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[Intervention Review]

Fenofibrate for diabetic retinopathy

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ABSTRACT

Background

Diabetic retinopathy (DR) remains a major cause of sight loss worldwide, despite new therapies and improvements in the metabolic control of people living with diabetes. Therefore, DR creates a physical and psychological burden for people, and an economic burden for society. Preventing the development and progression of DR, or avoiding the occurrence of its sight-threatening complications is essential, and must be pursued to save sight. Fenofibrate may be a useful strategy to achieve this goal, by reversing diabetes' effects and reducing inflammation in the retina, as well as improving dyslipidaemia and hypertriglyceridaemia.

Objectives

To investigate the benefits and harms of fenofibrate for preventing the development and progression of diabetic retinopathy in people with type 1 (T1D) or type 2 diabetes (T2D), compared with placebo or observation.

Search methods

We searched CENTRAL, MEDLINE, Embase, and three trials registers (February 2022).

Selection criteria

We included randomised controlled trials (RCTs) that included people with T1D or T2D, when these compared fenofibrate with placebo or with observation, and assessed the effect of fenofibrate on the development or progression of DR (or both).

Data collection and analysis

We used standard Cochrane methods for data extraction and analysis.

Our primary outcome was progression of DR, a composite outcome of 1) incidence of overt retinopathy for participants who did not have DR at baseline, or 2) advancing two or more steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale for participants who had any DR at baseline (or both), based on the evaluation of stereoscopic or non-stereoscopic fundus photographs, during the follow-up period. Overt retinopathy was defined as the presence of any DR observed on stereoscopic or non-stereoscopic colour fundus photographs.

Secondary outcomes included the incidence of overt retinopathy, reduction in visual acuity of participants with a reduction in visual acuity of 10 ETDRS letters or more, proliferative diabetic retinopathy, and diabetic macular oedema; mean vision-related quality of life, and serious adverse events of fenofibrate.

We used GRADE to assess the certainty of evidence.

Main results

We included two studies and their eye sub-studies (15,313 participants) in people with T2D. The studies were conducted in the US, Canada, Australia, Finland, and New Zealand; follow-up period was four to five years. One was funded by the government, the other by industry.

Compared to placebo or observation, fenofibrate likely results in little to no difference in progression of DR (risk ratio (RR) 0.86; 95% confidence interval (CI) 0.60 to 1.25; 1 study, 1012 participants; moderate-certainty evidence) in a population with and without overt retinopathy at baseline. Those without overt retinopathy at baseline showed little or no progression (RR 1.00, 95% CI 0.68 to 1.47; 1 study, 804 participants); those with overt retinopathy at baseline found that their DR progressed slowly (RR 0.21, 95% CI 0.06 to 0.71; 1 study, 208 people; test for interaction P = 0.02).

Compared to placebo or observation, fenofibrate likely resulted in little to no difference in either the incidence of overt retinopathy (RR 0.91; 95% CI 0.76 to 1.09; 2 studies, 1631 participants; moderate-certainty evidence); or the incidence of diabetic macular oedema (RR 0.39; 95% CI 0.12 to 1.24; 1 study, 1012 participants; moderate-certainty evidence).

The use of fenofibrate increased severe adverse effects (RR 1.55; 95% CI 1.05 to 2.27; 2 studies, 15,313 participants; high-certainty evidence).

The studies did not report on incidence of a reduction in visual acuity of 10 ETDRS letters or more, incidence of proliferative diabetic retinopathy, or mean vision-related quality of life.

Authors' conclusions

Current, moderate-certainty evidence suggests that in a mixed group of people with and without overt retinopathy, who live with T2D, fenofibrate likely results in little to no difference in progression of diabetic retinopathy. However, in people with overt retinopathy who live with T2D, fenofibrate likely reduces the progression.

Serious adverse events were rare, but the risk of their occurrence was increased by the use of fenofibrate.

There is no evidence on the effect of fenofibrate in people with T1D. More studies, with larger sample sizes, and participants with T1D are needed. They should measure outcomes that are important to people with diabetes, e.g. change in vision, reduction in visual acuity of 10 ETDRS letters or more, developing proliferative diabetic retinopathy; and evaluating the requirement of other treatments, e.g. injections of anti-vascular endothelial growth factor therapies, steroids.

PLAIN LANGUAGE SUMMARY

Is fenofibrate effective for diabetic retinopathy?

What was the aim of this review?

The aim of this review was to find out whether fenofibrate prevents people with either type 1 (T1D) or type 2 (T2D) diabetes from developing diabetic retinopathy (DR), or if they already had DR, whether it slows its progression, when compared with placebo or observation.

Key messages

- overall, fenofibrate likely made little to no difference in the progression of DR when compared with placebo (moderate-certainty evidence)

- for people with DR, their DR likely progressed slowly when they took fenofibrate (moderate-certainty evidence)

- although rare, side effects increased when people took fenofibrate (high-certainty evidence)

- more studies are needed; for example, studies that include people with type 1 diabetes, studies that take into account other treatments that people received, and importantly, studies that include outcomes that are important to people living with diabetes

What was studied in the review?

DR, a condition that occurs when the blood vessels in the back of your eye develop problems, is a major cause of sight loss worldwide and a burden to society. Preventing its occurrence, and if present, slowing or preventing its progression must be pursued to save sight. This review summarised the evidence about whether fenofibrate may be useful for this purpose (when compared to placebo or observation).

What are the main results of the review?

We found two studies. In total, they included 15,313 people with T2D, who were followed for four or five years. The studies were conducted in the US, Canada, Australia, Finland, and New Zealand. One was funded by the government, the other by industry.

For people with T2D, when those who may or may not have had DR were studied together, moderate-certainty evidence suggested that fenofibrate likely made little to no difference in the progression of DR when compared with placebo. However, when people with DR were studied on their own, the evidence suggested that their DR progressed slowly when they were taking fenofibrate. Serious adverse events were rare, but the risk of their occurrence increased for those who took fenofibrate (high-certainty evidence).

More studies are needed. For example, studies that include people with type 1 diabetes, and importantly, studies that include outcomes that are important to people living with diabetes, such as the number of people who experience a change in vision or sight loss, develop proliferative diabetic retinopathy (growth of new blood vessels), or require injections of anti-vascular endothelial growth factor therapies, or steroids. Health-related and vision-related quality of life measures, acceptability of the treatment to people using it, and costs of the treatment should be also included.

How up-to date is this review?

The review authors searched for studies published up to 1 February 2022.

Summary of findings 1. Fenofibrate for diabetic retinopathy

Fenofibrate compared to placebo or observation for diabetic retinopathy

Patient or population: people with type 2 diabetes
Setting: hospital settings
Intervention: fenofibrate
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with fenofibrate				
Progression of DR[a]	Study population 118 per 1000[c]	96 per 1000[d]	RR 0.86 (0.60 to 1.25)	1012[c,d] (1 RCT)	⊕⊕⊕⊖ Moderate[e]	Fenofibrate likely resulted in little to no difference in progression of DR (main analysis). Subgroup analysis, separating those with and without overt retinopathy at baseline, suggested a difference in progression (RR 1.00, 95% CI 0.68 to 1.47; 804 people without overt retinopathy) and (RR 0.21, 95% CI 0.06 to 0.71; 208 people with overt retinopathy; test for interaction P = 0.02)
Incidence of overt retinopathy[a,b]	Study population 223 per 1000 (216 per 1000[c])	203 per 1000 (169 to 243) (199 per 1000[c])	RR 0.91 (0.76 to 1.09)	1580 (1631[c]) (2 RCTs)	⊕⊕⊕⊖ Moderate[e]	
Incidence of a reduction in visual acuity of 10 ETDR letters or more	Not reported					
Incidence of PDR	Not reported					
Incidence of DMO[a]	Study population 24 per 1000	9 per 1000 (3 to 29)	RR 0.39 (0.12 to 1.24)	850 (1012[c]) (1 RCT)	⊕⊕⊕⊖ Moderate[e]	

	(20 per 1000[c])	(8 per 1000[c])			
Mean vision-related quality of life	Not reported				
SAE[a]	Study population		RR 1.55 (1.05 to 2.27)	15226 (15313[c]) (2 RCTs)	⊕⊕⊕⊕ High
	6 per 1000 (5 per 1000[c])	9 per 1000 (6 to 13) (8 per 1000[c])			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DMO:** diabetic macular oedema; **DR:** diabetic retinopathy; **ETDR:** the Early Treatment Diabetic Retinopathy Study; **OR:** odds ratio; **PDR:** proliferative diabetic retinopathy; **RCT:** randomised controlled trial; **RR:** risk ratio; **SAE**: serious adverse events

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]the data at 5 years
[b]the data at 4 years
[c]Calculated with the number of randomised participants
[d]In 1012 participants, there were 105 (20.5%) in the fenofibrate group and 103 (20.6%) in the placebo group with overt retinopathy at baseline.
[e]Downgraded one level for imprecision; sample sizes were less than the optimal information size, and the confidence intervals were wide and included no effect.

BACKGROUND

Description of the condition

Diabetic retinopathy (DR) is a neurovascular complication of diabetes mellitus, initiated by chronically high blood sugar levels. Cells of the neurovascular unit, including endothelial cells, pericytes, glial cells, and resident and circulating immune cells, are affected by the disease, with subsequent alterations in permeability and blood perfusion to the retina, resulting in retinal leakage and ischaemia (Stitt 2016). Depending on the extension of capillary loss, among other factors, this deficiency or lack of blood supply may lead to the formation of what are called 'new vessels'. New vessels are newly formed, abnormally fragile, blood vessels that develop in an attempt to bring blood and nourishment to the retina. The presence of new vessels defines proliferative diabetic retinopathy (PDR), a sight-threatening complication of DR (Evans 2014). New vessels can lead to sight loss as a result of them bleeding inside the eye (known as vitreous haemorrhage), or as a result of the formation of scarring tissue that accompanies them (so-called fibrovascular membranes), which can contract and detach the retina. As the blood vessels become weakened by the reduced number of cells, blood and fluid contained in them may leak out, leading to retinal oedema (accumulation of fluid in the retina). When fluid accumulates in the centre of the retina, the macula, diabetic macular oedema (DMO) ensues (Tan 2017). Besides vascular degeneration, loss of neural and supporting cells (glial cells) in the retina (neurodegeneration) occurs in DR, which also has an impact on vision.

One study estimated that globally, approximately 103 million people may have DR, and 29 million people may have sight-threatening stages of DR (Teo 2021). The study estimated that by 2045, 161 million people would have DR, and 45 million would have sight-threatening stages of DR. In addition to constituting a psychological and physical burden to the individual, DR also bears an economic burden to society. Several studies in Europe, US, and Asia have recently reported an association of higher medical costs with DR (Heintz 2010; Romero-Aroca 2016; Schmier 2009; Woung 2010; Zhang 2017). The total healthcare costs of DR in Sweden are up to approximately EUR 9.9 million per year, or EUR 106,000 per 100,000 inhabitants, when one considers a 4.8% prevalence of diabetes (Heintz 2010). A study in Singapore reported that the presence and severity of DR was associated with increased direct medical costs (Zhang 2017).

Description of the intervention

Strict control of blood glucose levels and blood pressure is essential to reduce the risk of sight loss from complications of DR, namely DMO, macular ischaemia, and PDR, but is often difficult to achieve. In some people with diabetes, sight-threatening complications may still occur, even if glucose levels and blood pressure are controlled. Laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factor (VEGF) drugs, and corticosteroids are used to treat DMO and PDR (Duh 2017; Evans 2014; Gross 2015; McCulloch 2017; Virgili 2018). These therapeutic modalities, although sight-saving in many cases, have inherent risks; and despite them, visual loss can still occur in a proportion of people who are unresponsive to them. Therapeutic strategies to prevent the development of the end-stage complications of DR would be expected to be more fruitful to save sight.

Fenofibrate, a fibrate indicated for the treatment of mixed dyslipidaemia and hypertriglyceridaemia, came to the market in 1975, and is widely used (Blane 1989; Guay 1999). Its cost is low. The main clinical effects are mediated through peroxisome proliferator-activated receptor (PPAR)-alpha activation, and consist of a moderate reduction in total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels, a marked reduction in triglycerides (TG), and an increase in high-density lipoprotein cholesterol (HDL-C).

How the intervention might work

PPAR-alpha is highly expressed in tissues with high mitochondrial and peroxisomal fatty-acid beta-oxidation rates, such as the retina (Ciudin 2013). It has been reported that PPAR-alpha is downregulated in the retinas of both type 1 and type 2 experimental diabetic models, and that high glucose is a cause of PPAR-alpha downregulation (Hu 2013). PPAR-alpha knockout mice develop vascular leakage, leukostasis, pericyte loss, capillary degeneration, and overexpression of inflammatory markers, all features observed in DR in humans (Hu 2013). Therefore, fenofibrate may help reverse the effects of diabetes in the retina. Other reported mechanisms through which fenofibrate may ameliorate DR include modulating Nrf2 signalling and NLRP3 inflammasome activation, and by cytochrome P450 epoxygenase (CYP)2C inhibition (Gong 2016; Liu 2017).

Why it is important to do this review

The number of people suffering from DR, as well as the number of people with diabetes are increasing worldwide (Teo 2021). As described above, laser photocoagulation, anti-VEGFs, and steroids are used routinely for the treatment of established DMO and PDR, but not to prevent their occurrence or to prevent the development and progression of DR (Aiello 2010; Boyer 2014; Gross 2015; Sivaprasad 2017; Virgili 2018). Fenofibrate may be useful for this purpose.

OBJECTIVES

To investigate the benefits and harms of fenofibrate for preventing the development and progression of diabetic retinopathy in people with type 1 or type 2 diabetes, compared with placebo or observation.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs). We planned to include ongoing or unpublished studies. We excluded post-trial follow-up studies.

Types of participants

Participants were people diagnosed with type 1 or type 2 diabetes (T1D; T2D). We included those who both did not have retinopathy, or who had non-proliferative diabetic retinopathy (NPDR) at baseline.

We excluded studies that only included participants with established complications of diabetic retinopathy (DR, i.e. diabetic macular oedema (DMO) and proliferative diabetic retinopathy

(PDR)). We included studies randomising participants with or without complications of DR (i.e. DMO or PDR) if the proportion of people with complications was low (i.e. less than 10%), or if data for people without complications were presented separately.

Types of interventions

Intervention: fenofibrate (any dose or regimen)

Comparison: placebo or observation

Types of outcome measures

Studies were included even if no outcome data were available, unless it was clear that none of the following outcomes were measured.

Primary outcomes

- Progression of diabetic retinopathy

Progression of diabetic retinopathy was considered a composite outcome of: 1) incidence of overt retinopathy for participants who did not have DR at baseline, or 2) advancing two or more steps for participants who had any DR at baseline in the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale, based on evaluation of stereoscopic or non-stereoscopic fundus photographs, during the follow-up period, or both (ETDRS 1991). Overt retinopathy was defined as the presence of any DR observed on stereoscopic or non-stereoscopic colour fundus photographs.

Secondary outcomes

- Incidence of overt retinopathy
- Mean change in visual acuity
- Incidence of a reduction in visual acuity of 10 ETDRS letters or more
- Incidence of PDR
- Incidence of DMO
- Additional treatments for DR (any laser, defined as any laser treatment including focal or grid, panretinal photocoagulation (PRP), or both; focal or grid laser and PRP (separately); anti-vascular endothelial growth factor (VEGFs), steroids, vitrectomy, other)
- Mean vision-related quality of life
- Incremental cost per Quality Adjusted Life years (QALY) gained
- Acceptability of the treatment
- Discontinuation of the treatment
- Adverse effects (serious adverse events (SAE))
- Adverse effects (rhabdomyolysis)
- Adverse effects (hepatic disorder, i.e. alanine aminotransferase elevated three times more than upper limit of normal)
- Adverse effects (pancreatitis)
- Adverse effects (Stevens-Johnson Syndrome)
- Adverse effects (others defined by original study authors)

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following databases for randomised controlled trials and controlled clinical trials. There were no restrictions on language or year of publication. The date of the search was 1 February 2022.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 2; which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 1 February 2022; Appendix 1);
- MEDLINE Ovid (1946 to 1 February 2022; Appendix 2);
- Embase Ovid (1980 to 1 February 2022; Appendix 3);
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 1 February 2022; Appendix 4);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 1 February 2022; Appendix 5);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp; searched 1 February 2022; Appendix 6).

Searching other resources

Two review authors (SYK, YK) independently searched the reference lists of identified clinical trials.

Data collection and analysis

Data extraction was undertaken using a previously piloted Excel data extraction sheet and Covidence.

Selection of studies

Two of three review authors (KI, SYK, SK) independently screened search results; discrepancies were resolved through discussion. We screened the list of titles and abstracts, and classified records as potentially eligible or not eligible. We obtained the full-text articles of all potentially eligible studies, which were independently reviewed by two reviewers (SYK, YK), who classified them as eligible or not eligible. Disagreements were resolved through discussion with other authors (KI, SK, NW, NL). We gave the primary reasons for exclusion in the Characteristics of excluded studies table.

Data extraction and management

Two of four review authors (SYK, NL, SK, YK) independently extracted data from trial reports and entered the data into Review Manager 5 (RevMan 5) and RevMan Web (Review Manager 2020; RevMan Web 2023). We resolved any discrepancies in data extraction through discussion. If we could not reach consensus, we consulted another review author (NW). When information in the full-text article was insufficient, we contacted the corresponding author of the original trial to request additional information. We used a data collection form, which we piloted prior to its use (Appendix 7). We planned to obtain English translations of any trials reported in non-English. However, none of the eligible studies were written in other languages. Therefore, translations were not needed. We obtained the data on outcomes specified in Types of outcome measures. For dichotomous outcomes, we collected data on the number of events and total participants randomised and followed in each trial arm. For continuous outcomes, we collected data on the mean and standard deviation or median and interquartile range in each trial arm.

Assessment of risk of bias in included studies

Two of four review authors (SYK, NL, SK, YK) independently assessed study quality, study limitations and the extent of potential bias by using the Cochrane RoB 1 tool, described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We considered the following domains.

- Sequence generation (selection bias)
- Allocation concealment (selection bias)
- Masking (blinding) of participants, personnel (performance bias)
- Masking (blinding) of outcomes assessors (detection bias)
- Incomplete outcome data (attrition bias)
- Selective outcome reporting (reporting bias)
- Other - other threats to validity

For each domain, we judged whether the trial authors made sufficient attempts to minimise bias in their study design. We made judgements using three measures: high, low, and unclear risk of bias. We recorded this judgement in the risk of bias tables and presented a summary risk of bias figure.

Measures of treatment effect

We measured treatment effect according to the data types described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022).

Dichotomous data

Variables in this group included the primary outcome, progression of DR, and the following secondary outcomes: incidence of overt retinopathy, incidence of a reduction in visual acuity of 10 ETDRS letters or more, incidence of PDR, incidence of DMO, additional treatments for DR, acceptability of the treatment, discontinuation of the treatment, and adverse effects. We reported dichotomous variables as risk ratios (RRs) with 95% confidence intervals (CIs).

Continuous data

We planned to report continuous variables, including differences between groups for mean change in visual acuity, quality of life scores, and incremental cost per QALY gained as mean difference with 95% CI (if normally distributed) or median and interquartile range (if not normally distributed). We planned to calculate the standardised mean difference (SMD) when trials used different scales for the same outcome measure.

Unit of analysis issues

Trials reporting one eye per person

When trials included outcomes based on one eye per person, there were no issues regarding unit of analysis. We documented how the trials selected the included eye.

Trials reporting two eyes per person

Ideally, these studies are adjusted for within-person correlation. We planned to collect data on the measure of effect and confidence interval and enter this into RevMan 5 or RevMan Web using the generic inverse variance method (Review Manager 2020; RevMan Web 2023). If trials reported both eyes without this adjustment, we planned to use the data and discuss the implications in the interpretation. When the results per person were reported using a scale that considered both eyes, we used these results, since in this case, there were no issues regarding the unit of analysis.

Dealing with missing data

We documented if loss to follow-up was high (over 20%), or unbalanced between treatment groups, as a potential source of attrition bias. We used data as reported in the trial publications, including any imputation for missing data.

Assessment of heterogeneity

We assessed heterogeneity between trials by visual inspection of forest plots, and by formal statistical tests of heterogeneity (Chi^2 test (Deeks 2022)).

Assessment of reporting biases

We searched both registered trials and published trials. We contacted researchers of the unpublished trials to provide data related to outcomes in this review, though we found that these trials were ongoing studies.

Data synthesis

We performed statistical analyses according to guidance from Cochrane Eyes and Vision. We pooled data using a fixed-effect model. When we conducted meta-analysis using data measured with different scales, we described the scales' characteristics.

Subgroup analysis and investigation of heterogeneity

We presented subgroup analysis undertaken in the included RCTs, but we did not undertake any subgroup analysis as part of the current review, as this was not possible.

Sensitivity analysis

We did not conduct any sensitivity analysis due to insufficient number of trials.

Summary of findings and assessment of the certainty of the evidence

We planned to report absolute risks and measures of effect in a summary of findings table, and provide an overall assessment of the certainty of the evidence for each outcome using the GRADE system (GRADEpro GDT). Two review authors (SYK, YK) independently undertook the GRADE assessment. Discrepancies were resolved by discussion. If we could not reach consensus, we consulted another review author (NW, NL).

We included these outcomes in the summary of findings table. We reported the results at three years.

- Progression of DR
- Incidence of overt retinopathy
- Incidence of a reduction in visual acuity of 10 ETDRS letters or more
- Incidence of PDR
- Incidence of DMO
- Mean vision-related quality of life
- Adverse effects (SAE)

RESULTS

Description of studies

Results of the search

The electronic searches yielded a total of 423 records (Figure 1). After removing 121 duplicates, the Cochrane Information Specialist (CIS) screened the remaining 302 records and removed 204 records that were not relevant to the scope of the review. We screened the remaining 98 records and obtained the full-text reports of 34 records for further assessment.

Figure 1. Study selection flow diagram

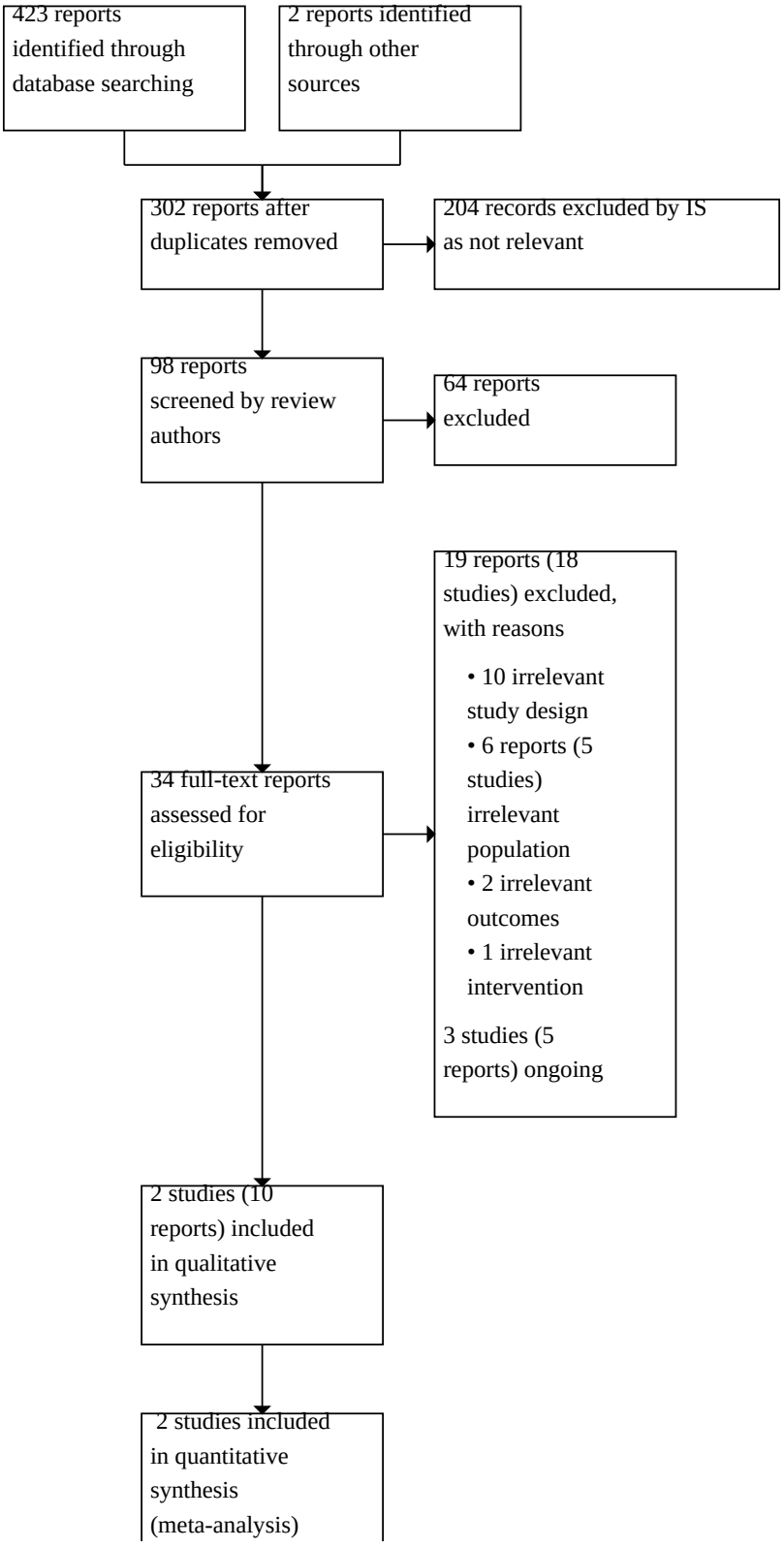


Figure 1. (Continued)

synthesis
(meta-analysis)

We included two studies (in 10 reports), excluded 18 studies (in 19 reports), and identified three ongoing studies (in 5 reports).

Included studies

Study design

We included two randomised controlled trials, both of which had an eye sub-study (ACCORD-Lipid; FIELD).

We included two studies, the Action to control cardiovascular risk in diabetes lipid trial (ACCORD-Lipid) and the Fenofibrate intervention and event lowering in diabetes study (FIELD (ACCORD-Lipid; FIELD)). Both were multicentre, double-masked, placebo-controlled RCTs, and each of them had an ophthalmological sub-study (ACCORD eye study of ACCORD-Lipid (ACCORD Eye Lipid), and FIELD ophthalmology sub-study). We describe the characteristics of these studies, including those of the eye sub-studies, in more detail below. Regarding eligibility criteria for the eye sub-studies, ACCORD Eye Lipid added one exclusion criterion to ACCORD-Lipid's criteria: history of proliferative diabetic retinopathy (PDR) that had been treated with laser photocoagulation or vitrectomy. FIELD ophthalmology sub-study added the following eligibility criteria to those of the FIELD main trial: two-field colour fundus photographs of both eyes had to show no evidence of PDR, severe non-proliferative diabetic retinopathy (NPDR), clinically significant DMO, or indication for, or evidence of, a history of laser treatment at a screening examination (this was done during the placebo run-in phase). Additionally, there were a number of other exclusions based on the presence of other ocular pathology or 'technical problems' (not specified which ones). ACCORD-Lipid was conducted in the United States and Canada. FIELD was conducted in Australia, Finland, and New Zealand. The follow-up period of ACCORD-Lipid was 4.7 years; FIELD was 5 years. The sample size of ACCORD-Lipid was calculated based on the primary outcome, which was not diabetic retinopathy (DR), but the number of participants included was lower than that required, based on the investigator's sample size calculation. For ACCORD Eye Lipid, a sample size calculation for the primary composite outcome related with advancing DR was provided, but like the full trial, this was not met. The sample size of FIELD was calculated based on each primary outcome, which were not DR, while in the FIELD ophthalmology sub-study, the sample size calculation was not given. The unit of assessment for the outcomes from ACCORD-Lipid, ACCORD Eye Lipid, and FIELD was the person. Outcomes reported in the FIELD ophthalmology sub-study were from worse affected eye, or right eye when both eyes were equally affected. ACCORD-Lipid was publicly funded, while FIELD was sponsored by industry.

Participants

See Characteristics of included studies tables (ACCORD-Lipid; FIELD). Combined, the two studies included 15,313 participants (ACCORD-Lipid: 5518, 36.0%; FIELD: 9795, 64.0%), with a predominance of males (total: 9962; 65.1%; ACCORD-Lipid: 3824, 38.4%; FIELD: 6138, 61.6%), and Caucasians (total: 12,867; 84.0%; ACCORD-Lipid: 3774, 29.3%; FIELD: 9093, 70.7%). The average age of participants was 62 years (ACCORD-Lipid: 62.3 ± 6.8 (mean ± SD); FIELD: 62.2 (SD was not specified in the original article)). Eye sub-studies included 2930 participants in total (ACCORD Eye Lipid: 1918, 65.6%; FIELD ophthalmology sub-study: 1012, 34.5%). The criteria for selection of participants for the sub-studies were as follows.

- All ACCORD-Lipid participants were recruited, and were assessed for eligibility for the ACCORD Eye Lipid sub-study, using the baseline information obtained in ACCORD-Lipid. Those who seemed eligible, were screened for eligibility. Informed consent was obtained from each participant specifically for the ACCORD Eye Lipid sub-study, and recruited.
- For FIELD, consents for the ophthalmology sub-study were obtained from only 22 FIELD sites' participants, not all FIELD participants. They were assessed for eligibility during the placebo run-in phase.

All participants in both studies had T2D.

Intervention

Both studies used fenofibrate as the intervention and placebo as the control, although different doses were used. The dose of fenofibrate in ACCORD-Lipid was 160 mg/day; in FIELD it was 200 mg/day. ACCORD-Lipid had intensive glycaemic control (HbA1c target < 6.0%) or standard therapy (7.0% ≤ HbA1c target ≤ 7.9%) arms to evaluate other interventions (tight glycaemic control) with a 2-by-2 factorial design. In ACCORD-Lipid, all participants received nutrition and physical activity counselling, a recommendation to use aspirin daily, and simvastatin 20 mg to 40 mg/day. Additionally, if participants had an additional risk factor for CVD, using an angiotensin-converting enzyme inhibitor was recommended. Current smokers received smoking cessation counselling. Participants' personal physicians received information about current guidelines for lipids and blood pressure management. In FIELD, all participants underwent an initial run-in period of 16 weeks before randomisation, consisting of 4 weeks with only diet advice, 6 weeks with single-blind placebo, and 6 weeks with single-blind fenofibrate. Their intention for the run-in period was to allow people time to discuss long-term participation with their families and their usual doctors, and for evaluation of the benefits of fenofibrate treatment on a background of recommended dietary advice. The active run-in period was to also determine to what extent any long-term clinical benefits of treatment correlated with the short-term effects of the drug to modify different lipid fractions.

Primary Outcome

Only the FIELD ophthalmology sub-study reported the incidence of overt retinopathy and the incidence of participants with overt retinopathy at baseline advancing two or more steps in the ETDRS severity scale separately.

Secondary Outcomes

The following outcomes were reported and obtained from the main ACCORD-Lipid trial: discontinuation of the treatment, severe adverse events (SAE), hepatic disorder, pulmonary embolism, and deep-vein thrombosis. The ACCORD Eye Lipid sub-study reported on incidence of overt retinopathy, and additional treatments for DR including focal/grid laser and PRP. FIELD reported additional treatment for DR, including any laser; additional treatments for DR, including focal/grid laser and PRP; discontinuation of the treatment; SAE; rhabdomyolysis; hepatic disorder; pancreatitis; pulmonary embolism; myositis; renal disease needing dialysis; and deep-vein thrombosis. The FIELD ophthalmology sub-study reported incidence of overt retinopathy, incidence of DMO, and additional treatment for DR, including vitrectomy. Following our protocol, we described all adverse events and SAE authors presented in their trials.

Neither study reported on the following outcomes: mean change in visual acuity; incidence of a reduction in visual acuity of 10 ETDRS letters or more; incidence of PDR; additional treatments for DR, including anti-vascular endothelial growth factor (VEGFs), steroids, and others; mean vision-related quality of life; incremental cost per QALY gained; or acceptability of the treatment.

Excluded studies

We excluded 18 studies (19 reports): 10 studies had an irrelevant study design, five studies (6 reports) had an irrelevant population, two measured irrelevant outcomes, and one study had an irrelevant intervention. See Characteristics of excluded studies for details.

Ongoing studies

We identified three ongoing studies (in 5 reports). We will assess and include them, as indicated, in future updates (FAME 1 EYE; NCT03439345; NCT04661358).

Risk of bias in included studies

Risk of bias of included studies are summarised in Figure 2 and Figure 3. ACCORD-Lipid's risk of bias was low for all domains, and ACCORD Eye Lipid's risk of bias was low for all domains. FIELD's risk of bias was low for all domains. For the FIELD ophthalmology sub-study, the risk of bias for the domain of selecting reporting was unclear; the other domains were at low risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item, presented as percentages across all included studies

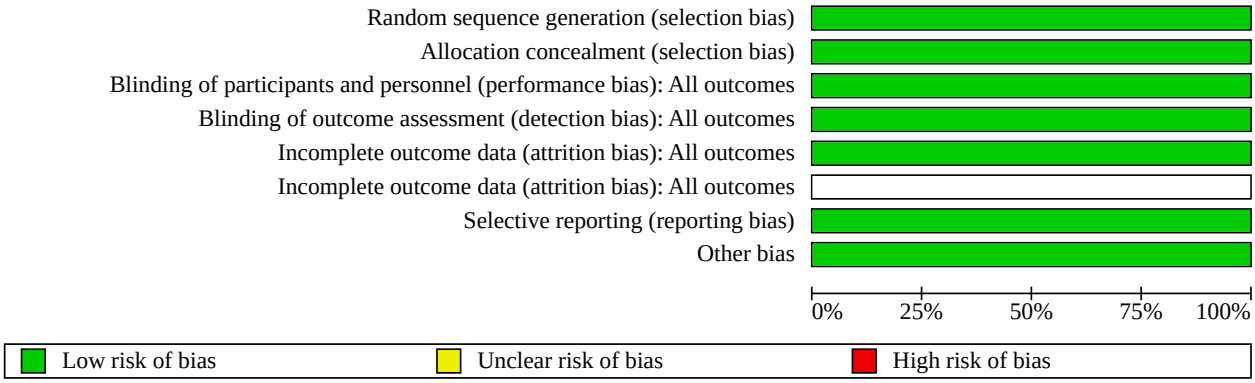
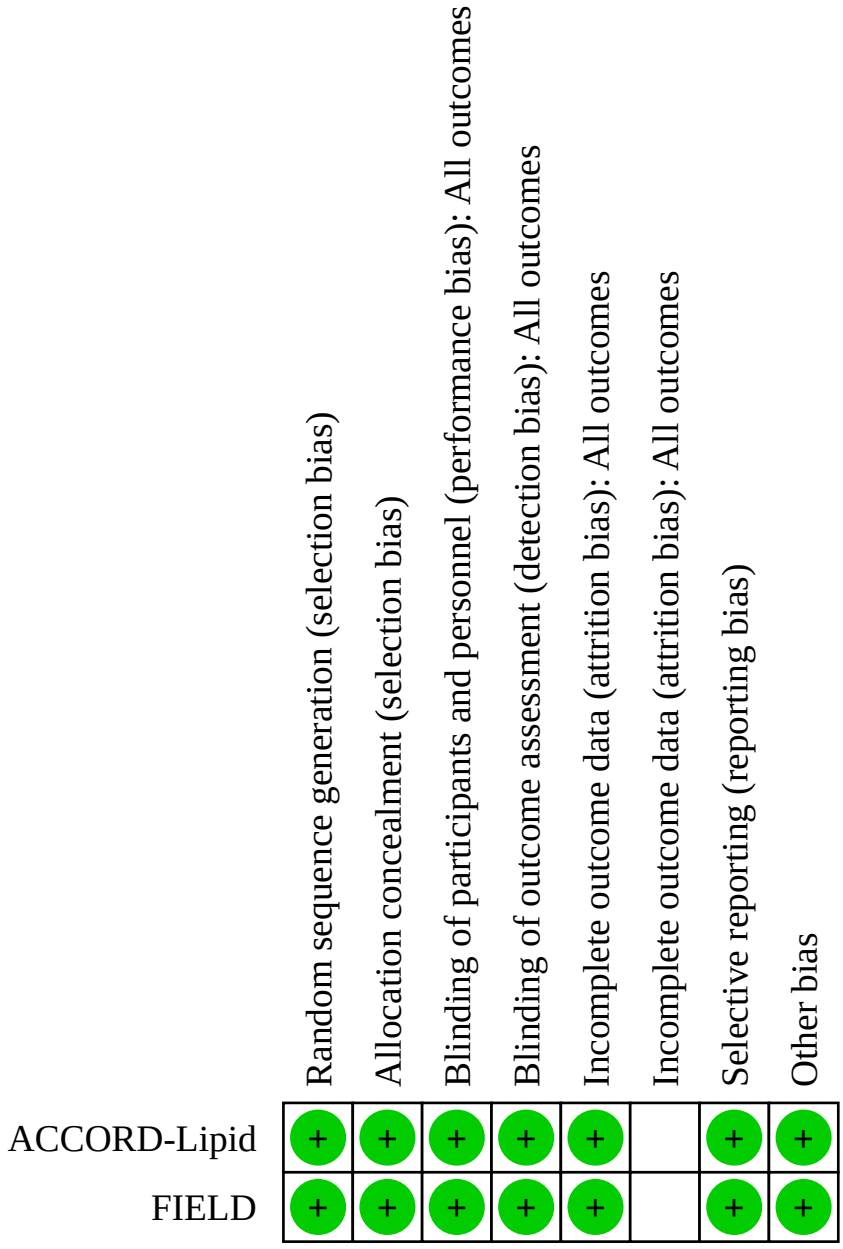


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



For sequence generation, randomisation was undertaken using permuted blocks in ACCORD-Lipid, and using a dynamic allocation method centrally in FIELD.

Therefore, the method of both trials' sequence generation was adequate.

Allocation

Both trials reported an adequate method of randomisation; one used permuted blocks and the other used a central computer system and dynamic allocation method.

Blinding

In both trials' participants, research personnel, and outcome assessors were masked to treatment allocation. Matching placebo was used in control groups.

Incomplete outcome data

In ACCORD-Lipid, data were missing for 56 participants (1.0%). This was a low proportion, but they did not provide the reasons for the missing data. We contacted the corresponding author of ACCORD Eye Lipid, who provided information on the number of participants whose data at baseline and 4-year follow-up did not exist (325 (16.9%)); therefore, risk of bias was judged to be low. In addition, 153 out of 325 were in the fenofibrate group (16.0%); 172 were in the placebo group (17.9%). Missing data were balanced between the groups. In FIELD, the number of missing data was 31 (0.31%); 9/31 withdrew their consents, and 22 were not followed up. The proportions were low, but they did not describe the reasons. In the FIELD ophthalmology sub-study, three participants withdrew their consents, and 124 were not followed up. Therefore, 127 (12.5%) participants were missing; the proportion was low, considering the number of outcomes' incidences. In addition, 67 of 127 were in the fenofibrate group (13.1%); 60 were in the placebo group (12.0%). The number missing was balanced between the groups. Therefore, we decided low risk for the FIELD ophthalmology sub-study.

Selective reporting

In ACCORD-Lipid, the authors stated their outcomes in the published protocol and reported all outcomes as defined (ACCORD-Lipid). Therefore, the risk of bias for this domain was considered low. In ACCORD Eye Lipid's protocol, we found that one outcome (change in visual acuity at four years compared with baseline) was different from that reported in the manuscript presenting the results. In the published protocol for the ACCORD Eye Lipid sub-study, the outcomes to be evaluated were: moderate vision loss or loss of 3 lines on the logarithmic minimum angle of resolution (LogMAR) visual acuity charts, legal blindness: 20/160 or worse, and severe vision loss of 5/200 or worse, all from baseline to year four. In contrast, in the main manuscript, they presented the results of the following outcomes instead: moderate vision loss, development of vision of 20/50 or worse from baseline, development of 20/200 or worse from baseline, worsening of ≥ 15 letters of visual acuity score, all from baseline to year four. However, this selective reporting did not affect the outcomes evaluated in our review, thus, we considered the risk of bias for ACCORD for the selective reporting domain to be low**.**

In FIELD, the authors stated their outcomes in the published protocols and reported them all, therefore, we classified the risks of bias as low (FIELD). We did not find a published protocol for the FIELD ophthalmology sub-study, so it was not clear if all outcomes prespecified for this study were reported; thus, we considered the risk of bias for this domain was unclear.

Other potential sources of bias

No other potential sources of bias were identified for ACCORD-Lipid or ACCORD Eye Lipid. It was not a cluster-randomised trial or cross-over trial. Baseline imbalance did not occur. Allocation concealment was adequate. No differential diagnostic activity was found. The vanguard phase did not affect the comparison. The risk of bias was graded low. In addition, ACCORD-Lipid was not funded by industry, but publicly funded. The study drugs were donated by the manufacturer, but they did not participate in the study design or conduct of the trial; neither data accrual or analysis, or manuscript preparation.

Regarding the FIELD or FIELD ophthalmology sub-study, we did not identify another potential source of bias, thus, the risk of bias for this domain was also low. Their methods in considering other potential source of bias were adequate. There was the run-in period, though it did not affect the randomisation. However, the FIELD and FIELD ophthalmology sub-study were sponsored by industry. Representatives of industry (i.e. sponsors) without voting rights attended meetings of the management committee. In the writing committee, some members had conflicts of interest with the sponsor. Both the writing committee and study management committee took part in the writing of the manuscript, and in making the decision to submit the manuscript for publication.

Effects of interventions

See: **Summary of findings 1** Fenofibrate for diabetic retinopathy

See Summary of findings 1.

ACCORD-Lipid randomised 2765 participants to fenofibrate and 2753 participants to placebo. The mean follow-up was 4.7 years. In the eye sub-study of ACCORD-Lipid, 959 participants were randomised to fenofibrate and 959 to placebo. FIELD randomised 4895 participants to fenofibrate and 4900 to placebo. The median follow-up was 5 years. In the FIELD ophthalmology sub-study, 512 participants were randomised to fenofibrate and 500 to placebo.

ACCORD-Lipid's data were collected from published studies and further information was provided by the authors; FIELD's data were collected from published studies.

The ACCORD Eye Lipid and FIELD ophthalmology sub-study used the ETDRS scale for DR severity. However, the ACCORD Eye Lipid sub-study used the ETDRS retinopathy severity scale for the person, in which both eyes are assessed and severity considers the retinopathy in both eyes. Steps ranged from 1 to 17, with more severe DR being given higher numbers. FIELD, however, graded the retinopathy using the ETDRS grading of the more severely affected eye (or of the right eye if both eyes were equally affected). The scale they used ranged from 1 to 13, with higher numbers given as the severity of DR increased.

We conducted meta-analysis for the following outcomes: incidence of overt retinopathy, additional treatments for DR including focal/grid laser and PRP, discontinuation of the treatment, and adverse effects including SAE, hepatic disorder, deep-vein thrombosis, and pulmonary embolism, as both trials provided data on these outcomes. We found no substantial heterogeneity in the outcomes we meta-analysed (I^2 = 0%), except discontinuation of the treatment (I^2 = 87%) and adverse effects (hepatic disorder I^2 = 82%). Meta-analysis was not possible for any of the other outcomes, including our primary outcome.

Following factors of the sensitivity analysis or subgroup analysis, we also described the results of the included studies, if applicable.

Fenofibrate compared to placebo or observation

Progression of diabetic retinopathy (DR)

Overall, fenofibrate likely resulted in little to no difference in the progression of DR at five years (risk ratio (RR) 0.86, 95% confidence interval (CI) 0.60 to 1.25; 1 study, 1012 participants; Analysis 1.1; moderate-certainty evidence). We downgraded one level for imprecision, since the sample size was less than the optimal information size (OIS), and crossed the line of no effect (Guyatt 2011; Schünemann 2022).

The FIELD ophthalmology sub-study reported that of those with overt retinopathy at baseline, 2.9% (3/105) of the fenofibrate group and 13.6% (14/103) of the placebo group progressed two or more stages in the ETDRS scale (RR 0.21, 95% CI 0.06 to 0.71; 1 study, 208 people; test for interaction P = 0.02; Analysis 1.1). In subgroup analysis, those without overt retinopathy at baseline showed little or no progression (RR 1.00, 95% CI 0.68 to 1.47; 1 study, 804 participants).

Incidence of overt retinopathy

The ACCORD Eye Lipid sub-study reported this outcome at four years; the FIELD ophthalmology sub-study at five years. In ACCORD Eye Lipid, 28.0% (120/429) of participants in the fenofibrate group and 31.9% (127/398) of participants in the placebo group developed this outcome at four years. In the FIELD ophthalmology sub-study, 11.3% (46/407) of participants in the fenofibrate group and 11.3% (45/397) of participants in the placebo group developed this outcome at five years. Fenofibrate likely resulted in little to no difference in the incidence of overt retinopathy (RR 0.91, 95% CI 0.76 to 1.09; 2 studies, 1580 participants; Analysis 1.2; moderate-certainty evidence). We downgraded one level for imprecision.

Excluding the industry-funded FIELD ophthalmology sub-study, the risk ratio was 0.88 (95% CI 0.72 to 1.09). On the other hand, excluding the study in which this outcome was measured at four years (rather than at five years, as stated in our protocol, i.e. excluding the ACCORD Eye Lipid trial), the risk ratio was 1.00 (95% CI 0.68 to 1.47).

Incidence of DMO

The FIELD ophthalmology sub-study reported this outcome at five years; 0.8% (4/512) of participants in the fenofibrate group and 2.0% (10/500) of participants in the placebo group developed DMO. Fenofibrate likely resulted in little to no difference in the incidence of DMO (RR 0.39, 95% CI 0.12 to 1.24; 1 study, 850 participants; moderate-certainty evidence; Analysis 1.3). We downgraded one level for imprecision.

Additional treatments for DR (any laser)

Only FIELD reported this outcome. In FIELD, 3.6% (178/4895) of participants in the fenofibrate group and 5.2% (253/4900) of participants in the placebo group received any laser treatment (including focal/grid, PRP, or both). Fenofibrate reduced the requirement for any laser when compared with placebo (RR 0.70 95%CI 0.58 to 0.85; 1 study, 9764 participants; Analysis 1.4).

Additional treatments for DR (focal/grid laser)

Both ACCORD Eye Lipid (at four years) and FIELD (at five years) reported this outcome. In ACCORD Eye Lipid, 2% (19/959) of participants in the fenofibrate group and 2.7% (26/959) of participants in the placebo group required focal/grid laser. In FIELD, 2.3% (115/4895) of participants in the fenofibrate group and 3.4% (167/4900) of participants in the placebo group required this treatment. Fenofibrate reduced the requirement for focal/grid laser (RR 0.69, 95% CI 0.56 to 0.86; 2 studies, 11,358 participants; Analysis 1.5).

Excluding the industry-funded FIELD Ophthalmology sub-study, the risk ratio was 0.71 (95% CI 0.40 to 1.28). On the other hand, excluding the study with this outcome measured at four years (rather than five, as established in our protocol, i.e. the ACCORD Eye Lipid trial) the risk ratio was 0.69 (95% CI 0.55 to 0.87).

Additional treatments for DR (PRP)

Both ACCORD Eye Lipid and FIELD reported this outcome. In ACCORD Eye Lipid at four years, 0.8% (8/959) of participants in the fenofibrate group and 1.6% (15/959) of participants in the placebo group required PRP. In FIELD at five years, 1.5% (75/4895) of participants in the fenofibrate group and 2.2% (108/4900) of participants in the placebo group required PRP. Fenofibrate reduced the requirement of PRP (RR 0.67, 95% CI 0.51 to 0.89; 2 studies, 11,347; Analysis 1.6).

Excluding the industry-funded FIELD study, the risk ratio was 0.52 (95% CI 0.22 to 1.22). Excluding the trial in which this outcome was measured at four years (rather than at five, as established in our protocol, i.e. the ACCORD Eye Lipid trial), the risk ratio was 0.70 (95% CI 0.52 to 0.93).

Additional treatments for DR (vitrectomy)

Only the FIELD ophthalmology sub-study reported this outcome. In FIELD, 0.4% (2/512) of participants in the fenofibrate group and 0.2% (1/500) of participants in the placebo group required vitrectomy. Fenofibrate may result in little to no difference in the requirement of vitrectomy (RR 1.96 95% CI 0.18 to 21.56; 1 study, 850 participants; Analysis 1.7; moderate-certainty evidence). We downgraded for imprecision because the CIs were wide, with few events.

Discontinuation of the treatment

Both ACCORD-Lipid and FIELD reported this outcome. In ACCORD-Lipid, 22.7% (628/2765) of participants in the fenofibrate group and 18.7% (516/2753) of participants in the placebo group discontinued treatment with fenofibrate during the trial. In FIELD, 19.5% (954/4895) of participants in the fenofibrate group and 19.4% (950/4900) of participants in the placebo group discontinued treatment with fenofibrate during the trial. Fenofibrate likely increased discontinuation of the treatment (RR 1.08, 95%CI 1.01 to 1.15; 2 studies, 15,226 participants; with heterogeneity, I^2 = 87%; Analysis 1.8).

Excluding the industry-funded FIELD study, the risk ratio was 1.21 (95% CI 1.09 to 1.34). Both studies were conducted with adequate methodology and reported outcomes at five years.

Adverse effects (serious adverse events (SAE))

Both ACCORD-Lipid and FIELD reported this outcome at five years. In ACCORD-Lipid, 1.0% (27/2765) of participants in the fenofibrate group and 0.7% (18/2753) of participants in the placebo group developed SAE. In FIELD, 0.8% (38/4895) of participants in the fenofibrate group and 0.5% (24/4900) of participants in the

placebo group developed SAE. While SAE were rare, the risk of their occurrence increased with the use of fenofibrate (RR 1.55, 95% CI 1.05 to 2.27; 2 studies, 15,226 participants; high-certainty evidence; Analysis 1.9).

Excluding the industry-funded FIELD study, the risk ratio was 1.49 (95% CI 0.82 to 2.70).

Adverse effects (rhabdomyolysis)

FIELD reported this outcome. In the fenofibrate group, 0.1% (3/4895) of participants and in the placebo group, 0.0% (1/4900) of participants developed rhabdomyolysis. Data suggested that fenofibrate might result in little to no difference in the development of rhabdomyolysis (RR 3.00 95% CI 0.31 to 28.87; 1 study, 9764 participants; Analysis 1.10). However, due to the rarity of this complication and the very wide 95% CI, this result is uncertain.

Adverse effects (hepatic disorder)

Both ACCORD-Lipid and FIELD reported this outcome. In ACCORD-Lipid, 1.9% (52/2765) of participants in the fenofibrate group and 1.5% (40/2753) of participants in the placebo group developed this outcome. In FIELD, 0.4% (22/4895) of participants in the fenofibrate group and 0.8% (38/4900) of participants in the placebo group developed this outcome. Fenofibrate likely resulted in little to no difference in the development of hepatic disorder (RR 0.95 95% CI 0.69 to 1.32; 1 study, 15,226 participants; with heterogeneity, I^2 = 82%; Analysis 1.11).

Excluding the industry-funded FIELD study, the risk ratio was 1.29 (95% CI 0.86 to 1.95).

Adverse effects (pancreatitis)

FIELD reported this outcome. In FIELD, 0.8% (40/4895) of participants in the fenofibrate group and 0.5% (23/4900) of participants in the placebo group developed pancreatitis. Fenofibrate increased the development of pancreatitis (RR 1.74 95% CI 1.04 to 2.90; 1 study, 9764 participants; Analysis 1.12).

Adverse effects (pulmonary embolism)

Both ACCORD-Lipid and FIELD reported this outcome. In ACCORD-Lipid, 0.0% (0/2765) of participants in the fenofibrate group and 0.0% (0/2753) of participants in the placebo group developed this outcome. In FIELD, 1.1% (53/4895) of participants in the fenofibrate group and 0.7% (32/4900) of participants in the placebo group developed this outcome. Fenofibrate likely increased the development of pulmonary embolism (RR 1.66 95% CI 1.07 to 2.57; 2 studies, 15,226 participants; Analysis 1.13).

Excluding the industry-funded FIELD study, fenofibrate resulted in little to no difference in pulmonary embolism, because no one in either group in ACCORD-Lipid developed this outcome.

Adverse effects (myositis)

FIELD reported this outcome. In FIELD, 0.0% (2/4895) of participants in the fenofibrate group and 0.0% (1/4900) of participants in the placebo group developed this outcome. Data suggested that fenofibrate might result in little to no difference in the development of myositis (RR 2.00 95% CI 0.18 to 22.08; 1 study, 9764 participants; Analysis 1.14).

Adverse effects (renal disease needing dialysis)

Only FIELD reported this outcome. In FIELD, 0.3% (16/4895) of participants in the fenofibrate group and 0.4% (21/4900) of participants in the placebo group developed this outcome. Fenofibrate resulted in little to no difference in the development of renal disease needing dialysis (RR 0.76 95% CI 0.40 to 1.46; 1 study, 9764 participants; Analysis 1.15).

Adverse effects (deep-vein thrombosis)

Both ACCORD-Lipid and FIELD reported this outcome. In ACCORD-Lipid, 0% (0/2765) of participants in the fenofibrate group and 0% (0/2753) of participants in the placebo group developed this outcome. In FIELD, 1.4% (67/4895) of participants in the fenofibrate group and 1.0% (48/4900) of participants in the placebo group developed this outcome. Fenofibrate resulted in little to no difference in the development of deep vein thrombosis (RR 1.40 95% CI 0.97 to 2.02; 2 studies, 15,226 participants; Analysis 1.16).

Excluding the industry-funded FIELD study, fenofibrate resulted in little to no difference in deep-vein thrombosis, because no one in either group of ACCORD-Lipid developed this outcome.

DISCUSSION

Summary of main results

We included two randomised controlled trials (RCTs; N = 15,226), each of which included an eye sub study (ACCORD-Lipid; FIELD).

Moderate-certainty evidence from one sub-study found that fenofibrate likely resulted in little to no difference in the progression of diabetic retinopathy (DR) with a mixed population (with and without overt retinopathy), but likely resulted in slow progression of DR in a population with overt retinopathy at baseline.

Moderate-certainty evidence found that fenofibrate likely resulted in little to no difference in the incidence of overt retinopathy (two studies) or diabetic macular oedema (DMO; one study).

High-certainty evidence found that fenofibrate increased serious adverse events overall.

However, only the FIELD ophthalmology sub-study reported on our primary outcome, progression of DR. Thus, meta-analysis was not possible. The FIELD ophthalmology sub-study reported that in a mixed group of people with and without overt retinopathy, fenofibrate likely resulted in little to no difference in progression of DR. Because of the small sample size (N = 850) compared with the optimal information size (OIS), this finding should be interpreted cautiously (Guyatt 2011; Schünemann 2022). The degree of certainty was moderate. However, subgroup analysis by the presence of overt retinopathy at baseline suggested a difference in progression. For the secondary outcome, incidence of overt retinopathy, we conducted meta-analysis and found that compared to placebo or observation, fenofibrate likely resulted in little to no difference in the incidence of overt retinopathy. Because of the imprecision due to the small sample size (N = 1580) compared with the OIS, this result should be also interpreted with caution, as we assessed the certainty of the evidence to be moderate.

For the incidence of DMO, fenofibrate likely resulted in little to no difference, but here, due to the imprecision because of the small sample size (N = 850) compared with the OIS, we assessed the

certainty of the evidence as moderate; yet again, results should be interpreted with caution. Fenofibrate reduced the requirement of any laser, focal/grid laser, and panretinal photocoagulation. Fenofibrate might result in little to no difference in the need for vitrectomy. With imprecision due to the small sample size (N = 850) and few events (n = 3), this result should also be interpreted cautiously. Fenofibrate likely increased discontinuation of the treatment.

Regarding adverse effects, the use of fenofibrate increased severe adverse events with high-certainty evidence. The use of fenofibrate also increased pancreatitis, and likely increased pulmonary embolism. Fenofibrate likely resulted in little to no difference in the development of hepatic disorder and might result in little to no difference in the development of rhabdomyolysis or myositis. Fenofibrate resulted in little to no difference in the development of renal disease needing dialysis and deep-vein thrombosis.

Neither ACCORD-Lipid nor FIELD examined any of the other outcomes specified in our review, including mean change in visual acuity, incidence of a reduction in visual acuity of 10 ETDRS letters or more, incidence of proliferative diabetic retinopathy, additional treatments for DR including anti-vascular endothelial growth factor (VEGFs) or steroids, mean vision-related quality of life, incremental cost per quality-adjusted life year gained, acceptability of the treatment, or adverse effects (Steven-Johnson syndrome). At present, there are no other preventive measures besides glycaemia, blood pressure, and lipid control that could potentially reduce the risk of progression and complications of DR. Therefore, new prophylactic strategies are needed. Recent trials have demonstrated that intravitreal anti-VEGF use in eyes with moderately severe and severe non-proliferative DR may lead to an improvement in retinopathy levels, measured using the diabetic retinopathy severity scale (Brown 2021; Maturi 2021). Further evidence is required to support the use of fenofibrate in people with, or at risk of developing DR. LENS, FAME 1 eye, and Fenofibrate for prevention of DR worsening studies will hopefully provide this evidence (FAME 1 EYE; NCT03439345; NCT04661358).

Overall completeness and applicability of evidence

We included two studies conducted in the US, Canada, Australia, Finland, and New Zealand. Participants were 40 to 79 years old, with a higher proportion of males (65.1%) and Caucasians (84.0%); all had type 2 diabetes (T2D). Participants were similar in age and gender in both trials. We are not confident that the results are generalisable to people of other races or ages, or those with type 1 diabetes (T1D), without further evidence from new studies.

No studies examined the: mean change in visual acuity, incidence of a reduction in visual acuity of 10 ETDRS letters or more, incidence of proliferative diabetic retinopathy (PDR), additional treatments for DR, mean vision-related quality of life, incremental cost per quality adjusted life years (QALY) gained, acceptability of the treatment, or adverse effects (Steven-Johnson syndrome).

Regarding ongoing trials, LENS's participants had any diabetes mellitus except gestational diabetes, FAME 1 eye's participants had T1D, and Fenofibrate for Prevention of DR Worsening's participants were either T1D or T2D. We await publication of the data from their outcomes, progression of DR, incidence of DMO, additional treatments including laser, anti-VEGFs, steroid, and vitrectomy, and visual acuity from three ongoing trials, cost-effectiveness from LENS, and health-related quality of life from LENS and FAME 1 eye.

On applicability of the data: fenofibrate likely results in little to no difference in the progression of diabetic retinopathy, but not in a group of people with overt retinopathy at baseline (FIELD sub-study); and reduces the requirement for any laser treatment (FIELD), and for laser treatment including focal/grid and panretinal photocoagulation (ACCORD-Lipid sub-study; FIELD sub-study). However, these findings should be interpreted with caution, as stated above. In addition, fenofibrate increases severe adverse events, pancreatitis, and pulmonary embolism.

Quality of the evidence

We included two high-quality RCTs comprising a total of 15,313 participants (ACCORD-Lipid: 5518; ACCORD Eye Lipid: 1918; FIELD: 9795; FIELD ophthalmology sub-study: 1012). These were multi-centre RCTs, using matching placebo, with appropriate sequence generation and allocation concealment. We assessed ACCORD-Lipid as low risk of bias. The sample size of ACCORD-Lipid was calculated based on the primary outcome, which was not DR. Despite its large sample size, the number of participants included was lower than required, based on the investigator's sample size calculation (ACCORD-Lipid). In ACCORD Eye Lipid, a sample size calculation for the primary composite outcome, related with advancing DR, was provided, but similar to the full trial, this was not met. We detected selective reporting bias, but it did not affect the outcomes evaluated in our review, therefore, we considered the risk of bias for ACCORD Eye lipid for the selective reporting domain to be low. We considered FIELD to have a low risk of bias and large sample size (FIELD). The sample size of FIELD was calculated based on each primary outcome, none of which were DR. FIELD was supported by industry, which took part in the design of the trial, the writing of the manuscripts, and presenting of the results of the trial. In the FIELD ophthalmology sub-study, the sample size calculation was not given. The FIELD ophthalmology sub-study had no published protocol, and its reporting bias was unclear. The bias of other domains was adequate.

Results for the outcomes from the eye sub-studies for both trials should be interpreted with caution (Summary of findings 1). We assessed the certainty of the evidence for the progression of DR as moderate, because of imprecision due to small sample size (N = 850) compared with the OIS (Guyatt 2011; Schünemann 2022). We assessed moderate-certainty evidence for the incidence of overt retinopathy, downgrading due to imprecision related to small sample size (N = 1580) comparing with the OIS, and moderate-certainty evidence for incidence of DMO, due to imprecision related to small sample size (N = 850).

We found no reason to downgrade the certainty of the evidence for additional treatment for DR (any laser (FIELD)), or additional treatment for DR (focal/grid laser and PRP (ACCORD-Lipid sub-study; FIELD)), therefore, both of these outcomes were supported by high-certainty evidence. Moderate-certainty evidence supported the need for additional treatments for DR (vitrectomy), downgraded for imprecision due to only 850 participants and few events (n = 3 (FIELD sub-study).

For discontinuation of treatment, we included data at five years from both studies, with adequate study designs and a large sample size (N = 15,226), but we detected inconsistency (I^2 = 87%). We

found no reasons to downgrade the certainty of evidence for severe adverse events, because of adequate study designs and a large sample size (N = 15,226). There was high-certainty evidence that fenofibrate increases the risk of severe adverse events overall, and deep-vein thrombosis (N = 15226) in particular. Other adverse effects reported few events, rhabdomyolysis (4/9764), myositis (3/9764); and heterogeneity between studies, hepatic disorder (N = 15,226), pulmonary embolism (N = 15,226). Only FIELD reported rhabdomyolysis (N = 9764), pancreatitis (N = 9764), and renal disease needing dialysis (N = 9764), thus reducing the sample size.

Potential biases in the review process

We followed Cochrane guidelines to undertake this review. None of the authors of this review have any potential conflicts of interest to report. Therefore, there should be no potential bias introduced in this review.

We did introduce several changes in the methodology for this review compared with our plan at the protocol stage (Inoue 2019). We made these changes before initiating the literature searches and data extraction. All changes are detailed in the Differences between protocol and review section.

Agreements and disagreements with other studies or reviews

Two other systematic reviews have been published that evaluated the effects of fenofibrate on DR. There were some differences between them and our review.

Czupryniak 2016 set out to estimate the effects of micronized fenofibrate alone or with a statin on microvascular complications (retinopathy, nephropathy, or neuropathy) in people with T2D. They searched PubMed between January 1990 and November 2015. They included ACCORD-Lipid, FIELD, their sub-studies, and the MacuFen study (Massin 2014). They reported results similar to our review, that fenofibrate reduced the incidence of advancing two or more steps in the ETDRS scale in people with overt retinopathy; the composite outcome of advancing three or more steps in the ETDRS scale; the need for laser treatment for DMO and proliferative DR, and the lack of progression of DR in those without overt retinopathy at baseline. The real difference came from their inclusion of the MacuFen study, which found that fenofibrate reduced total macular volume in participants with DMO. Our review found little or no difference in the incidence of DMO, but we excluded those with DMO at baseline.

Elkjaer 2020 examined whether systemic treatments would prevent or delay the progression of DR in people with diabetes. The treatments included fenofibrate, intensive glycaemic control, medications to reduce blood pressure, combination treatment, and others, which covered a wider scope than our review. They searched for prospective studies, including RCTs, written in English, in PubMed and Embase, without limiting the type of diabetes or systematic treatments. They included 13 studies, two of which covered fenofibrate (ACCORD-Lipid; FIELD). They also reported that fenofibrate only reduced progression of DR in participants with overt retinopathy; it reduced the need for laser treatment, the risk of a two-step progression of DR grade, DMO, or laser treatment, when compared with placebo.

Su 2019 published the protocol of a systematic review investigating the effects of fenofibrate on people with DR. They plan to search for RCTs in CENTRAL, PubMed, Embase, CINAHI, ACMD, CBM, CNKI, VIP, and WANG-FANG without limitations on the study period.

AUTHORS' CONCLUSIONS

Implications for practice

Current, moderate-certainty evidence suggests that in a mixed group of people with and without overt retinopathy, who live with type 2 diabetes (T2D), fenofibrate likely results in little to no difference in progression of diabetic retinopathy (DR). However, in people with overt retinopathy who live with T2D, fenofibrate likely reduces the progression.

Serious adverse events were rare, but the risk of their occurrence was increased by the use of fenofibrate.

There is no evidence on the effect of fenofibrate in people with type 1 diabetes (T1D).

Implications for research

Further studies are needed to determine the possible beneficial effects of fenofibrate in people living with diabetes.

Participants in the randomised controlled trials (RCTs) included in this review had all T2D. Therefore, research is needed to determine the effect of fenofibrate in people with T1D.

Only one sub-study contributed data on progression of diabetic retinopathy (DR), incidence of diabetic macular oedema (DMO), and additional treatments for DR (especially vitrectomy), therefore, the number of participants was small compared with the optimal information size (OIS). Although two sub-studies contributed data on the incidence of overt retinopathy, the number of participants was still small compared with the OIS on this outcome. To establish high-certainty evidence, future studies should be powered appropriately.

Future studies should consider evaluating other important outcomes, e.g. other measures of visual acuity (e.g. mean change in visual acuity, and proportion of people experiencing a reduction in visual acuity of 10 ETDRS letters or more, i.e. the Early Treatment Diabetic Retinopathy Study); the incidence of proliferative diabetic retinopathy; use of more recently introduced treatments for complications of DR, including anti-vascular endothelial growth factor and steroids; health-related and vision-related quality of life; cost-effectiveness; and acceptability of the treatment. Involving people living with diabetes in the design of future trials is essential to ensure that outcomes that are important to people with the disease are included.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ACCORD-Lipid

Study characteristics	
Methods	**Types of study:** parallel-group randomised controlled trial
	Number of exclusion after randomisation: fenofibrate: 0 (substudy: NI), placebo: 0 (substudy: NI)
	Losses to follow-up: fenofibrate: 27 (substudy: 153), placebo: 29 (substudy: 172)
	Number randomised: fenofibrate: 2765 (substudy: 959), placebo: 2753 (substudy: 959)
	Number analysed: fenofibrate: 2765 out of 2765 (substudy: 806 out of 959), placebo: 2753 out of 2753 (substudy: 787 out of 959)
	The method of handling missing data: NI
	Power calculation conducted prior to the commencement of the study: yes

ACCORD-Lipid *(Continued)*

Planned sample size by power calculation: 5800 (substudy: NI)

Planned power: the trial had 87% power to detect an observed 20% reduction in the primary outcome (substudy: the trial had 91% power to detect an observed 20% reduction in the primary outcome)

Planned primary time point the trialists had defined (year/month /date): participants will be treated and followed for 4 to 8 years (approximate mean, 5.6 years); (substudy: participants were evaluated at 4-year follow-up with 7FIELD ETDRS images. Information was collected annually about whether laser or vitrectomy performed; visual acuity done every 2 years to determine moderate visual loss, defined as worsening in either eye of 3 or more ETDRS lines on ETDRS VA chart.)

Other specific addition of statistical methods: NI

Another intervention: yes

Unit of randomisation: person

Unit of analysis: person

Participants

Countries where the participants were recruited: the US and Canada

Single centre or multicentre: multicentre

Setting: clinical sites

Number of recruiting centres: 77

Baseline characteristics

fenofibrate

- Number of participants: 2765
- Men, n (%): 1914 (69.2%)
- Age, years, mean (SD): 62.2 (6.7)
- Caucasian, n (%): 1909 (69.0%)
- Non-Caucasian, n (%): 856 (31.0%)
- T1D, n (%): 0 (0.0%)
- T2D, n (%): 2765 (100.0%)
- Overt retinopathy, n (%): NI
- DR status none, n (%): NI
- DR status mild, n (%): NI
- DR status moderate NPDR, n (%): NI
- DR status severe NPDR, n (%): NI
- DR status PDR, n (%): NI
- T-chol (mg/dL), mean (SD): 174.4 (36.8)
- LDL-C (mg/dL), mean (SD): 100 (30.3)
- HDL-C (mg/dL), mean (SD): 38 (7.8)
- Triglyceride (mg/dL), median (IQR): 164 (114 to 232)
- HbA1c (%), mean (SD): 8.3 (1.0)

substudy:

- Number of participants: 806
- Men, n (%): 559 (69.4%)
- Age, years, mean (SD): 61.9 (6.2)
- Caucasian, n (%): 584 (72.5%)
- Non-Caucasian, n (%): 222 (27.5%)
- T1D, n (%): 0 (0.0%)
- T2D, n (%): 806 (100.0%)

ACCORD-Lipid *(Continued)*

- Overt retinopathy, n (%): 377 (46.8%)
- DR status none, n (%): 429 (53.2 %)
- DR status mild, n (%): 141 (17.5%)
- DR status moderate NPDR, n (%): 230 (28.5%)
- DR status severe NPDR, n (%): 2 (0.2%)
- DR status PDR, n (%): 4 (0.5%)
- T-chol (mg/dL), mean (SD): NI
- LDL-C (mg/dL), mean (SD): 96.5 (29.7)
- HDL-C (mg/dL), mean (SD): 38.6 (7.8)
- TG (mg/dl), mean (SD): 190.1 (111.3)
- HbA1c (%): 8.2 (1.0))

placebo

- Number of participants: 2753
- Men, n (%): 1910 (69.4%)
- Age, years, mean (SD): 62.3 (6.9)
- Caucasian, n (%): 1865 (67.7%)
- Non-Caucasian, n (%): 888 (32.3%)
- T1D, n (%): 0 (0.0%)
- T2D, n (%): 2753 (100.0%)
- Overt retinopathy, n (%): NI
- DR status none, n (%): NI
- DR status mild, n (%): NI
- DR status moderate NPDR, n (%): NI
- DR status severe NPDR, n (%): NI
- DR status PDR, n (%): NI
- T-chol (mg/dL), mean (SD): 175.7 (37.9)
- LDL-C (mg/dL), mean (SD): 101.1 (31.0)
- HDL-C (mg/dL), mean (SD): 38.2 (7.8)
- TG (mg/dL), median (IQR): 160 (112 to 227)
- HbA1c (%), mean (SD): 8.3 (1.0)

substudy:

- Number of participants: 787
- Men, n (%): 533 (67.7%)
- Age, years, mean (SD): 61.5 (6.5)
- Caucasian, n (%): 553 (70.3%)
- Non-Caucasian, n (%): 234 (29.7%)
- T1D, n (%): 0 (0.0%)
- T2D, n (%): 787 (100.0%)
- Overt retinopathy, n (%): 389 (49.4%)
- DR status none, n (%): 398 (50.6%)
- DR status mild, n (%): 155 (19.7%)
- DR status moderate NPDR, n (%): 224 (28.5%)
- DR status severe NPDR, n (%): 4 (0.5%)
- DR status PDR, n (%):, mean (SD): 6 (0.8%)
- T-chol (mg/dL), mean (SD): NI
- LDL-C (mg/dL), mean (SD): 97 (30.1)
- HDL-C (mg/dL), mean (SD): 38.5 (7.9)
- TG (mg/dL), mean (SD): 187.9 (112.4)
- HbA1c (%): 8.2 (1.0))

ACCORD-Lipid *(Continued)*

Equivalence of baseline characteristics: yes

Inclusion criteria:

- T2D defined according to the 1997 ADA criteria for ≥ 3 months
- An HbA1c level (obtained < 3 months before anticipated date of randomisation) of (a.) 7.5% to 11%: (i) If on insulin < 1 U/kg and on 0 or 1 oral agent or (ii) If not on insulin, and on 0, 1, or 2 oral agents (b.) 7.5% to 9%: (i) If on insulin < 1 U/kg and on 2 oral agents, (ii) If on insulin > 1 U/kg and 0 oral agents, or (iii) If not on insulin and on 3 oral agents
- Stable diabetes therapy for > 3 months
- Age at randomisation (a.) 40 to 79 yr (inclusive) for anyone with a history of clinical CVD, or (b.) 55 to 79 yr (inclusive) for anyone without a history of clinical CVD (the age eligibility was modified on the basis of the results of the vanguard phase, so some participants were aged ≥ 80 yr at randomisation)
- At high risk for CVD events, defined as (a.) presence of clinical CVD (prior MI, stroke, arterial revascularisation, angina with ischaemic changes on ECG at rest, changes on a graded exercise test, or positive cardiac imaging test results; (b.) If no clinical CVD, evidence in the past 2 yr suggesting high likelihood of CVD (1 risk factor: microalbuminuria, ankle-brachial index < 0.9, left ventricular hypertrophy by ECG or echocardiography, or > 50% stenosis of a coronary, carotid, or lower extremity artery); or (c.) presence of ≥ 2 of the following factors that increase CVD risk: > LDL-C 130 mg/dL treated with lipid lowering medication or untreated, low HDL-C (< 40 mg/dL for men and < 50 mg/dL for women), systolic BP > 140 mm Hg or diastolic BP > 95 mm Hg treated with BP-lowering medication or untreated, current cigarette smoking, or BMI > 32
- Lipids measured within the previous 12 months with (a.) estimated LDL-C off statin therapy of 60 mg/dL to 180 mg/dL, and (b.) HDL-C < 55 mg/dL for women or African Americans or HDL-C < 50 mg/dL for all other sex and race groups, and triglycerides < 750 mg/dL on no therapy, or < 400 mg/dL on treatment with lipid-lowering drugs

Exclusion criteria:

- History of hypoglycaemic coma/seizure within last 12 months
- Hypoglycaemia requiring 3rd party assistance in last 3 months with concomitant glucose < 60 mg/dL
- History consistent with T1D
- Unwilling to do frequent capillary blood glucose self-monitoring or unwilling to inject insulin several times a day
- BMI > 45 kg/m^2
- Serum creatinine > 1.5 mg/dL obtained within the previous 2 months
- Transaminase > 2 times upper limit of normal or active liver disease
- Any ongoing medical therapy with known adverse interactions with the glycaemic interventions (e.g. corticosteroids, protease inhibitors)
- Cardiovascular event or procedure (as defined for study entry) or hospitalisation for unstable angina within last 3 months
- Current symptomatic heart failure, history of NYHA Class III or IV congestive heart failure at any time, or ejection fraction (by any method) < 25%
- A medical condition likely to limit survival to < 3 years or a malignancy other than non-melanoma skin cancer within the last 2 years
- Any factors likely to limit adherence to interventions, e.g. dementia, alcohol or substance abuse, plans to move in the next 2 years, history of unreliability in medication taking or appointment keeping, significant concerns about participation in the study from spouse, significant other, or family members, or lack of support from primary health care provider
- Failure to obtain informed consent from participant
- Currently participating in another clinical trial.
- Living in the same household as an already randomised ACCORD participant
- Any organ transplant
- Weight loss > 10% in last 6 months
- Pregnancy, currently trying to become pregnant, or of child-bearing potential and not practising birth control
- Participants with recurrent requirements for phlebotomy or transfusion of red blood cells

ACCORD-Lipid *(Continued)*

- Known hypersensitivity to statins or fibrates
- Requirements for use of erythromycin, clarithromycin, cyclosporine, systemic azole antifungals, or nefazodone or trazodone (all of which have reported interactions with either statins or fibrates)
- Refusal to stop current lipid-lowering drugs
- History of pancreatitis
- Untreated or inadequately treated thyroid disease
- Breastfeeding
- Documented previous occurrence of myositis/myopathy
- Pre-existing gallbladder disease

In the substudy, one more criteria was added:

- History of proliferative diabetic retinopathy that had been treated with laser photocoagulation or vitrectomy

Interventions	**Intervention Characteristics** fenofibrate • number of people randomised: 2765 (substudy: 959) • drug name: fenofibrate • dose (mg/day): 160 mg/day • frequency(/day):1 • route of administration: oral placebo • number of people randomised: 2753 (substudy: 959) • drug name: placebo • dose (mg/day): identical dose • frequency(/day): 1 • route of administration: oral Another intervention for both groups • All participants received nutrition and physical activity counselling, and a recommendation to use aspirin daily • For participants with histories of MI, congestive heart failure, nephropathy, or 1 additional risk factor for CVD, treatment with an angiotensin-converting enzyme inhibitor was recommended • Current smokers received smoking cessation counselling • All participants were randomised to have intensive (HbA1c target < 6) or standard (HbA1c 7 to 7.9; approx 7.5%) glycaemic control • Information on current guidelines for lipids and blood pressure treatment was provided by the study to participants' personal physicians • All participants received simvastatin 20 mg/day to 40mg/day
Outcomes	Primary outcome • The first occurrence of a major cardiovascular event, including nonfatal MI, nonfatal stroke, or death from cardiovascular causes (substudy: • The progression of DR of 3 steps on the ETDRS scale or progression to PDR that requires photocoagulation and/or vitrectomy) Secondary outcome • Expanded macrovascular outcome: the combination of the primary end point plus any revascularization and hospitalisation for congestive heart failure

ACCORD-Lipid *(Continued)*

- Major coronary artery disease events: fatal events, nonfatal MI, and unstable angina
- Nonfatal MI
- Total stroke: combined fatal and nonfatal stroke
- Nonfatal stroke
- Total mortality
- Cardiovascular mortality
- Congestive heart failure: death or hospitalisation for heart failure (with documented clinical and radiologic evidence)

(substudy:

- Change in visual acuity at 4 years compared with baseline:
  - Moderate vision loss or loss of 3 lines on the log minimum angle of resolution visual acuity charts
  - Legal blindness: 20/160 or worse at 4 years
  - Severe vision loss: 5/200 (20/50, 20/200) at 4 years
- Rates of cataract extraction
- Rates of photocoagulation and/or vitrectomy
- The development or progression of DMO)

Outcomes reported in manuscript:

- Discontinuation of the treatment

(substudy:

- Incidence of overt retinopathy
- Focal/grid laser
- PRP)

Adverse effects: reported

- Serious adverse event
- Hepatic disorder
- Pulmonary embolism
- Deep-vein thrombosis

Unit of measure: person

Planned length of follow-up: participants to be treated and followed for 4 to 8 years (approximate mean 5.6 years)

Actual length of follow-up: the mean duration of follow-up for the primary outcome was 4.7 years. The study report only provided the mean.

Identification	**Full study name:** The action to control cardiovascular risk in diabetes lipid trial (substudy: The action to control cardiovascular risk in diabetes eye study) **Clinical trial registration number and name of register:** ClinicalTrials.gov number NCT00000620 for the ACCORD study (substudy: NCT00542178 for the ACCORD Eye study) **Authors name:** ACCORD study group (substudy: Emily Y. Chew; ACCORD Eye study group) **Institution:** the Department of Medicine, Columbia University College of Physicians and Surgeons (substudy: National Eye Institute) **Email:** hng1@columbia.edu (substudy: echew@nei.nih.gov) **Address:** the Department of Medicine, Columbia University College of Physicians and Surgeons, Rm. PH10-305, New York, NY 10032 (substudy: the National Institutes of Health, Bldg. 10, Clinical Research Center, Rm. 3-2531, 10 Center Dr., Mail Stop Center 1204, Bethesda, MD 20892)

ACCORD-Lipid *(Continued)*

Notes	**Date of enrolment of the first participant:** early 2001 (substudy: October 2003) **Date of the final follow-up date of the last participant:** June 2009 (substudy: June 2009) **Source of funding:** the National Heart, Lung, and Blood Institute, the National Institutes of Health, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Eye Institute, the National Institute on Aging, and the Centers for Disease Control and Prevention. General Clinical Research Centers provided support at many sites. These companies donated study medications, equipment, or supplies: Abbott Laboratories, Amylin Pharmaceutical, AstraZeneca Pharmaceuticals, Bayer HealthCare, Closer Healthcare, GlaxoSmithKline Pharmaceuticals, King Pharmaceuticals, Merck, Novartis Pharmaceuticals, Novo Nordisk, Omron Healthcare, Sanofi-Aventis U.S., and Takeda Pharmaceuticals. **Sub-group analyses reported by the authors:** yes **Were trial investigators contacted?** We contacted and received missing data for the substudy **Declaration of interest:** Dr. Goff - grant support or pending grant support from Merck, and money for serving as a data and safety monitoring board member for a trial of a diabetes medication from Takeda Dr. Cushman - consulting fees from Novartis, Takeda, Sanofi-Aventis, Bristol-Myers Squibb, King Pharmaceuticals, Daiichi–Sankyo, Gilead, Theravance, Pharmacopeia, and Sciele, and grant support or pending grant support from Novartis, GlaxoSmithKline, and Merck Dr. Ginsberg - advisory fees from Merck, Merck–Schering Plough, and Bristol-Myers Squibb–AstraZeneca; consulting fees from Merck, Abbott–AstraZeneca, Bristol-Myers Squibb, Roche, Isis–Genzyme, GlaxoSmithKline, Novartis, Pfizer, and Regeneron–Sanofi-Aventis; grant support or pending grant support from Merck, Isis–Genzyme, Roche, and AstraZeneca; payment for development of education presentations from Pfizer; and payment for travel and accommodation expenses from all these companies Dr. Ela - payment for development of education presentations from Pfizer, Abbott Pharmaceuticals, and Merck–Schering Plough Dr. Gerstein - consulting fees from Sanofi-Aventis, GlaxoSmithKline, Eli Lilly, Novo Nordisk, AstraZeneca, Bristol-Myers Squibb, Roche, Medtronic, Merck, Bayer, Bioavail, and Jansen Ortho; grant support or pending grant support from Sanofi-Aventis, GlaxoSmithKline, Novo Nordisk, Merck, Pronova, and Roche; honoraria from Sanofi-Aventis, GlaxoSmithKline, Solvay, Boehringer Ingelheim, Servier, Bayer, Eli Lilly, Novo Nordisk, and Takeda; and payment for travel and accommodation expenses from all these companies Dr. Schubart - participated in trials sponsored by Sanofi-Aventis, Merck, and Johnson & Johnson No other potential conflict of interest relevant to this article was reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally on the trial's website with the use of permuted blocks to maintain concealment of study-group assignments
Allocation concealment (selection bias)	Low risk	Randomization was performed centrally on the trial's website with the use of permuted blocks to maintain concealment of study-group assignments.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	They used placebo; this study was a fully masked randomised trial.

ACCORD-Lipid *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was a fully masked randomised trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The proportion of loss to follow up was low and balanced. We did not find the reason.
Selective reporting (reporting bias)	Low risk	In ACCORD Eye Lipid, the visual outcomes reported in the published protocol are different to those listed and presented in the main sub-study results manuscript. However, as this change does not affect the outcomes we were investigating in our review, we considered the risk of bias for the domain selective reporting to be low.
Other bias	Low risk	None

FIELD

Study characteristics	
Methods	**Types of study:** parallel-group randomised controlled trial **Number of exclusion after randomisation:** fenofibrate: 0 (substudy: 0), placebo: 0 (substudy: 0) **Losses to follow-up:** fenofibrate:12; 4 more withdrew consent (substudy: 67; none withdrew consent), placebo: 10; 5 more withdrew consent (substudy: 57; 3 more withdrew consent) **Number randomised:** fenofibrate: 4895 (substudy: 512), placebo: 4900 (substudy: 500) **Number analysed:** fenofibrate: 4852 out of 4895 (substudy: 429 out of 512); placebo: 4856 out of 4900 (primary outcome was assessed) (substudy: 421 out of 500) **The method of handling missing data:** NI **Power calculation conducted prior to the commencement of the study:** yes (substudy: NI) **Planned sample size by power calculation:** 9795 (substudy: NI) **Planned power:** the trial had 80% power to detect a 22% reduction in CHD events. This also provide 90% power to detect a 25% relative reduction in CHD events. (substudy: NI) **Planned primary time point the trialists had defined (year/month /date):** this outcome could occur anytime during the minimum follow-up time of 5 years (60 months) (substudy: planned period was 5 years (60 months) on average) **Other specific addition of statistical methods:** NI **Another intervention:** no **Unit of randomisation**: person **Unit of analysis**: person (substudy: eye)
Participants	**Countries where the participants were recruited:** Australia, Finland, and New Zealand **Single centre or multi centres: multicentre** **Setting:** hospital clinics and community base sources **Number of recruiting centres:** 63 (substudy: 22)

FIELD *(Continued)*

Baseline characteristics

fenofibrate

- Number of participants: 4895
- Men, n (%): 3071 (62.7%)
- Age, years, mean (SD): 62.2 (6.8)
- Caucasian, n (%): 4534 (92.6%)
- Non-Caucasian, n (%): 361 (7.4%)
- T1D, n (%): 0 (0.0%)
- T2D, n (%): 4895 (100.0%)
- Overt retinopathy, n (%): NA
- DR status none, n (%): NA
- DR status mild, n (%): NA
- DR status moderate NPDR, n (%): NA
- DR status severe NPDR, n (%): NA
- DR status PDR, n (%): NA
- T-chol (mmol/L), mean (SD): 5.0 (0.7)
- LDL-C (mmol/L), mean (SD): 3.1 (0.6)
- HDL-C (mmol/L), mean (SD): 1.1 (0.3)
- TG (mmol/L), median (IQR): 1.7 (1.3 to 2.3)
- HbA1c (%), median (IQR): 6.9 (6.1 to 7.8)

substudy

- Number of participants: 512
- Men, n (%): NI
- Age, years, mean (SD): NI
- Caucasian, n (%): NI
- Non-Caucasian, n (%): NI
- T1D, n (%): 0 (0.0%)
- T2D, n (%): 512 (100.0%)
- Overt retinopathy, n (%): 105 (20.5%)
- DR status none, n (%): 407 (79.5%)
- DR status mild, n (%):88 (17.2%)
- DR status moderate NPDR, n (%): 14 (2.7%)
- DR status severe NPDR, n (%): 3 (0.6%)
- DR status PDR, n (%): 0 (0.0%)
- T-chol (mmol/L), mean (SD): NI
- LDL-C (mmol/L), mean (SD): NI
- HDL-C (mmol/L), mean (SD): NI
- TG (mmol/L), median (IQR): NI
- HbA1c (%), median (IQR): NI

placebo

- Number of participants: 4900
- Men, n (%): 3067 (62.6%)
- Age, years, mean (SD): 62.2 (6.9)
- Caucasian, n (%):4559 (93.0%)
- Non-Caucasian, n (%): 341 (7.0%)
- T1D, n (%): 0 (0.0%)
- T2D, n (%): 4900 (100.0%)
- Overt retinopathy, n (%): NA

FIELD *(Continued)*

- DR status none, n (%): NA
- DR status mild, n (%): NA
- DR status moderate NPDR, n (%): NA
- DR status severe NPDR, n (%): NA
- DR status PDR, n (%): NA
- T-chol (mmol/L), mean (SD): 5.0 (0.7)
- LDL-C (mmol/L), mean (SD): 3.1 (0.7)
- HDL-C (mmol/L), mean(SD): 1.1 (0.3)
- TG (mmol/L), median (IQR): 1.7 (1.3 to 2.3)
- HbA1c (%), median (IQR): 6.9 (6.1 to 7.8)

substudy

- Number of participants: 500
- Men, n (%): NI
- Age, years, mean (SD): NI
- Caucasian, n (%): NI
- Non-Caucasian, n (%): NI
- T1D, n (%): 0 (0.0%)
- T2D, n (%): 500 (100.0%)
- Overt retinopathy, n (%): 103 (20.6%)
- DR status none, n (%): 397 (79.4%)
- DR status mild, n (%): 78 (15.6%)
- DR status moderate NPDR, n (%): 21 (4.2%)
- DR status severe NPDR, n (%): 4 (0.8%)
- DR status PDR, n (%): 0 (0.0%)
- T-chol (mmol/L), mean (SD): NI
- LDL-C (mmol/L), mean (SD): NI
- HDL-C (mmol/L), mean (SD): NI
- TG (mmol/L), median (IQR): NI
- HbA1c (%), median (IQR): NI

Equivalence of baseline characteristics: yes

Inclusion criteria:

- Male or female, aged 50 to 75 years
- T2D with age at diagnosis > 35 years (currently using any of diet, tablets or insulin); for Maori, Pacific Islanders, Australian Aborigines and Torres Strait Islanders, the eligible age of diagnosis was > 25 years, provided there had been at least 1 year of treatment without insulin
- On the basis of diabetes, considered to be at higher risk for coronary heart disease than the general population
- No clear indication for any cholesterol-lowering treatment: the person was not already taking any cholesterol-lowering drug and neither the person, nor the person's doctor considered a definite need to do so
- T-chol level 3 to 6.5 mmol/L, plus either
  - T-chol-to-HDL-C ratio of ≥ 4.0
  - bloodTG level >1.0 mmol/L
- No clear contraindication to study therapy in the view of the treating physician
- No other predominant medical problem that might limit compliance with 5 years of study treatment, or compromise long-term participation and clinic attendance in the trial

In the substudy, one more criteria was added:

FIELD *(Continued)*

- Two-field colour fundus photographs of both eyes showed no evidence of PDR, severe NPDR, clinically significant DMO, or indication for, or evidence of a history of laser treatment at a screening examination done during the placebo run-in phase

Exclusion criteria:

- Serum TG > 5 mmol/L in the baseline fasting blood sample
- Concurrent treatment with any other lipid-lowering agent
- Serum creatinine > 130 µmol/L
- Known chronic liver disease, transaminases > 2 × upper limit of normal or symptomatic gall-bladder disease
- MI or hospital admission for unstable angina within 3 months
- Female of child-bearing potential, unless sterilized or on reliable, approved methods of contraception, including oral contraceptives
- Concurrent cyclosporin treatment (or a condition likely to result in organ transplantation and the need for cyclosporin during the next 5 years)
- Known allergy to any fibrate drug or known photosensitivity
- Unwilling or unable to consent to enter the study, with the understanding that follow-up was planned to continue for more than 5 years

In the substudy, one more criteria was added:

- A number of other ocular pathologies or technical problems

Interventions	fenofibrate • Number of people randomised: 4895 (substudy: 512) • Drug name: fenofibrate • Dose (mg/day): 200 mg/day • Frequency (/day): 1 • Route of administration: oral placebo • Number of people randomised: 4900 (substudy: 500) • Drug name: matching placebo • Dose (mg/day): NA • Frequency (/day):1 • Route of administration: oral Another intervention for both groups There was a run-in phase for all participants that consisted of three periods before randomisation. 1. 4-week diet only 2. 6-week single-masked placebo 3. 6-week single-masked active run-in period on comicronised fenofibrate 200 mg once daily
Outcomes	Primary outcome: • The first occurrence of either non-fatal MI or death from coronary heart disease substudy: • Progression of DR at least a 2-step increase in ETDRS grade after 2 years or more of follow-up for all participants; (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 outcomes:

FIELD *(Continued)*

- Major CVD events (coronary heart disease events, total stroke, and other cardiovascular death combined)
- Total CVD events (major cardiovascular disease events plus coronary and carotid revascularisation)
- Coronary heart disease death
- Total CVD deaths
- Haemorrhagic and nonhaemorrhagic stroke
- Coronary and peripheral revascularisation procedures
- Cause-specific non-coronary heart disease mortality
- Total mortality

substudy:

- One-step progression
- Incidence or progression of DMO
- The occurrence or progression of hard exudates
- Laser treatment
- Vitrectomy
- The occurrence of cataract (including surgery)
- Deterioration of visual acuity by two lines (Snellen chart)
- Incidence of over retinopathy
- Composite end point reflecting the development of significant retinal pathology included any of a 2-step progression of retinopathy grade, new DMO, or laser treatment

Tertiary outcomes:

- Vascular and neuropathic amputations
- Nonfatal cancers
- Progression of renal disease
- Hospital admission for angina pectoris
- Number and duration of all hospital admissions
- Laser treatment for DR

Outcomes reported in manuscript:

- Laser treatment
- Focal/grid laser
- PRP
- Discontinuation of the treatment

substudy:

- Progression of DR
- Incidence of overt retinopathy
- Incidence of DMO
- Laser treatment
- Vitrectomy

Adverse effects: reported

- Serious adverse events
- Rhabdomyosis
- Pancreatitis
- Deep-vein thrombosis
- Pulmonary embolism
- Myositis
- Renal disease needing dialysis

FIELD *(Continued)*

	Unit of measure: person (substudy: worst eye)
	Planned length of follow-up: 5 years
	Actual length of follow-up: reported a median of 5 years
Identification	**Full study name:** The fenofibrate intervention and event lowering in diabetes study (substudy: ophthalmology substudy)
	Clinical trial registration number and name of register: International standard randomised controlled trial, number ISRCTN64783481
	Authors name: AC Keech
	Institution: NHMRC Clinical Trials Centre, University of Sydney
	Email: tony@ctc.usyd.edu.au
	Address: FIELD study, NHMRC Clinical Trials Centre, University of Sydney, Building F, 88 Mallet Street, Camperdown, NSW 2050, Australia
Notes	**Date of enrolment of the first participant:** NI
	Date of the final follow-up date of the last participant: NI
	Source of funding: grant from Laboratoires Fournier SA, Dijon, France, and the National Health and Medical Research Council of Australia
	Subgroup analyses reported by the authors: yes
	Were trial investigators contacted?: yes, but they did not reply.
	Declaration of interest: some members of the writing committee (ACK, PM, PAS, JO'D, TMED, M-RT, RJS, LTL, MCdE, PGC) 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 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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out using a dynamic allocation method.
Allocation concealment (selection bias)	Low risk	Randomisation was done by central computer, using a dynamic allocation method with stratification for important prognostic factors, including age, sex, previous myocardial infarction, lipid levels, and urinary albumin concentration.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants took micronised fenofibrate 200 mg once daily or matching placebo. 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.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	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.
Incomplete outcome data (attrition bias)	Low risk	The proportion of missing data was low and balanced between groups. However, we did not find the reason.

FIELD *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	We were unable to find a published protocol for the FIELD ophthalmology substudy. Thus, we considered the risk of bias for selective reporting of the FIELD ophthalmology substudy to be unclear, as a result.
Other bias	Low risk	None

ADA: American Diabetes Association; **BMI**: body mass index; **BP**: blood pressure; **CVD**: cardiovascular disease; **DMO**: diabetic macular oedema; **DR**: diabetic retinopathy; **ECG**: electrocardiography; **ETDRS**: the early treatment diabetic retinopathy study; **HDL-C**: high density lipoprotein cholesterol; **HbA1c**: glycated haemoglobin A1C; **IQR**: interquartile range; **LDL-C**: low density lipoprotein cholesterol; **MI**: myocardial infarction; **NA**: not available; **NI**: no information; **NPDR**: non-proliferative diabetic retinopathy; **NYHA**: New York Heart Association; **PDR**: proliferative diabetic retinopathy; **PRP**: pan retinal photocoagulation; **SD**: standard deviation; **T-chol**: total cholesterol; **TG**: triglycerides; **T1D:** type 1 diabetes; **T2D:** type 2 diabetes

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACCORDION 2016	Irrelevant intervention
ACTRN 12618000592246	Irrelevant population
Borona 2021	Irrelevant population
Bronson 2010	Irrelevant study design
Cui 2018	Irrelevant population
Elam 2011	Irrelevant study design
Fazio 2009	Irrelevant study design
Feher 2005	Irrelevant study design
FIELD 2008	Irrelevant study design
Fuessl 2008	Irrelevant study design
Grigoryeva 2011	Irrelevant study design
Massin 2014	Irrelevant population
Matthews 2011	Irrelevant study design
NCT04140201	Irrelevant outcomes
NCT04885153	Irrelevant outcomes
O'Connor 2011	Irrelevant study design
Srinivasan 2018	Irrelevant population
Valentine 2013	Irrelevant study design

Characteristics of ongoing studies *[ordered by study ID]*

FAME 1 EYE

Study name	The fenofibrate and microvascular events in type 1 diabetes eye: a randomised trial to evaluate the efficacy on retinopathy and safety of fenofibrate in adults with type 1 diabetes. A multicentre double-blind placebo-controlled study in Australia and internationally
Methods	**Types of study:** parallel-group randomised controlled trial **Number of exclusion after randomisation:** **Losses to follow-up:** fenofibrate:, placebo: **Number randomised:** fenofibrate:, placebo: **Number analysed:** fenofibrate: out of, placebo: out of **The method of handling missing data:** **Power calculation conducted prior to the commencement of the study (yes or no):** **Planned sample size by power calculation:** 450 (NI regarding power calculation) **Planned power:** **Planned primary time point the trialists had defined (year/month /date):** 36 months **Other specific addition of statistical methods:** **Another intervention (yes/no):** **Unit of randomisation**: person **Unit of analysis**:
Participants	**Where the participants were recruited:** Hong Kong, New Zealand, and Australia **Single centre or multicentre:** multicentre **Setting:** clinic **Number of recruiting centres:** 21 **Baseline Characteristics** fenofibrate • Number of participants: • Men, n (%): • Age, years, mean (SD): • Caucasian, n (%): • Non-Caucasian, n (%): • T1D, n (%): • T2D, n (%): • Overt retinopathy, n (%): • DR status none, n (%): • DR status mild, n (%): • DR status moderate NPDR, n (%): • DR status severe NPDR, n (%): • DR status PDR, n (%): • T-chol (mmol/L), mean (SD):

FAME 1 EYE *(Continued)*

- LDL-C (mmol/L), mean (SD):
- HDL-C (mmol/L), mean (SD):
- TG (mmol/L), median (IQR):
- HbA1c (%), median (IQR):

placebo

- Number of participants:
- Men, n (%):
- Age, years, mean (SD):
- Caucasian, n (%):
- Non-Caucasian, n (%):
- T1D, n (%):
- T2D, n (%):
- Overt retinopathy, n (%):
- DR status none, n (%):
- DR status mild, n (%):
- DR status moderate NPDR, n (%):
- DR status severe NPDR, n (%):
- DR status PDR, n (%):
- T-chol (mmol/L), mean (SD):
- LDL-C (mmol/L), mean (SD):
- HDL-C (mmol/L), mean (SD):
- TG (mmol/L), median (IQR):
- HbA1c (%), median (IQR):

Equivalence of baseline characteristics:

Inclusion criteria:

- Men or non-pregnant women (on acceptable contraception) with T1D according to standard criteria; T1D defined as either (a.) T1D diagnosed below 40 years of age and insulin therapy commencing within one year of T1D diagnosis, or (b.) T1D diagnosed at or after 40 years of age along with: i) documented history of ketoacidosis, and/or ii) documented history of very low or undetectable C-peptide (fasting < 200 nmol/L or 0.2 pmol/L), and/or iii) documented history of T1D related autoantibody/ies (anti-GAD, anti-A2, anti-ZnT8)
- Age 18 years or over
- eGFR must exceed 30 mL/min/1.73 m^2
- Must have at least one eligible eye with NPDR (ETDRS scale 35 to 53 inclusive) confirmed by current retinal photography within the last 3 months (irrespective of prior laser therapy); any eye having undergone prior pan-retinal laser therapy is not eligible, but prior focal, macular or grid laser does not exclude that eye from eligibility
- All types of insulin therapy, with no restriction by level of HbA1c
- Willing and able to comply with all study requirements, including treatment, assessment and clinic visit attendances
- Able to personally read and understand the Participant information and consent form and provide written, signed, and dated informed consent to participate in study

Exclusion criteria:

- Definite indication for, or contraindications to fibrate treatment (other lipid drugs, e.g. statins, ezetimibe, fish oils allowed)
- Need for bilateral intra-ocular treatment or laser photocoagulation therapy within the next 3 months (this exclusion only applies to retinal laser photocoagulation treatment onto the posterior pole, i.e. laser correction of corneas for short-sightedness is not an exclusion criterion)
- Prior bilateral PRP treatment for DR
- Prior bilateral intra-ocular injection(s) within the last 6 months

FAME 1 EYE *(Continued)*

- Bilateral cataract surgery within the last 6 months
- Planned bilateral cataract surgery within the next 12 months
- History of any other non-diabetic eye disease that is, or is likely to affect bilateral vision
- History of photosensitive skin rash or myositis
- Abnormal thyroid function (untreated)
- Liver function tests exceeding 3 x ULN
- Persistent elevated unexplained blood CK level above normal range
- Documented fasting triglyceride levels > 6.5 mmol/L
- History of pancreatitis, deep-vein thrombosis, or pulmonary embolism
- Use of investigational drugs in the prior 8 weeks
- Any unstable condition in last 3 months, including active sepsis, diabetic ketoacidosis
- MI, unstable angina, stroke, or heart failure within last 6 months
- Diagnosed cancer with ongoing treatment or prognosis anticipated at < 5 years
- Any obstacle to regular follow-up, including scheduled clinic attendances
- Prior or planned organ transplantation (including islet cell) with subsequent continued immunosuppression therapy

Interventions	**Intervention Characteristics** fenofibrate • Number of people randomised: • Drug name: fenofibrate • Frequency (/day): 1 • Dose (mg/day): 145 • Route of administration: oral placebo • Number of people randomised: • Drug name: placebo • Frequency (/day): 1 (lactose) • Dose (mg/day): • Route of administration: oral Another intervention for both group (yes/no):
Outcomes	Primary outcome: • Occurrence of clinically significant retinopathy progression, defined as comprising 2-step progression of ETDRS scale (to at least moderately severe grade), occurrence of clinically significant DMO, need for laser treatment, need for intraocular anti-VEGF or corticosteroid therapy or vitrectomy adjudicated to be for retinopathy Secondary outcomes: • Individual components of the primary end point • Visual Acuity • Retinal vessel calibre and geometry • Macular volume and thickness by OCT • Urine albumin:creatinine ratio • eGFR (measured 8 weeks after treatment withdrawal) • Measures of peripheral neuropathy (symptoms, monofilament testing, vibration, and temperature sensation) • Autonomic neuropathy: QTc and RR intervals on yearly ECGs • Total cardiovascular events, including MI (including silent MI by ECGs), stroke, sudden cardiac death, hospitalisation for acute coronary syndrome, or any revascularization requirement

FAME 1 EYE *(Continued)*

	• Frequency of foot ulcer and non-traumatic amputation • Lipid and lipoprotein levels • Biomarkers and molecular markers • Quality of life questionnaire Outcomes reported in manuscript: Adverse effects: **Unit of measure**: **Planned length of follow up**: 36 months **Actual length of follow up:**
Starting date	March 2016
Contact information	**Name:** Liping Li **Institution:** NHMRC Clinical Trials Centre, The University of Sydney **Email:** fame1eye@ctc.usyd.edu.au **Address:** Medical Foundation Building 92-94 Parramatta Road Camperdown NSW 2050
Notes	**Date of enrolment of the first participant:** November 2016 **Date of the final follow-up date of the last participant (if any):** **Source of funding:** NHMRC Clinical Trials Centre, University of Sydney (Australia), Mylan EPD Europe, National Health and Medical Research Council (Australia), Juvenile Diabetes Research Foundation (Australia) **Were trial investigators contacted?** yes **Declaration of interest:**

NCT03439345

Study name	A randomised placebo-controlled trial of fenofibrate to prevent progression of non-proliferative retinopathy in diabetes
Methods	**Types of study:** parallel-group randomised controlled trial **Number of exclusion after randomisation:** **Losses to follow-up:** fenofibrate:, placebo: **Number randomised:** fenofibrate:, placebo: **Number analysed:** fenofibrate: out of, placebo: out of **The method of handling missing data:** **Power calculation conducted prior to the commencement of the study (yes or no):** **Planned sample size by power calculation:** 1151 (NI regarding power calculation) **Planned power:** **Planned primary time point the trialists had defined (year/month /date):** this outcome could occur anytime during the minimum follow-up time of 5 years (60 months)

NCT03439345 *(Continued)*

Other specific addition of statistical methods:

Another intervention (yes/no): no

Unit of randomisation: person

Unit of analysis:

Participants	**Countries where the participants were recruited:** United Kingdom **Single centre or multicentre:** multicentre **Setting:** National Health Service (NHS) **Number of recruiting centres:** 16 **Baseline Characteristics** fenofibrate • Number of participants: • Men, n (%): • Age, years, mean (SD): • Caucasian, n (%): • Non-Caucasian, n (%): • T1D, n (%): • T2D, n (%): • Overt retinopathy, n (%): • DR status none, n (%): • DR status mild, n (%): • DR status moderate NPDR, n (%): • DR status severe NPDR, n (%): • DR status PDR, n (%): • T-chol (mmol/L), mean (SD): • LDL-C (mmol/L), mean (SD): • HDL-C (mmol/L), mean (SD): • TG (mmol/L), median (IQR): • HbA1c (%), median (IQR): placebo • Number of participants: • Men, n (%): • Age, years, mean (SD): • Caucasian, n (%): • Non-Caucasian, n (%): • T1D, n (%): • T2D, n (%): • Overt retinopathy, n (%): • DR status none, n (%): • DR status mild, n (%): • DR status moderate NPDR, n (%): • DR status severe NPDR, n (%): • DR status PDR, n (%): • T-chol (mmol/L), mean (SD): • LDL-C (mmol/L), mean (SD): • HDL-C (mmol/L), mean (SD):

NCT03439345 *(Continued)*

- TG (mmol/L), median (IQR):
- HbA1c (%), median (IQR):

Equivalence of baseline characteristics: yes

Inclusion criteria:

- Capable of giving informed consent
- Diabetes mellitus (any type except gestational diabetes)
- Observable DR/maculopathy, defined based on NHS Scotland grading criteria as: R1 in both eyes or R2 in one/both eyes at the most recent retinal screening assessment; or M1 in one/both eyes at any retinal screening assessment in the past 3 years
- Willing to either complete electronic questionnaires or conduct telephone interviews for collection of data once every 6 months
- Age minimum: 18 years

Exclusion criteria:

- Clinically significant DR (defined as R3 or R4 or M2 in one or both eyes)
- History of gallbladder disease (cholecystitis, symptomatic gallstones, cholecystectomy)
- History of acute or chronic pancreatitis
- ALT or AST > 2 X ULN according to local NHS laboratory reference range at screening visit
- ALT or AST > 2.5 X ULN according to local NHS laboratory reference range at randomisation visit
- CK > 3 X ULN according to local NHS laboratory reference range at screening visit
- CK > 3 X ULN according to local NHS laboratory reference range at randomisation visit
- eGFR < 40 mL/min/1.73m^2 at screening visit
- eGFR < 30mL/min/1.73m^2 at randomisation visit
- Cirrhosis of any aetiology, or any other serious hepatic disease (investigator opinion)
- Female who is pregnant, breastfeeding, currently trying to become pregnant, or of child-bearing potential and not practising birth control
- Ongoing vitamin K antagonist (warfarin, phenindione, acenocoumarol), cyclosporine, colchicine, ketoprofen, daptomycin, fibrate therapy, or treatment with rosuvastatin 40 mg daily
- Previous myositis, myopathy or rhabdomyolysis of any cause, or diagnosed hereditary muscle disorder
- Ongoing renal replacement therapy
- Any previous organ transplant
- Previous reported intolerance to any fibrate
- Medical history that might limit the individual's ability to take trial treatments for the duration of the study (e.g. severe respiratory disease, history of cancer within last 5 years other than non-melanoma skin cancer; or recent history of alcohol or substance misuse)
- Any other significant disease or disorder, which in the opinion of the Investigator, may either put the participant at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial
- Enrolment in any other study or trial
- The intervention being investigated in another trial has the potential to interact with fenofibrate therapy
- Not adherent to active run-in treatment

Interventions	Fenofibrate • Number of people randomised: • Drug name: fenofibrate • Frequency (/day): • Dose (mg/day): 145 mg • Route of administration: oral Placebo

NCT03439345 *(Continued)*

	• Number of people randomised: • Drug name: placebo • Frequency (/day): • Dose (mg/day): NA • Route of administration: oral
Outcomes	Primary outcome • Progression to clinically significant DR/maculopathy Secondary outcomes • Any progression of DR/maculopathy • Components of the primary outcome (progression to clinically significant DR/maculopathy; retinal laser therapy; vitrectomy; intra-vitreal injection of medication for treatment of DR/maculopathy) reported separately • Cost-effectiveness (incremental cost per QALY gained) • Quality of life (according to the EQ-5D questionnaire) • The development of hard exudates within 1 disc diameter of the macula • Incidence of DMO • Total cost to the health service • Visual acuity • Visual function (according to the VFQ-25 questionnaire) • Change in urine albumin:creatinine ratio • The occurrence of major cardiovascular events (MI, stroke, coronary, and peripheral revascularisation) • Minor and major non-traumatic lower limb amputation (minor, defined as distal to the ankle; or major, defined as through or proximal to the ankle) Outcomes reported in manuscript: Adverse effects: **Unit of measure**: **Planned length of follow-up**: 48 months **Actual length of follow-up:**
Starting date	July 2018
Contact information	**Authors name:** David Preiss **Institution:** LENS trial, University of Oxford **Email:** lens@ndph.ox.ac.uk **Address:** LENS trial, CTSU Richard Doll Building, University of Oxford Roosevelt Drive OXFORD, OX3 7LF
Notes	**Date of enrolment of the first participant:** 23 July 2018 **Date of the final follow-up date of the last participant:** NI **Source of funding:** National Institute for Health Research (United Kingdom), NHS Scotland Diabetic Retinopathy Screening Collaborative, University of Aberdeen, University of Dundee, University of Edinburgh, and University of Glasgow **Were trial investigators contacted?:** yes

NCT03439345 *(Continued)*	
	Declaration of interest:

NCT04661358	
Study name	A Randomized Clinical Trial Evaluating Fenofibrate for Prevention of Diabetic Retinopathy Worsening
Methods	**Types of study:** parallel-group randomised controlled trial **Number of exclusion after randomisation:** **Losses to follow-up:** fenofibrate:, placebo: **Number randomised:** fenofibrate:, placebo: **Number analysed:** fenofibrate: out of, placebo: out of **The method of handling missing data:** **Power calculation conducted prior to the commencement of the study (e.g. yes or no):** **Planned sample size by power calculation:** 910 (NI regarding power calculation) **Planned power:** **Planned primary time point the trialists had defined (year/month /date):** the time flame is 4 years (48 months). **Other specific addition of statistical methods:** **Another intervention (yes/no):** no **Unit of randomisation:** person **Unit of analysis**:
Participants	**Countries where the participants were recruited:** the United States **Single centre or multicentre:** multicentre **Setting:** clinics, institution, or university **Number of recruiting centres:** 42 **Baseline characteristics** fenofibrate • Number of participants: • Men, n (%): • Age, years, mean (SD): • Caucasian, n (%): • Non-Caucasian, n (%): • T1D, n (%): • T2D, n (%): • Overt retinopathy, n (%): • DR status none, n (%): • DR status mild, n (%): • DR status moderate NPDR, n (%): • DR status severe NPDR, n (%):

NCT04661358 *(Continued)*

- DR status PDR, n (%):
- T-chol (mmol/L), mean (SD):
- LDL-C (mmol/L), mean (SD):
- HDL-C (mmol/L), mean (SD):
- TG (mmol/L), median (IQR):
- HbA1c (%), median (IQR):

placebo

- Number of participants:
- Men, n (%):
- Age, years, mean (SD):
- Caucasian, n (%):
- Non-Caucasian, n (%):
- T1D, n (%):
- T2D, n (%):
- Overt retinopathy, n (%):
- DR status none, n (%):
- DR status mild, n (%):
- DR status moderate NPDR, n (%):
- DR status severe NPDR, n (%):
- DR status PDR, n (%):
- T-chol (mmol/L), mean (SD):
- LDL-C (mmol/L), mean (SD):
- HDL-C (mmol/L), mean (SD):
- TG (mmol/L), median (IQR):
- HbA1c (%), median (IQR):

Equivalence of baseline characteristics: yes

Inclusion criteria:

- Age ≥18 years and < 80 years
- T1D or T2D
- At least one eye with the following: (a.) mild to moderately severe NPDR (defined by ETDRS DR severity level 35 to 47), confirmed by central Reading Center grading of fundus photographs; (b.) best-corrected E-ETDRS visual acuity letter score of ≥ 79 (approximate Snellen equivalent 20/25 or better)
- If only one eye is eligible, the non-study eye must have at least microaneurysms (DR severity level 20)

Exclusion criteria:

- Current centre-involved DMO based on clinical exam or thickness measured with OCT: (a.) Zeiss Cirrus: CST ≥ 290 µm in women or ≥ 305 µm in men; (b.) Heidelberg Spectralis: CST ≥ 305 µm in women or ≥ 320 µm in men
- Any prior treatment for DMO or DR, other than focal/grid laser. If the eye has a history of focal/grid laser, it must be at least 12 months prior
- History of intraocular anti-VEGF or corticosteroid treatment within the prior year for any indication
- Decreased renal function, defined as requiring dialysis or central laboratory eGFR value < 45 mL/min/1.73 m^2

Interventions	Fenofibrate • Number of people randomised: NI • Drug name: fenofibrate

NCT04661358 *(Continued)*	• Frequency (/day): 1 • Dose (mg/day): 160 mg • Route of administration: oral Placebo • Number of people randomised: NI • Drug name: placebo • Frequency (/day): 1 • Dose (mg/day): 160 mg • Route of administration: oral
Outcomes	Primary outcome • Worsening of DR Secondary outcomes • Intraocular procedure undertaken to treat DR or DMO including PRP, intraocular anti-VEGF, corticosteroid, focal/grid laser or vitrectomy • Incidence of centre-involved DMO • Incidence of centre-involved DMO with vision loss • Visual acuity loss from any cause Outcomes reported in manuscript Adverse effects: NI **Unit of measure**: **Planned length of follow-up**: 4 years **Actual length of follow-up:**
Starting date	March 2021
Contact information	**Authors name:** Emily Y Chew **Institution:** Jaeb Center for Health Research **Email:** drcrnet@jaeb.org **Address:** NI **Declaration of interest:** NI
Notes	

ALT: alanine aminotransferase; **AST:** aspartate aminotransferase; **CK:** creatine kinase; **CST:** central subfield thickness; **DMO:** diabetic macular oedema; **DR:** diabetic retinopathy; **eGFR:** estimated glomerular filtration rate; **ETDRS:** the early treatment diabetic retinopathy study severity scale; **HbA1c:** glycated Hemoglobin A1C; **HDL-C:** high density lipoprotein cholesterol; **IQR:** interquartile range; **LDL-C:** low density lipoprotein cholesterol; **NI:** no information; **NPDR:** non-proliferative diabetic retinopathy; **OCT:** optical coherence tomography; **SD:** standard deviation; **TG**: triglycerides; **T1D:** type 1 diabetes; **T2D**: type 2 diabetes; **PDR:** proliferative diabetic retinopathy; **PRP:** panretinal photocoagulation; **ULN:** the upper limit of normal; **VEGF:** vascular endothelial growth factor

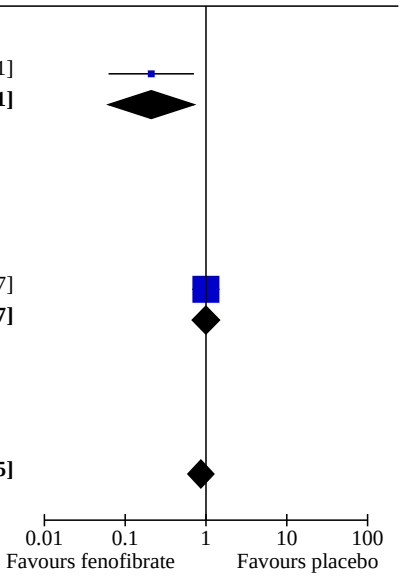
DATA AND ANALYSES

Comparison 1. Fenofibrate vs placebo (5 year)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Progression of diabetic retinopathy	1	1012	Risk Ratio (IV, Fixed, 95% CI)	0.86 [0.60, 1.25]
1.1.1 With overt retinopathy at baseline	1	208	Risk Ratio (IV, Fixed, 95% CI)	0.21 [0.06, 0.71]
1.1.2 Without overt retinopathy at baseline	1	804	Risk Ratio (IV, Fixed, 95% CI)	1.00 [0.68, 1.47]
1.2 Incidence of overt retinopathy	2	1580	Risk Ratio (IV, Fixed, 95% CI)	0.91 [0.76, 1.09]
1.3 Incidence of DMO	1	850	Risk Ratio (IV, Fixed, 95% CI)	0.39 [0.12, 1.24]
1.4 Additional treatments for diabetic retinopathy (any laser)	1	9764	Risk Ratio (IV, Fixed, 95% CI)	0.70 [0.58, 0.85]
1.5 Additional treatments for diabetic retinopathy (focal/grid laser)	2	11358	Risk Ratio (IV, Fixed, 95% CI)	0.69 [0.56, 0.86]
1.6 Additional treatments for diabetic retinopathy (panretinal photocoagulation)	2	11347	Risk Ratio (IV, Fixed, 95% CI)	0.67 [0.51, 0.89]
1.7 Additional treatments for diabetic retinopathy (vitrectomy)	1	850	Risk Ratio (IV, Fixed, 95% CI)	1.96 [0.18, 21.56]
1.8 Discontinuation of the treatment	2	15226	Risk Ratio (IV, Fixed, 95% CI)	1.08 [1.01, 1.15]
1.9 Adverse effects (serious adverse event)	2	15226	Risk Ratio (IV, Fixed, 95% CI)	1.55 [1.05, 2.27]
1.10 Adverse effects (rhabdomyolysis)	1	9764	Risk Ratio (IV, Fixed, 95% CI)	3.00 [0.31, 28.87]
1.11 Adverse effects (hepatic disorder)	2	15226	Risk Ratio (IV, Fixed, 95% CI)	0.95 [0.69, 1.32]
1.12 Adverse effects (pancreatitis)	1	9764	Risk Ratio (IV, Fixed, 95% CI)	1.74 [1.04, 2.90]
1.13 Adverse effects (pulmonary embolism)	2	15226	Risk Ratio (IV, Fixed, 95% CI)	1.66 [1.07, 2.57]
1.14 Adverse effects (myositis)	1	9764	Risk Ratio (IV, Fixed, 95% CI)	2.00 [0.18, 22.08]
1.15 Adverse effects (renal disease needing dialysis)	1	9764	Risk Ratio (IV, Fixed, 95% CI)	0.76 [0.40, 1.46]
1.16 Adverse effects (deep-vein thrombosis)	2	15226	Risk Ratio (IV, Fixed, 95% CI)	1.40 [0.97, 2.02]

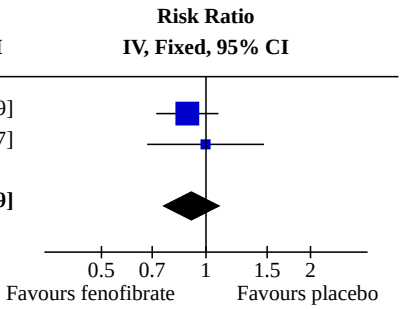
Analysis 1.1. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 1: Progression of diabetic retinopathy

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
1.1.1 With overt retinopathy at baseline						
FIELD	3	105	14	103	9.2%	0.21 [0.06 , 0.71]
Subtotal (95% CI)		**105**		**103**	**9.2%**	**0.21 [0.06 , 0.71]**
Total events:	3		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.51 (P = 0.01)						
1.1.2 Without overt retinopathy at baseline						
FIELD	46	407	45	397	90.8%	1.00 [0.68 , 1.47]
Subtotal (95% CI)		**407**		**397**	**90.8%**	**1.00 [0.68 , 1.47]**
Total events:	46		45			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**512**		**500**	**100.0%**	**0.86 [0.60 , 1.25]**
Total events:	49		59			
Heterogeneity: Chi² = 5.71, df = 1 (P = 0.02); I² = 82%						
Test for overall effect: Z = 0.78 (P = 0.44)						
Test for subgroup differences: Chi² = 5.71, df = 1 (P = 0.02), I² = 82.5%						



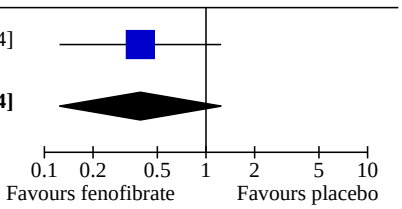
Analysis 1.2. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 2: Incidence of overt retinopathy

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
ACCORD-Lipid	120	401	127	375	77.9%	0.88 [0.72 , 1.09]
FIELD	46	407	45	397	22.1%	1.00 [0.68 , 1.47]
Total (95% CI)		**808**		**772**	**100.0%**	**0.91 [0.76 , 1.09]**
Total events:	166		172			
Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 1.05 (P = 0.30)						
Test for subgroup differences: Not applicable						



Analysis 1.3. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 3: Incidence of DMO

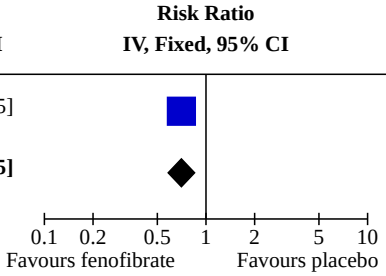
Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
FIELD	4	429	10	421	100.0%	0.39 [0.12 , 1.24]
Total (95% CI)		**429**		**421**	**100.0%**	**0.39 [0.12 , 1.24]**
Total events:	4		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						
Test for subgroup differences: Not applicable						



Analysis 1.4. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 4: Additional treatments for diabetic retinopathy (any laser)

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
FIELD	178	4879	253	4885	100.0%	0.70 [0.58 , 0.85]
Total (95% CI)		**4879**		**4885**	**100.0%**	**0.70 [0.58 , 0.85]**
Total events:	178		253			

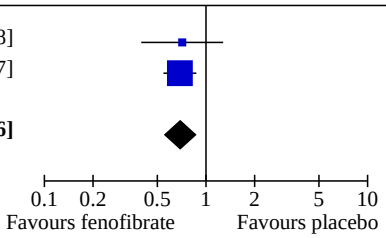
Heterogeneity: Not applicable
Test for overall effect: Z = 3.66 (P = 0.0003)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 5: Additional treatments for diabetic retinopathy (focal/grid laser)

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
ACCORD-Lipid	19	807	26	787	13.9%	0.71 [0.40 , 1.28]
FIELD	115	4879	167	4885	86.1%	0.69 [0.55 , 0.87]
Total (95% CI)		**5686**		**5672**	**100.0%**	**0.69 [0.56 , 0.86]**
Total events:	134		193			

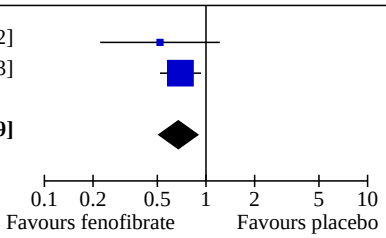
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 3.31 (P = 0.0009)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 6: Additional treatments for diabetic retinopathy (panretinal photocoaculation)

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
ACCORD-Lipid	8	802	15	781	10.5%	0.52 [0.22 , 1.22]
FIELD	75	4879	108	4885	89.5%	0.70 [0.52 , 0.93]
Total (95% CI)		**5681**		**5666**	**100.0%**	**0.67 [0.51 , 0.89]**
Total events:	83		123			

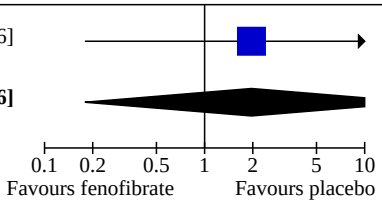
Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.80 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 7: Additional treatments for diabetic retinopathy (vitrectomy)

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
FIELD	2	429	1	421	100.0%	1.96 [0.18 , 21.56]
Total (95% CI)		**429**		**421**	**100.0%**	**1.96 [0.18 , 21.56]**
Total events:	2		1			

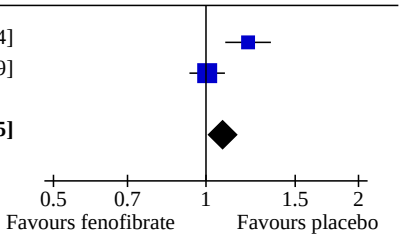
Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 8: Discontinuation of the treatment

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
ACCORD-Lipid	628	2738	516	2724	37.7%	1.21 [1.09 , 1.34]
FIELD	954	4879	950	4885	62.3%	1.01 [0.93 , 1.09]
Total (95% CI)		**7617**		**7609**	**100.0%**	**1.08 [1.01 , 1.15]**
Total events:	1582		1466			

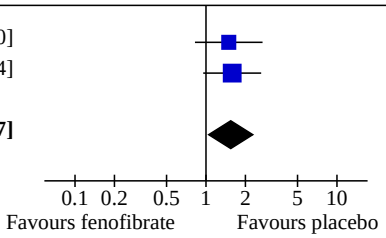
Heterogeneity: Chi² = 7.70, df = 1 (P = 0.006); I² = 87%
Test for overall effect: Z = 2.32 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 9: Adverse effects (serious adverse event)

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
ACCORD-Lipid	27	2738	18	2724	42.4%	1.49 [0.82 , 2.70]
FIELD	38	4879	24	4885	57.6%	1.59 [0.95 , 2.64]
Total (95% CI)		**7617**		**7609**	**100.0%**	**1.55 [1.05 , 2.27]**
Total events:	65		42			

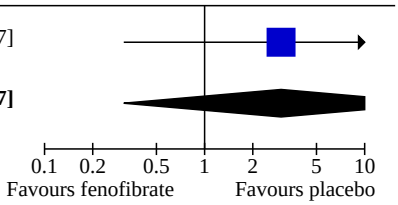
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 2.21 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 10: Adverse effects (rhabdomyolysis)

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
FIELD	3	4879	1	4885	100.0%	3.00 [0.31 , 28.87]
Total (95% CI)		**4879**		**4885**	**100.0%**	**3.00 [0.31 , 28.87]**
Total events:	3		1			

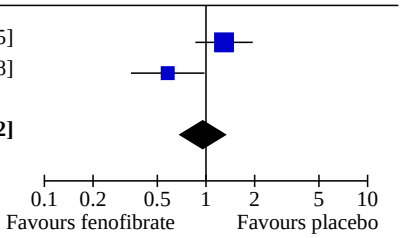
Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 11: Adverse effects (hepatic disorder)

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
ACCORD-Lipid	52	2738	40	2724	62.1%	1.29 [0.86 , 1.95]
FIELD	22	4879	38	4885	37.9%	0.58 [0.34 , 0.98]
Total (95% CI)		**7617**		**7609**	**100.0%**	**0.95 [0.69 , 1.32]**
Total events:	74		78			

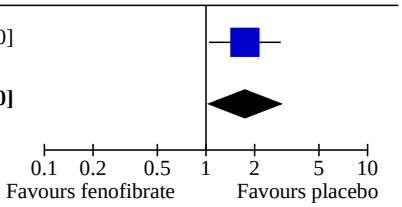
Heterogeneity: Chi² = 5.61, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 12: Adverse effects (pancreatitis)

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
FIELD	40	4879	23	4885	100.0%	1.74 [1.04 , 2.90]
Total (95% CI)		**4879**		**4885**	**100.0%**	**1.74 [1.04 , 2.90]**
Total events:	40		23			

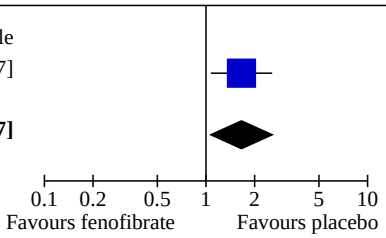
Heterogeneity: Not applicable
Test for overall effect: Z = 2.13 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 13: Adverse effects (pulmonary embolism)

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
ACCORD-Lipid	0	2738	0	2724		Not estimable
FIELD	53	4879	32	4885	100.0%	1.66 [1.07 , 2.57]
Total (95% CI)		**7617**		**7609**	**100.0%**	**1.66 [1.07 , 2.57]**
Total events:	53		32			

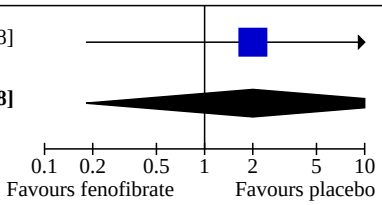
Heterogeneity: Not applicable
Test for overall effect: Z = 2.27 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 14: Adverse effects (myositis)

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
FIELD	2	4879	1	4885	100.0%	2.00 [0.18 , 22.08]
Total (95% CI)		**4879**		**4885**	**100.0%**	**2.00 [0.18 , 22.08]**
Total events:	2		1			

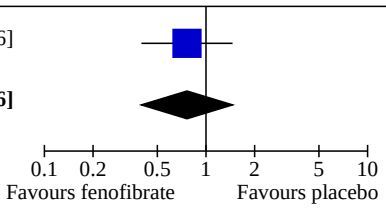
Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 15: Adverse effects (renal disease needing dialysis)

Study or Subgroup	fenofibrate Events	fenofibrate Total	placebo Events	placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
FIELD	16	4879	21	4885	100.0%	0.76 [0.40 , 1.46]
Total (95% CI)		**4879**		**4885**	**100.0%**	**0.76 [0.40 , 1.46]**
Total events:	16		21			

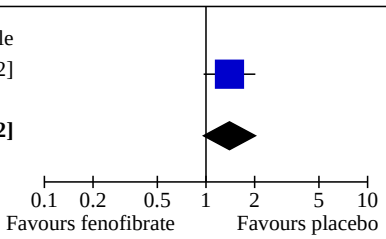
Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Fenofibrate vs placebo (5 year), Outcome 16: Adverse effects (deep-vein thrombosis)

Study or Subgroup	fenofibrate Events	Total	placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
ACCORD-Lipid	0	2738	0	2724		Not estimable
FIELD	67	4879	48	4885	100.0%	1.40 [0.97 , 2.02]
Total (95% CI)		**7617**		**7609**	**100.0%**	**1.40 [0.97 , 2.02]**
Total events:	67		48			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.78 (P = 0.08)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Diabetic Retinopathy] explode all trees
#2 (diabet* or proliferative or non-proliferative) near/4 retinopath*
#3 diabet* near/3 (eye* or vision or visual* or sight*)
#4 retinopath* near/3 (eye* or vision or visual* or sight*)
#5 DR near/3 (eye* or vision or visual* or sight*)
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Fenofibrate] this term only
#8 fenofibrate or phenofibrate
#9 antara or controlip or durafenat or fenoglide or fenobeta or fenofanton or lipofen or lipanthyl or lipantil or liparison or livesan or lofibra or normalip or procetofen or procetofene or secalip or supralip or tricor or triglide
#10 #7 or #8 or #9
#11 #6 and #10

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. random$.ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. trial.ab,ti.
6. (group or groups).ab,ti.
7. or/1-6
8. exp animals/
9. exp humans/
10. 8 not (8 and 9)
11. 7 not 10
12. exp Diabetic Retinopathy/
13. ((diabet$ or proliferative or non-proliferative) adj4 retinopath$).tw.
14. diabetic retinopathy.kw.
15. (diabet$ adj3 (eye$ or vision or visual$ or sight$)).tw.
16. (retinopath$ adj3 (eye$ or vision or visual$ or sight$)).tw.
17. (DR adj3 (eye$ or vision or visual$ or sight$)).tw.
18. or/12-17
19. Fenofibrate/
20. (fenofibrate or phenofibrate).tw.
21. (antara or controlip or durafenat or fenoglide or fenobeta or fenofanton or lipofen or lipanthyl or lipantil or liparison or livesan or lofibra or normalip or procetofen or procetofene or secalip or supralip or tricor or triglide).tw.
22. or/19-21
23. 18 and 22
24. 11 and 23

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp Diabetic Retinopathy/
34. ((diabet$ or proliferative or non-proliferative) adj4 retinopath$).tw.
35. diabetic retinopathy.kw.
36. (diabet$ adj3 (eye$ or vision or visual$ or sight$)).tw.
37. (retinopath$ adj3 (eye$ or vision or visual$ or sight$)).tw.
38. (DR adj3 (eye$ or vision or visual$ or sight$)).tw.
39. or/33-38
40. Fenofibrate/
41. (fenofibrate or phenofibrate).tw.
42. (antara or controlip or durafenat or fenoglide or fenobeta or fenofanton or lipofen or lipanthyl or lipantil or liparison or livesan or lofibra or normalip or procetofen or procetofene or secalip or supralip or tricor or triglide).tw.
43. or/40-42
44. 39 and 43
45. 32 and 44

Appendix 4. ISRCTN search strategy

(fenofibrate OR phenofibrate OR tricor) AND diabetic retinopathy

Appendix 5. ClinicalTrials.gov search strategy

(fenofibrate OR phenofibrate OR tricor) AND (diabetic retinopathy)

Appendix 6. WHO ICTRP search strategy

diabetic retinopathy = Condition AND fenofibrate OR phenofibrate OR tricor = Intervention

Appendix 7. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	• **Parallel-group RCT***i.e. people randomised to treatment* • **Cluster-RCT***i.e. communities randomised to treatment* • **Cross-over RCT** • Other, specify Exclusions after randomisation Losses to follow-up Number randomised/analysed How were missing data handled? *e.g. available case analysis, imputation methods* Reported power calculation (Y/N)*, if yes, sample size and power* Unusual study design/issues	*Eyes or Unit of randomisation/ unit of analysis*
Participants		
Two eyes included in study, both eyes received same treatment, *briefly specify how analysed (best/worst/average/both and adjusted for within-person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye*		
Country		
Setting Ethnic group Equivalence of baseline characteristics (Y/N)	Total number of participants	*This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up, please indicate.*
Number (%) of men and women		
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (N =) Comparator (N =)		• *Number of people randomised to this group* • *Drug (or intervention) name* • *Dose* • *Frequency*

(Continued)

	• *Route of administration*
Outcomes	
Primary and secondary outcomes *as defined in study reports*	*List outcomes* *Adverse events reported (Y/N)*
Notes	
Date conducted	*Specify dates of recruitment of participants mm/yr to mm/yr*
Full study name: *(if applicable)* Reported subgroup analyses (Y/N) Were trial investigators contacted?	
Sources of funding	
Declaration of interest	

HISTORY

Protocol first published: Issue 4, 2019

CONTRIBUTIONS OF AUTHORS

IK produced the first draft of the protocol; NL edited the subsequent draft

SYK, NL, SK, and NW reviewed and commented on the protocol draft

SYK, SK, and KI screened abstracts

SYK and YK reviewed full texts and identified eligible studies

SYK, NL, SK, and YK extracted data and estimated risk of bias

SYK, YK, NW, NL were involved in estimation of GRADE

SYK produced the first draft of the manuscript

NL edited the subsequent draft; NL, IK, SK, YK and NW reviewed and commented on the subsequent draft. All authors approved the final manuscript for submission.

DECLARATIONS OF INTEREST

SYK: none

NL: none

YK: none

SK: none

KI: none

NW: none related to the present review

SOURCES OF SUPPORT

Internal sources

- None, Other

  None

External sources

- Public Health Agency, UK

  The HSC Research and Development (R&D) Division of the Public Health Agency funds the Cochrane Eyes and Vision editorial base at Queen's University Belfast.
- Queen's University Belfast, UK

  Gianni Virgili, Co-ordinating Editor for Cochrane Eyes and Vision's work is funded by the Centre for Public Health, Queen's University of Belfast, Northern Ireland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following changes were made to the original protocol (Inoue 2019).

We limited the inclusion of studies to RCTs whose intervention group's participants took fenofibrate throughout the trial.

We changed the inclusion criteria of participants. In our original protocol, participants were people diagnosed with T1D or T2D, and we included those who did not have retinopathy or who had DR at baseline. We did not mention we would exclude people with the established complications of DR (i.e. DMO/PDR). In the final protocol we followed, we excluded studies including only participants with established complications of DR, which were evaluating the effect of fenofibrate on the established complications (rather than on preventing them). Studies randomising participants with complications were included in this review if only a small proportion of participants had established complications of DR at baseline (i.e. less than 10%), or if data for people without complications were presented separately and could be extracted.

We searched electronic databases for the European Association for the Study of Diabetes (EASD) congress and the European Association for the Study of Diabetes Eye Complications Study Group (EASDEC) congress from 1990 to the present instead of handsearching.

We changed some of secondary outcomes' names, proportion of participants with a reduction in visual acuity of 10 letters or more, and proportion of participants in which treatment is discontinued to incidence of a reduction in visual acuity of 10 ETDRS letters or more, and discontinuation of the treatment.

Our original protocol established that all outcomes would be investigated at one, three, and five years. We changed the protocol to include outcomes measured at 3 ± 1, and 5 ± 1 years, instead of 3 years ± 6 months and 5 years ± 6 months, and we included the 4-year data with the 5-year data.

Four reviewers (SYK, NL, SK, YK) engaged in data extraction, and assessment of risk bias in included studies, and data management using Covidence, Excel, RevMan 5, RevMan Web.

In unit of analysis, we included results that reported using per person (as done in ACCORD-Lipid using the ETDRS scale which considers the grading of DR from both eyes), and the worse eye or right eye when both eyes had the same retinopathy severity, for ocular outcomes (i.e. incidence of overt retinopathy and additional treatments for DR (focal/grid and PRP)) in conducting meta-analysis.

Though we did not conduct subgroup analysis due to insufficient numbers of trials, we changed the definition of with or without overt retinopathy at baseline (ETDRS scale; Final Retinopathy Severity Scale for Persons of step 3 or less, or step 4 or greater (i.e. step 3 suggests the existence of microaneurysms detected in both eyes; step 4 suggests the existence of mild NPDR in one eye)) in subgroup analysis to that of with or without overt retinopathy at baseline (we used the original study authors' definitions) in subgroup analysis.

Reviewers (SYK, NL, YK, NW) agreed and prepared the summary of findings.

INDEX TERMS

Medical Subject Headings (MeSH)

*Diabetes Mellitus, Type 1; *Diabetes Mellitus, Type 2 [complications] [drug therapy]; *Diabetic Retinopathy [drug therapy]; *Fenofibrate [adverse effects]; *Macular Edema [drug therapy] [etiology]; *Retinal Diseases

MeSH check words

Humans