Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial

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Summary

Background Laser treatment for diabetic retinopathy is often associated with visual field reduction and other ocular side-effects. Our aim was to assess whether long-term lipid-lowering therapy with fenofibrate could reduce the progression of retinopathy and the need for laser treatment in patients with type 2 diabetes mellitus.

Methods The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a multinational randomised trial of 9795 patients aged 50–75 years with type 2 diabetes mellitus. Eligible patients were randomly assigned to receive fenofibrate 200 mg/day (n=4895) or matching placebo (n=4900). At each clinic visit, information concerning laser treatment for diabetic retinopathy—a prespecified tertiary endpoint of the main study—was gathered. Adjudication by ophthalmologists masked to treatment allocation defined instances of laser treatment for macular oedema, proliferative retinopathy, or other eye conditions. In a substudy of 1012 patients, standardised retinal photography was done and photographs graded with Early Treatment Diabetic Retinopathy Study (ETDRS) criteria to determine the cumulative incidence of diabetic retinopathy and its component lesions. Analyses were by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN64783481.

Findings Laser treatment was needed more frequently in participants with poorer glycaemic or blood pressure control than in those with good control of these factors, and in those with a greater burden of clinical microvascular disease, but the need for such treatment was not affected by plasma lipid concentrations. The requirement for first laser treatment for all retinopathy was significantly lower in the fenofibrate group than in the placebo group (164 [3·4%] patients on fenofibrate *vs* 238 [4·9%] on placebo; hazard ratio [HR] 0·69, 95% CI 0·56–0·84; p=0·0002; absolute risk reduction 1·5% [0·7–2·3]). In the ophthalmology substudy, the primary endpoint of 2-step progression of retinopathy grade did not differ significantly between the two groups overall (46 [9·6%] patients on fenofibrate *vs* 57 [12·3%] on placebo; p=0·19) or in the subset of patients without pre-existing retinopathy (43 [11·4%] *vs* 43 [11·7%]; p=0·87). By contrast, in patients with pre-existing retinopathy, significantly fewer patients on fenofibrate had a 2-step progression than did those on placebo (three [3·1%] patients *vs* 14 [14·6%]; p=0·004). An exploratory composite endpoint of 2-step progression of retinopathy grade, macular oedema, or laser treatments was significantly lower in the fenofibrate group than in the placebo group (HR 0·66, 95% CI 0·47–0·94; p=0·022).

Interpretation Treatment with fenofibrate in individuals with type 2 diabetes mellitus reduces the need for laser treatment for diabetic retinopathy, although the mechanism of this effect does not seem to be related to plasma concentrations of lipids.

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Introduction

Diabetic retinopathy has become the leading cause of vision loss and blindness in working-age adults in both developed and developing countries.[1,2] Visual loss results mainly from central macular oedema, and less frequently from proliferative diabetic retinopathy. The onset of diabetic retinopathy is characterised by vasodilation and hyperperfusion, followed by capillary loss and ischaemia. Leakage of protein and fluid from damaged capillaries leads to oedema at the macula, the focal centre of the retina, together with lipid and protein deposits termed hard exudates. The development of these pathological changes is strongly related to hyperglycaemia in type 2 diabetes.[3,4]

Laser treatment to photocoagulate ischaemic retina and leaking microaneurysms has been proven in clinical trials to slow or prevent further vision loss from diabetic retinopathy.[2,5,6] Although successful, laser treatment is frequently associated with visual field reduction and other ocular side-effects,[7] and so any treatment that could reduce the need for the use of lasers would be an important advance. Medical management of risk factors associated with diabetic retinopathy is also important in slowing the progression of retinal disease.[8–10] Although there is clear evidence of an association between diabetic retinopathy and glycaemia, duration of diabetes, raised blood pressure, and microalbuminuria, neither control of glycaemia nor blood pressure has fully prevented the progression of diabetic retinopathy, underscoring the importance of also assessing the management of other potential risk factors.

Raised serum cholesterol and triglyceride concentrations have been reported to be associated with both the

development and severity of diabetic retinopathy.[11–13] Increased lipid concentrations have also been linked in several studies to the development of macular oedema,[14–17] or to hard exudate deposition or proliferative retinopathy.[17–20] However, there is uncertainty regarding the beneficial effects of lipid lowering treatment for the management of diabetic retinopathy.[21,22]

Nonetheless, the associations between raised lipid concentrations and the presence and severity of diabetic macular oedema and retinal hard exudate deposition highlight the potential for possible benefits from lipid-lowering drug therapy. Although statins have proven unsuccessful in preventing diabetic retinopathy,[23] previous studies of peroxisome proliferator-activated receptor (PPAR)α agonists—also known as fibrates—in small numbers of patients have found beneficial effects on retinal[24–27] and macular hard exudates.[28,29]

The aim of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was to assess whether long-term lipid-lowering therapy with fenofibrate could reduce macrovascular and microvascular outcomes in type 2 diabetes. Previously, we found that, in patients with type 2 diabetes and adequate glycaemic and blood pressure control, there was a significant relative reduction of almost a third in the rate of first laser treatment events for retinopathy after an average of 5 years treatment with fenofibrate 200 mg a day.[30] Here, we report in detail on the effects of fenofibrate therapy on ophthalmic complications, and attempt to identify the underlying pathologies being treated in patients receiving laser treatment.

Methods

Patients

Participants in FIELD have been described in detail elsewhere.[30,31] Briefly, individuals were eligible for inclusion if they were aged between 50 and 75 years, had type 2 diabetes according to WHO criteria, and had an initial plasma total cholesterol concentration of 3·0–6·5 mmol/L and a total cholesterol/HDL-cholesterol ratio of 4·0 or more, or a plasma triglyceride concentration of 1·0–5·0 mmol/L, without requiring lipid-modifying treatment at study entry. Individuals with significant renal impairment (plasma creatinine >130 μmol/L), chronic liver disease, or symptomatic gallbladder disease, or who had experienced a cardiovascular event within the 3 months before recruitment were excluded.

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

See Online for webtable 1

Procedures

9795 patients were eligible for inclusion, and were randomly assigned to receive micronised fenofibrate 200 mg once daily (Laboratoires Fournier, Dijon, France) or matching placebo. Patients were seen for scheduled study visits at 4–6 month intervals over a planned period of 5 years on average against a background of usual care from their health-care professionals. Information concerning any history of retinopathy was recorded at baseline, but retinal photography was not gathered routinely from participants in the main study. All

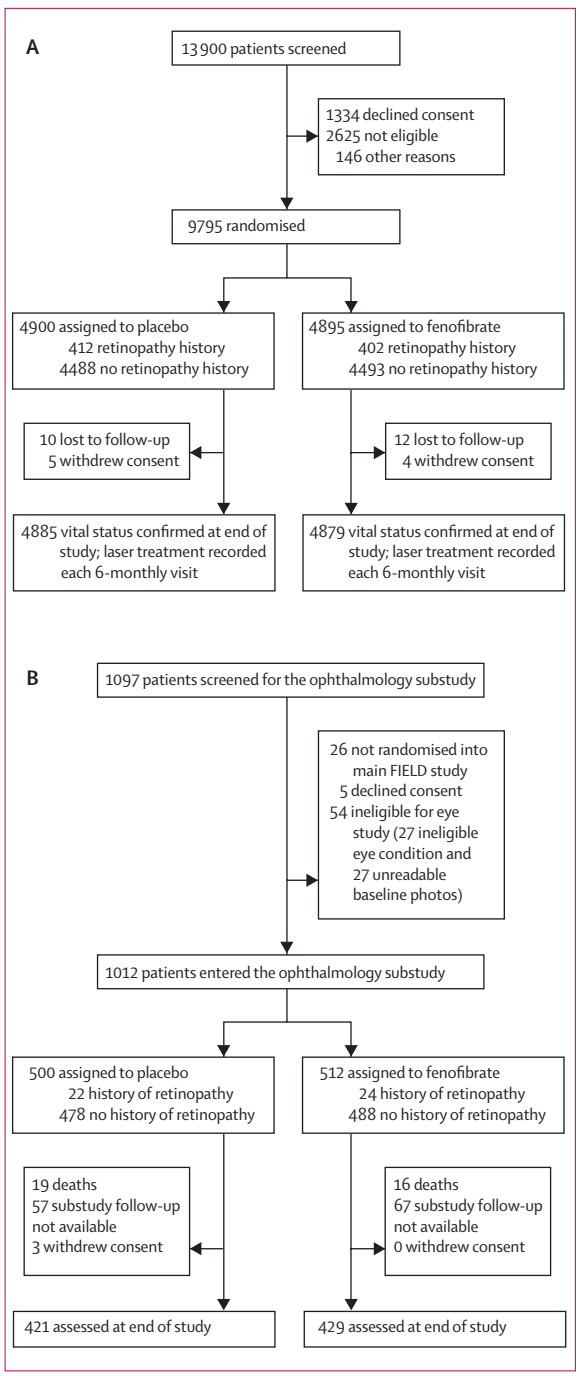

Figure 1: **Trial profile**
(A) FIELD study. (B) Ophthalmology substudy.

instances of laser photocoagulation therapy for diabetic retinopathy were then recorded routinely at every follow-up visit, and supporting documentation was requested subsequently. The occurrence of laser treatment for retinopathy was a prespecified tertiary endpoint of the main FIELD study. There were no constraints in the study protocol, however, regarding the use of laser treatment for diabetic retinopathy in trial participants, which remained at the discretion of each patient's usual doctors. As such, use of laser treatment in the FIELD study reflects current clinical practice, and would not be expected to have differed systematically between groups.

Documentation regarding the use of laser treatment was adjudicated, masked to treatment allocation, by at least two ophthalmologists involved in the FIELD study (PM, PAS) to ascertain the reason for each episode of laser treatment. New laser treatment events were recorded when the date of laser treatment was at least 10 weeks after the previously reported course of treatment. All instances of laser treatment were classified as either laser treatment for macular oedema, or for proliferative retinopathy without macular involvement. Where involvement of the macula as the underlying pathology could not be reliably determined from supporting documentation (87 cases only), these cases were classified as laser treatment for proliferative retinopathy without macular involvement. Participants in whom laser treatment was identified as being for treatment of capsular opacity, iridotomy, retinal breaks, or for other non-diabetic conditions, were excluded from the analysis.

At 22 of 63 FIELD sites, patients were also approached to participate in an ophthalmology substudy involving serial retinal photography. Consenting patients were eligible provided that two-field colour fundus photographs of both eyes showed no evidence of proliferative retinopathy, severe non-proliferative retinopathy, clinically significant macular oedema, or indication for, or evidence of a history of laser treatment at a screening examination done during the placebo run-in phase. A number of other ocular pathologies or technical problems also rendered patients ineligible.

Retinopathy status and severity were assessed from two-field 45° colour fundus photographs of the macula (stereoscopic) and a disc/nasal field taken at the baseline, 2 year, 5 year, and end of study examinations as part of the FIELD follow-up, to look for long-term changes and possible effects of treatment. Grading of retinopathy and macular oedema was done by the study ophthalmologists (PM, PAS), or a trained photographic grader (MSM), who were masked to treatment allocation, in accordance with adapted Early Treatment Diabetes Retinopathy Study (ETDRS) criteria, from grade 10 to 99 (webtable 1).[5,32]

Before retinal photography, pupils were dilated with 1% tropicamide, which was repeated to achieve adequate pupil dilation (at least 6 mm in diameter). Colour retinal

	Placebo (n=4900)		Fenofibrate (n=4895)	
	Number of patients (%)	Number of treatments	Number of patients (%)	Number of treatments
0	4662 (95%)	0	4731 (97%)	0
1	121 (2%)	121	85 (2%)	85
2	48 (1%)	96	38 (0·8%)	76
3	27 (0·6%)	81	17 (0·4%)	51
4	15 (0·3%)	60	9 (0·2%)	36
5	10 (0·2%)	50	8 (0·2%)	40
6–12	17 (0·3%)	127	7 (0·1%)	49
Cumulative total	238 (5%)	535	164 (3%)	337*

*p=0·0003 for difference in incidence density rates by treatment assignment (Poisson test).

Table 1: **Number of laser treatment courses per patient during follow-up and cumulative totals by allocated treatment group**

	No laser treatment (n=9393)	Laser treatment (n=402)	p value
General characteristics			
Sex (male)	5864 (62·4%)	274 (68·2%)	0·020
Ethnic origin (white)	8728 (92·9%)	365 (90·8%)	0·106
Age at visit 1 (years)	62·3 (6·9)	61·5 (6·7)	0·032
Diabetes duration (years)	5·0 (2·0–9·0)	12·0 (8·0–16·0)	<0·0001
BMI (kg/m²)	29·8 (26·8–33·5)	29·6 (27·0–33·4)	0·868
Waist–hip ratio	0·94(0·88–0·98)	0·95(0·91–1·00)	<0·0001
Systolic blood pressure (mm Hg)	140·3 (15·3)	144·9 (16·2)	<0·0001
Diastolic blood pressure (mm Hg)	82·0 (8·5)	83·0 (9·5)	0·024
Current smoker	892 (9·5%)	30 (7·5%)	0·171
Ex-smoker	4747 (50·5%)	197 (49·0%)	0·547
Clinical history			
Previous cardiovascular disease	2036 (21·7%)	95 (23·6%)	0·352
Myocardial infarction	466 (5·0%)	19 (4·7%)	0·832
Stroke	324 (3·4%)	23 (5·7%)	0·016
Angina	1136 (12·1%)	51 (12·7%)	0·722
Peripheral vascular disease	670 (7·1%)	42 (10·4%)	0·012
Coronary revascularisation (CABG or PTCA)	348 (3·7%)	15 (3·7%)	0·978
History of hypertension	5329 (56·7%)	217 (54·0%)	0·275
Any microvascular disease	1767 (18·8%)	258 (64·2%)	<0·0001
Diabetic retinopathy	614 (6·5%)	200 (49·8%)	<0·0001
Diabetic neuropathy	1238 (13·2%)	157 (39·1%)	<0·0001
Diabetic nephropathy	243 (2·6%)	36 (9·0%)	<0·0001
Laboratory data			
Total cholesterol (mmol/L)	5·04 (0·70)	5·04 (0·69)	0·862
LDL cholesterol (mmol/L)	3·07 (0·65)	3·07 (0·68)	0·847
HDL cholesterol (mmol/L)	1·10 (0·26)	1·10 (0·27)	0·689
Triglyceride (mmol/L)	1·74 (1·34–2·33)	1·71 (1·33–2·27)	0·642
Fasting glucose (mmol/L)	8·4 (7·0–10·2)	11·0 (8·9–13·0)	<0·0001
HbA_{1c} (%)	6·8% (6·1–7·7)	8·3% (7·2–9·4)	<0·0001
Creatinine (μmol/L)	77·6 (15·8)	77·3 (16·5)	0·720
Homocysteine (μmol/L)	9·5 (8·0–11·5)	10·1 (8·3–12·4)	0·0001
Dyslipidaemia	3569 (38·0%)	141 (35·1%)	0·237
Microalbuminuria	1727 (18·4%)	123 (30·6%)	<0·0001
Macroalbuminuria	257 (2·7%)	56 (13·9%)	<0·0001

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Baseline cardiovascular medication			
Antithrombotic	2923 (31·1%)	145 (36·1%)	0·036
Aspirin	2695 (28·7%)	134 (33·3%)	0·044
Antithrombotic (excluding aspirin)	292 (3·1%)	16 (4·0%)	0·327
Angiotensin-converting enzyme inhibitors	3127 (33·3%)	154 (38·3%)	0·037
Angiotensin II receptor antagonist	504 (5·4%)	18 (4·5%)	0·438
β blocker	1368 (14·6%)	54 (13·4%)	0·528
Calcium antagonist	1813 (19·3%)	79 (19·7%)	0·862
Nitrate	525 (5·6%)	25 (6·2%)	0·591
Diuretic	1424 (15·2%)	61 (15·2%)	0·994
Baseline blood-glucose-lowering medication			
Diet alone	2602 (28·1%)	6 (1·7%)	<0·0001
Metformin alone	1699 (18·1%)	22 (5·5%)	<0·0001
Sulfonylurea alone	1568 (16·7%)	43 (10·7%)	0·001
Metformin+sulfonylurea	2173 (23·1%)	147 (36·6%)	<0·0001
Other oral agent	19 (0·2%)	0 (0·0%)	0·367
Metformin and/or sulfonylurea+other agent	155 (1·7%)	15 (3·7%)	0·002
Insulin alone	529 (5·6%)	78 (19·4%)	<0·0001
Insulin+oral agent	648 (6·9%)	91 (22·6%)	<0·0001

Data are n (%), mean (SD), or median (IQR). BMI=body-mass index. CABG=coronary artery bypass graft surgery. PTCA=percutaneous transluminal coronary angioplasty.

Table 2: **Baseline characteristics of participants requiring or not requiring laser treatment during the study**

See Online for webtable 2

photographs were taken of two fields in both eyes according to guidelines of the EURODIAB study by using a suitable retinal camera.[33] The macular field was imaged so that the optic disc was at the nasal end of the field. The disc/nasal field was imaged with the optic disc positioned one disc-diameter from the temporal edge of the field. A single photograph of any other significant retinal pathology was also taken. Existing fundus cameras at different sites were used so that there was some variability in the photographic angle taken; however, the camera did not differ between treatment groups at any site. All but two sites provided photographs in a non-digital format. After film processing, the slides were analysed at either of the two grading centres in Australia and Finland (from baseline to study end) and the grading of 100 patients was cross-checked between the grading sites for quality assessment and concordance, which were high (weighted κ values were 0·74 for grade of diabetic retinopathy, 1·0 for presence of macular oedema).

Macular oedema was characterised by the presence of thickening of the retina. Clinically significant macular oedema was defined as having any one of the three following criteria: retinal thickening at or within 500 μm of the centre of the macula; hard exudates at or within 500 μm of the centre of the macula associated with macular oedema; and zone(s) of retinal thickening at least one disc area in size, any part of which is within one disc diameter of the centre of the macula.[6] Macular oedema was graded according to whether it was absent, present but not clinically significant (not involving the foveal centre), or present and clinically significant (involving the foveal centre). Hard exudates were graded as absent or present and, when present, were graded by comparison with standard photographs by use of the hard exudate scale of the modified ETDRS system (webtable 2).[32]

The main objective of the substudy was to assess the effects of treatment on progression of diabetic retinopathy. This was defined as at least a 2-step increase in ETDRS grade (webtable 1) after 2 years or more of follow-up for all patients, and was also subclassified as (1) secondary (2-step progression of existing retinopathy in those with a baseline grade of 20 or more) and (2) primary (2-step progression to retinopathy in those with a baseline grade of 15 or less). Secondary endpoints included one-step progression, the occurrence or progression of macular oedema, of hard exudates, and the occurrence of laser treatment, vitrectomy surgery, and cataract (including surgery), and deterioration of visual acuity by two lines (Snellen chart). In the substudy, the development of new retinopathy was defined as grade 20 or greater in the ETDRS classification after 2 years or more of follow-up in patients with grade 15 or less at baseline. A post-hoc exploratory composite endpoint reflecting the development of significant retinal pathology included any of a 2-step progression of retinopathy grade, new macular oedema, or laser treatment.

Statistical analysis

All analyses were done on an intention-to-treat basis. Treatment differences for baseline characteristics were analysed with χ^2 tests for categorical variables, *t* tests for continuous variables, or if the distribution of the data was non-normal, the Wilcoxon rank-sum test. Cox proportional hazards analysis was used to compute hazard ratios (HR) and 95% CI to assess the effect of fenofibrate treatment on the time to first laser treatment event. Where appropriate, p values were computed with the log-rank test. Cumulative incidence curves of the time to first laser treatment event according to the main underlying cause, and by treatment group, were calculated with the Kaplan-Meier method. For multiple event analysis, a Poisson model on the number of laser treatment courses was used. The Poisson analysis yields an incidence density ratio (analogous to the HR), reflecting the relative change in event rate per unit time (per month in this case) for the fenofibrate group relative to the placebo group. For the substudy, in all participants, the most severely affected eye at baseline was used for the analysis, but photographs of both eyes were graded. In cases of equal severity at baseline, the values for the right eye were used. For low-count events, the conditional binomial exact test was used. For analyses including outcomes measured at intervals, interval-censored proportional hazards methods were used. All statistical inferences were drawn with a two-sided p value of 0·05. All statistical analyses were done with SAS version 9.1 or ACCoRD (Analysis of Censored and Correlated Data).

The FIELD study is registered as an International Standard Randomised Controlled Trial, number ISRCTN64783481.

Role of the funding source

The study was designed by an independent management committee and an ophthalmology working group, and was coordinated by the National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Australia. Two non-voting representatives of the main sponsor attended meetings of the management committee. 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. The writing committee and study management committee had final responsibility for the decision to submit for publication.

Results

Of the 9795 participants randomised into the FIELD study, 4895 were assigned to receive fenofibrate and 4900 were assigned to receive matching placebo. 8·3% (412 participants in the placebo group and 402 in the fenofibrate group) of patients self-reported a history of diagnosed retinopathy before study entry, and 91·7% (4488 of those allocated placebo and 4493 allocated fenofibrate) reported no history of retinopathy. The fenofibrate and placebo treatment groups were well matched in terms of baseline characteristics, as reported previously.[30] Follow-up for any instances of laser treatment for retinopathy was complete to the end of study for over 99% of the patients who were still alive (figure 1).

402 (4·1%) of patients underwent laser treatment for diabetic retinopathy during follow-up. Almost half of all patients receiving on-study laser treatment required several courses of therapy (total of 872 courses, range 2–12 courses per patient; table 1). The baseline characteristics and medications of those who went on to require or not require laser treatment were strikingly different (table 2). Patients receiving laser treatment during the study were more likely to be male, had a 7-year longer average duration of diabetes, a marginally higher waist-hip ratio, around a 5 mm Hg higher average systolic blood pressure, and were more likely to have had a stroke or peripheral vascular disease than were those who did not require laser treatment. They were also more likely to have reported prior microvascular complications, including retinopathy, neuropathy, and nephropathy at baseline. Furthermore, fasting plasma glucose concentrations and HbA_{1c} levels were higher in patients needing laser treatment than in those who did not need it (table 2), despite more aggressive therapy for their diabetes. Homocysteine levels were significantly higher in patients needing laser treatment; such patients were also more likely to have measured microalbuminuria or macroalbuminuria. No differences were seen in baseline concentrations of blood lipids, including total cholesterol, HDL cholesterol, calculated LDL cholesterol, or triglycerides. Participants receiving laser treatment were significantly more likely at baseline to have been prescribed antithrombotic medication (mainly aspirin), and angiotensin-converting enzyme (ACE) inhibitors, and non-dietary blood glucose-lowering therapies (mainly metformin, sulfonylureas, or insulin) than were those not needing laser treatment (table 2), reflecting their longer diabetes duration, worse glycaemic control, and consequently greater prevalence of vascular complications. At the end of the study, use of these treatments was even higher in patients receiving laser treatment, particularly the use of insulin therapy (webtable 3).

See Online for webtable 3

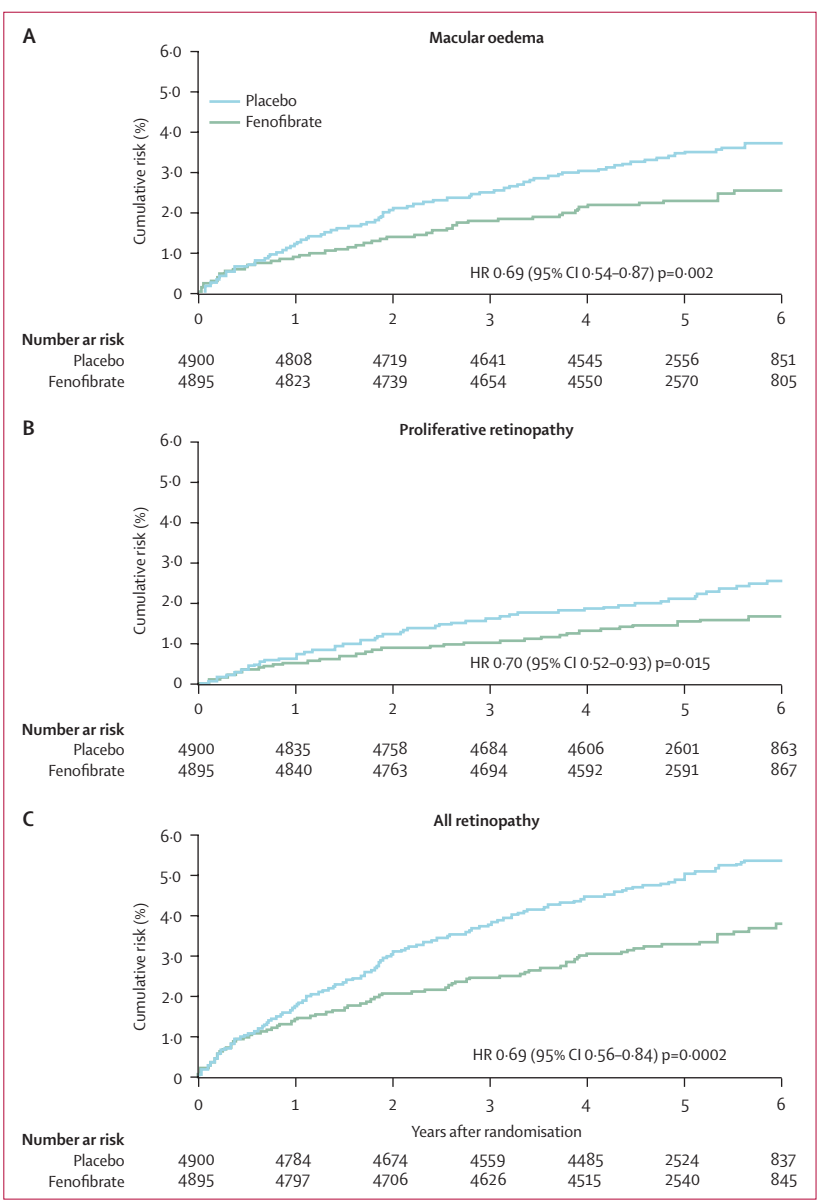

Figure 2: **Cumulative risk curves of time to event of any first laser treatment, by treatment group**
Macular oedema indicates laser treatment where the macula was involved; proliferative retinopathy shows cases without macular involvement; all retinopathy includes all first instances of laser treatment for any diabetic retinopathy.

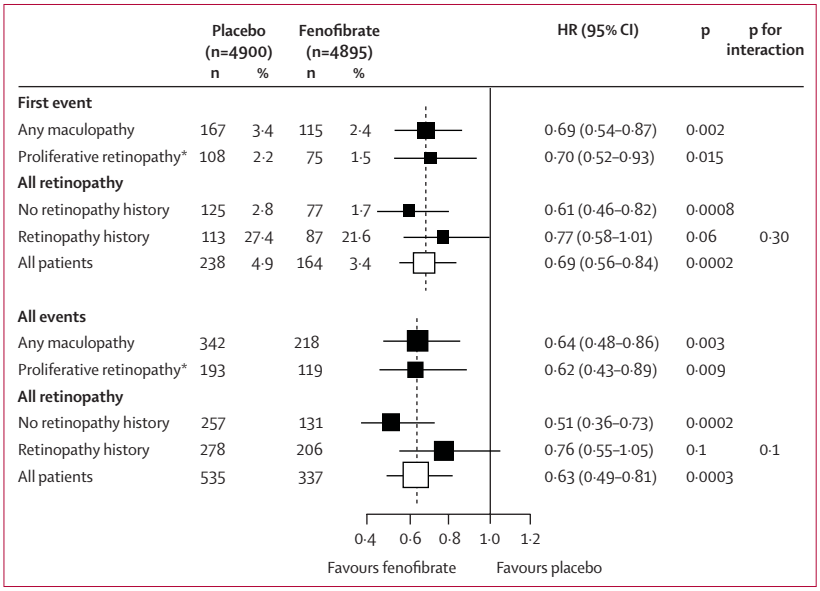

Figure 3: **Effect of fenofibrate on first and all laser treatment events**
Counts for each underlying pathology are shown; for first events, a patient was counted only once under each type of pathology listed; for all events, all courses of laser treatment for each type of pathology are counted (Poisson method). *Without macular involvement.

	ETDRS grading	Placebo: number needing laser treatment/number in group (%)*	Fenofibrate: number needing laser treatment/number in group (%)*
Absent	10	1/357 (0·28%)	1/363 (0·28%)
Questionable	14 and 15	1/40 (2·5%)	0/44 (0%)
Minimal, non-proliferative	20	3/52 (5·8%)	0/41 (0%)
Mild, non-proliferative	35	4/26 (15·3%)	2/47 (4·3%)
Moderate, non-proliferative	43	10/21 (47·6%)	1/14 (7·1%)
Moderately severe non-proliferative or worse	47–99	4/4 (100%)	1/3 (33·3%)
Total		23/500 (4·6%)	5/512† (1·0%)

*Each percentage expresses the number of patients needing laser treatment as a proportion of the total number with that Early Treatment Diabetic Retinopathy Study (ETDRS) grade of retinopathy at baseline. †Fewer first instances of laser treatment in those allocated to fenofibrate than in those allocated to placebo, p=0·0004.

Table 3: **Stage of diabetic retinopathy (ETDRS grading) at baseline of the worse eye in patients needing laser treatment in the ophthalmology substudy**

465 of the 872 courses of laser treatment done during the FIELD study were first laser treatments deemed to be for macular oedema or proliferative retinopathy. Most of these first laser treatments were for macular oedema alone or associated with proliferative retinopathy (282; 61% of first treatments), with the remainder (183; 39%) being for proliferative retinopathy without macular involvement. Baseline lipid concentrations did not differ between those whose first laser treatment was given for macular oedema compared with proliferative retinopathy (data not shown).

The requirement for first laser treatment for any retinopathy was significantly lower in the fenofibrate group than in the placebo group (238 [4·9%] patients in the placebo group *vs* 164 [3·4%] patients in the fenofibrate group; HR 0·69, 95% CI 0·56–0·84; p=0·0002), corresponding to an absolute risk reduction of 1·5% (0·7–2·3). There were similar estimated relative reductions in the number of patients needing first laser treatment for any maculopathy (31% reduction with fenofibrate, 95% CI 13–46; p=0·002) and in those needing such treatment for proliferative retinopathy (30% reduction with fenofibrate, 7–48; p=0·015), corresponding to absolute risk reductions of 1·1% (0·4–1·7) and 0·7% (0·1–1·2), respectively (figure 2 and figure 3). These effect sizes remained almost identical after adjustment for the main baseline characteristics predicting the need for laser treatment (data not shown). For each pathology, visible separation of the cumulative incidence curves emerged within 8 months of starting fenofibrate treatment, with progressively greater benefits accumulating over time (figure 2).

The relative effects of fenofibrate seemed to be larger in those without (39% reduction, 95% CI 18–54; p=0·0008) than with (23% reduction, –1 to 42; p=0·06) a history of retinopathy, although the difference was not statistically significant (p value for heterogeneity 0·30; figure 3). The risk of first laser treatment in the placebo group over an average of 5 years was about 3% in those without a history of retinopathy and 27% in those with such a history (figure 3); consequently, the absolute risk reduction was much larger in patients with a history of retinopathy: if treated with fenofibrate, there would be 5·8 fewer first laser treatments per 100 patients (number needed to treat [NNT] 17) in those with a history of retinopathy compared with 1·1 fewer treatments per 100 patients treated (NNT 90) in those without a history of retinopathy.

Of the 872 total courses of laser treatment, 535 were given to 238 (4·9%) patients on placebo, and 337 to 164 (3·4%) patients on fenofibrate (relative reduction with fenofibrate 37%, 95% CI 19–51; p=0·0003; figure 3). There was a relative reduction in the need for laser treatment of 36% (95% CI 14–52; p=0·003) with fenofibrate treatment in those with any maculopathy, and of 38% (11–57; p=0·009) in those with proliferative retinopathy (figure 3). Although the relative effects of fenofibrate seemed to be larger in those without (49% reduction, 95% CI 27–64, p=0·0002) than with (24% reduction, –5 to 45; p=0·10) a history of retinopathy, these differences were not statistically significant (p value for heterogeneity 0·1). These differences represent an average of 2·8 fewer events per 100 patients treated with fenofibrate over 5 years without a history of retinopathy, compared with 16·2 fewer events per 100 patients treated with fenofibrate over 5 years with a history of retinopathy.

The safety profiles of fenofibrate and matching placebo were much the same over an average of 5 years follow-up, with small increases seen only in the rare clinical events of pancreatitis and pulmonary embolism.[30] Increases in both plasma creatinine (average around 15% at 1 year) and plasma homocysteine (average around 41% at 1 year)

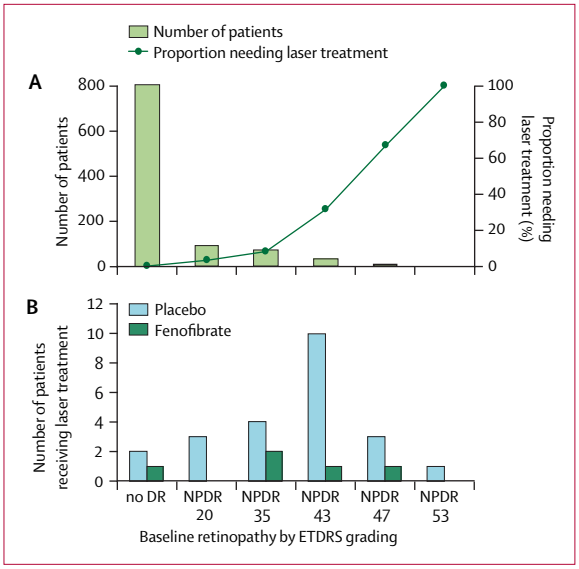

Figure 4: **Ophthalmology substudy**
(A) Distribution of patients and proportion of laser treatment events by ETDRS grading of retinopathy at baseline; (B) number of laser treatment events in each treatment group by ETDRS grading of retinopathy at baseline.

	Placebo group (n=500)	Fenofibrate group (n=512)	p value
Intercurrent events			
Laser treatment (one or more) for diabetic retinopathy	23 (4·6%)	5 (1·0%)	0·0004
Vitrectomy surgery	1 (0·2%)	2 (0·4%)	0·73
Cataract or cataract surgery	28 (5·6%)	37 (7·2%)	0·29
2-step progression of retinopathy (primary endpoint)			
All patients	57 (12·3%)	46 (9·6%)	0·19
No pre-existing retinopathy	43 (11·7%)	43 (11·4%)	0·87*
Pre-existing retinopathy	14 (14·6%)	3 (3·1%)	0·004*
Other outcomes diagnosed at scheduled eye visits (2 years, 5 years, study end)			
1-step progression of retinopathy grade	106 (22·9%)	104 (21·8%)	0·69
Occurrence of new retinopathy	45 (12·3%)	46 (12·1%)	0·96
Occurrence of new hard exudates	14 (3·1%)	16 (3·5%)	0·78
Any progression of hard exudates	2 (14·3%)	2 (13·3%)	0·99
2-line worsening in visual acuity (Snellen chart)	90 (29·1%)	97 (30·7%)	0·67
Occurrence of any macular oedema	10 (2·2%)	4 (0·8%)	0·09
Composite outcome of significant retinal pathology			
Any of 2-step progression of retinopathy grade, macular oedema, or laser treatment (either eye)	75 (16·1%)	53 (11·1%)	0·022

Data are n (%). *p value for interaction between treatment effects in those with and without pre-existing retinopathy=0·019.

Table 4: **Main outcomes for the ophthalmology substudy**

concentrations were seen soon after the commencement of active treatment, but levels of both were found to reverse over 6–8 weeks after drug withdrawal at the end of the study.[30]

1012 (10·3% of the whole study population) participants, recruited from 22 participating study centres, further consented to, and were eligible for participation in, the ophthalmology substudy. Patients who were recruited to the substudy were much the same as those not participating (data not shown), including in terms of baseline concentrations of blood lipids. Participants had a slightly lower rate of previous cardiovascular disease (16% *vs* 22%), and less history of retinopathy (4·5% *vs* 8·7%) compared with those who did not participate in the substudy. Of the participants in the substudy, 850 (84%; 421 allocated to placebo, 429 allocated to fenofibrate) were followed up with detailed eye examinations to the end of the study (figure 1). 127 (12·5%) patients were missing end of study follow-up data, including 67 (6·6%) with no data for any point during follow-up in the substudy.

Of the 1012 patients recruited into the substudy, around 80% had no or questionable diabetes-related retinopathy at baseline (ETDRS grades 10, 14, or 15), and a low risk for subsequent laser treatment (<3%; table 3). ETDRS scores at baseline were well balanced between the two groups (table 3). The risk of needing laser treatment increased with increasing baseline ETDRS grades of retinopathy (table 3 and figure 4). 28 patients in the substudy required a first laser intervention for diabetic eye disease; most of whom had minimal to moderately severe non-proliferative diabetic retinopathy (ETDRS grades 20–47). The use of drug treatments, including antihypertensives, antidiabetic therapy, and statins, was either similar or greater in participants on placebo than in those on fenofibrate by the end of the study (webtable 4).

See Online for webtable 4

The primary endpoint of 2-step progression of retinopathy grade did not differ significantly between the two groups (table 4). However, in patients with pre-existing retinopathy, significantly fewer patients on fenofibrate had a 2-step progression than did those on placebo (three [3·1%] patients on fenofibrate *vs* 14 [14·6%] on placebo; p=0·004). By contrast, the number of patients without pre-existing retinopathy who had a 2-step progression was much the same in the two groups (43 [11·4%] *vs* 43 [11·7%]; p=0·87). The treatment effect within these two main subgroups differed signficantly (test for interaction p=0·019).

23 patients in the placebo group and five in the fenofibrate group received one or more laser treatments over the course of the study (HR 0·21, 95% CI 0·08–0·54; p=0·0004; table 3 and figure 4). The occurrence of new retinopathy was not reduced by fenofibrate, nor was the occurrence or progression of hard exudates (table 4). Worsening in visual acuity did not differ significantly between groups (table 4), nor did numbers showing equivalent improvement. There were fewer instances of macular oedema in those treated with fenofibrate than in those on placebo (p=0·09). The risk of the composite endpoint of any of 2-step progression of retinopathy grade, development of macular oedema, or one or more laser treatments (either eye) was significantly lower in the fenofibrate group than in the placebo group (HR 0·66, 95% CI 0·47–0·94; p=0·022; table 4).

Discussion

Our results show that treatment with micronised fenofibrate—in addition to therapies for hyperglycaemia and other risk factors for retinopathy—reduces the need for laser treatment for diabetic retinopathy in individuals with type 2 diabetes. This reduction was mainly associated with a lower prevalence of macular oedema as the underlying cause of diabetic retinopathy, although the need for treatment for proliferative retinopathy without macular involvement was also reduced by a similar amount. These findings are supported by less progression of pre-existing retinopathy with fenofibrate and the suggestion of less macular oedema in the ophthalmology substudy, in which the frequency of the exploratory composite endpoint of progression, macular oedema, or laser treatment was about a third lower in the fenofibrate group relative to the placebo group. Of interest is that the benefit of treatment in the substudy was largely seen in patients with pre-existing retinopathy and that there was not a significant reduction in 2-step progression of retinopathy grade in patients without pre-existing disease. No differences were seen in the substudy in terms of deterioration in visual acuity, or the development or progression of hard exudates, but those eligible for the substudy were a low-risk sample, offering limited power to explore these outcomes, and the numbers of all events in the substudy were small.

A somewhat greater reduction in the relative risk of laser treatment was seen when all laser treatment events were assessed, suggesting that there is a continuing benefit beyond the first treatment. Perhaps most striking was the apparent rapid onset of benefit of fenofibrate therapy, with divergence in the need for laser treatment evident within about 8 months of treatment allocation. Although the reduction in the relative risk of laser treatment with fenofibrate seemed to be more pronounced in patients without a history of diabetic eye disease, this might have been due to previously undiagnosed retinopathy in many of these patients subsequently undergoing laser treatment. Further, the estimated absolute risk reduction was much larger in patients with a history of diabetic eye disease.

The actual mode(s) of action of fenofibrate responsible for achieving these reported benefits are unclear. Fenofibrate is a lipid-modifying agent, and after 4 months of treatment had reduced total cholesterol concentrations by 11%, LDL-cholesterol concentrations by 12%, and triglyceride concentrations by 29%, and had increased HDL-cholesterol concentrations by 5%.[30] However, the effect on individual lipid parameters was attenuated over the course of the study, and there was no clinically important difference in HDL-cholesterol concentrations at study completion between the two groups.[30] Additionally, none of these lipid concentrations at baseline seemed to affect the likelihood of developing retinopathy requiring laser treatment, despite small trials of both fibrates and statins suggesting improvements in ocular findings.[24–29,34–37] Nonetheless, it is possible that intraretinal lipid transport rather than serum lipid concentrations might be more important in the pathogenesis of diabetic retinopathy.[38]

Even though the requirement over 5 years for laser treatment was strongly associated with higher baseline concentrations of fasting glucose and of HbA_{1c}, fenofibrate did not reduce either of these markers of diabetes control.[30] Neither did fenofibrate lower systolic blood pressure, also strongly associated with laser requirement, by as much (average <2 mm Hg lower than with placebo) as reported in the ADVANCE trial of perindopril plus indapamide in diabetes (decrease of 5·6 mm Hg), in which reductions in eye events were not statistically significant.[39] Furthermore, the benefits observed in the FIELD study were achieved against a background of medical care that, by the end of the study, included the use of ACE inhibitors or angiotensin II receptor blockers in more than 60% of patients in both groups, with all antihypertensive drug therapy classes being more commonly used over time in the placebo group than in the fenofibrate group.[30] Additionally, significantly more statin use occurred in the placebo than fenofibrate group over time.[30]

These findings suggest that the mechanisms of benefit of fenofibrate in diabetic retinopathy must go beyond the effects of this drug on lipid concentrations or to lower blood pressure, and might be conferred mainly by other means. If so, this could indicate a mechanism of action that operates even when lipid concentrations have been controlled effectively by statin therapy and blood pressure by antihypertensive treatment.

Progressive microvascular ischaemia with vascular leak occurring within the ischaemic retina or, in more severe cases, new vessel proliferation and its sequelae, are the main features of diabetic retinopathy. Macular oedema, however, is the most frequent cause of both threatened and actual visual loss.[40] The mechanisms by which fenofibrate might improve microvascular outcomes are yet to be fully elucidated. PPARα agonists are reported to inhibit the vascular endothelial growth factor (VEGF) pathway important in angiogenesis, inflammation, and cell migration,[41] all thought to have a role in the progression of diabetic retinopathy. Fenofibrate has been shown to regulate retinal endothelial cell survival and to prevent apoptotic cell death.[42] The drug has also been shown to stimulate expression of VEGF mRNA in the retina via the AMP-activated protein kinase (AMPK) signal transduction pathway. VEGF may be increased early in the course of diabetic retinopathy as a mechanism to maintain the integrity of the endothelial vascular bed.[43] Fenofibrate has also been shown to improve endothelial-dependent vascular reactivity.[43] Together, these studies suggest that fenofibrate might prevent the need for laser treatment in diabetic retinopathy by inhibiting apoptosis of retinal endothelial cells, preventing

cellular migration, and reducing local inflammatory processes, with implications for pathological processes such as retinal capillary leakage.

There have been suggestions that inflammation might be involved in the progression of diabetic retinopathy. The concentration of the RANTES cytokine is raised in individuals with severe non-proliferative diabetic retinopathy, compared with those with less severe non-proliferative retinopathy.[44] Furthermore, monocyte chemoattractant protein 1 (MCP1) and intercellular adhesion molecule 1 (ICAM1) are upregulated within the retinal tissue in advanced diabetic retinopathy.[44] In hepatocytes, fenofibrate was shown to inhibit protein production induced by tumour necrosis factor alpha (TNFα) and mRNA expression of RANTES.[45] In a double-blind controlled clinical trial of patients with hypertriglyceridaemia and various components of the metabolic syndrome, fenofibrate (160 mg/day) lowered fasting and postprandial concentrations of soluble ICAM1 levels.[46] Fenofibrate exhibits anti-migratory properties on endothelial cells by inhibiting VEGF-mediated Akt phosphorylation.[47]

There is evidence also that the pro-inflammatory cytokines interleukin 1β and TNFα are raised in the serum and vitreous of patients with proliferative diabetic retinopathy compared with healthy controls.[48] In a randomised placebo-controlled trial, 12 weeks of fenofibrate treatment reduced concentrations of the pro-inflammatory TNFα, interleukin 6, and interleukin 1β in plasma, as well as markers for endothelial dysfunction,[49] although results from other studies are needed to confirm these findings. Fenofibrate could also have a protective role in the progression of diabetic retinopathy by inhibiting oxidative stress. Malondialdehyde is a lipid peroxide that is formed as a result of raised concentrations of reactive oxygen species. Malondialdehyde is raised in patients with type 1 diabetes with retinopathy.[50] One study has shown that fenofibrate treatment (200 mg daily for 3 months) decreases plasma malondialdehyde concentrations in patients with type 2 diabetes.[51] Lastly, omega-3 polyunsaturated fatty acids are thought to be protective against hypoxic retinopathy,[52] but available evidence does not suggest that fenofibrate increases omega-3 concentrations in human beings.[53]

The results of FIELD demonstrate a clear reduction in the need for laser treatment, and possible reduction in development of macular oedema, from the use of a lipid lowering agent in type 2 diabetes mellitus; these findings are especially important in view of the burden of type 2 diabetes mellitus worldwide,[54] and the disappointment of recent studies of medical treatment for diabetic retinopathy.[39,55–57] Fenofibrate might have anti-apoptotic, anti-inflammatory, and anti-oxidative effects and might also improve vascular reactivity, thus attenuating progression of diabetic retinopathy and the need for laser treatment. Additional studies of oxidative stress and vascular inflammation in FIELD patients will be important to further define the mechanisms underlying microvascular benefit, and could also usefully inform strategies for other new drug development.

The ophthalmological findings related to the FIELD study have a number of strengths and limitations. The effects of therapy on laser treatment are robust and consistent within the main trial and the substudy. Limitations of the study include that laser treatment was one of a number of tertiary outcomes in the main trial, that data on the reason for laser treatment was collected retrospectively in about 10% of patients receiving laser treatment, and that there were 127 (12·5%) without follow-up data at the end of the substudy, including 67 (6·6%) without any follow-up data in the substudy. Another limitation is that only patients in the smaller substudy had retinal photographs taken, from which to validate the extent of retinopathy before laser treatment. Further, the effects of fenofibrate within the substudy were driven mainly by patients with pre-existing disease, whereas, paradoxically the relative reduction of laser treatment in the main trial seemed to be greater in those with no history of eye disease. This finding could possibly relate to undetected retinopathy at baseline in many of these patients who subsequently had laser treatment, but who were not part of the substudy. Consequently, although the effects on laser treatment are clear cut, the determination of the stage of the disease at which to intervene should be considered exploratory. Further evidence from ongoing trials such as ACCORD[58] might provide confirmatory evidence in this regard.

The substantial benefits of fenofibrate on need for laser treatment for diabetic retinopathy are likely to be additive to those benefits arising from tight control of blood glucose and blood pressure in the management of type 2 diabetes mellitus, and emerge rapidly after treatment is commenced. The retinal benefits argue for consideration of using fenofibrate in the management of diabetic eye disease, and should be considered in the context of the other effects reported with fenofibrate in the FIELD study.[30]

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A full list of all FIELD study collaborators can be found in: The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366:** 1849–61.

Conflict of interest statement

Some members of the writing committee (ACK, PM, PAS, JO'D, TMED, M-RT, RJS, LTL, MCdE, PGC) have had the costs of participation in scientific meetings and/or contributions to advisory boards, or doing other research reimbursed by the pharmaceutical industry. ACK is a listed applicant on a patent application in relation to some of the findings contained in this scientific report. DCC is an employee of the study sponsor. MSM, EW, AM, RLO'C, and DT have no conflict of interest to declare.

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