Effect of Fenofibrate Therapy on Laser Treatment for Diabetic Retinopathy: A Meta-Analysis of Randomized Controlled Trials

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Diabetic eye disease (retinopathy and maculopathy) remains a leading cause of blindness and impaired vision, and it is also the only major cause that is increasing in most regions of the world (1). While good control of blood glucose and blood pressure modestly reduces the risk 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 α, thereby lowering circulating triglycerides and modestly raising HDL cholesterol. A hypothesis-generating tertiary outcome of a major cardiovascular trial suggested that prolonged fenofibrate therapy reduces the need for retinal laser treatment (2), and a substudy with a composite diabetes eye outcome, embedded within another trial, further supported this hypothesis (3). No data are 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 1,000 participants with diabetes and with intended follow-up over 1 year. Trials were identified in literature searches of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL), conducted on 20 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and first laser treatment for diabetic retinopathy or maculopathy were extracted from publications or obtained from unpublished data sought from investigators or data repositories.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-effect 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 than in 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 Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial previously published data on retinal laser treatment and changes in lipids. Individual participant data for eye laser treatment for the Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid trial were obtained from the National Heart, Lung, and Blood Institute Data Repository and trial investigators, while changes in lipids were extracted from published data. Investigators from the Lipids in Diabetes Study (LDS), which was terminated early due to withdrawal of cerivastatin (an intervention being tested along with fenofibrate in a 2 × 2 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 a weighted mean follow-up of 4.0 years. Fenofibrate reduced mean triglycerides by 29–51 mg/dL (20–30%), mean total cholesterol by 6–22 mg/dL (3–12%), and mean LDL cholesterol by 0–14 mg/dL (0–12%) compared with placebo at 1 year across these trials.

During follow-up, 892 (4.6%) participants received retinal laser treatment. A total of 391 (4.0%) participants allocated fenofibrate and 501 (5.1%) participants allocated placebo received laser

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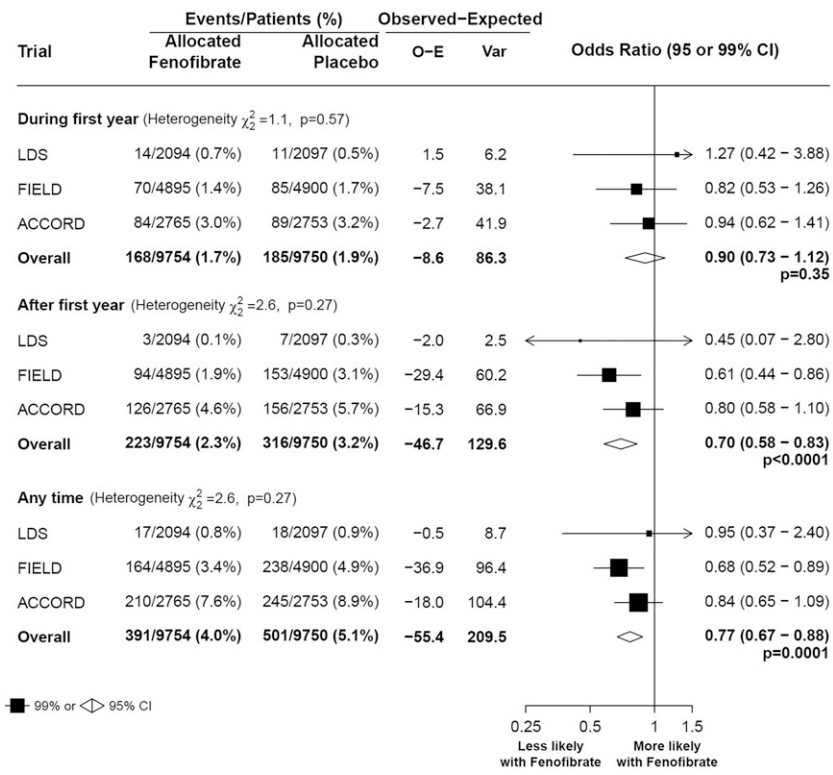

Figure 1–The effect of fenofibrate therapy on laser treatment for diabetic retinopathy. O–E, observed–expected. Var, variance. For each trial, O−E is calculated from 2 × 2 contingency tables. OR is calculated by taking ln(OR) to be (O−E)/V with normal variance 1/V, where V = Var (O–E). Totals of (O−E) and of V yield inverse-variance–weighted averages of the ln(OR) values. For the FIELD trial, digitization software was used to extract numbers of events in the first year vs. later years.

treatment, a 23% reduction (OR 0.77; 95% CI 0.67–0.88; *P* = 0.0001) in the odds of laser treatment (Fig. 1) with no significant heterogeneity between the trials. This equates to a number needed to treat 88 (95% CI 59–162) participants over 4 years. There was a nonsignificant 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 under way 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 Fenofibrate and Microvascular Events in Type 1 Diabetes Eye (FAME 1 Eye) trial (NCT01320345; 450 participants with type 1 diabetes), the Lowering Events in Non-proliferative Retinopathy in Scotland (LENS) trial (NCT03439345; 1,150 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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Author Contributions. D.P. conceived the study. R.R.H., L.L., and H.N.G. were investigators on contributing trials. D.P., E.S., R.L.C., and L.L. conducted the analyses. D.P. drafted the manuscript. D.P., E.S., R.R.H., R.L.C., L.L., H.N.G., and J.A. contributed critical intellectual content, made important revisions to the manuscript, and contributed to the discussion. D.P. 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.

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