FIELD Study Analysis

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)[1] study was a double-blind, randomized, controlled trial conducted in 63 centres Australia, New Zealand and Finland.

Entry criteria included:

- type 2 diabetes mellitus (World Health Organization criteria)
- age 50 to 75 years old
- TC 3.0 – 6.5 mmol/L
- plus TC/HDL rati ≥ 4 or TG 1.0 to 5.0 mmol/L
- no clear indication for, or treatment with, lipid-modifying therapy

Exclusion criteria:

- renal impairment CR >130 µmol/L
- chronic liver disease or symptomatic gall bladder disease
- cardiovascular event within 3 months before recruitment

Endpoints Included in the FIELD Study

- Primary endpoint: nonfatal MI or death from CHD
- Secondary outcomes:
  - total cardiovascular disease events (major cardiovascular disease events plus coronary and carotid revascularisation)
  - coronary heart disease death
  - total cardiovascular disease deaths
  - haemorrhagic and nonhaemorrhagic stroke
  - coronary and peripheral revascularization procedures
  - cause-specific non-coronary heart disease mortality
  - total mortality
- Tertiary outcomes
  - vascular and neuropathic amputations
  - nonfatal cancers
  - progression of renal disease
  - laser treatment for diabetic retinopathy
  - hospital admission for angina pectoris
  - number and duration of all hospital admissions

FIELD was designed to assess the effects of long-term fenofibrate treatment on coronary morbidity and mortality in patients with type 2 diabetes. FIELD was intended to be the definitive, large, clinical, endpoint trial evaluating fibrate therapy in the diabetes population.

Patients in the FIELD study were randomized to receive fenofibrate (Lipidil) 200 mg or placebo and followed every 4 to 6 months. Any changes in therapy for diabetes or comorbid conditions, including lipid-lowering therapy, were made by the patients' primary care doctor or specialist physician. Newsletters were used to communicate findings from major lipid trials (such as the landmark Heart Protection Study[2]) to patients and their physicians.

As presented, FIELD was a "negative trial." Clinical outcomes showed that fenofibrate was associated with an 11% non-significant reduction in primary outcome of first MI or CHD death. There was a significant 24% reduction in nonfatal MI and a non-significant increase in fatal CHD. Secondary outcomes showed that total cardiovascular disease events (major cardiovascular disease events plus coronary and carotid revascularization) were significantly

reduced by 11%. There were significant reductions in coronary and peripheral revascularization procedures. Cause-specific non-coronary heart disease mortality, total mortality, coronary heart disease death, total cardiovascular disease deaths and haemorrhagic and nonhaemorrhagic stroke were not significantly affected. Of the tertiary outcomes. there was a reduction in the progression of renal disease (placebo 11% vs. fenofibrate 10%) and regression (placebo 8% vs. fenofibrate 9%). As well, laser treatment for diabetic retinopathy was reduced by 1.6% ARR.

In the prespecified subgroup analysis, treatment significantly benefits patients with no prior cardiovascular disease with significant 19% RRR (relative risk reduction), 2% ARR (absolute risk reduction). Patients under 65 years of age showed significant 20% RRR. Patients with low HDL (defined as <1.03 mmol/L for males, and <1.29 mmol/L for females) gained significant benefit as did patients with TC <4.5 and LDL <3.0. Patients with high TG, HTN, dyslipidemia and the metabolic syndrome demonstrated borderline benefit. Cox regression analysis showed fenofibrate reduced CHD events by 19% (p=0.01) and total cardiovascular events by 15% (p=0.004).

The study showed that fenofibrate was generally well tolerated. Serious adverse effects were low (<1%) and included pancreatitis (placebo 0.5% vs. fenofibrate 0.8%). There was small increased risk of pulmonary embolism and deep vein thrombosis.

FIELD: A negative trial?

The results of FIELD were disappointing and less than compelling. Was this a negative trial? For CHD death and nonfatal MI in the total population, the answer is yes. However, for nonfatal MI (24% RRR), total cardiovascular disease events (11% RRR), primary prevention (19% RRR; 2% ARR; NNT 50), patients over 65 years of age (20% RRR), patients with low HDL and patients with TC <4.5 or LDL <3.0, there was significant benefit.

The problems with FIELD relate to study design, enrollment criteria, background risk and lipid-lowering contamination. The study used rigorous endpoints. Broader primary endpoints, such as those used in the Collaborative Atorvastatin Diabetes Study (CARDS)[3], could have yielded a positive outcome. The entry criteria allowed enrollment of a low-risk population. Low placebo event rates (1.2% nonfatal MI or death from CHD, and 0.7% stroke) were less than half of those rated in HPS[2] or VA-HIT[4]. Event rates were even lower in those enrolled without prior cardiovascular disease. As we have seen in other trials (e.g., Prevention of Events with Angiotensin-Converting Enzyme Inhibition [PEACE][5] and Ischemia Management with Accupril post-bypass Graft via Inhibition of angiotensin coNverting Enzyme [IMAGINE][6]), it is difficult to yield positive results in patients with very low placebo event rates.

Furthermore, the low triglyceride entry criteria in FIELD yielded an enrollment population with a picture of dyslipidemia that was not typical of the “diabetic dyslipidemic”. Benefits of fibrate treatment may have been obscured by doubling of statin use in the placebo group and greater discontinuation of fibrate in patients on fenofibrate therapy. FIELD was not really a placebo-controlled study as opposed to a study of fibrate therapy versus usual care.

In spite of the high utilization of statins, FIELD investigators were still able to measure benefit from fibrate therapy in primary prevention in the population with diabetes, that was identical to HPS patients without coronary artery disorder. The microvascular benefits of fibrates on renal progression and diabetic retinopathy demand further investigation.

Will the FIELD study affect the Canadian Diabetes Association guidelines for the management of dyslipidemia in people with diabetes?[7]

CDA Dyslipidemia Management Guidelines:

A) **In cases where LDL-C is the predominant abnormality, a statin should be prescribed *(Grade A, level 1)***
B) **In cases where TGs are 1.5- 4.5 mmol/L, HDL-C is < 1.0 mmol/L, and LDL-C is at target, either a fibrate or statin can be prescribed *(Grade A, Level 1)***
C) **In cases of marked hyper TG (>4.5), a fibrate should be prescribed *(Grade D, consensus)***
D) **When single drug treatment fails to optimize the lipid profile, a second drug from another class can be added *(Grade B, Level 2)***

CDA Guidelines Can J Diab Dec 2003; 27 (Suppl 2; S58-S65)

Based on the evidence from FIELD, I would expect the CDA Dyslipidemia Management Guidelines to remain unchanged. Statins remain first line for primary LDL abnormalities. Fibrates remain an option for moderate hypertriglyceridemia when LDL is at target and fibrates remain first line therapy in cases of marked hypertriglyceridemia.

Even in studies of aggressive lipid lowering, such as Treating to New Targets (TNT)[8] or Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)[9], there are still significant event rates in the population that is treated aggressively. Lowering these event rates further will require either more aggressive LDL reduction with combination agents (such as cholesterol absorption inhibitors), or dual lipid modulation with agents that raise HDL, shift LDL atherogenicity or provide pleiotropic anti-inflammatory benefit beyond their lipid-lowering capabilities. Combination lipid-lowering therapy will be essential in the future in order to have an impact cardiovascular event rates, particularly in the population of patients with diabetes; fibrate therapy would seem suited to the task. More definitive answers may emerge in late 2007, from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study[10].

1) Keech A et al for the FIELD study investigators. *Lancet* 2005;366(9500):1849-61.

2) *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.

3) Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA Neil HAW, Livingstone SJ Thomason MJ, Mackness MI, Charlton-Menys V and Fuller JH 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. *The Lancet* 2004; ***364:****685-696*.

4) Robins S. *Current Opinions in Lipidology* 2003;14:575-583.

5) The PEACE Trial Investigators. *N Engl J Med* 2004;351:2058-2068.

6) IMAGINE Trial presented at European Society of Cardiology September 2005. http://www.imaginetrial.org/

7) CDA Guidelines *Can J Diab* 2003; 27 (Suppl 2; S58-S65)

8) LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart J-C, Gotto AM, Greten H, . Kastelein JJP, Shepherd J and Wenger NK, for the Treating to New Targets (TNT) Investigators. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. *N Engl J Med* 2005; 352:1425-1435.

9) Pedersen TR, Faergeman O, Kastelein JPP, Olsson AG, Tikkanen MJ, Holme I, Lytken Larsen M, Bendiksen FS, Lindahl C, Szarek M and Tsai J for the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group.High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction The IDEAL Study: A Randomized Controlled Trial. *JAMA*, November 16, 2005—Vol 294, No. 19 2437-2445.

10)ACCORD http://www.accordtrial.org/public/index.cfm#