subjects.² Whereas statins effectively lower LDL levels, they do not effectively correct this dyslipidaemia. Fibrates improve HDL levels and lower triglycerides, however they have been used in only a few studies to date that have been designed to show benefit through cardiovascular event rate reductions.^{3,4,5} Furthermore, these studies have included very few subjects with diabetes mellitus.

This lack of clinical outcome data for fibrate treatment in diabetes is to be addressed later in the year, with the eagerly awaited release of results from the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study. This is the largest ever trial in patients with type 2 diabetes and is designed to provide the first fully randomised evidence as to whether treatment with fenofibrate confers clinical benefit on cardiovascular events in type 2 diabetes mellitus. The relative risk of CHD is increased 2-4 times⁶ in patients with type 2 diabetes and CHD is the leading cause of death.

All guidelines, however identify HDL as a major risk factor, and although statin treatment effectively reduces event rates by 30-35% over 5 years, the absolute risk for CHD in treated patients with low HDL levels still remains higher than in those without dyslipidaemia but who have been untreated with statins.¹ Fibrates such as fenofibrate,

however, are effective in increasing levels of HDL-C and decreasing plasma TG,⁷ the predominant lipid abnormalities found in patients with type 2 diabetes and in patients with the metabolic syndrome.

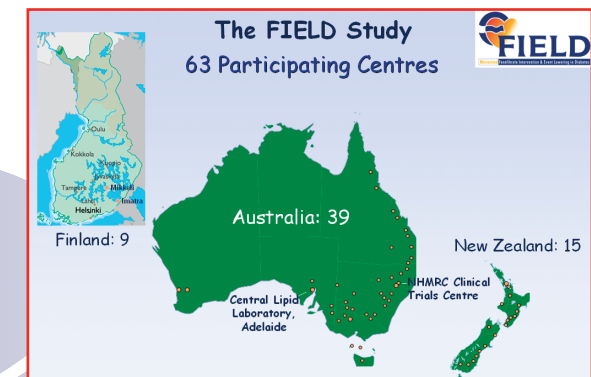


Fig. 1

The FIELD study will thus provide invaluable information and unequivocal data on the effect of fenofibrate on CHD event rates in patients with type 2 diabetes. The trial results should thus finally cement the place of this fibrate as an important therapeutic approach for reducing further the unfavourably high CHD risk associated with type 2 diabetes mellitus.

Russell Scott - Clinical Professor of Medicine and Director of Lipid and Diabetes research, Christchurch School of Medicine, New Zealand.

References

- ¹ 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. *The Lancet* 2002; 360:23-33.
- ² Feingold KR, Grunfield C, Pang M, Doerrler W, Krauss RM: LDL subclass phenotypes and triglyceride metabolism in non-insulin dependent diabetes. *Arterioscler Thromb* 1992; 12:1496-1502.
- ³ Helsinki Heart Study. Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors and incidence of coronary disease. *N Eng J Med* 1987; 347:1237-45.
- ⁴ Veterans Affairs - High Density Lipoprotein Intervention Trial. *JAMA* 2001; 285:1585-91.
- ⁵ Rubins HB et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol. *N Eng J Med* 2004; 1999; 341:410-8.
- ⁶ Krams H (ed.). The St Vincent declaration: diabetes care and research in Europe. Geneva, Switzerland: World Health Organisation, 1992.
- ⁷ Keating GM, Ormrod D. Micronized Fenofibrate. An updated review of its clinical efficacy in the management of dyslipidaemia. *Drugs* 2002; 62:1909-44.

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Your Feedback

For further information or if you wish to comment on any aspect of this newsletter: pressenquiries@webershandwick.com



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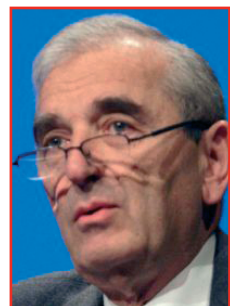
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Diabetic Dyslipidaemia



Dyslipidaemia is extremely common among patients with type 2 diabetes. Typically diabetic dyslipidaemia is characterised by elevated triglycerides (TG), reduced high-density lipoprotein cholesterol (HDL-C) levels, and normal levels of low-density lipoprotein cholesterol (LDL-C) but the LDL particles are small and dense.¹ This lipid profile is also associated with metabolic syndrome.

Current European guidelines recommend that patients with diabetes should have LDL-C levels below 2.5 mmol/l,² yet about 84% of men and 89% of women with type 2 diabetes have LDL-C greater than 2.6 mmol/l.³ Furthermore, almost 50% of people with type 2 diabetes have triglyceride levels above 1.7 mmol/l and about 25% have a TG level above 2.3 mmol/l.³ Triglyceride levels >1.7mmol/l are regarded as markers of increased cardiovascular risk.

An issue of concern with many current guidelines for diabetic dyslipidaemia is that although they recognise elevated triglycerides and lowered HDL-C as powerful markers that should be used to guide therapy, they do not set treatment goals related to these specific indicators.² Support to formalise indicators as treatment goals has been growing, and in April 2005, the International Diabetes Federation (IDF) published a global consensus statement presenting a new worldwide definition of the metabolic syndrome. For the first time globally, this lists the specific primary aims of therapy in metabolic syndrome - to lower TG (as well as lowering ApoB and non-HDL cholesterol), raise HDL-C levels, and reduce LDL-C levels.⁴

Therapeutic options

Six principal treatment options exist for diabetic dyslipidaemia: cholesterol absorption inhibitors, anion-exchange resins, nicotinic acid, fish oils, HMG CoA reductase inhibitors (statins) and fibrates. In practice statins and fibrates are the mainstays of treatment, and these are listed as the primary options for therapy in the new IDF consensus statement.⁴

However, despite the widespread use of statins, a large number of clinical coronary events still occur⁵ and many patients with diabetic

dyslipidaemia are considered to be at high risk.⁶ Stratification of coronary events according to patients' baseline HDL-C levels indicates that more events occur (irrespective of whether patients receive a statin or placebo) in those with lower concentrations of HDL-C.⁷

The future of therapy

This situation may soon change, with the release of results from the landmark FIELD trial, which is examining the effect of fenofibrate on coronary mortality and morbidity in a wide range of diabetic populations.⁸ Based on studies such as the Diabetes Atherosclerosis Intervention Study,⁹ it has been speculated that fenofibrate is a highly appropriate choice in diabetic dyslipidaemia, as it specifically targets HDL-C and TG, and a positive result from FIELD will undoubtedly add weight to the argument that current targets for therapy should include these markers. FIELD has become one of the most eagerly awaited outcomes trials of recent years, and could transform both treatment and outcomes for patients with diabetic dyslipidaemia.

Professor George Steiner – Professor of Medicine and Physiology at University of Toronto and Director of the Lipid Research Clinic at Toronto General Hospital.

References

- Syvänne M, Taskinen MR. Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. *The Lancet* 1997; 350 Suppl 1:S120-3.
- De Backer G, Ambrosioni E, Borch-Johnsen K et al. European Guidelines on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2003; 24:1601-10.
- Taskinen, MR. Diabetic Dyslipidaemia. *Atheroscler Suppl.* 2002 May; 3:47-51.
- http://www.idf.org/webdata/docs/IDF_Metasyndrome_definition.pdf accessed August 22 2005.
- Feher MD. Diabetes: preventing coronary heart disease in a high risk group. *Heart* 2004; 90: iv18-21.
- Tenebaum A, Fisman EZ. Which of the best lipid-modifying strategy in metabolic syndrome and diabetes: fibrates, statins, or both? *Cardiovascular Diabetology* 2004; 3:10.
- 4S Investigators. Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). *The Lancet* 1995; 345:1274-5.
- The FIELD study investigators. The need for a large-scale trial of fibrate therapy in diabetes: the rationale and design of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Cardiovascular Diabetology* 2004; 3:9.
- Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *The Lancet* 2001; 357:905-10.

Trials on Trial



Fibrates have been a mainstay of lipid management for many years.¹ They decrease plasma triglycerides (TG), increase high density lipoprotein -cholesterol (HDL-C),² and exert anti-atherogenic effects by regulating fibrinolysis, vascular inflammation and haemostasis.³ As a result, fibrates are seen as the treatment of choice for those patient populations who have dyslipidaemia characterised by high TG levels and low levels of HDL-C, such as those with type 2 diabetes and the metabolic syndrome.

Recently, fibrates have been attracting increasing attention for their potential in greater cardiovascular risk reduction, above and beyond those demonstrated by the statin class.

Lessons from LDL-C

The effect of statins on diabetic dyslipidaemia has been studied extensively over the years, and data from a number of pivotal studies including West of Scotland Coronary Prevention Study (WOSCOPS), Scandinavian Simvastatin Survival Study (4S) and Heart Protection Study (HPS) have shown broadly that the number of coronary events in diabetics could be reduced with statin therapy, largely due to its effect on low-density lipoprotein cholesterol (LDL-C).^{4,5,6} As a consequence, statins have become very widely used in clinical practice. However, it has become clear that simply reducing LDL-C does not eliminate coronary events, and that low levels of HDL-C predicts an increased CAD risk regardless of LDL-C level.⁷

Beyond LDL-C: the impact of fibrates

Fibrates have also been examined in diabetic sub-populations of major large-scale studies including the Helsinki Heart Study (HHS), Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), and Bezafibrate Infarction Prevention Trial (BIP), all of which confirmed the importance of raising HDL-C and lowering TG as targets in reducing risk.^{8,9,10}

HHS showed that over the five years of the study, treatment with a fibrate (gemfibrozil) increased the concentration of HDL-C by a mean of 11%, decreased serum total cholesterol by 10%, and lowered LDL-C and TG by 11% and 35% respectively (Fig.2). Increased HDL-C and decreased LDL-C were shown to be predictive of cardiac deaths.⁸ A particularly significant finding was that the main benefits of gemfibrozil treatment were seen in those who had one or more features of the metabolic syndrome.¹

Similar results were obtained from BIP and VA-HIT. In BIP the frequency of the primary end point (fatal or nonfatal myocardial infarction or sudden death) was 13.6% on bezafibrate versus 15.0% on placebo.⁹ In VA-HIT the primary end point (fatal or non-fatal MI) was reduced from 21.7% in the placebo group to 17.3% in the fibrate group.¹⁰

In all three studies it was clearly shown that those with higher baseline TG concentrations derived an especially large benefit from fibrate treatment.¹

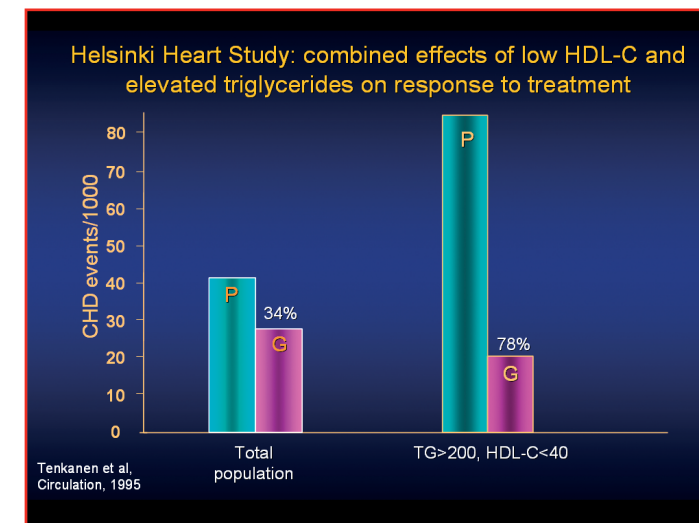


Fig. 2

Looking ahead to FIELD

As these studies have shown, fibrates effectively target HDL-C and TG, and are considered highly appropriate for patients with these types of lipid abnormalities, such as those with type 2 diabetes or the metabolic syndrome. However, although many of the larger fibrate studies have included diabetic subgroups, until the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, no large scale trials of these agents had been conducted specifically in diabetes.¹¹ FIELD will build on the positive results from the previous fibrate trials, and further clarify the role for fenofibrate in a very broad range of diabetic patient types.

The FIELD trial will generate clinical data on similar numbers of people with diabetes to statin trials and enlarge the range of lipid profiles studied and the number of events in such populations.

The FIELD trial will also help physicians determine how effective and how cost-effective lipid-modifying therapy with fenofibrate is for people with type 2 diabetes.

Professor Juan Carlos Pedro-Botet Montoya – The University Hospital of Barcelona

References

- Barter P. Reconsidering the value of fibrates: lessons from the trials. *Br J Diabetes Vasc Dis* 2003; 3:162-7.
- Keating GM, Ormrod D. Micronized Fenofibrate. An updated review of its clinical efficacy in the management of dyslipidaemia. *Drugs* 2002; 62:1909-1944.
- Fruchart J-C, Staels B, Duriez P. The role of fibric acids in atherosclerosis. *Curr Atheroscler Rep* 2001; 3:83-92.
- West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation* 1998; 97:1440-5.
- Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). *The Lancet* 1995; 345:1274-5.
- Collins R, Armitage J, Parish S et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *The Lancet* 2003; 361:2005-16.
- Després J-P. Increasing High-Density Lipoprotein Cholesterol: An Update on Fenofibrate. *Am J Cardio* 2001; 88: 30N-36N.
- Manninen V, Elo O, Frick H et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-51.
- 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.
- Robins SJ, Collins D, Wittes JT et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA* 2001; 285:1585-1591.
- The FIELD Investigators. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, a randomized, placebo-controlled trial: baseline characteristics and short-term effects of fenofibrate. *Cardiovascular Diabetology* 2005; 4:13.