

The effect of fenofibrate therapy on laser treatment for diabetic retinopathy: a meta-analysis of randomized controlled trials

Short title: fenofibrate and diabetic retinopathy

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Diabetic eye disease (retinopathy and maculopathy) remains a leading cause of blindness and impaired vision. It is also the only major cause that is increasing in most regions of the world¹. Whilst good control of blood glucose and blood pressure modestly reduces the risk of and progression of microvascular disease, these approaches can be difficult to achieve, require monitoring, and may have undesired side-effects. Fenofibrate is an inexpensive lipid-modifying agent that activates the peroxisome proliferator-activated receptor alpha, thereby lowering circulating triglycerides and modestly raising HDL-cholesterol. A hypothesis-generating tertiary outcome of a major cardiovascular trial suggested that prolonged fenofibrate therapy may reduce the need for retinal laser treatment², and a sub-study with a composite diabetes eye outcome, embedded within another trial, further supported this hypothesis³. No data is available from major trials of other fibrates. The primary aim of this analysis was to evaluate the effect of prolonged treatment with fenofibrate on the need for laser treatment of diabetic eye disease in major trials conducted in participants with type 2 diabetes.

We performed a systematic review and meta-analysis of randomized placebo-controlled trials investigating the effects of fenofibrate therapy in at least 1000 participants with diabetes and with intended follow up of over 1 year. Trials were identified in literature searches of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, conducted on 20th December 2020. Changes in lipids at 1 year and first laser treatment for diabetic retinopathy or maculopathy were extracted from publications or obtained from unpublished data sought from investigators or data repositories. Trial-specific odds ratios (ORs) for first laser treatment were calculated and combined in fixed effects meta-analyses using Peto's one-step statistic. In a hypothesis-generating analysis, based on knowledge that lipid modification tends to have greater benefits on cardiovascular disease outcomes in later years

compared to the first year, we also separately assessed the effects of fenofibrate therapy on the need for laser therapy in the first year and later years.

We identified three large placebo-controlled trials of fenofibrate therapy, all primarily designed to investigate its effects on cardiovascular outcomes in participants with type 2 diabetes^{2,4,5}. Eligibility in these trials did not include the presence or absence of retinopathy. The FIELD trial previously published data on retinal laser treatment and changes in lipids. Individual participant data for eye laser treatment for the ACCORD-Lipid trial were obtained from the NHLBI Data Repository and trial investigators, while changes in lipids were extracted from published data. Investigators from the Lipids in Diabetes Study, which was terminated early due to withdrawal of cerivastatin (an intervention being tested along with fenofibrate in a 2x2 factorial design), provided unpublished summary data for both laser treatment and lipids. Together, these trials included 19,504 participants and accumulated about 80,000 patient-years of follow up with weighted mean follow up of 4.0 years. Fenofibrate reduced mean triglycerides by 29-51mg/dL (20-30%), mean total cholesterol by 6-22mg/dL (3-12%) and mean LDL-cholesterol by 0-14mg/dL (0-12%) compared with placebo at one year across these trials.

During follow up, 892 (4.6%) participants received retinal laser treatment. 391 (4.0%) participants allocated fenofibrate and 501 (5.1%) participants allocated placebo received laser treatment, a 23% reduction (OR 0.77; 95% confidence interval (CI) 0.67–0.88; p=0.0001) in the odds of laser treatment (**Figure 1**) with no significant heterogeneity between the trials. This equates to a number needed to treat of 88 (95% CI 59–162) participants over 4 years. There was a non-significant 10% (OR 0.90; 95% CI 0.73–1.12) reduction in the odds of laser

treatment within the first year followed by a significant 30% (OR 0.70; 95% CI 0.58–0.83) reduction thereafter, suggesting that benefit accumulates over time.

In conclusion, in a combined analysis of large cardiovascular trials conducted to date, fenofibrate treatment reduced the need for retinal laser treatment by over 20% compared with placebo. To receive worldwide regulatory approvals allowing widespread use of this generically available and simple treatment to reduce the risk of progressive diabetic retinopathy and maculopathy, it will be necessary to conduct randomized trials primarily designed to test its effect on diabetic eye outcomes. Such studies are underway in participants with established diabetic retinopathy who are at higher risk of progressive diabetic eye disease than participants in the prior cardiovascular trials. These include the FAME-1-EYE trial (NCT01320345; 450 participants with type 1 diabetes), the LENS trial (NCT03439345; 1150 participants with type 1 or type 2 diabetes) and the newly announced Randomized Clinical Trial Evaluating Fenofibrate for Prevention of Diabetic Retinopathy Worsening (NCT04661358; 910 participants with type 1 or type 2 diabetes).

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Duality of Interest: DP is chief investigator, and ES and JA are coinvestigators, for the LENS trial which has received fenofibrate and matching placebo tablets from Mylan free of charge; RRH reports research support from AstraZeneca, Bayer and Merck Sharp & Dohme, and personal fees from Anji Pharmaceuticals, Bayer, Novartis and Novo Nordisk; HG is medical advisor for the Randomized Clinical Trial Evaluating Fenofibrate for Prevention of Diabetic Retinopathy Worsening; RLC and LL declare no competing interests.

Author Contributions: DP conceived the study; RRH, LL and HG were investigators on contributing trials; DP, ES, RLC, LL conducted the analyses; DP drafted the manuscript; DP, ES, RRH, RC, LL, HG, JA contributed critical intellectual content, made important revisions to the manuscript and contributed to the discussion; DP is the guarantor of this work and, as such, had full access to all the data in this study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Registration: the meta-analysis is registered at Open Science Framework (see <https://osf.io/8ewcp>)

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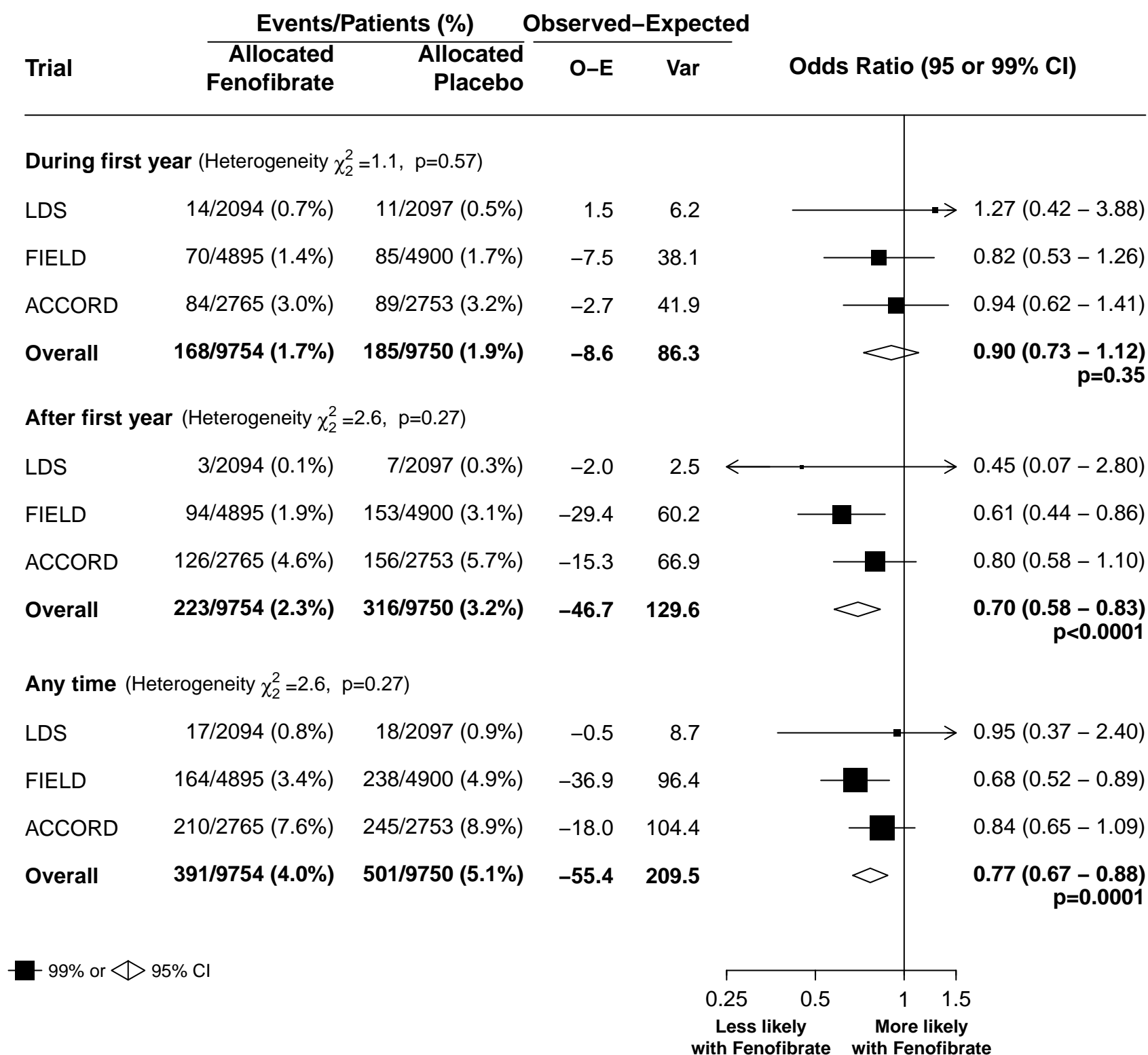
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Figure Titles and Footnotes:

Figure 1. The effect of fenofibrate therapy on laser treatment for diabetic retinopathy

Footnote: O–E=observed–expected. Var=variance. For each trial, O–E is calculated from 2×2 contingency tables. Odds ratio is calculated by taking \ln odds ratio to be $(O-E)/V$ with normal variance $1/V$, where $V=\text{Var}(O-E)$. Totals of $(O-E)$ and of V yield inverse–variance weighted averages of the \ln odds ratio values. For the FIELD trial, digitization software was used to extract numbers of events in the first year vs. later years.

Figure 1: Effect of fenofibrate therapy on laser treatment for diabetic retinopathy



O–E=observed–expected. Var=variance. For each trial, O–E is calculated from 2 × 2 contingency tables. Odds ratio is calculated by taking \ln odds ratio to be (O–E)/V with normal variance 1/V, where V=Var (O–E). Totals of (O–E) and of V yield inverse–variance weighted averages of the \ln odds ratio values.

For FIELD trial, appropriate digitization software was used to extract relevant data.