Effects of fenofibrate on cardiovascular events in patients with diabetes, with and without prior cardiovascular disease

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study

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Effects of fenofibrate on cardiovascular events in patients with diabetes, with and without prior cardiovascular disease: the FIELD study

Running title: Fenofibrate treatment and previous CVD

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Abstract

Background

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, comparison of the effect of fenofibrate on cardiovascular disease (CVD) between those with prior CVD and without was a prespecified subgroup analysis.

Methods

The effects of fenofibrate on total CVD events and its components in patients who did (*n*=2131) and did not (*n*=7664) have a history of CVD were computed by Cox proportional-hazards modeling and compared by testing for treatment-by-subgroup interaction. The analyses were adjusted for commencement of statins, use of other CVD medications and baseline covariates. Effects on other CVD endpoints were explored.

Results

Patients with prior CVD were more likely than those without to be male, to be older (by 3.3 years), to have had a history of diabetes for 2 years longer at baseline, and to have diabetic complications, hypertension, and higher rates of use of insulin and CVD medications. Discontinuation of fenofibrate was similar between the subgroups, but more patients with prior CVD than without, and also more placebo than fenofibrate-assigned patients, commenced statin therapy. The borderline difference in the effects of fenofibrate between those who did (HR 1.02; 95% CI, 0.86–1.20) and did not have prior CVD (HR 0.81; 95% CI, 0.70–0.94; heterogeneity *P*=0.045) became nonsignificant after adjustment for baseline covariates and other CVD medications (HR 0.96; 95% CI 0.81–1.14 vs HR 0.78; 95% CI 0.67–0.90) (heterogeneity *P*=0.06).

Conclusions

Our findings do not support treating patients with fenofibrate differently on the basis of any history of CVD, in line with evidence from other trials.

Keywords

Fibrates; cardiovascular risk factors; type 2 diabetes; cardiovascular disease; subgroup analysis

Introduction

In people with diabetes, who are already at higher risk of cardiovascular disease (CVD), a prior CVD event more than doubles the risk of having a major CVD event and approximately triples the risk of cardiovascular death.[1]

Cholesterol-lowering treatments may be used to modify the characteristic diabetic dyslipidemic pattern.[2] People with type 2 diabetes have low high-density lipoprotein (HDL) cholesterol levels and high triglyceride levels,[3, 4] both of which are associated with higher risks of CHD.[5-7] Fibrates are more effective in reducing triglyceride levels and possibly raising HDL cholesterol levels than HMG–CoA reductase inhibitors (statins),[8 9] and may reduce CVD in people with diabetes.[10-12]

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, treatment with fenofibrate compared with placebo over an average of 5 years resulted in a nonsignificant 11% relative risk reduction (95% CI -5% to 25%) in the primary outcome, coronary events (CHD death or nonfatal myocardial infarction).[6] Fenofibrate treatment significantly reduced the prespecified outcome for subgroup comparisons— a composite of total CVD events (coronary events, stroke, and coronary and carotid revascularisation) by 11% (*P*=0.035).[6] Subgroup comparisons specified in the main protocol included the effects of treatment in patients with a history of CVD compared with patients with no such history. Total cardiovascular events were reduced by fenofibrate treatment in those with no prior CVD (HR 0.81; 95% CI, 0.70–0.94), but not in those with CVD (HR 1.02; 95% CI, 0.86–1.20; interaction *P*=0.045). These results generated considerable discussion. Therefore, this paper examines these findings in more detail.

Methods

Study design

Detailed descriptions of the FIELD study design and baseline characteristics have been published.[6 13] Between February 1998 and November 2000, people with type 2 diabetes

aged between 50 and 75 years were recruited from hospitals and other sources, and 9795 were randomly allocated to either daily micronised fenofibrate 200 mg (Laboratoires Fournier, Dijon, France) or matching placebo. They were followed up for a median of 5 years.[6] Lipid criteria for entry to the study included plasma total cholesterol 3.0–6.5 mmol/L (115–250 mg/dl), plus a total-to-HDL cholesterol ratio ≥4.0 or plasma triglyceride levels of 1.0–5.0 mmol/L (40–195 mg/dl), with no clear indication for or treatment with, lipid-modifying therapy at study entry. The study design allowed for the commencement of other lipid-lowering therapies during the study at the discretion of the patient's usual physician. Exclusion criteria included renal impairment (serum creatinine >130 μmol/L(1.47 mg/dL)), chronic liver disease, symptomatic gallbladder disease, and any CVD event within three months before recruitment.

The prespecified outcome for subgroup analyses was total CVD, a composite of coronary events (CHD death and nonfatal myocardial infarction), stroke, and coronary and carotid revascularization. Effects on this composite and its components are presented.

Patients were categorized as those with and those without CVD before randomization. Prior CVD was defined as a reported history of myocardial infarction, stroke, angina (stable or unstable), coronary revascularization (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty and/or stenting), claudication, peripheral arterial vascular disease, or peripheral arterial revascularization.

All major CVD events and deaths were adjudicated by the Outcomes Assessment Committee blinded to treatment allocation and using prespecified definitions.

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

Statistical methods

For baseline characteristics, categorical outcomes were compared by suitable χ^2 tests, while continuous outcomes were compared by *t* tests, or if the distribution of the data was non-normal, the Wilcoxon rank–sum test.

Change from baseline lipid levels was analyzed using linear models predicting lipid levels at 1 year, 2 years, and study close. The baseline lipid level was included as a covariate in the model along with CVD group and treatment group. The prior-CVD-by-treatment interaction term in the model was tested to determine whether effects of treatment on lipid levels differed between those with and those without prior CVD.

Standard log-rank methods were used without adjustment for covariates to determine the statistical significance of the effect of treatment on outcomes within each level of a subgroup.[14] Cox proportional hazards modeling was used to compute the hazard ratio (HR) and its 95% confidence intervals (CIs) and to allow adjustment for baseline covariates (where specified).[15, 16] The following baseline covariates were adjusted for: sex, age (in 5-year groups), diabetes duration (0–2, 3–10, >10 years), smoking status (current vs not current), prior cancer, peripheral nerve damage (detected via monofilament test), systolic blood pressure (mmHg), total cholesterol (mmol/L), HDL cholesterol (mmol/L), hemoglobin A_{1c} (%) and plasma creatinine (mol/L). A test for treatment-by-prior-CVD-subgroup interaction (heterogeneity) in the proportional-hazards model was performed to determine whether the hazard ratio for the effect of treatment on outcome events differed according to prior history of CVD.[17, 18] When this test was no significant, the overall estimate of the treatment effect in the combined groups (rather than any subgroup-specific estimates) was considered the most valid estimate of treatment efficacy. Although total CVD was the prespecified primary endpoint for subgroup analyses, we also included the components of total CVD as an exploratory analysis and consider these analyses hypothesis generating rather than hypothesis confirming.[18]

We undertook additional analyses incorporating adjustment for nonstudy lipid-lowering therapy (statins) and other cardiovascular medications during follow-up because the proportions of patients taking these drugs in the two treatment groups were different, as were the proportions taking them in the prior-CVD subgroups. Adjustment for the use of these medications incorporated a penalized Cox model which adjusted the risk of a CVD event occurring individually for the period during which a patient took statins or other cardiovascular medications (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics and antiplatelet agents) according to external estimates of their effects on CVD event rates.[19] Analyses were further adjusted for the baseline characteristics previously listed.

All analyses were according to intention-to-treat to maintain the benefit of a randomized comparison. Results were not adjusted for multiple comparisons as outcomes were highly correlated.[18] All analyses used SAS (version 9.2; SAS Institute Inc., Cary, NC, USA).

Funding and ethical approval

The FIELD trial was funded by Laboratoires Fournier SA (now part of Abbott) and grants from the National Health and Medical Research Council, Australia. It was designed by an independent management committee, and coordinated by the NHMRC Clinical Trials Centre, University of Sydney. All patients provided written informed consent. The study protocol was approved by local institutional and national ethics committees and the study was performed in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines.

Results

Baseline characteristics

Of 9795 patients, 2131 (21.8%) had a history of a prior CVD at baseline. Prior CVD events included; myocardial infarction (5.0% of patients), stroke (3.5%), angina (12.1%), and coronary revascularization (3.7%).

Although the baseline characteristics of the two treatment groups in the main study were well matched,[6] the baseline characteristics of those with and without prior CVD differed substantially (Table 1). Participants with prior CVD were more likely to be male, were on average 3.3 years older, had a longer average duration of history of diabetes (2 years longer), and were more likely to have microvascular complications of diabetes, to be smokers, to have hypertension, and to have high HbA_{1c}, serum creatinine or homocysteine levels. Baseline lipid levels in the two groups were statistically significantly different although very similar in absolute terms. Those patients with prior CVD were also more likely to use insulin, less likely to be managed by diet and had more frequent use of most other CVD medications (Table 1). Complete data were available for all variables except diabetes duration, which was missing for 17 patients, who were excluded from the multivariable analyses.

Lipids and the effect of fenofibrate treatment

There were small but statistically significant differences between participants with and without prior CVD in their pattern of lipid response to treatment (Figure 1). At 12 months after randomization the effect of fenofibrate in raising HDL cholesterol and lowering LDL cholesterol and triglyceride levels was greater in those with no prior CVD than in those with prior CVD (all $P<0.05$). At 24 months after randomization, differences in treatment effect between prior CVD subgroups were seen for HDL cholesterol ($P=0.046$) and triglycerides ($P=0.002$). At study close, differences were seen for LDL cholesterol ($P=0.01$) and triglycerides ($P=0.006$).

Compliance with trial medication and use of other drugs

Over the course of the study, those allocated placebo had a higher uptake of lipid-lowering therapy (mainly statins) than those allocated fenofibrate (17% and 8%, respectively, averaged over the study period). There was also a higher uptake of statins among participants with prior CVD than those without and a slightly higher uptake of other CVD medications.[6, 13, 19] Patients with prior CVD discontinued fenofibrate therapy more often

than those with no prior CVD (14% and 9%, respectively) (Figure 2). Discontinuing fenofibrate because of a possible adverse drug reaction was more common in the subgroup with no prior CVD ($P<0.001$), but discontinuing due to a hospital admission was more common in the prior-CVD group ($P=0.003$).

Unadjusted effect of treatment on outcomes

The unadjusted effect of fenofibrate on future total CVD events differed by prior CVD status (interaction $P=0.05$). There was an independently significant reduction in the risk of a CVD event (HR 0.81; 95% CI, 0.70–0.94; $P=0.004$) in the group without prior CVD whereas in the prior-CVD group, there was no significant effect of treatment (HR 1.02; 95% CI, 0.86–1.20, $P=0.9$).[6]

Components of total CVD

An exploratory analysis of the major components of the total-CVD composite outcome showed a statistically significant difference in treatment effect between those with and those without prior CVD for coronary events (interaction $P=0.03$) but not stroke ($P=0.56$) nor revascularization ($P=0.053$) (Figure 3). For coronary events there was an independently significant reduction in the risk of an event (HR 0.75; 95% CI, 0.59–0.94, $P=0.01$) in the group without prior CVD whereas in the prior-CVD group, there was no significant effect of treatment (HR 1.08; 95% CI, 0.84–1.38, $P=0.55$).

Adjusted analyses of treatment effect

Even after the adjustment for uneven uptake of statins and other cardiovascular medications across treatment arms, the treatment-by-prior-CVD interaction term remained significant (statins only $P=0.05$; statins plus other CVD medications $P=0.04$) (Figure 4). However, after adjustment for baseline covariates, differences in treatment effects were no longer apparent ($P=0.06$).

Discussion

In this prespecified FIELD substudy, fenofibrate reduced total CVD events (the prespecified outcome for subgroup analyses) in those patients with no prior history of CVD, but did not in patients with a history of CVD before recruitment to the trial. However, when the difference between the patient groups with and without prior CVD was formally tested for interaction, the difference between them was only marginally significant, and was no longer significant after adjustment for baseline covariates.

Those with prior CVD were more likely to be receiving other CVD medications, including statins. Analyses were adjusted to account for differential uptakes of various medications on a per patient basis. However, the adjustment for use of statins and other CVD drugs had surprisingly little influence on the degree of heterogeneity, so it is unlikely that the marginal heterogeneity of treatment effects between prior-CVD subgroups was due to use of these other medications. Although those with prior CVD had more risk factors, this was not an explanation, as we have established that fenofibrate is equally effective in patients with different numbers of (1 to 4) risk factors (data not shown)

The components of total CVD analyzed in an exploratory analysis were coronary events, stroke, and coronary and carotid revascularization. Coronary events and revascularizations showed a similar pattern of treatment effects, with greater event reductions in the group with no prior CVD; however, only for coronary events were the treatment effects in the groups with and without prior CVD statistically different.

The analysis of prior CVD subgroups was one of 11 subgroup comparisons that were predefined.[6] Although subgroup comparisons were kept to a minimum of clinically important factors, and all used the same prespecified composite endpoint, the probability of finding at least one false-positive result for heterogeneity of treatment effect was 43%. This increased probability of a type I error, combined with the fact that the *P* value for the comparison was only of borderline significance, suggests this result could well be a chance finding.

Data from other fibrate monotherapy trials do not support lack of benefit in those with a history of CVD. The VA-HIT trial in men with prior CHD, low HDL cholesterol and normal LDL cholesterol showed that gemfibrozil significantly reduced the risk of CVD events (nonfatal myocardial infarction, coronary death, and stroke) by 32% in the 769 with diabetes (P=0.004).[12] In the Helsinki Heart Study, gemfibrozil reduced major coronary events (CHD death or nonfatal MI) by 68% in 135 men who had initial hypercholesterolemia and no history of CVD, although men with diabetes comprised only 3% of the study population and the effect in them was not independently significant.[20] Furthermore, the ACCORD trial, which examined the effect of fenofibrate in people with diabetes on a background of routine open-label statin therapy, also showed no difference in treatment effects between those with and those without prior CVD (heterogeneity P=0.45),[21] although there was no significant overall effect on the primary endpoint was shown overall. Lastly, a recent meta-analysis showed independently significant benefits of fibrate therapy in those with and without prior CVD, without statistical heterogeneity.[22]

Atherosclerosis develops over decades, and most people with diabetes already have subclinical evidence of this at the time their diabetes is diagnosed.[23] Accordingly, there are no particular reasons *a priori* to expect that the potential effects of an intervention would differ between those with or without prior clinical CVD events. On the other hand, because fenofibrate is a peroxisome-proliferator agonist and has anti-inflammatory effects as well as improving dyslipidemic profiles, larger effects of fenofibrate in those without prior CVD related to the role of cardiovascular inflammation are theoretically feasible.[24] The recent meta-analysis of fibrate trials suggested that fibrates may be particularly beneficial for patients with high triglyceride and low HDL cholesterol levels, who are at particularly high risk of CVD events.[22]

Introduction of statins during follow-up varied, but measures were introduced to allow for this in the statistical analyses. It is possible that the method used to adjust for uptake of these drugs did not fully account for its effects. The statin adjustment used independent

estimates derived from meta-analyses of large clinical trials;[19] this method does not incorporate possibly different absolute effects of statins in those with diabetes who have and have not had CVD.[25]

In conclusion, statins remain the cornerstone of lipid-modifying therapy in people with diabetes. Our detailed analyses showed no evidence of heterogeneity in the effect of fenofibrate given as well as statins between patients who had a history of CVD at baseline and those who did not. Patients already taking fenofibrate who have a CVD event may still benefit from continuing fenofibrate, particularly if they have elevated triglycerides and low HDL levels,[6, 21, 26] or are at risk of microvascular complications.[21, 27-29]

Acknowledgments

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Conflict of interest

JS has received an honorarium from Fournier. ACK and AT have received honoraria from pharmaceutical companies (including Fournier Pharma, now part of Abbott) and are on advisory panels for pharmaceutical companies. All other authors report no conflicts of interest.

Figure legends

Figure 1

Mean (SE) differences between fenofibrate and placebo in changes from baseline for plasma lipid levels, according to prior history of cardiovascular disease (CVD) (solid lines) or no prior CVD (dotted lines). Baseline measurements are the mean of Visit 2 (12 weeks before randomization) and Visit 3 (6 weeks before randomization), before the run-in on active treatment.

Figure 2

Average percentages of patients in each treatment arm who commenced other lipid-lowering treatment (A) or discontinued study treatment (B) per year, by prior CVD status.

Figure 3

A. Effects of fenofibrate in patients with prior cardiovascular disease (CVD) (*n*=2131) and without prior CVD (*n*=7664) on total CVD events, the prespecified composite endpoint for subgroup comparisons.

B. Exploratory analyses of the effects of fenofibrate in patients with and without prior CVD for the components of the composite total-CVD endpoint.

Figure 4

Effect of fenofibrate on total CVD events in those without and without prior CVD after adjustments for uptake of statins, other CVD medications and baseline characteristics.

Table 1: Baseline characteristics of patients with and patients without prior CVD

Characteristics	Prior CVD (*n*=2131)	No prior CVD (*n*=7664)	*P**
General characteristics			
Male (%)	1448 (67.9)	4690 (61.2)	<0.001
Age at Visit 1 (years, mean [SD])	64.8 (6.5)	61.5 (6.8)	<0.001
Diabetes duration (years, median [IQR])	7 (3–12)	5 (2–9)	<0.001
Systolic blood pressure (mmHg, mean [SD])	142.4 (15.6)	139.9 (15.2)	<0.001
Diastolic blood pressure (mmHg, mean [SD])	81 (8.7)	82 (8.5)	<0.001
Current smoker (%)	242 (11.4)	680 (8.9)	<0.001†
Clinical history (%)			
History of hypertension‡	1461 (68.6)	4085 (53.3)	<0.001
Microvascular disease‡	706 (33.1)	1319 (17.2)	<0.001
Laboratory data§			
Total cholesterol (mmol/L, mean [SD])	4.98 (0.69)	5.05 (0.71)	<0.001
(mg/dL, mean [SD]))	192 (27)	195 (27)	
LDL cholesterol (mmol/L, mean [SD])	3.03 (0.65)	3.08 (0.65)	0.002
(mg/dL, mean [SD]))	117 (25)	119 (25)	
HDL cholesterol (mmol/L, mean [SD])	1.06 (0.25)	1.11 (0.26)	<0.001
(mg/dL, mean [SD]))	41 (10)	43 (10)	
Triglyceride (mmol/L, median [IQR])	1.79 (1.35–2.40)	1.72 (1.34–2.30)	0.009
(mg/dL, mean [SD]))	158 (119–212)	152 (119–204)	
Hemoglobin A_{1c} (%, median [IQR])	7.0 (6.3–8.0)	6.8 (6.1–7.7)	<0.001
Baseline cardiovascular medication (%)			
Antiplatelets (including aspirin)	1222 (57.3)	1633 (21.3)	<0.001
ACE Inhibitors	882 (41.4)	2399 (31.3)	<0.001
Angiotensin II receptor antagonist	107 (5.0)	415 (5.4)	0.47
Beta blocker	616 (28.9)	806 (10.5)	<0.001
Calcium antagonists	656 (30.8)	1236 (16.1)	<0.001
Nitrate	510 (23.9)	40 (0.5)	<0.001
Diuretic	475 (22.3)	1010 (13.2)	<0.001
Baseline blood-glucose-lowering medication (%)			
Diet alone	432 (20.3)	2176 (28.4)	<0.001
Metformin alone	321 (15.1)	1400 (18.3)	<0.001
Insulin (± oral agents)	412 (19.3)	934 (12.2)	<0.001

* *P* value from chi-square test for categorical variables, *t* test for normally distributed continuous variables or Wilcoxon rank–sum test for non-normally distributed continuous variables.

† *P* value for smoking status (current, ex-smoker or never smoked) from 3 x 2 chi-square test.

‡ Self reported at Visit 1

§ Mean of Visit 2 and Visit 3, except for HbA1c and creatinine (mean of Visit 1 and Visit 3) and homocysteine (Visit 3)

CVD = cardiovascular disease; SD = standard deviation; IQR = interquartile range; LDL = low-density lipoprotein; HDL = high-density lipoprotein

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HDL cholesterol (mmol/L, mean [SD])	1.06 (0.25)	1.11 (0.26)	<0.001
(mg/dL, mean [SD]))	41 (10)	43 (10)	
Triglyceride (mmol/L, median [IQR])	1.79 (1.35–2.40)	1.72 (1.34–2.30)	0.009
(mg/dL, mean [SD]))	158 (119–212)	152 (119–204)	
Hemoglobin A_{1c} (%, median [IQR])	7.0 (6.3–8.0)	6.8 (6.1–7.7)	<0.001
Baseline cardiovascular medication (%)			
Antiplatelets (including aspirin)	1222 (57.3)	1633 (21.3)	<0.001
ACE Inhibitors	882 (41.4)	2399 (31.3)	<0.001
Angiotensin II receptor antagonist	107 (5.0)	415 (5.4)	0.47
Beta blocker	616 (28.9)	806 (10.5)	<0.001
Calcium antagonists	656 (30.8)	1236 (16.1)	<0.001
Nitrate	510 (23.9)	40 (0.5)	<0.001
Diuretic	475 (22.3)	1010 (13.2)	<0.001
Baseline blood-glucose-lowering medication (%)			
Diet alone	432 (20.3)	2176 (28.4)	<0.001
Metformin alone	321 (15.1)	1400 (18.3)	<0.001
Insulin (± oral agents)	412 (19.3)	934 (12.2)	<0.001

* *P* value from chi-square test for categorical variables, *t* test for normally distributed continuous variables or Wilcoxon rank–sum test for non-normally distributed continuous variables.

† *P* value for smoking status (current, ex-smoker or never smoked) from 3 x 2 chi-square test.

‡ Self reported at Visit 1

§ Mean of Visit 2 and Visit 3, except for HbA1c and creatinine (mean of Visit 1 and Visit 3) and homocysteine (Visit 3)

CVD = cardiovascular disease; SD = standard deviation; IQR = interquartile range; LDL = low-density lipoprotein; HDL = high-density lipoprotein

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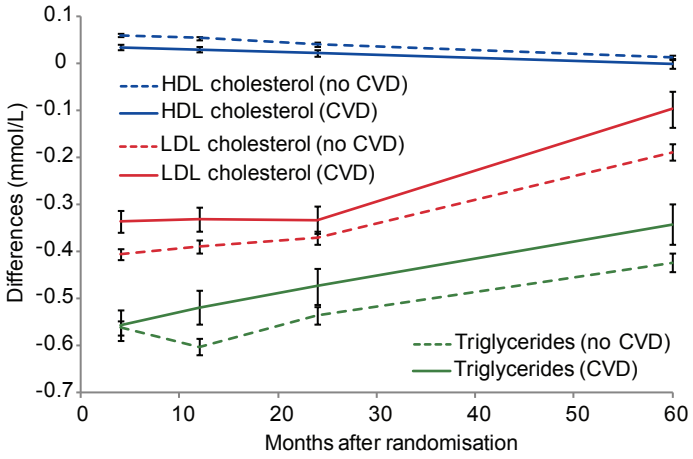
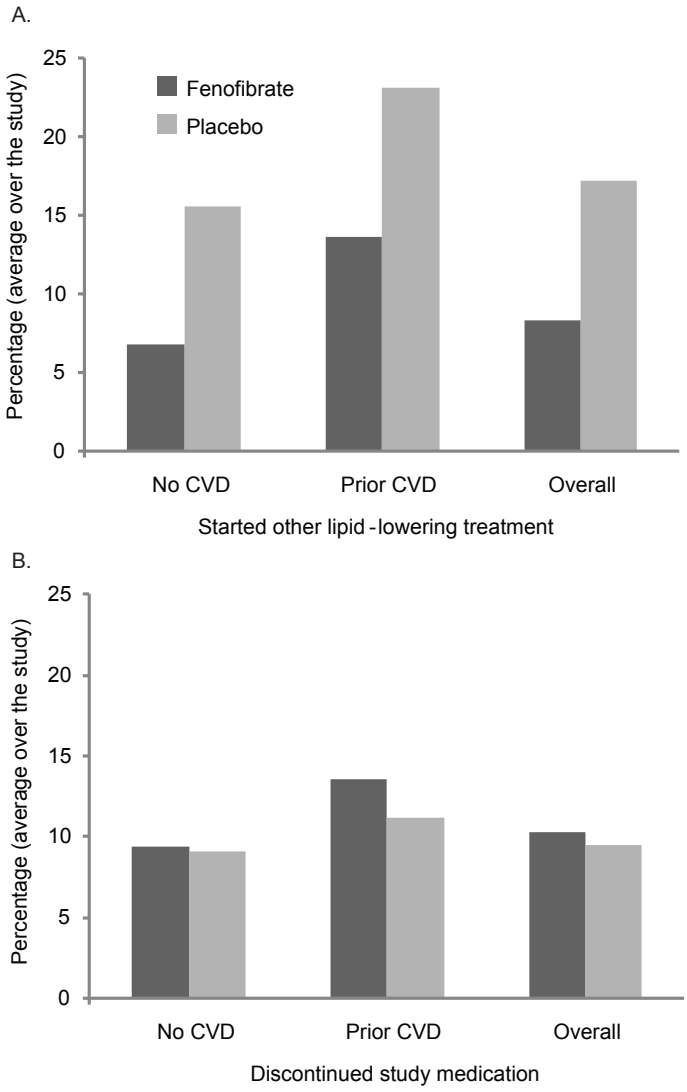
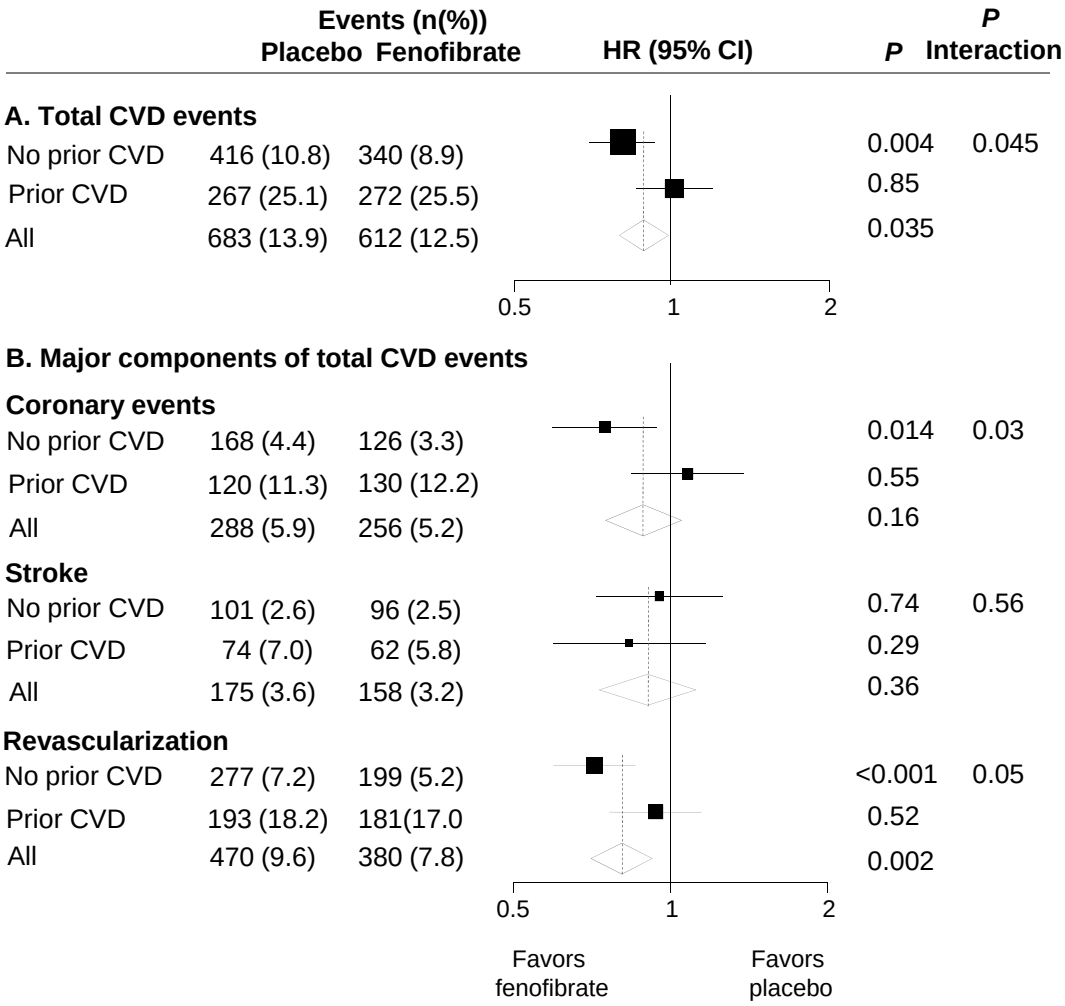
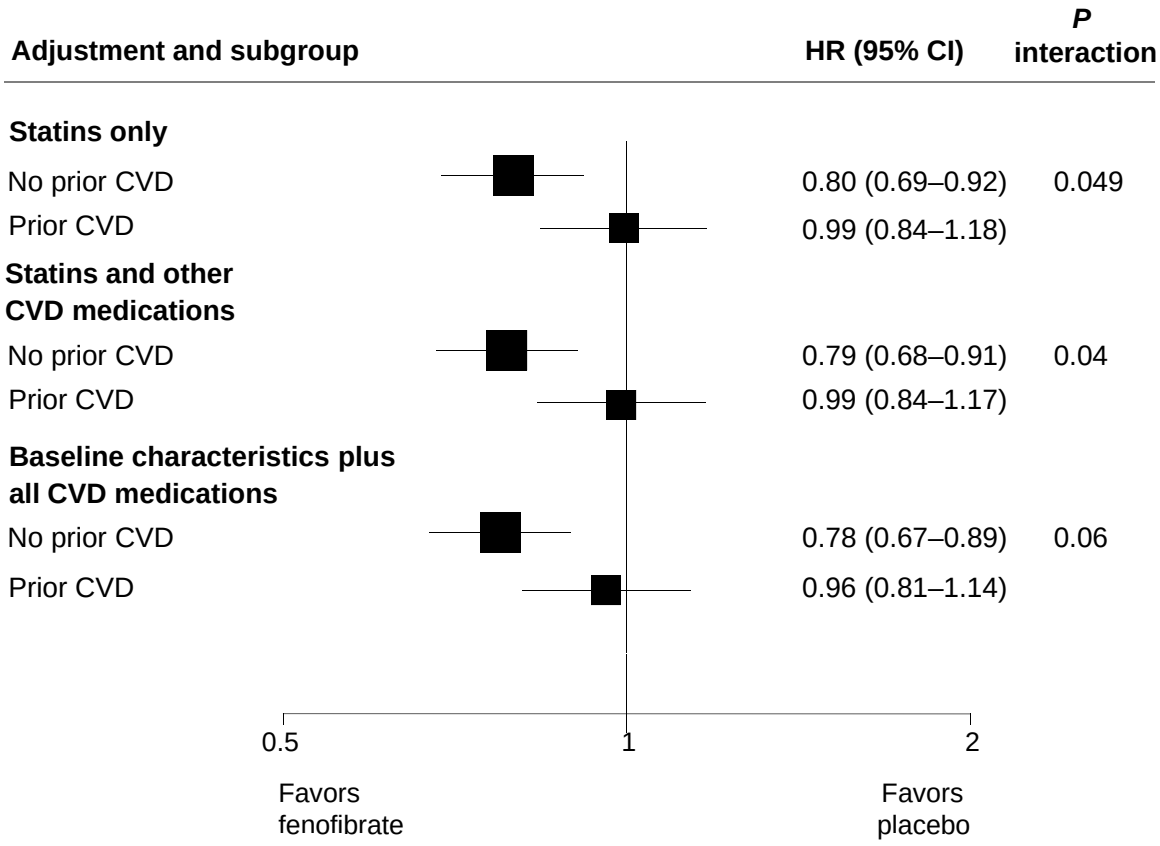
Figure


0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
Differences (mmol/L)
HDL cholesterol (no CVD)
HDL cholesterol (CVD)
LDL cholesterol (no CVD)
LDL cholesterol (CVD)
Triglycerides (no CVD)
Triglycerides (CVD)
0
10
20
30
40
50
60
Months after randomisation


A.
Percentage (average over the study)
25
20
15
10
5
0
Fenofibrate
Placebo
No CVD
Prior CVD
Overall
Started other lipid-lowering treatment
B.
Percentage (average over the study)
25
20
15
10
5
0
No CVD
Prior CVD
Overall
Discontinued study medication


Events (n(%))
Placebo Fenofibrate
HR (95% CI)
P
P Interaction
A. Total CVD events
No prior CVD 416 (10.8) 340 (8.9) 0.004 0.045
Prior CVD 267 (25.1) 272 (25.5) 0.85
All 683 (13.9) 612 (12.5) 0.035
0.5
1
2
B. Major components of total CVD events
Coronary events
No prior CVD 168 (4.4) 126 (3.3) 0.014 0.03
Prior CVD 120 (11.3) 130 (12.2) 0.55
All 288 (5.9) 256 (5.2) 0.16
Stroke
No prior CVD 101 (2.6) 96 (2.5) 0.74 0.56
Prior CVD 74 (7.0) 62 (5.8) 0.29
All 175 (3.6) 158 (3.2) 0.36
Revascularization
No prior CVD 277 (7.2) 199 (5.2) <0.001 0.05
Prior CVD 193 (18.2) 181(17.0 0.52
All 470 (9.6) 380 (7.8) 0.002
0.5
1
2
Favors fenofibrate
Favors placebo


Adjustment and subgroup
HR (95% CI)
P interaction
Statins only
No prior CVD
0.80 (0.69–0.92)
0.049
Prior CVD
0.99 (0.84–1.18)
Statins and other CVD medications
No prior CVD
0.79 (0.68–0.91)
0.04
Prior CVD
0.99 (0.84–1.17)
Baseline characteristics plus all CVD medications
No prior CVD
0.78 (0.67–0.89)
0.06
Prior CVD
0.96 (0.81–1.14)
0.5
1
2
Favors fenofibrate
Favors placebo