Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial

*The FIELD study investigators**

Summary

Background Patients with type 2 diabetes mellitus are at increased risk of cardiovascular disease, partly owing to dyslipidaemia, which can be amenable to fibrate therapy. We designed the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study to assess the effect of fenofibrate on cardiovascular disease events in these patients.

Methods We did a multinational, randomised controlled trial with 9795 participants aged 50–75 years, with type 2 diabetes mellitus, and not taking statin therapy at study entry. After a placebo and a fenofibrate run-in phase, we randomly assigned patients (2131 with previous cardiovascular disease and 7664 without) with a total-cholesterol concentration of 3·0–6·5 mmol/L and a total-cholesterol/HDL-cholesterol ratio of 4·0 or more or plasma triglyceride of 1·0–5·0 mmol/L to micronised fenofibrate 200 mg daily (n=4895) or matching placebo (n=4900). Our primary outcome was coronary events (coronary heart disease death or non-fatal myocardial infarction); the outcome for prespecified subgroup analyses was total cardiovascular events (the composite of cardiovascular death, myocardial infarction, stroke, and coronary and carotid revascularisation). Analysis was by intention to treat. The study was prospectively registered (number ISRCTN 64783481).

Findings Vital status was confirmed on all but 22 patients. Averaged over the 5 years' study duration, similar proportions in each group discontinued study medication (10% placebo *vs* 11% fenofibrate) and more patients allocated placebo (17%) than fenofibrate (8%; p<0·0001) commenced other lipid treatments, predominantly statins. 5·9% (n=288) of patients on placebo and 5·2% (n=256) of those on fenofibrate had a coronary event (relative reduction of 11%; hazard ratio [HR] 0·89, 95% CI 0·75–1·05; p=0·16). This finding corresponds to a significant 24% reduction in non-fatal myocardial infarction (0·76, 0·62–0·94; p=0·010) and a non-significant increase in coronary heart disease mortality (1·19, 0·90–1·57; p=0·22). Total cardiovascular disease events were significantly reduced from 13·9% to 12.5% (0·89, 0·80–0·99; p=0·035). This finding included a 21% reduction in coronary revascularisation (0·79, 0·68–0·93; p=0·003). Total mortality was 6·6% in the placebo group and 7·3% in the fenofibrate group (p=0·18). Fenofibrate was associated with less albuminuria progression (p=0·002), and less retinopathy needing laser treatment (5·2% *vs* 3·6%, p=0·0003). There was a slight increase in pancreatitis (0·5% *vs* 0·8%, p=0·031) and pulmonary embolism (0·7% *vs* 1·1%, p=0·022), but no other significant adverse effects.

Interpretation Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce total cardiovascular events, mainly due to fewer non-fatal myocardial infarctions and revascularisations. The higher rate of starting statin therapy in patients allocated placebo might have masked a moderately larger treatment benefit.

Lancet 2005; 366: 1849–61

Published online November 14, 2005 DOI:10.1016/S0140-6736(05)67667-2

See **Comment** page 1829

*Investigators listed at end of report

Correspondence to: The FIELD study investigators, c/o NHMRC Clinical Trials Centre, Mallett St Campus, University of Sydney, NSW 2006, Australia **FIELDTrial@ctc.usyd.edu.au**

Introduction

The prevalence of type 2 diabetes mellitus is rapidly increasing worldwide. Rates of coronary heart disease at any given age are three–four-fold higher in patients with type 2 diabetes than in those without, and the risk of coronary heart disease is higher across all levels of cholesterol.[1,2] The high rates of pre-hospital, in-hospital, and subsequent mortality after myocardial infarction reduce life expectancy by an average of 5–10 years.[3,4] Hence, type 2 diabetes contributes to the overall burden of premature morbidity and mortality from coronary heart disease to a greater extent than expected by its prevalence in the community.

Although total-cholesterol and LDL-cholesterol concentrations for age and sex in those with diabetes are usually similar to or lower than those in non-diabetic populations,[5] their lipid patterns differ. First, LDL-cholesterol particles are smaller and denser in individuals with diabetes than in those without diabetes,[6] so that similar LDL-cholesterol levels mask a higher number of LDL particles. Second, people with diabetes generally have lower HDL-cholesterol and higher triglyceride concentrations,[7,8] which are associated with an increased risk of cardiovascular disease.[9,10]

This pattern of dyslipidaemia typical of type 2 diabetes can be corrected with fibrates. Although the effects of fenofibrate on lipid fractions can vary with the population under study, a fall of 15% or more in total cholesterol and LDL cholesterol has often been reported.[11] In parallel, an increase in HDL cholesterol of 10–15% is expected, together with substantial reductions in plasma triglycerides of about 30%.[11] Many doctors therefore believe that fibrates are a logical drug treatment for diabetic dyslipidaemia.

The Helsinki Heart Study[12] tested long-term fibrate (gemfibrozil) use in men with hypercholesterolaemia without previous coronary disease. Fibrates lowered coronary events more in people with diabetes than in others in a post-hoc analysis, though the difference was not separately significant.[13] The overall reduction in coronary events was greater than would have been expected on the basis of lowering of LDL cholesterol alone. More recently, several other studies have reported beneficial effects of fibrates in individuals with diabetes or metabolic syndrome. First, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial (VA-HIT)[14] reported that gemfibrozil reduced recurrent events in patients with coronary heart disease and low HDL-cholesterol concentrations, with greater relative benefits seen in those with diabetes or insulin resistance than in those without. Second, the findings of the Bezafibrate Infarct Prevention (BIP) trial[15] showed greater cardiovascular disease event reductions in those with metabolic syndrome. These reports were also post-hoc analyses. In the Saint Mary's Ealing Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) study[16] of 150 patients with diabetes without previous cardiovascular disease, there was a significant reduction in ischaemic events, including electrocardiographic changes. In the Diabetes Atherosclerosis Intervention Study (DAIS)[17] of 418 individuals with diabetes and angiographically documented coronary disease, established coronary atherosclerosis progressed less in those assigned fenofibrate than in those assigned matching placebo over 3 years; there were also fewer clinical events with treatment, but this finding was not significant and the study was not designed to examine clinical outcomes.

Thus, despite its potentially important role in reducing cardiovascular risk in the setting of diabetes, no large clinical-endpoint trials of fibrate therapy specifically in people with diabetes have been done. We therefore designed the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study to assess the effects on coronary morbidity and mortality of long-term treatment with fenofibrate to raise HDL-cholesterol concentrations and lower triglyceride levels in patients with type 2 diabetes and total blood cholesterol concentrations of less than 6·5 mmol/L.

Methods

Patients

A detailed description of the design of the FIELD study—a double-blind, placebo-controlled trial done in 63 centres in Australia, New Zealand, and Finland—has been published.[18] In brief, patients with type 2 diabetes diagnosed according to WHO criteria[1] and aged 50–75 years were randomly allocated between February, 1998, and November, 2000, to once-daily micronised fenofibrate 200 mg (Laboratoires Fournier, Dijon, France) or matching placebo capsules. Patients were recruited from hospital clinics and community-based sources. All individuals had an initial plasma total-cholesterol concentration of between 3·0 mmol/L and 6·5 mmol/L, plus either a total-cholesterol/HDL-cholesterol ratio of 4·0 or more or a plasma triglyceride concentration of between 1·0 mmol/L and 5·0 mmol/L, with no clear indication for, or treatment with, lipid-modifying therapy at study entry. Exclusion criteria included renal impairment (blood creatinine >130 μmol/L), known chronic liver disease or symptomatic gallbladder disease, and a cardiovascular event within the 3 months before recruitment.

All patients provided written informed consent. The study protocol was approved by local and national ethics committees and was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Patients' management and procedures

All patients had to complete a 16-week run-in period, comprising 4 weeks of dietary modification, 6 weeks of single-blind placebo, and 6 weeks of single-blind fenofibrate therapy, during which time we confirmed eligibility for randomisation and documented baseline biochemical variables on several occasions. The purpose of the active run-in period was to assess whether the effects of fenofibrate treatment differed in individuals with larger short-term responses in lipid levels compared with those with smaller responses. There was no formal restriction on subsequent randomisation related to compliance during the run-in period.

Randomisation was done by central computer, using a dynamic allocation method[19] with stratification for important prognostic factors, including age, sex, previous myocardial infarction, lipid levels, and urinary albumin concentration. Allocated treatment was taken as a single daily dose with breakfast.

Patients were seen for scheduled study visits at 4–6-monthly intervals over a planned period of 5 years on average against a background of usual care from their health-care professionals. Decisions about changes in therapy for diabetes or co-morbid conditions, including lipid-lowering therapy, were at the discretion of the patient's primary-care doctor or specialist physician. We communicated new findings of major lipid trials, such as the Heart Protection Study,[20] to patients and their doctors through newsletters. The Sydney coordinating centre advised local investigators if any patient's fasting plasma cholesterol level exceeded 6·5 mmol/L or plasma triglyceride level exceeded 8·0 mmol/L on two successive visits up to 1 year apart; this information was also then provided to the patient's usual doctor.

At every study visit, compliance was verified by return pill count, allocated treatment was dispensed, and concomitant medication recorded. Any adverse events were documented and a clinical examination done, including weight and blood pressure. Post-randomisation fasting blood samples were taken at baseline, at 4, 8, and 12 months, yearly thereafter, and at study close, for plasma lipids,

plasma creatinine, and alanine aminotransferase. Plasma glucose, haemoglobin A1c (HbA1c), apolipoproteins A1, A2, and B, lipoprotein a, insulin, C-peptide, fibrinogen and homocysteine, urine albumin, and urine creatinine were measured periodically during follow-up. Creatine phosphokinase was measured regularly up to 12 months, and thereafter only if unexplained muscle pain was reported. Baseline albumin excretion values were calculated as the mean of two measurements from spot morning urine samples, then remeasured at year 2 and study close. An electrocardiograph (ECG) was recorded at baseline, at 2 and 5 years, and at study close.

In a subgroup of Australian patients, fasting blood and urine samples were taken 6–8 weeks after study closure for measurement of blood creatinine, homocysteine, glucose, lipids and fibrinogen, HbA1c, urine albumin, and urine creatinine.

All blood and urine samples were analysed in one of two central laboratories in Adelaide, Australia, and Helsinki, Finland. Both laboratories participated in national quality assurance schemes for all analytes and were aligned for lipid and HbA1c analyses through the Canadian External Quality Assurance Laboratory in Vancouver. Methods used to measure lipids were accredited by the Centers for Disease Control Lipid Standardisation Program.

All myocardial infarctions, strokes, and deaths—ie, all major cardiovascular disease events and all other deaths—were adjudicated by an outcomes assessment committee unaware of treatment allocation with definitions specified before the study began. A diagnosis of myocardial infarction required at least two of three criteria: ECG changes, ischaemic symptoms, or raised cardiac enzymes. A stroke required evidence of sudden onset of focal neurological deficits, lasting at least 24 h, with cerebral imaging excluding haemorrhage to confirm an ischaemic stroke. Cause-specific mortality was classified into major categories of coronary, other vascular, cancer, and other non-cardiovascular disease subtypes. More detailed definitions have been published previously.[18]

All potentially serious adverse drug reactions were reported to the Sydney coordinating centre within 24 h, and all other serious adverse events within 10 days. Local investigators were informed: 1) when there had been a rise in plasma creatinine to more than 160 μmol/L; 2) if the plasma concentrations of alanine aminotransferase exceeded three times the upper limit of normal; or 3) if the plasma level of creatine phosphokinase was more than twice the upper limit of normal. For each of these circumstances, a detailed protocol dealing with repeat measurement and consideration of temporary or permanent cessation of study medication was followed.

Study monitors from the Australian, New Zealand, or Finnish project offices reviewed study progress and data, including adverse events, at every site two to three times per year. Members of the trial's independent safety and data monitoring committee and the unblinded statistician were the only personnel to view data by treatment allocation. The safety and data monitoring committee reviewed the safety data every 6 months and undertook two formal interim analyses of numbers of deaths from coronary heart disease.

The primary endpoint was the first occurrence of either non-fatal myocardial infarction or death from coronary heart disease. Secondary outcomes included major cardiovascular disease events (coronary heart disease events, total stroke, and other cardiovascular death combined), total cardiovascular disease events (major cardiovascular disease events plus coronary and carotid revascularisation), coronary heart disease death, total cardiovascular disease deaths, haemorrhagic and non-haemorrhagic stroke, coronary and peripheral revascularisation procedures, cause-specific non-coronary heart disease mortality, and total mortality. Tertiary outcomes comprised vascular and neuropathic amputations, non-fatal cancers, the progression of renal disease, laser treatment for diabetic retinopathy, hospital admission for angina pectoris, and the number and duration of all hospital admissions.

Statistical analysis

During recruitment, the number of participants who had had a previous myocardial infarction fell short of that originally planned for enrolment and the sample size was increased from 8000 to 9795. In December, 2002, the primary endpoint for the study was amended from coronary heart disease death to coronary heart disease events (coronary heart disease death plus non-fatal myocardial infarction) to maintain the study's power, after a blinded review of overall rates of discontinuation of study medication, commencement of open-label lipid-lowering treatment, and cardiovascular disease event rates. For this new primary outcome, 500 events and 5 years' median follow-up were needed to ensure 80% power to detect a 22% reduction in coronary heart disease events based on an intention-to-treat method of analysis. This effect corresponded to an underlying 27% risk reduction in those taking fenofibrate and assumed a drop-out rate of study medication of 18% and a rate of starting statin therapy (ie, drop-in rate) of 23% overall by study closure. We made a conservative assumption of a larger starting rate of statin treatment in those allocated placebo than in those allocated fenofibrate (16% *vs* 7% averaged over the study, reaching 32% *vs* 16% at study close),[21] as well as a larger starting rate of statins in patients with previous cardiovascular disease than in those without. Statin therapy was assumed to offer the same 27% reduction in coronary heart disease events as fenofibrate.

Because of the two formal interim analyses done during the study, the p value at the final analysis for the primary outcome needed to be less than 0·047 to be significant. We assessed the effects of treatment on the outcome of total cardiovascular disease events in prespecified subgroups defined at baseline, including those with and without previous cardiovascular disease, men and women,

those aged younger than 65 years and 65 years or older, and the presence and absence of the metabolic syndrome as defined by NCEP ATPIII[22] and its individual components. Additional prespecified subgroups included total-cholesterol concentration (<4·5, 4·5–5·5, >5·5 mmol/L) and LDL-cholesterol concentration (<3·0, 3·0–3·5, >3·5 mmol/L).

We had a predefined statistical analysis plan. We used standard log-rank methods without adjustment for covariates to ascertain the significance of the effect of treatment on the first coronary event (coronary heart disease death and non-fatal myocardial infarction).[23,24] We used Cox proportional hazards modelling to compute the hazard ratio (HR) and its 95% CIs, and in a sensitivity analysis adjusted for baseline covariates.[24] Similarly, we used the log-rank and Cox methods for time-to-event outcomes for all secondary endpoints. The main analysis for every subgroup was a test for interaction in the Cox model to ascertain whether the HR for treatment effect on total cardiovascular disease events differed significantly between the various categories. A global test for interaction was also done for the primary set of subgroups. Displays of times to event for each treatment group of all primary and secondary outcomes and for discontinuation of study medication or drop-in to other lipid therapy used estimates derived from the Kaplan-Meier method.[25] We estimated drop-out rate and drop-in rate of starting statins averaged over the study from the area under the curves up to 5 years. Where appropriate, we analysed categorical outcomes with χ^2 tests and continuous outcomes with standard regression methods. Continuous variables are presented as mean (SD) or median (IQR). Because of the expected use of other lipid-lowering therapy during the trial, we specified an additional analysis to estimate treatment effects on cardiovascular disease events in a Cox regression analysis with new use of statins as a time-dependent covariate. We did this analysis, using non-randomised data, to assess the possible confounding of fenofibrate effect by differing rates of statin use.

Results are unadjusted for multiple comparisons. Analysis was intention to treat, and we used the SAS statistical software package (version 8.2) for all analyses.

The study is registered as an International Standard Randomised Controlled Trial, ISRCTN 64783481.

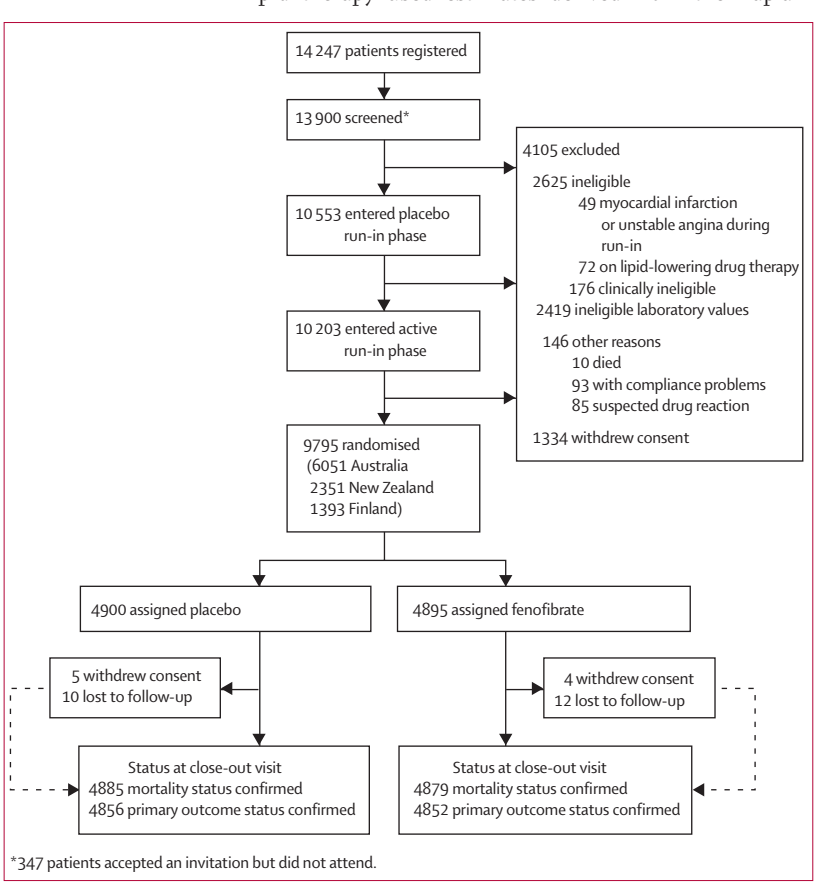


Figure 1: **Trial profile**

Role of the funding source

The study was designed by an independent study management committee and coordinated by the National Health and Medical Research Council Clinical Trials Centre (CTC), University of Sydney, Australia. Two non-voting representatives of the main sponsor attended meetings of the management committee. Members of the committee were responsible for preparation of the manuscript after all study-related data had been reviewed. The sponsor of the study had no role in data collection or data analysis. The writing committee had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. In the three countries, 14 247 patients were registered, of whom 4900 were randomised to placebo and 4895 to fenofibrate. Women comprised 37% (n=3657) of the sample, 40% (n=3955) were aged 65 years or older at screening, and 22% (n=2131) had previous cardiovascular disease. The two treatment groups were well matched for baseline characteristics, including use of cardiovascular and glucose-lowering therapies (table 1). 5820 patients (59%) met the prespecified definition of low HDL cholesterol (<1·03 mmol/L in men, <1·29 mmol/L in women) and 5093 (52%) had high triglyceride concentrations (>1·7 mmol/L); 3710 patients (38%) had both of these features, to meet the definition of dyslipidaemia.

By the end of the trial (close-out visits from January to May, 2005, median 5 years after randomisation), 950 of the patients allocated placebo (19%) and 954 of those allocated fenofibrate (20%) had discontinued study medication, corresponding to drop-out rates of 10% and 11% averaged over the 5-year study period. Most drop-outs related to deteriorating health, laboratory abnormalities, withdrawal of patient's consent, and minor possible

adverse drug reactions, the respective frequencies of which were similar between groups. We continued to follow up patients who had discontinued therapy until death or study close; 22 patients were lost to follow-up and were assumed to be alive at the end of the study; a further 65 patients were not evaluable for morbidity at study close-out such that the primary outcome was confirmed in all but 87 participants (0·9%). There were 34 eligibility protocol violations, including 20 patients who were subsequently found not to fulfil WHO criteria for the diagnosis of diabetes. All these patients were included in the analysis.

Serum lipid profiles and non-study lipid-lowering therapy

Table 2 shows the absolute differences in plasma lipids between groups. Allocation to fenofibrate resulted in reductions relative to placebo in plasma total-cholesterol concentration of 11%, LDL-cholesterol level of 12%, and triglyceride concentrations of 29%, and increases in levels of HDL cholesterol of 5% after 4 months of treatment. These differences decreased in the total population over time particularly in those patients receiving additional lipid-lowering drugs. In those patients not receiving lipid-lowering drugs, fenofibrate allocation produced initial mean differences relative to placebo that were very similar to the full cohort. These differences were maintained for levels of total cholesterol, LDL cholesterol, and triglycerides, but differences in HDL cholesterol had decreased by study close from 5% to 2% (table 2).

Levels of apolipoprotein A1, A2, and B were also affected by fenofibrate. Compared with placebo, allocation to fenofibrate increased concentrations of apolipoprotein A1 and A2 by 3·9% and 28%, and reduced levels of apolipoprotein B by 13·6% at 4 months, with differences at study close of 1·8%, 23·7%, and –7·5%, respectively. In those not starting other lipid-lowering treatment, changes at study close indicated durable effects on apolipoproteins A2 (24·5%) and B (15·7%), with some attenuation of the effects on apolipoprotein A1 (2·0%).

There was a progressive increase in the proportion of patients who were prescribed additional lipid-lowering drugs as well as of patients who discontinued study therapy (figure 2). By study end, 1776 patients allocated placebo were taking non-study lipid-lowering agents, compared with 944 patients allocated fenofibrate. This pattern corresponded with an average use of non-study lipid-lowering agents over the entire study of 17% in the placebo group and 8% in the fenofibrate group ($p<0·0001$). In 93% (n=1657) and 94% (n=890) of patients, respectively, this additional drug was a statin. In patients allocated placebo who commenced other lipid-lowering therapy, 74% (n=1318) remained on the study drug, whereas for those allocated fenofibrate, the equivalent proportion was 62% (n=581; $p<0·0001$).

	Placebo (n=4900)	Fenofibrate (n=4895)
General characteristics		
Male	3067 (63%)	3071 (63%)
White	4559 (93%)	4534 (93%)
Age at visit 1 (years, mean [SD])	62·2 (6·9)	62·2 (6·8)
Diabetes duration (years, median [IQR])*	5 (2–10)	5 (2–10)
Body-mass index (kg/m², median [IQR])	29·8 (26·7–33·4)	29·8 (26·8–33·6)
Waist-to-hip ratio (median [IQR])	0·94 (0·88–0·98)	0·94 (0·88–0·98)
Blood pressure (mm Hg, mean [SD])		
Systolic	141 (15)	140 (15)
Diastolic	82 (9)	82 (9)
Current smoker	460 (9%)	462 (9%)
Ex-smoker	2490 (51%)	2454 (50%)
Clinical history		
Previous cardiovascular disease	1063 (22%)	1068 (22%)
Myocardial infarction	255 (5%)	230 (5%)
Stroke	182 (4%)	164 (3%)
Angina	588 (12%)	600 (12%)
Peripheral vascular disease	354 (7%)	357 (7%)
Coronary revascularisation (CABG or PTCA)	168 (3%)	195 (4%)
History of hypertension*	2768 (56%)	2776 (57%)
Microvascular disease*	998 (20%)	1026 (21%)
Retinopathy*	412 (8%)	402 (8%)
Neuropathy*	687 (14%)	707 (14%)
Nephropathy*	135 (3%)	144 (3%)
Laboratory data†‡		
Total cholesterol (mmol/L, mean [SD])	5·03 (0·71)	5·04 (0·69)
LDL cholesterol (mmol/L, mean [SD])	3·07 (0·66)	3·07 (0·64)
HDL cholesterol (mmol/L, mean [SD])	1·10 (0·26)	1·10 (0·26)
Triglycerides (mmol/L, median [IQR])	1·73 (1·34–2·30)	1·74 (1·34–2·34)
HbA1c (%, median [IQR])	6·9 (6·1–7·8)	6·9 (6·1–7·8)
Plasma creatinine (μmol/L, mean [SD])	77·4 (15·7)	77·7 (15·9)
Homocysteine (μmol/L, median [IQR])	9·6 (8·0–11·4)	9·5 (7·9–11·6)
Dyslipidaemia§	1824 (37%)	1886 (39%)
Microalbuminuria¶	925 (19%)	925 (19%)
Macroalbuminuria¶	157 (3%)	156 (3%)
Baseline cardiovascular medication		
Any antithrombotic	1569 (32%)	1574 (32%)
Aspirin	1455 (30%)	1448 (30%)
Other	170 (4%)	165 (3%)
Angiotensin-converting enzyme inhibitor	1725 (35%)	1716 (35%)
Angiotensin II receptor antagonist	265 (5%)	280 (6%)
β blocker	748 (15%)	757 (15%)
Calcium antagonist	983 (20%)	1013 (21%)
Nitrate	306 (6%)	260 (5%)
Diuretic	780 (16%)	798 (16%)
Baseline blood-glucose-lowering medication		
Diet alone	1284 (26%)	1258 (26%)
Metformin alone	823 (17%)	828 (17%)
Sulfonylurea alone	799 (16%)	809 (17%)
Metformin+sulfonylurea	1196 (24%)	1207 (25%)
Other oral agent	10 (<1%)	9 (<1%)
Metformin and/or sulfonylurea+other oral agent	100 (2%)	93 (2%)
Insulin alone	286 (6%)	283 (6%)
Insulin+oral agent	402 (8%)	408 (8%)

CABG=coronary artery bypass grafting, PTCA=percutaneous transluminal coronary angioplasty. Data are number (%) unless otherwise indicated. *Reported at visit 1. †Mean of visit 2 and visit 3 for lipids, mean of visit 1 and visit 3 for HbA1c and creatinine, and visit 3 only for homocysteine. ‡To convert mmol/L to mg/dL: for cholesterols multiply by 38·67, for triglycerides multiply by 88·6. §Defined as low HDL cholesterol (<1·03 mmol/L for men, <1·29 mmol/L for women) with high triglycerides (>1·7 mmol/L). ¶Microalbuminuria defined as urine albumin/creatinine ratio 3·5–35 mg/mmoL, macroalbuminuria defined as urine albumin/creatinine ratio >35 mg/mmoL.

Table 1: **Baseline characteristics and medication**

Clinical outcomes

There were 544 primary outcome events. Fenofibrate was associated with a non-significant 11% relative reduction in the primary outcome of first myocardial infarction or coronary heart disease death (table 3 and figure 3). This finding corresponds to a significant 24% relative reduction in non-fatal myocardial infarction, with a non-significant

	Plasma concentrations at baseline (mean [SD])		Absolute (mmol/L) and relative (%) differences between treatment groups in plasma lipid concentrations after randomisation*				Plasma concentrations at study close (mean [SD])	
	Placebo	Fenofibrate	4 months	1 year	2 years	Study close	Placebo	Fenofibrate
Full cohort (fenofibrate n=4895, placebo n=4900)								
Total cholesterol	5·03 (0·71)	5·04 (0·69)	−0·58 (−11·4%)	−0·58 (−11·6%)	−0·56 (−11·1%)	−0·33 (−6·9%)	4·56 (0·90)	4·23 (0·78)
LDL cholesterol	3·07 (0·66)	3·07 (0·64)	−0·39 (−12·0%)	−0·38 (−11·9%)	−0·36 (−11·7%)	−0·17 (−5·8%)	2·60 (0·78)	2·43 (0·65)
HDL cholesterol	1·10 (0·26)	1·10 (0·26)	0·05 (5·1%)	0·05 (4·5%)	0·04 (3·5%)	0·01 (1·2%)	1·12 (0·29)	1·13 (0·30)
Triglycerides	1·93 (0·88)	1·95 (0·87)	−0·56 (−28·6%)	−0·58 (−30·2%)	−0·52 (−27·4%)	−0·41 (-21·9%)	1·87 (0·96)	1·47 (0·78)
Started other lipid-lowering therapy (fenofibrate n=944, placebo n=1776)								
Total cholesterol	5·2 (0·67)	5·25 (0·69)	−0·42 (−8·0%)	−0·39 (−7·6%)	−0·33 (−6·5%)	−0·08 (−1·6%)	4·12 (0·88)	3·98 (0·85)
LDL cholesterol	3·31 (0·63)	3·23 (0·64)	−0·24 (−6·6%)	−0·19 (−5·5%)	−0·15 (−4·6%)	0·02 (0·7%)	2·18 (0·74)	2·13 (0·66)
HDL cholesterol	1·08 (0·25)	1·03 (0·24)	0·05 (4·6%)	0·03 (2·8%)	0·01 (1·7%)	−0·01 (−0·5%)	1·12 (0·28)	1·05 (0·29)
Triglycerides	2·08 (0·99)	2·22 (0·99)	−0·54 (−24·6%)	−0·55 (−24·8%)	−0·45 (−21·0%)	−0·24 (−10·9%)	1·84 (0·97)	1·74 (0·96)
Did not start other lipid-lowering therapy (fenofibrate n=3951, placebo n=3124)								
Total cholesterol	4·87 (0·68)	4·99 (0·69)	−0·63 (−12·5%)	−0·66 (−13·1%)	−0·68 (−13·4%)	−0·66 (−13·1%)	4·82 (0·80)	4·29 (0·74)
LDL cholesterol	2·93 (0·64)	3·03 (0·64)	−0·44 (−13·6%)	−0·45 (−14·3%)	−0·48 (−15·3%)	−0·46 (−14·7%)	2·84 (0·70)	2·50 (0·63)
HDL cholesterol	1·11 (0·27)	1·11 (0·26)	0·05 (5·1%)	0·05 (4·8%)	0·04 (4·0%)	0·02 (2·1%)	1·13 (0·29)	1·15 (0·30)
Triglycerides	1·85 (0·81)	1·89 (0·83)	−0·57 (−29·6%)	−0·60 (−31·6%)	−0·55 (−29·1%)	−0·51 (−27·3%)	1·88 (0·95)	1·41 (0·72)

*Fenofibrate minus placebo. p<0·05 for all differences between groups at every timepoint shown, except in patients who started other lipid-lowering therapy, for HDL cholesterol and LDL cholesterol at study close.

Table 2: **Plasma concentration of lipids at baseline and study close, with treatment group differences during follow-up**

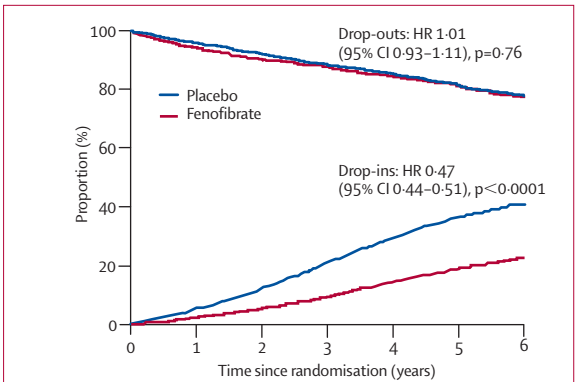
See Lancet Online for webtables 1 and 2 and webfigures 1 and 2

increase in fatal coronary heart disease. We noted no significant excess of any particular cause of coronary heart disease death (webtable 1), with slightly fewer other cardiovascular disease deaths seen in the fenofibrate group than in the placebo group.

For the secondary outcome of total cardiovascular disease events (the composite of cardiovascular disease death, myocardial infarction, stroke, and coronary and carotid revascularisation), there was a significant 11% reduction with fenofibrate (table 3 and figure 3). This benefit was due mainly to the reduction in non-fatal myocardial infarction together with a significant 21% relative reduction in coronary revascularisation. Differences in total cardiovascular disease events emerged mainly after 2 years, and with 5-year rates of total cardiovascular disease events of 13·9% and 12·5%. Other secondary outcomes (including stroke, fatal cardiovascular disease events, coronary heart disease mortality, and all-cause mortality) did not differ significantly between groups (table 3).

The rate of progression to albuminuria was significantly reduced by fenofibrate. 539 (11%) patients allocated placebo progressed from normoalbuminuria to micro-albuminuria or from microalbuminuria to macro-albuminuria, compared with 466 fenofibrate-allocated patients (10%), whereas 400 (8%) and 462 (9%) regressed. This represents 2·6% more patients allocated fenofibrate than placebo regressing or not progressing (p=0·002; webtable 2). A similar effect of treatment was seen on urinary albumin concentration unadjusted for urinary creatinine (p=0·001). The number of patients that needed dialysis at any time after randomisation was 21 in those allocated placebo and 16 in those assigned fenofibrate. More controls (253) than patients allocated fenofibrate (178) needed one or more laser treatments for retinopathy (1·6% difference, p=0·0003; webfigure 1). The effect of fenofibrate was very similar in reducing laser therapy when confined to the subgroup of patients without retinopathy at baseline (p=0·001).

Figure 4 summarises the analyses of total cardiovascular disease events in the primary set of prespecified subgroups. Treatment effects were significantly larger in the patients with no previous cardiovascular disease than in those with previous cardiovascular disease, and in younger (<65 years) rather than older patients. We noted a significant 19% reduction in total cardiovascular disease events in patients with no previous cardiovascular disease (p=0.004; webfigure 2), with a significant 20% reduction also in patients aged younger than 65 years (p=0·003). Patients with the metabolic syndrome were generally at



Numbers at risk: drop-outs

Placebo	4900	4668	4464	4272	4087	2260	711
Fenofibrate	4895	4598	4392	4236	4041	2257	731

Numbers at risk: drop-ins

Placebo	4900	4602	4228	3749	3291	1677	510
Fenofibrate	4895	4739	4540	4290	3972	2107	671

Figure 2: **Kaplan-Meier curves of compliance with study medication (shown as time to permanent discontinuation) and cumulative risk curves of uptake of other lipid-lowering agents, by treatment group**

	Placebo (n=4900)		Fenofibrate (n=4895)		HR (95% CI)	Log-rank p
	Number (%)*	Rate/1000 person-years at risk	Number (%)*	Rate/1000 person-years at risk		
Primary outcome						
Coronary events	288 (6%)	11·7	256 (5%)	10·4	0·89 (0·75–1·05)	0·16
Coronary heart disease mortality	93 (2%)	3·7	110 (2%)	4·4	1·19 (0·90–1·57)	0·22
Non-fatal myocardial infarction	207 (4%)	8·4	158 (3%)	6·4	0·76 (0·62–0·94)	0·010
Secondary outcome						
Total cardiovascular disease events	683 (14%)	29·0	612 (13%)	25·8	0·89 (0·80–0·99)	0·035
Cardiovascular disease mortality	127 (3%)	5·1	140 (3%)	5·6	1·11 (0·87–1·41)	0·41
Total mortality	323 (7%)	12·9	356 (7%)	14·2	1·11 (0·95–1·29)	0·18
Total stroke	175 (4%)	7·1	158 (3%)	6·4	0·90 (0·73–1·12)	0·36
Non-haemorrhagic stroke	158 (3%)	6·4	144 (3%)	5·8	0·91 (0·73–1·14)	0·43
Coronary revascularisation	364 (7%)	15·0	290 (6%)	11·9	0·79 (0·68–0·93)	0·003
All revascularisation†	471 (10%)	19·7	380 (8%)	15·8	0·80 (0·70–0·92)	0·001

*Only first event for each patient counted in each row. †Includes coronary, carotid, and all other peripheral revascularisation.

Table 3: **Effect of treatment on primary and secondary outcomes[15]**

higher risk of an event, but did not have significantly greater benefit from fenofibrate than the others. Differences in treatment effects in these prespecified subgroups might indicate chance variation in the overall effect (global interaction test p=0·27). We also undertook a post-hoc subgroup analysis on the primary outcome of

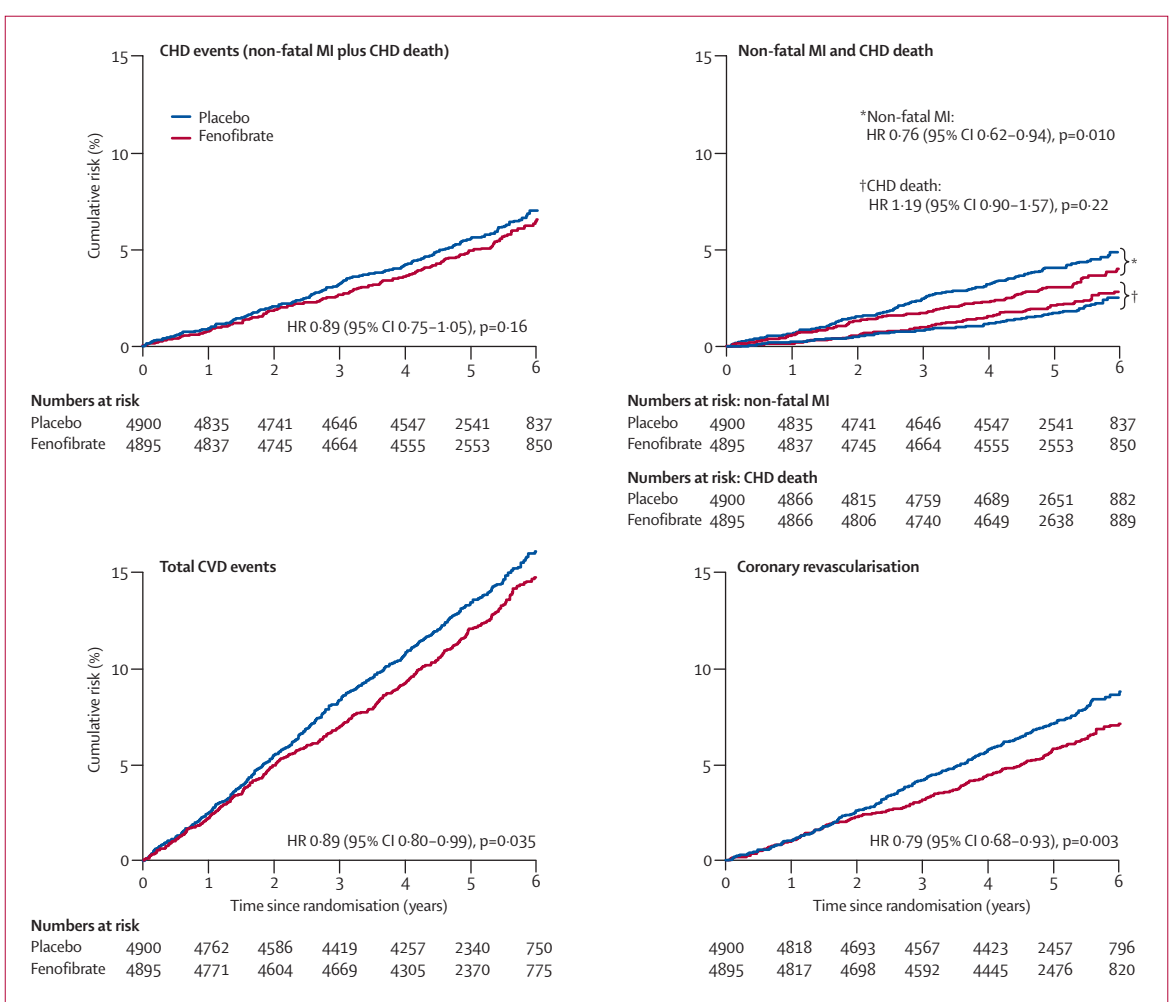


Figure 3: **Cumulative risk curves of time to first events**
CHD=coronary heart disease. MI=myocardial infarction. CVD=cardiovascular disease.

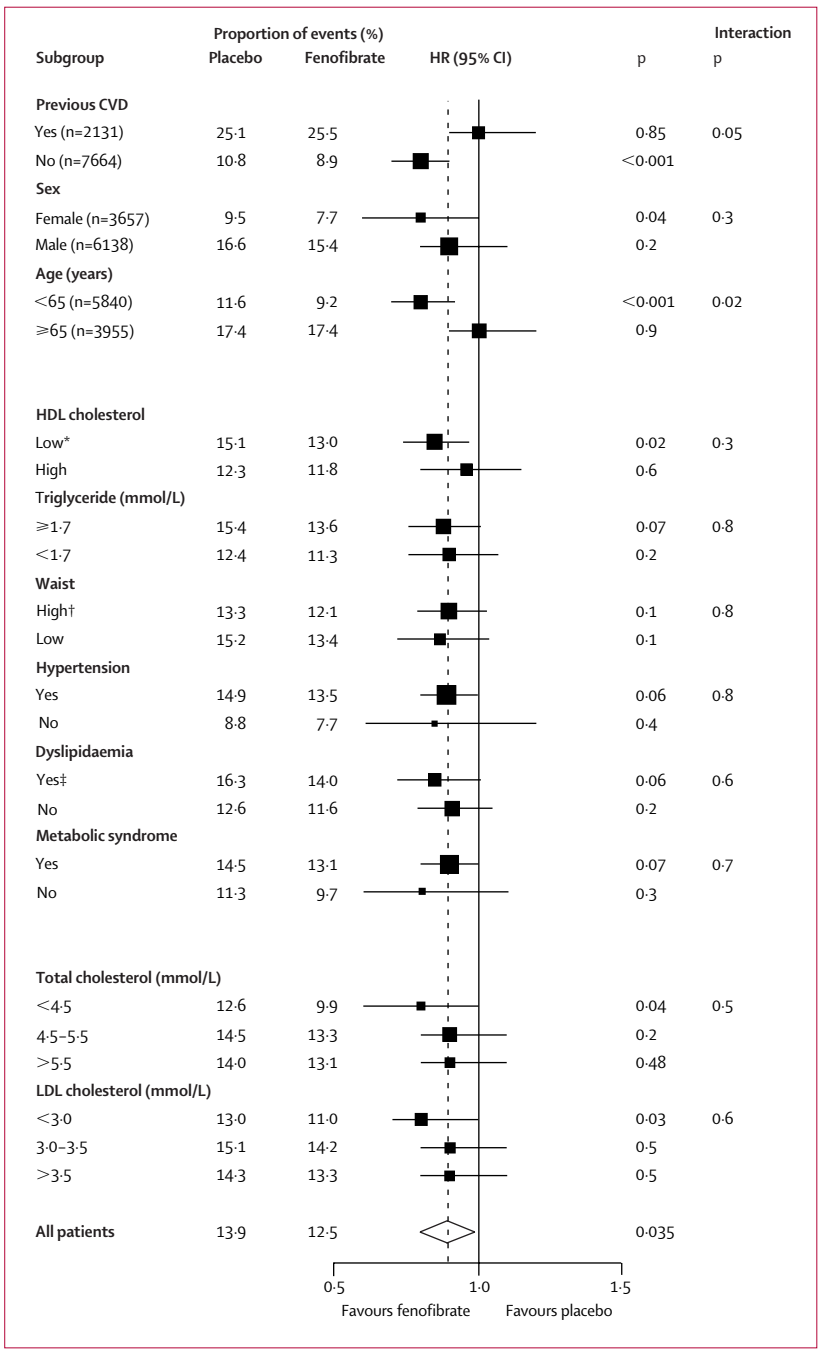


Figure 4: **Effect of fenofibrate treatment on total cardiovascular disease (CVD) events (CVD death, myocardial infarction, stroke, coronary, or carotid revascularisation)**
*<1·03 mmol/L for men, <1·29 mmol/L for women. †>102 cm for men, >88 cm for women. ‡Low HDL cholesterol plus high triglyceride.

See Lancet Online for webfigures 2 and 3 and webtable 3

coronary heart disease events; this showed a reduction in coronary heart disease events in the subgroup of patients with no previous cardiovascular disease (webfigure 2) but not in those with previous cardiovascular disease (interaction p=0·03). The relative risk reduction in total cardiovascular disease events of 19% for patients without previous cardiovascular disease corresponds to an absolute risk reduction of 2·0% or the equivalent of needing to treat 50 patients for 5 years to prevent one or more cardiovascular disease events in one patient. Similarly for the entire cohort, the relative risk reduction of 11% in total cardiovascular disease events corresponds to an absolute risk reduction of 1·4% or the equivalent of needing to treat around 70 patients for 5 years to prevent one or more cardiovascular disease events in one patient.

The rate of starting other lipid-lowering treatments differed among subgroups (webfigure 3). The average rate for those with previous cardiovascular disease (19%) was higher than for those without (11%), in both treatment groups combined, but the difference in rates between the placebo and fenofibrate groups was similar for both subgroups (for previous cardiovascular disease, about 23% in placebo-allocated and 14% in fenofibrate-allocated patients, or a 9% difference between treatment groups; no previous cardiovascular disease, 16% and 7%, or 9% difference). Similar differences in statin use between treatment groups were also seen in the younger compared with the older subgroups (both 9% differences).

The differences between treatment groups in starting rates of other lipid-lowering therapy were larger in individuals with higher baseline total-cholesterol and LDL-cholesterol levels. In both instances, this trend was associated with non-significant trends to lesser effects of treatment on total cardiovascular disease event reduction with the higher baseline total-cholesterol and LDL-cholesterol levels.

The greater use of non-study lipid-lowering therapy in patients allocated placebo resulted in an attenuation of differences in plasma lipid concentrations. In patients who did not begin such treatment, differences in plasma LDL-cholesterol, total-cholesterol, and triglyceride concentrations were maintained. However, an attenuation in the differences in HDL-cholesterol levels arose even in those not starting statins (table 2).

After adjustment for new lipid-lowering therapy, in a time dependent Cox regression analysis, fenofibrate reduced the risk of coronary heart disease events by 19% (p=0·01) and of total cardiovascular disease events by 15% (p=0·004). The corresponding estimated reductions in risk associated with starting statin therapy in these analyses were 49% (p<0·001) for coronary heart disease events and 26% (p<0·001) for total cardiovascular disease events, respectively, indicating the effects of both patient selection onto other lipid-lowering treatment and the effect of statin therapy (webtable 3). Alternatively, if patients were simply censored at the time of starting lipid-lowering therapy, then the estimated effect of fenofibrate on the relative reduction in coronary heart disease events was 14% (p=0·10).

The increases in concomitant cardiovascular and glucose-lowering medications, except for lipid-lowering medications, were similar in both treatment groups (table 4) with little likely effect on the fenofibrate effect on the primary outcome. The greater use of coronary revascu-

	Placebo group (n=4900)		Fenofibrate group (n=4895)	
	Change from baseline (%)	Number (%) at final visit*	Change from baseline (%)	Number (%) at final visit*
Cardiovascular medication				
Any antithrombotic	24·0	2744 (56%)	22·7	2688 (55%)
Aspirin	18·2	2348 (48%)	17·2	2291 (47%)
Other	9·2	622 (13%)	9·1	613 (13%)
Angiotensin-converting enzyme inhibitor	12·7	2348 (48%)	9·8	2197 (45%)
Angiotensin II receptor antagonist	14·8	991 (20%)	13·8	956 (20%)
β blocker	11·0	1290 (26%)	8·6	1179 (24%)
Calcium antagonist	7·1	1335 (27%)	5·4	1277 (26%)
Digoxin	5·6	201 (4%)	5·8	242 (5%)
Diuretic	7·7	1157 (24%)	5·0	1043 (21%)
Nitrate	5·6	577 (12%)	5·8	543 (11%)
Lipid-lowering agent†	36·0	1776 (36%)	19·0	944 (19%)
Blood-glucose-lowering medication				
Oral	9·9	3818 (78%)	9·7	3829 (78%)
Insulin	15·9	1464 (30%)	15·9	1467 (30%)

*Within 3 months of study close. †For this category only, defined as the cumulative number of patients who had used non-study lipid-lowering treatment for more than 3 months at any time. Signficant differences at study close: angiotensin-converting enzyme inhibitors p=0·003, β blockers p=0·011, diuretics p=0·006, digoxin p=0·045, lipid-lowering agents p=<0·0001.

Table 4: **Patients on concominant medication between baseline and study close**

larisation in the placebo group (7·4% *vs* 5·9%, a difference of 1·5%) was due to a 0·9% greater use of revascularisation after a primary coronary heart disease event and a 0·6% greater use before a primary outcome event or study close. Consequently, the greater use of coronary revascularisation in the placebo group could only produce a small diminution in fenofibrate effect.

Safety outcomes

Fenofibrate was generally well tolerated and had a good safety profile irrespective of concomitant therapy (table 5); similar numbers of patients in the placebo and fenofibrate groups discontinued treatment (figure 2). Only 24 (0·5%) patients on placebo and 38 (0·8%) on fenofibrate had possible serious adverse drug reactions. One patient on placebo, and three allocated fenofibrate had rhabdomyolysis, which in each case fully resolved; none of these patients was taking statin therapy. Patients allocated to fenofibrate were at greater risk for pancreatitis than those on placebo, but the numbers were small (23 [0·5%] *vs* 40 [0·8%]; p=0·031). There was also a small increased risk of pulmonary embolism (p=0·022) and deep venous thrombosis (p=0·074) associated with fenofibrate. There were similar numbers of patients with newly diagnosed cancers in the two groups (table 5).

Concentrations of creatine phosphokinase of more than five times the upper limit of normal arose at least once in 15 patients on fenofibrate and in ten controls (table 5). Routinely measured alanine aminotransferase concentrations reached three or more times the upper limit of normal at least once in 38 patients on placebo and 22 in the fenofibrate group. Six cases of clinical hepatitis were reported in each group. During the study, plasma creatinine remained an average of 10–12 μmol/L higher in the fenofibrate group, which had a median concentration of 91 μmol/L at study close compared with 80 μmol/L in placebo-allocated patients (p<0·001). In the subset of 661 patients restudied 8 weeks after ceasing study medications at the end of the trial, the plasma creatinine fell from a median of 92 μmol/L to 77 μmol/L in those previously allocated to fenofibrate, and from 82 μmol/L to 79 μmol/L in those allocated placebo.

Plasma homocysteine was an average of 3·7 μmol/L higher in the fenofibrate group at the end of the study, with a median concentration of 15·1 μmol/L compared with 11·2 μmol/L in placebo-allocated patients. In the subset of patients restudied after the end of the study, plasma homocysteine concentrations fell from a median of 15·0 μmol/L to 9·5 μmol/L in the fenofibrate group, and from 10·7 μmol/L to 9·5 μmol/L in the placebo group. Median HbA1c was 6·9% at entry and 6·9% at the end of the study in the placebo group, and 6·9% and 7·0%, respectively, in the fenofibrate group. The median fasting plasma glucose was 8·5 mmol/L at entry and 7·9 mmol/L at close of the study in the placebo group, and 8·5 mmol/L and 7·6 mmol/L in the fenofibrate group. The median blood pressure was 140/82 mm Hg at entry and 138/78 mm Hg at study close in the placebo group, compared with 140/82 mm Hg and 136/77 mm Hg, respectively, in the fenofibrate group. Median bodyweight was 86 kg at baseline in both groups and did not differ between groups at the end of the study.

Discussion

This large and scientifically rigorous study provided mixed results on the effects of fenofibrate in individuals with type 2 diabetes. Our findings indicate that fenofibrate did not significantly reduce the risk of the primary trial outcome of major coronary events. However, fenofibrate did reduce the risk of total cardiovascular disease events, particularly through the prevention of non-fatal myocardial infarctions and coronary revascularisations. Further, fenofibrate significantly reduced microvascular-associated complications and proved to be generally well tolerated in patients with type 2 diabetes.

	Placebo (n=4900)	Fenofibrate (n=4895)
Any serious adverse event*		
Death, other than cardiovascular causes	196 (4%)	216 (4%)
Cancer	148 (3%)	168 (3%)
Respiratory disease	16 (<1%)	19 (<1%)
Trauma	12 (<1%)	11 (<1%)
Other	20 (<1%)	18 (<1%)
Non-fatal events*	3346 (68%)	3361 (69%)
Gastrointestinal	927 (19%)	975 (20%)
Cardiac	807 (17%)	727 (15%)
Musculoskeletal	739 (15%)	755 (15%)
Tumour-related†	661 (14%)	643 (13%)
Genitourinary	568 (12%)	607 (12%)
Special senses‡	527 (11%)	499 (10%)
Vascular (non-cardiac)	439 (9%)	418 (9%)
Respiratory	342 (7%)	384 (8%)
Newly diagnosed cancer	373 (8%)	393 (8%)
Colorectal	60 (1%)	67 (1%)
Prostate	59 (1%)	65 (1%)
Other gastrointestinal	49 (1%)	47 (1%)
Respiratory	41 (<1%)	45 (<1%)
Breast	38 (<1%)	37 (<1%)
Urinary	31 (<1%)	24 (<1%)
Clinically important events in <2% of patients*		
Deep-vein thrombosis	48 (1·0%)	67 (1%)
Pulmonary embolism	32 (0·7%)	53 (1%)
Pancreatitis	23 (0·5%)	40 (0·8%)
Myositis	1 (<1%)	2 (<1%)
Rhabdomyolysis	1 (<1%)	3 (<1%)
Renal disease needing dialysis	21 (<1%)	16 (<1%)
Laboratory variable measurements		
Raised alanine aminotransferase		
3–5×upper limit of normal	26 (<1%)	11 (<1%)
>5×upper limit of normal	12 (<1%)	11 (<1%)
Raised creatine phosphokinase		
5–10×upper limit of normal	7 (<1%)	11 (<1%)
>10×upper limit of normal	3 (<1%)	4 (<1%)
Raised creatinine		
>200 μmol/L	48 (1%)	73 (2%)

Data are number (%) *Other than primary and secondary cardiovascular outcomes. †Includes invasive cancers, in-situ cancers, non-melanoma skin cancers, and benign tumours. ‡Includes cataract and other eye and ear conditions.

Table 5: **Clinical and laboratory evidence of safety of fenofibrate**

Results of systematic reviews of randomised trials of lipid-modifying therapies show clear evidence of benefit from cholesterol-lowering therapy for a broad cross section of patients at risk for cardiovascular disease.[26,27] This conclusion is based mainly on trials of statin therapy and is largely consistent with the effect of statins in reducing LDL cholesterol, with a one-fifth to one-quarter reduction in cardiovascular disease events per mmol/L LDL cholesterol reduction, corresponding to roughly a one-third reduction in risk from currently used statin regimens.[28] By contrast with the large reductions in LDL cholesterol of 20–35% often achieved with statin therapy, the effects of fibrates on LDL cholesterol are much smaller, and somewhat varied—no fall was reported with gemfibrozil in VA-HIT and we report a fall of only 13% with fenofibrate. Nevertheless, fibrates tend to raise HDL-cholesterol concentrations to a similar or greater extent than do statins, lower triglycerides more effectively, and reduce cardiovascular disease events. The effect of fibrates on cause-specific mortality is less clear though, with smaller numbers of patients included in studies, especially of currently used therapies.[26]

Before publication of the report of the Cholesterol Treatment Trialists' Collaboration,[27] there had been no systematic reviews of lipid modifying therapy confined to patients with diabetes,[28] but there is now strong evidence of similar relative benefits of statin therapy in these, compared with other, patients. Conversely, the evidence from HHS,[13] VA-HIT,[14] and BIP[15] in patients with diabetes or metabolic syndrome suggest possible larger than average benefits of fibrate therapy in patients with diabetes than in those without.

In FIELD, however, this was not the case. Overall, the effects of fenofibrate on cardiovascular events were less than planned for in the study design. Our trial was designed to detect a 22% reduction in coronary heart disease events in the intention-to-treat analysis, corresponding to a 27% reduction for those taking fenofibrate. The study achieved its planned follow-up duration of 5 years and exceeded the target number of primary outcome events needed to attain at least 80% power to identify such effects. The large study sample also allowed for differential statin use between groups on a scale similar to that we encountered.

The reduction in coronary heart disease events we noted is less than that reported in other randomised trials of fibrate therapy, particularly in patients with diabetes and low HDL-cholesterol concentrations in the VA-HIT trial[14] or with metabolic syndrome (in a post-hoc analysis) in the BIP trial.[15] By contrast with these studies, in FIELD we noted no greater treatment effect in patients with features of metabolic syndrome than in those without. However, VA-HIT and BIP were both secondary prevention studies with different patients' characteristics and lipid profiles, limiting direct comparisons.

The yearly rates of death from coronary heart disease or non-fatal myocardial infarction of 1·2%, and of stroke events of 0·7%, noted in the placebo group of the FIELD study are very similar to the rates in the CARDS study of primary prevention of cardiovascular disease in type 2 diabetes.[29] The event rates in FIELD were even lower in patients with no previous cardiovascular disease. The FIELD event rates were less than half the corresponding rates in the groups with diabetes in the Heart Protection Study[20] and the secondary prevention fibrate study, VA-HIT. The low background cardiovascular event rates in FIELD might indicate the broader community-based selection of patients for the trial.

Why was the treatment effect not as great as expected? First, there was a significantly greater use of statin therapy in patients allocated placebo than in those on fenofibrate, presumably in response to non-study lipid measurements. Results of a prespecified analysis, with adjustment for statin use suggest a significant reduction with fenofibrate in the primary outcome of coronary heart disease events and total cardiovascular disease events. However, this analysis also shows a larger than anticipated reduction in

the risk of events arising after starting statin therapy, probably due to both statin treatment effects and patient selection effects when other lipid-lowering treatment is started. Consequently, the estimated treatment effects of both fenofibrate and added statin therapy in this non-randomised comparison should be interpreted cautiously. The possible masking of the effects of fenofibrate treatment by different rates of statin use can be alternatively estimated by assuming that statin uptake reduced the risk of all future cardiovascular events by a third. If the uptake of statin therapy occurred uniformly across different strata of risk, this would correspond to an underlying treatment benefit of fenofibrate of 17%, whereas if such therapy was used predominantly in patients at high risk, differential statin use might have masked an 18–20% risk reduction. Consequently, the greater use of statins in placebo-allocated patients provides only a partial explanation.

A second possible explanation relates to the unexpectedly small difference in HDL-cholesterol concentrations between the two groups. The average increase in the fenofibrate group compared with the placebo group, as seen within the active run-in period[21] and also within the first few months of randomisation, was smaller than in previous non-diabetic cohorts, but is similar to that of other diabetic cohorts.[14,17] Further, the HDL-cholesterol concentrations in the two treatment groups converged as the study progressed, to the extent that about a third of the initial difference remained at study end. This pattern was noted in individuals who did and who did not use statins during the trial, suggesting a diminution of effect of long-term treatment on this lipid fraction. In view of the durable differences in total cholesterol, LDL-cholesterol, and triglyceride concentrations between groups in those who did not start statin therapy, the explanation for this observation is unclear. However, it is noteworthy that patients with diabetes in the VA-HIT trial had a smaller increase in HDL-cholesterol levels but a larger reduction in cardiovascular disease events than others, lending support to analyses showing that changes in HDL-cholesterol concentrations were not the major predictor of the clinical benefits of fibrates in that study.

Allocation to fenofibrate was associated with various biochemical non-lipid effects, including those on homocysteine, creatinine, and HbA1c. Fibrates increase homocysteine; gemfibrozil apparently less than fenofibrate.[30] How much these changes contributed to the results of the study is uncertain. The median plasma homocysteine concentration increased by about 4 μmol/L in the fenofibrate-allocated group compared with the placebo group. Epidemiological data suggest an increase in risk of 10–20% in cardiovascular events could be associated with this difference,[31] but whether changes in homocysteine are causal for cardiovascular disease or an epiphenomenon is unknown, and to date there is no randomised evidence that lowering homocysteine levels reduces cardiovascular disease events. Fenofibrate-associated changes in creatinine have not been reported to be related to a fall in glomerular filtration rate[32] and therefore seem unlikely to be clinically significant. The minor HbA1c changes are also unlikely to have contributed much to the final outcome. All three of these changes were fully reversed within 6–8 weeks of stopping fenofibrate.

Another unexplained result is the observation of a significant reduction in non-fatal cardiovascular disease events while there was a non-significant excess in fatal cardiovascular disease events. This occurrence lessened the effect of treatment on the composite outcomes of coronary heart disease events and total cardiovascular disease events, and so we examined whether it was related to differential rates of other treatments for cardiovascular disease after an initial non-fatal ischaemic cardiovascular disease event. However, the increased use of most ancillary treatments was quite similar for both randomised groups by study close out, and the greater use of statins in the placebo group arose mostly before the patient's first cardiovascular disease event. Consequently, use of ancillary treatment does not explain the larger effect on non-fatal compared with fatal outcomes, although statin therapy might have reduced coronary heart disease deaths to a moderately greater extent in the placebo group than in the fenofibrate group.

We noted a non-significant excess in non-cardiovascular disease deaths, as also reported in some other fibrate trials.[26,33] However, this apparent excess was not attributable to any specific cause of death, nor was it linked to a significant increase in any specific non-fatal non-cardiovascular disease event, such as invasive cancers, and so remains consistent with a chance finding. Fenofibrate was generally very well tolerated and appeared safe. There was no greater rate of discontinuation of study medication in those allocated fenofibrate overall or in association with adverse events. Pancreatitis has been previously reported with fenofibrate use. The small excess of venous thromboembolic events has not been previously reported, nor are we aware of any thrombotic tendency from this treatment.

We noted an important effect of treatment with fenofibrate on the progression of albuminuria, as reported previously in DAIS.[34] Additionally, we noted a favourable effect of fenofibrate on the need for retinal laser therapy. Taken together, these findings suggest a beneficial effect of fenofibrate on the microvasculature, which cannot be explained by changes in HbA1c or concomitant medications, or by the minor reduction in blood pressure in the fenofibrate group. The mechanisms of these effects are unknown.

There was possible heterogeneity in the effect of fenofibrate between some of the prespecified subgroups in the study. For example, by contrast with the significant reduction in major cardiovascular events in patients without previous cardiovascular disease as well as in patients younger than age 65 years, there was no apparent

treatment-related benefit in those with previous cardiovascular disease and in patients older than age 65 years. These differences in outcomes between subgroups did not seem to be explained by either the differential use of statin therapy or differences in the proportions of fatal to non-fatal events in these subgroups.

FIELD provides information to help guide clinicians on the future use of fenofibrate in patients with type 2 diabetes. The results are likely to be of particular importance among patients without previous cardiovascular disease and in settings where both the prevention of non-fatal macrovascular events and microvascular complications are judged important. Fenofibrate should be considered in the context of the well established benefits of statin therapy, where its main use will probably be in combination therapy. This question is being addressed directly in the ongoing ACCORD trial.[35] Meanwhile, our results do provide substantial information about the safety of fenofibrate, which was well tolerated when used alone or in combination.

Writing committee
A Keech, R J Simes, P Barter, J Best, R Scott, M R Taskinen, P Forder, A Pillai, T Davis, P Glasziou, P Drury, Y A Kesäniemi, D Sullivan, D Hunt, P Colman, M d'Emden, M Whiting, C Ehnholm, M Laakso.

Management committee
Executive committee members—P Barter, J Best, A Keech (study chairman and principal investigator), R Scott, R J Simes, M-R Taskinen
Other—P Colman, M d'Emden, T Davis, P Drury, C Ehnholm, P Glasziou, D Hunt, YA Kesäniemi, M Laakso, D Sullivan, M Whiting; J-C Ansquer, B Fraitag (non-voting sponsor representatives).

Outcomes assessment committee
N Anderson, G Hankey, D Hunt (chairman), S Lehto, S Mann, M Romo; L P Li (outcomes officer, in attendance).

Safety and data monitoring committee
C Hennekens, S MacMahon (chairman), S Pocock, A Tonkin, L Wilhelmsen; P Forder (unblinded statistician, in attendance).

Site principal investigators
Australia—H Akauola, F Alford, P Barter, I Beinart, J Best, S Bohra, S Boyages, P Colman, H Connor, D Darnell, T Davis, P Davoren, F Lepre, F De Looze, M d'Emden, A Duffield, R Fassett, J Flack, G Fulcher, S Hamwood, D Harmelin, R Jackson, W Jeffries, M Kamp, L Kritharides, L Mahar, V McCann, D McIntyre, R Moses, H Newnham, G Nicholson, R O'Brien, K Park, N Petrovsky, P Phillips, G Pinn, D Simmons, K Stanton, B Stuckey, D R Sullivan, M Suranyi, M Suthers, Y Tan, M Templer, D Topliss, J H Waites, G Watts, T Welborn, D Wilson, R Wyndham.
Finland—H Haapamäki, A Kesäniemi, M Laakso, J Lahtela, H Levänen, J Saltevo, H Södervik, M-R Taskinen, M Vanhala
New Zealand—J Baker, A Burton, P Dixon, J Doran, P Drury, P Dunn, N Graham, A Hamer, J Hedley, P Manning, I McPherson, S Morris, C Renner, R Scott, R Smith, M Wackrow, S Young.

Co-investigators and site coordinators
Australia—J Alcoe, C Allan, J Amerena, C Anderson-Stanford, N Arnold, T Arsov, D Ashby, C Atkinson, L Badhni, M Balme, D Barton, B Batrouney, C Beare, T Beattie, J Beggs, C Bendall, C Bendall, A Benz, D Black, A Bond, R Bradfield, J Bradshaw, S Brearley, D Bruce, J Burgess, M Callary, J Campbell, H Carr, K Chambers, J Chow, S Chow, K Ciszek, P Clifton, P Clifton-Bligh, V Clowes, P Coates, C Cocks, S Cole, D Colquhoun, M Correcha, S Coverdale, M Croft, J Crowe, W Davis, J Dunn, S Edwards, R Elder, S El-Kaissi, L Emery, M England, O Farouque, M Fernandez, B Fitzpatrick, N Francis, P Francis, P Freeman, A Fuller, V Gaylard, C George, C Gillzan, C Glatthaar, J Goddard, V Grange, T Greenaway, J Griffin, A Grogan, S Guha, J Gustafson, P S Hamblin, I Hamilton-Craig, T Hannay, C Hardie, A Harper, G Hartl, A Harvey, S Havlin, K Haworth, P Hay, L Hay, B Heenan, R Hesketh, A Heyworth, M Hines, G Hockings, A Hodge, L Hoffman, L Hoskin, M Howells, D Hunt, A Hunt, W Inder, D Irvine, D Jackson, C Jang, K Kearins, P Kee, J Keen, D Kilpatrick, J Kindellan, M Kotowicz, E Lahz, A Lassig, M Layton, S Lean, H Legg, E Lim, F Long, L Lucas, D Ludeman, C Ludeman-Robertson, M Lyall, L Lynch, C Maddison, B Malkus, A Marangou, F Margrie, N Martyn, K Matthiesson, J Matthiesson, S Maxwell, V Maxwell, K McCarthy, A McElduff, H McKee, J McKenzie, K McLachan, P McNair, M Meischke, A Merkel, C Miller, E Morrison, A Morton, W Mossman, A Mowat, J Muecke, P Murie, S Murray, P Nadorp, S Nair, J Nairn, A Nankervis, K Narayan, N Nattrass, J Ngui, S Nicholls, V Nicholls, C Nolan, J A Nye, E Nye, D O'Neil, M O'Neill, S O'Rourke, J Pearse, C Pearson, L Pittis, D Playford, L Porter, L Porter, R Portley, M Powell, C Preston, S Pringle, J Raffaele, G Ramnath, J Ramsden, G Rayment, S Roffe, S Rosen, G Ross, Z Ross, J Rowe, D Rumble, S Ryan, N Sachithanandan, J Sansom, L Sefert, E Shanahan, J Shepherd, G Sherman, R Siddall, D Silva, S Simmons, R Simpson, A Sinha, R Slobodniuk, M Smith, P Smith, S Smith, V Smith-Orr, L Socha, T Stack, K Steed, K Steele, J Stephensen, P Stevens, G Stewart, C Strakosch, M Sullivan, S Sunder, J Sunderland, E Tapp, J Taylor, D Thorn, A Tolley, D Torpy, G Truran, F Turner, J Turner, S Varley, J Wallace, J Walsh, J Walshe, G Ward, B Watson, J Watson, A Webb, F Werner, E White, A Whitehouse, N Whitehouse, S Wigg, E Wilmshurst, G Wittert, B Wong, M Wong, S Worboys, S Wright, S Wu, J Yarker, M Yeo, K Young, J Youssef, R Yuen, H Zeimer, R W Ziffer.
Finland—A Aura, A Friman, J Hanninen, J Henell, A Hiukka, N Hyvärinen, M Ikonen, A Itkonen, A Jantunen, A Jarva, T Jerkkola, V Jokinen, J Juutilainen, H Kähkönen, T Kangas, P Karja-Koskenkari, L Karjalainen, M Karttunen, P Kauranen, S Kortelainen, H Koukkunen, L Kumpulainen, T Laitinen, M Laitinen, S Lehto, R Lehto, E Leinonen, M Lindström-Karjalainen, A Lumiaho, J Mäkela, K Makinen, L Mannermaa, T Mård, M Metso, J Miettinen, V Naatti, S Paavola, P Pajunen, S Pöykkö, A Pulkkinen, J Ripatti, S Ruotsalainen, A Salo, M Siiskonen, A Soppela, J Starck, I Suonranta, A Toivonen, L Ukkola, K Valli, S Vehkavaara, J Virolainen.
New Zealand—P Allan, W Arnold, W Bagg, K Balfour, P Ball, B Ballantine, C Barker, C Barker, F Bartley, E Berry, G Braatvedt, A Campbell, T Clarke, R Clarke, A Claydon, S Clayton, P Cresswell, R Cutfield, J Delahunt, A Dissnayake, C Eagleton, C Ferguson, C Florkowski, D Fry, P Giles, M Gluyas, C Grant, P Guile, M Guolo, P Hale, M Hammond, M Hammond, P Healy, M Hills, J Hinge, J Holland, B Hyne, A Ireland, A Johnstone, S Jones, G Kerr, K Kerr, M Khant, J Krebs, L Law, B Lydon, K MacAuley, R McEwan, P McGregor, B McLaren, L McLeod, J Medforth, R Miskimmin, J Moffat, M Pickup, E Reda, C Ross, A Ryalls, D Schmid, N Shergill, H Snell, L Stevens, A Waterman, V Watts.

Coordinating centre teams
NHMRC clinical trials centre, Sydney—S Blakesmith, K Jayne, E Keirnan, P Newman, G Ritchie, A Rosenfeld (project directors), E Beller, P Forder, V Gebski, A Pillai (study statisticians), S Copt, S Heritier, A Kirby, R O'Connell (validation statisticians), C Sutton (data systems manager), C Anderson, T Biddle, S-Y Chan, S Czyniewski, A Dobbie, S Doshi, A Dupuy, S Eckermann, M Edwards, N Fields, K Flood, S Ford, C French, S Gillies, C Greig, M Groshens, J Gu, M Guo, Y Guo, W Hague, S Healey, L Hones, Z Hossain, M Howlett, J Lee, L-P Li, F Liang, T Matthews, J Micallef, I Minns, S Mulray, A Nguyen, F Papuni, A Patel, J Pearse, R Pike, M Pena, K Pinto, D Schipp, J Schroeder, B Sim, L Snaith, T Sourjina, R Taylor, P Vlagsma, S Walder, R Walker, J Zhang, B Zhong, A Keech (deputy director), R J Simes (director).
Helsinki project office—A Kokkonen, A Leppämäki, P Narva, A Salo, A-M Syrjänen, M-R Taskinen (director).
Christchurch project office—C Lintott, R Scott (director).

Central laboratories
SouthPath Laboratories, Flinders Medical Centre, Adelaide, Australia—L Clark, J Leach, M Pejakovic, R Tirimacco, M Whiting.
National Public Health Institute Laboratories, Helsinki, Finland—C Ehnholm, M Ikonen, M Kajosaari, L Råman, J Sundvall, M Tukianen.

Laboratoires Fournier SA liaison
Dijon—J C Ansquer, B Fraitag, D Crimet, F Aubin, F Golly, I Sirugue, C Foucher, K Le Malicot.
Sydney—P Aubonnet.

Conflict of interest statement

Some members of the writing committee (AK, RJS, PB, JB, RS, M-RT, TD, YAK, DS, PC, Md'E, and ML) have had the costs of participating in scientific meetings and/or contributing to advisory boards or doing other research reimbursed by the pharmaceutical industry. YAK holds stocks in one pharmaceutical company. All other members of the wrwiting committee declare that they have no conflict of interest.

Acknowledgments

This study is supported by a grant from Laboratoires Fournier SA, Dijon, France, and is being coordinated independently by the National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney, Australia, and overseen by the study management committee. The study is also supported by the National Health and Medical Research Council, Australia (Unit grant, Project grant, and Fellowships to AK and JS). We thank the National Heart Foundation, Australia, Diabetes Australia, Diabetes New Zealand, and the Finnish Diabetes Association for endorsing the study. The assistance of Medfiles, Finland, and DataPharm Australia staff is gratefully acknowledged as is the Australian Institute of Health and Welfare for providing assistance with searching of the National Death Index. We also thank R Pike, J C Ansquer, C Foucher, and K Le Malicot for their assistance with the preparation of this manuscript; and the many patients who participated in the FIELD study.

References

1 Barrett-Connor E, Orchard T. Diabetes and heart disease. In: National Diabetes Data Group. Diabetes data compiled 1984. Washington: US Department of Health and Human Services, XVI-XVI-41, 1985.

2 Stamler J, Vaccaro O, Neaton JD, Westworth D. Diabetes and other risk factors and the 12-year cardiovascular mortality for men screened for the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; **16:** 434–44.

3 Zuanetti G, Latini R, Maggioni AP, et al. Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 study. *J Am Coll Cardiol* 1993; **22:** 1788–94.

4 Keech AC, Colquhoun D, Best J, et al. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. *Diabetes Care* 2003; **26:** 2713–21.

5 Laakso M, Voutilainen E, Sarlund H, et al. Serum lipids and lipoproteins in middle aged non-insulin dependent diabetics. *Atherosclerosis* 1985; **56:** 271–81.

6 Feingold KR, Grunfeld C, Pang M, et al. LDL subclass phenotypes and triglyceride metabolism in non-insulin dependent diabetes. *Arterioscler Thromb* 1992; **12:** 1496–502.

7 Wilson PWF, Kannel WB, Anderson KM. Lipids, glucose intolerance and vascular disease: The Framingham Study. *Monogr Atheroscler* 1985; **13:** 1–11.

8 Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. *Diabetologia* 2003; **46:** 733–49.

9 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.

10 Assmann G, Schulte H. Triglycerides and atherosclerosis; results from the Prospective Cardiovascular Munster Study. *Arterioscler Rev* 1991; **22:** 51–57.

11 Keating GM, Ormrod D. Micronised fenofibrate: an updated review of its clinical efficacy in the management of dyslipidaemia. *Drugs* 2002; **62:** 1909–44.

12 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.

13 Koskinen P, Mänttäri M, Manninen V, Huttunen JK, Heinonen OP, Frick MH. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 1992; **15:** 820–25.

14 Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin and cardiovascular disease. Subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med* 2002; **162:** 2597–604.

15 Tenenbaum A, Motro M, Fisman EZ, Tanne D, Boyko V, Behar S. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. *Arch Intern Med* 2005; **165:** 1154–60.

16 Elkeles RS, Diamond JR, Poulter C, et al. Cardiovascular outcomes in type 2 diabetes: a double-blind placebo-controlled study of bezafibrate—the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. *Diabetes Care* 1998; **21:** 641–48.

17 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. *Lancet* 2001; **357:** 905–10.

18 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. *Cardiovasc Diabetol* 2004; **3:** 9.

19 Signorini DF, Leung O, Simes RJ, Beller E, Gebski VJ, Callaghan T. Dynamic balanced randomization for clinical trials. *Stat Med* 1993; **12:** 2343–250.

20 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; **361:** 2005–16.

21 The FIELD Study Investigators. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, a randomized, placebo-controlled trial: baseline characteristics and short-term effects of fenofibrate [ISRCTN 64783481]. *Cardiovasc Diabetol* 2005; **4:** 13.

22 Anon. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. *JAMA* 2001; **285:** 2487–97.

23 Peto R, Pike MC, Armitage P, et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976; **34:** 585–612.

24 Peto R, Pike MC, Armitage P, et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient, 2: analysis and examples. *Br J Cancer* 1977; **35:** 1–39.

25 Collett D. Modeling survival data in medical research. London: Chapman & Hall, 1994.

26 Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. Effect of different antilipidemic agents and diets on mortality: a systemic review. *Arch Intern Med* 2005; **165:** 725–30.

27 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005; **366:** 1267–78.

28 Gami AS, Montori VM, Erwin PJ, Khan MA, Smith SA. Systematic review of lipid lowering for primary prevention of coronary heart disease in diabetes. *BMJ* 2003; **326:** 528–29.

29 Colhoun HM, Betteridge DJ, Durrington PN, et al. 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.

30 Syvanne M, Whittall RA, Turpeinen U, et al. Serum homocysteine concentrations, gemfibrozil treatment, and progression of coronary atherosclerosis. *Atherosclerosis* 2004; **172:** 267–72.

31 Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA* 2002; **288:** 2015–222.

32 Hottelart C, El Esper N, Rose F, Hachard JM, Fournier A. Fenofibrate increases creatininemia by increasing metabolic production of creatinine. *Nephron* 2002; **92:** 536–41.

33 Heady JA, Morris JN, Oliver MF. WHO clofibrate/cholesterol trial: clarifications. *Lancet* 1992; **340:** 1405–06.

34 Ansquer JC, Foucher C, Rattier S, Taskinen MR, Steiner G, for the DAIS investigators. Fenofibrate reduces progression to microalbuminuria over 3 years in the placebo-controlled study in type 2 diabetes: results from Diabetes Atherosclerosis Intervention Study (DAIS). *Am J Kidney Dis* 2005; **45:** 485–93.

35 ACCORD. http://www.accordtrial.org/public/index.cfm (accessed Oct 24, 2005).