Diabetic retinopathy is an ocular manifestation of a systemic disease, diabetes mellitus. Although largely successful treatments developed over the past nearly 50 years, including focal and pan-retinal laser photocoagulation, vitrectomy surgery, and more recently, intravitreal injections of corticosteroids and biological agents directed at vascular endothelial growth factor, all have been local therapies within the eye itself and it seems reasonable to suppose that systemic treatments, directed at the systemic metabolic disease, also may have beneficial effects on its ocular sequelae. That has been the basis of previous clinical trials investigating the role of blood glucose and blood pressure control to prevent retinopathy and other complications in type 1 and type 2 diabetes. It is also the premise underlying the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study, a component of the much larger ACCORD Study, which focused on systemic therapies to prevent cardiovascular events in subjects with type 2 diabetes who already had experienced one cardiovascular event or who were considered at high risk for one.

The major results of the ACCORD Eye Study were published in 2010, and further analyses appear in this issue of Ophthalmology (see article on page XXX). Results of the overall study, dealing with cardiovascular outcomes, appeared in separate publications in 2010 and 2011. Briefly, the ACCORD Study (and its eye substudy) was a randomized controlled clinical trial with 3 components: extremely rigorous reduction of hyperglycemia to a hemoglobin A1c level of less than 6.0% (treatment group) versus 7.0% to 7.9% (control group); reduction of systolic blood pressure to less than 140 mmHg (treatment group) versus 140 mmHg or less (control group); and lipid control with simvastatin and an antioxidant (control group) plus fibric acid derivative or antioxidant (treatment group). Lowering in Diabetes trial. There are some caveats, however. First, as the present ACCORD Eye Study report indicates, significant retardation of retinopathy progression was observed only in study subjects with mild retinopathy at baseline, but not in those with either no retinopathy or with moderate to severe retinopathy. Second, there was no effect of any of the therapies, lower blood glucose, lower systolic blood pressure, or antilipid, on photographically demonstrable macular edema (optical coherence tomography was not used in the ACCORD Eye Study), but subjects with macular edema were less than 10% of the study population, and macular edema in these individuals was considered mild.

The ACCORD Eye Study has reached major conclusions about control of blood glucose and blood pressure and the use of antilipidemic agents, but has raised important questions. The lipid arm of this study is of particular interest, showing benefit from the simvastatin-plus-fibrate combination for retinopathy progression, but not for cardiovascular outcomes, compared with simvastatin alone. Fibric acid derivatives were introduced therapeutically nearly 40 years ago, and fenofibrate itself appeared 35 years ago. Yet, although they have impressive effects on serum lipid levels that are considered harmful, they have not demonstrated reduction in cardiovascular mortality in human subjects and therefore have been used less widely clinically than the statins. Ophthalmologists generally have not prescribed systemic medications for eye diseases (some cases of uveitis, glaucoma, and ocular infectious diseases

*In prespecified subgroup analyses, the simvastatin-plus-fenofibrate group showed a borderline significant \( P = 0.057 \) for interaction benefit in cardiovascular outcomes in subjects with atherogenic hyperlipidemia, that is, elevated plasma triglycerides and lowered high-density lipoprotein cholesterol.
have been occasional exceptions), and the prescription of drugs that are indicated primarily for cardiovascular disease and hyperlipidemia has been considered the province of cardiologists and other internal medicine practitioners. In light of the ACCORD Eye Study and Fenofibrate Intervention and Event Lowering in Diabetes results, perhaps this should change.16 At the least, ophthalmologists should communicate to their colleagues in other specialties that, whereas fenofibrate may have little benefit for cardiovascular disease, it seems to have a considerable preventive effect on progression of diabetic retinopathy. Also, its effect on diabetic macular edema was not tested adequately in the ACCORD Eye Study and merits further investigation in that regard. Like most systemic drugs, fenofibrate does have some adverse systemic effects.17–20 These seem to be limited to occasional elevation of liver enzymes, but rarely to clinical hepatic dysfunction.19,20 Diabetic subjects with borderline renal function may experience elevation of serum creatinine, but this seems to be reversible with discontinuation of fenofibrate.20 There also may be a differential effect of fenofibrate by gender. The overall ACCORD Study results showed a significant beneficial effect of the simvastatin-plus-fenofibrate combination for cardiovascular end points in men, but a borderline, even potentially harmful, effect in women (P = 0.01 for interaction).5 In the initial ACCORD Eye Study publication,4 the major reduction in diabetic retinopathy progression appeared in males (see reference 4, Table 1 for subgroup analyses), whereas there was no pronounced effect in women. The P value for interaction for this comparison was 0.11. This result of a protocol-specified subgroup analysis is not significant, and perhaps less so if corrected for multiple comparisons (22 in all),4 but certainly is suggestive, especially considering its parallelism with the cardiovascular results. With these caveats in mind, combination systemic therapy for diabetic retinopathy deserves further attention from ophthalmologists and merits further investigation in areas that were covered incompletely or not at all by the ACCORD Eye Study: in stages of diabetic retinopathy other than mild disease, as an adjunct to current intraocular therapies for diabetic macular edema and proliferative retinopathy, and in basic studies to pinpoint mechanisms of action and to determine if there is a true differential effect by gender. The best scientific studies answer important questions, but raise others. The ACCORD Eye Study is no exception.

References