Reduction in Risk of Progression of Diabetic Retinopathy
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The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (ClinicalTrials.gov number, NCT00000620) was designed primarily to study the effects of intensive glycemic control on cardiovascular events in persons with type 2 diabetes. The ACCORD Eye study (NCT00542178), described by the ACCORD Study Group and ACCORD Eye Study Group in this issue of the Journal, is a subgroup study of the larger ACCORD trial, designed to examine effects of several medical interventions on the progression of diabetic retinopathy. A sample of 4065 of the 10,251 participants in ACCORD was targeted for the eye study; complete data were obtained for 2856 subjects.

The authors assert that limiting the progression of diabetic retinopathy is important because doing so would limit the occurrence of proliferative retinopathy, a severe threat to vision. Perhaps more critical, in my view, is that retinopathy is a concomitant or precursor of systemic microvascular complications, such as renal disease, as well as of neuropathy and macrovascular complications. For these reasons, the report of the ACCORD Eye study has great importance, particularly because of the increasing prevalence of diabetes related to the aging of the population and also the increasing prevalence at younger ages, which is likely to be related to obesity.

In the ACCORD Eye analysis, intensive glycemic control resulted in a 33% reduction in the relative risk of progression of diabetic retinopathy in a relatively short period (4 years). In contrast, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study (NCT00145925), another study of patients with type 2 diabetes, showed no significant effect of glycemic control on severe diabetes related to ocular end points. The sample size was smaller in the ADVANCE trial (with 791 participants in the intensive-therapy group and 811 in the standard-therapy group) than in the ACCORD Eye trial (with 1429 and 1427 participants, respectively), and the odds ratio for severe diabetes related to ocular end points with the use of tighter glycemic control was in a protective direction in ADVANCE. A previous trial in persons with type 2 diabetes found beneficial effects of tight glycemic control on retinopathy, although the effect took longer to become significant. In addition, in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, which was performed in persons with type 1 diabetes, the results were substantially the same. The specific effects of intensive glycemic control on the odds of proliferative retinopathy in the DCCT/EDIC study are of interest. However, the effects on proliferative disease were not discussed directly, possibly because of the limited number of cases.

An exciting finding is the 40% reduction in the odds of having progression of retinopathy that is conveyed by fenofibrate (taken along with simvastatin) in the ACCORD Eye study over a 4-year period. This occurred in concert with a decrease in the serum triglyceride level by roughly 20 mg per deciliter (22.6 mmol per liter) in the fenofibrate group, as compared with the placebo group, occurring over the first year of treatment and maintained through the end of the study. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (Current Controlled Trials number, ISRCTN64783481) previously reported a protective effect of fenofibrate on laser treatment for proliferative diabetic retinopathy, but there was no evidence of a concomitant decrease in se-
rum triglyceride levels.\textsuperscript{4} In the ACCORD Eye trial, the effect of fenofibrate was independent of glycemia. Whether an enhanced effect of fenofibrate in the ACCORD Eye study is the result of an interaction with simvastatin will be an interesting topic for further research.

Some may find the lack of an apparent beneficial effect of intensive blood-pressure control on progression of retinopathy in the ACCORD Eye study surprising. However, blood pressure has not been a significant factor for the incidence or progression of retinopathy in patients with type 2 diabetes in observational studies.\textsuperscript{5,6} Higher blood pressure has been found to be associated with the incidence or progression of retinopathy in patients with type 1 diabetes and those with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS; ISRCTN75451837). The range of blood pressures in the ACCORD Eye trial was relatively small, and the duration of lowered pressure was relatively short. It may be that a longer follow-up period would be needed to show either a protective effect of blood-pressure lowering at the levels achieved in the ACCORD study or an increase to significance of the nonsignificant deleterious effect of intensive blood-pressure control that was found in the study. It is also possible that there is little effect of blood-pressure control in persons of the age and with the risk factors of the ACCORD Eye participants.

Although change in visual acuity was not a primary outcome of the ACCORD Eye study, data on this important functional result are provided. No significant beneficial effect on moderate vision loss was shown for any of the interventions.

There are many differences among studies of risk factors for the progression of retinopathy that might lead to the observed variation in their results. The means of ascertainment of retinopathy severity has not been uniform across studies. Even when photographs are taken, the protocols for photography may vary, as may the grading techniques and severity scales used. In addition, comparing findings between patients with type 1 diabetes and those with type 2 diabetes is not always appropriate. Finally, the inadequacy of some sample sizes and the use of repeated testing may also color our interpretation of study findings.

Overall, the ACCORD Eye trial has added substantially to our knowledge and confidence about the importance of glycemic control in the progression of diabetic retinopathy. The findings also strongly suggest the need for further evaluation of the potential importance of fenofibrate in our armamentarium of treatments for this condition.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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