

After FIELD: should fibrates be used to prevent cardiovascular disease in diabetes?



The typical dyslipidaemia in patients with diabetes is raised serum triglycerides, reduced HDL cholesterol, and a near-normal LDL cholesterol.¹ Fibrate drugs reduce triglycerides effectively and increase HDL cholesterol. However, major clinical guidelines recommend statins rather than fibrates as first-line lipid-lowering therapy in patients with diabetes, because of a lack of definitive data that fibrates prevent cardiovascular disease (CVD) in diabetes.²⁻⁴

In today's *Lancet*, the FIELD investigators report on the efficacy and safety of 200 mg fenofibrate in preventing CVD in patients with type 2 diabetes.⁵ Overall there was a non-significant 11% reduction in the primary endpoint of coronary heart disease events, and a significant 11% reduction in total CVD events, mainly because of reductions in non-fatal myocardial infarction and coronary revascularisations. There was a non-significant 19% increase in cardiac mortality. As expected after recent statin trials,^{6,7} many FIELD participants (on average 17% of the placebo group, 8% of the fenofibrate group) started statin therapy during the trial. The investigators had predicted this level of statin use and had expected it to reduce the observed effect on coronary heart disease. However, modelling the effect of actual statin use on the trial, they conclude that at best the true underlying effect of fenofibrate on coronary heart disease is a reduction of about 15-19% rather than the predicted 27%. FIELD is a well-conducted study but does not give clear answers on the efficacy and safety of fenofibrate, partly because the results contain some important subgroup findings.

Participants both with (n=2131) and without (n=7664) a history of CVD were included in FIELD. The non-significant 11% reduction in CHD events comprised a 25% reduction in those without previous CVD and a non-significant 8% increase in those with previous CVD. Total CVD events fell by 19% in those without a history of CVD, but there was no effect in those with previous CVD. The FIELD authors note that rates of additional statin use do not account for the difference in treatment effect by CVD status. These differences in treatment effects between CVD groups in FIELD are at borderline significance (p=0.05 for coronary heart disease, p=0.03

for CVD), although the global test for interaction across all subgroups tested is non-significant. Although the secondary prevention subgroup was just a fifth of the total sample, it contains a lot of information, as the event rates were much higher (about 2.5 fold for CVD). It is unclear whether differences in effect between these groups can be dismissed as being due to chance. Although the data are consistent with a modest treatment effect in those with established CVD, they do not provide convincing evidence that such a benefit exists. Conversely, although the data are consistent with a treatment effect in the primary prevention group much greater than the overall 11% reduction, this has not been shown conclusively either. Using gemfibrozil, another fibrate, a difference in effect by previous CVD status was found in an underpowered analysis in the Helsinki Heart Study.⁸ By contrast, the VA-HIT investigators found a large reduction in CVD events in individuals with a history of CVD, including those with diabetes, who were using gemfibrozil.⁹

FIELD is an important study because, although it does not involve a direct comparison, it allows us to ask whether fibrates could reasonably replace statins as first choice for primary or secondary prevention of CVD. The answer is that the evidence of benefit from FIELD is not sufficient to warrant a change in the current guidelines. Together, statin trials in patients with diabetes provide more convincing evidence of a substantial benefit than FIELD does.^{6,7,10,11} In a systematic review of the effects of statins on CVD outcomes, myocardial infarction or coronary death fell by 23% for every 1 mmol/L reduction in LDL cholesterol, with no difference in effect between diabetic and non-diabetic patients.¹² Stroke fell by 17% for every 1 mmol/L reduction in LDL cholesterol.

At present, most guidelines state that fibrate therapy could be considered for reducing triglycerides or increasing HDL in those at or very near target levels for LDL cholesterol, either as combination or sole therapy. Target lipid levels vary between guidelines (table) but are around 2.6 mmol/L for LDL cholesterol, with an optional target of 1.8 mmol/L in the USA in those with previous CVD.²⁻⁴ A triglyceride concentration of less than 1.7 mmol/L and an HDL cholesterol above 1.15 mmol/L

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	LDL cholesterol	HDL cholesterol	Triglycerides
European Joint Societies ²	2.5	Not a goal	Not a goal
American Diabetes Association ³	2.6†	1.15 men, 1.4 women	1.7
Adult Treatment Panel III ⁴	2.6†	1.15 men, 1.4 women	1.7

*Some guidelines give non-HDL targets alternative. †Goal of 1.8 mmol/L is considered a therapeutic option in those with established CVD.

Table: Guideline target level for LDL cholesterol, HDL cholesterol, and triglyceride (mmol/L) for patients with diabetes*

in men and 1.4 mmol/L in women are considered goals of therapy in the USA. In Europe, whilst triglycerides and HDL cholesterol levels outside these values are considered suboptimal, they are not formalised goals of therapy. Do the FIELD results provide any evidence to support the use of fibrates in those already at target LDL cholesterol levels? As in the CARDS trial of 10 mg atorvastatin versus placebo in diabetic patients,⁶ about a quarter of patients in FIELD were already at the target of 2.6 mmol/L for LDL cholesterol at entry. Baseline levels of LDL cholesterol did not significantly alter the effect in either study, so the best estimate of efficacy in those below target at entry is the overall treatment effect. Because the treatment effect was substantially greater in CARDS than in FIELD, the FIELD data do not support choosing fenofibrate over additional statin therapy for primary prevention of CVD in patients with LDL cholesterol at target level.

Data on efficacy and safety of using a statin and a fibrate in combination will have to await the ACCORD trial due to report in 2010.¹³ Meanwhile, the FIELD investigators conclude that their study provides reassurance that combination therapy with statins and fenofibrate is safe. Given this conclusion, it would have been useful for the safety data for the subgroup of patients exposed to combination therapy to have been presented, and to know whether the combination therapy is limited to any particular statins. It should also be noted that, although non-fatal myocardial infarction was reduced by 24%, cardiac mortality showed a non-significant increase of 19%, largely reflecting an increase in sudden cardiac deaths in the fenofibrate group against a similar rate of fatal myocardial infarction. Should this increase in sudden deaths be a concern? Although event numbers were small, there was also an increase in deep venous thrombi and pulmonary emboli in the fenofibrate group. These differences could partly reflect lower event numbers in the placebo arm

attributable to a higher drop-in rate with a statin, and for sudden deaths are within the bounds of what might be expected given the varying manifestations of coronary disease. Nonetheless, ongoing safety monitoring is warranted. Meanwhile the beneficial effects of fenofibrate on albumin-creatinine ratio, albuminuria, and laser incidence are reassuring. Reporting by the FIELD investigators of the subset of about 1000 patients who had serial retinal photographs taken will provide more definitive evidence of any effect of fenofibrate on retinopathy rates.

In summary the results from this well-executed trial do not warrant a recommendation for increased fenofibrate use in patients with diabetes, nor do they provide convincing evidence of the benefit of fenofibrate therapy in patients already at target serum LDL cholesterol.

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Total lymphocyte counts and ART in resource-limited settings

The widespread implementation of programmes for antiretroviral therapy (ART) has dramatically reduced AIDS-related morbidity and mortality in the developed world, which has created a moral imperative to bring ART programmes to areas in the developing world with a high prevalence of HIV. The international community has increasingly rallied behind this notion and ART programmes are expanding, albeit slowly, in every corner of the world. As the prices of antiretroviral drugs continue to fall,¹ the cost and availability of laboratory monitoring of patients has become an important limiting factor in the expansion of ART programmes in the countries most affected by the pandemic. Clinical assessment alone has proven inadequate to assess the need for ART² and CD4 counting is too expensive to be made widely available.

Total lymphocyte counts (TLCs), made as part of complete blood counts, are simple, relatively inexpensive, and are more likely to be widely available than CD4 counts. TLCs are an attractive alternative indicator of need for ART for many programmes with limited financial, material, and human resources. Most of the countries with explosive HIV epidemics—mainly in sub-Saharan Africa—have limited excess human-resource capacity and underdeveloped health-care infrastructures, limiting the development of new ART programmes of the scale needed.³ Therefore, simpler and less costly clinical tools to determine who should receive priority for ART in settings where sophisticated laboratories are not available is a pressing research need.^{1,4}

TLCs are highly positively correlated with CD4 counts in Indian⁵ and African people with HIV⁶ not receiving ART. CD4 cell counts are the main tool in industrialised countries to assess an individual's need for ART. Many studies have examined the value of TLCs in predicting CD4 cell counts below 200 per μL ^{5,7,8} but have found significant limitations in terms of sensitivity, specificity, and positive predictive value. Algorithms which add haemoglobin or packed cell volume into decision trees along with TLCs seem to improve clinical utility in patients

in South Africa,⁹ the USA,¹⁰ and Brazil.¹¹ However, it is unclear whether these algorithms will function as well in populations in which malaria is more common, and whether the correlation between TLCs and CD4 counts is the most clinically valid comparison to make.

In today's issue of *The Lancet*, David Dunn and colleagues¹² report a meta-analysis, which assesses the utility of TLCs in determining when to start ART in HIV-infected children. These investigators determined clinical thresholds for baseline TLCs that are correlated directly with risk of later mortality. This approach will probably result in better predictive value of TLCs, as it avoids the imperfect correlation with an intermediate predictor of mortality. Using this approach in adults, Bedell and colleagues¹³ previously showed that a baseline TLC of 1400 per μL is associated with a similar relative hazard for mortality as a baseline CD4 count of 200 per μL in HIV-infected adults receiving ART. This is the same methodological approach which established cell counts of 200 per μL as an important clinical threshold in adults starting ART.¹⁴

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