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The Effects of Medical Management on the Progression of Diabetic Retinopathy in Persons with Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Eye Study

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Purpose: To report additional ocular outcomes of intensive treatment of hyperglycemia, blood pressure, and dyslipidemia in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.

Design: Double 2×2 factorial, multicenter, randomized clinical trials in people with type 2 diabetes who had cardiovascular disease or cardiovascular risk factors. In the glycemia trial, targets of intensive and standard treatment were: hemoglobin A1c <6.0% and 7.0% to 7.9%, respectively, and in the blood pressure trial: systolic blood pressures of <120 and <140 mmHg, respectively. The dyslipidemia trial compared fenofibrate plus simvastatin with placebo plus simvastatin.

Participants: Of the 3472 ACCORD Eye Study participants enrolled, 2856 had 4-year data (85% of survivors).

Methods: Eye examinations and fundus photographs were taken at baseline and year 4. Photographs were graded centrally for retinopathy severity and macular edema using the Early Treatment Diabetic Retinopathy Study (ETDRS) methods.

Main Outcome Measures: Three or more steps of progression on the ETDRS person scale or treatment of retinopathy with photocoagulation or vitrectomy.

Results: As previously reported, there were significant reductions in the primary outcome in the glycemia and dyslipidemia trials, but no significant effect in the blood pressure trial. Results were similar for retinopathy progression by 1, 2, and 4 or more steps on the person scale and for ≥2 steps on the eye scale. In the subgroup of patients with mild retinopathy at baseline, effect estimates were large (odds ratios, ~0.30; $P < 0.001$), but did not reach nominal significance for participants with no retinopathy or for those with moderate to severe retinopathy at baseline.

Conclusions: Slowing of progression of retinopathy by intensive treatment of glycemia was observed in ACCORD participants, whose average age and diabetes duration were 62 and 10 years, respectively, and who had cardiovascular disease or cardiovascular risk factors. The effect seemed stronger in patients with mild retinopathy. Similar slowing of progression was observed in patients treated with fenofibrate, with no effect observed with intensive blood pressure treatment. This is the second study to confirm the benefits of fenofibrate in reducing diabetic retinopathy progression, and fenofibrate should be considered for treatment of diabetic retinopathy. *Ophthalmology 2014;■:1–9 © 2014 by the American Academy of Ophthalmology.*

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The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial included 3 randomized comparisons that evaluated the effects of intensive blood glucose and blood pressure control and the combination of fenofibrate and statin versus statin monotherapy therapy for dyslipidemia on the occurrence of cardiovascular events in patients with type 2 diabetes who also had established cardiovascular disease or additional cardiovascular risk factors.[1] As previously reported, none of the 3 intensive treatments were demonstrated to have a beneficial effect on the primary

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cardiovascular outcome.[2–5] After 3.5 years of follow-up, the glycemia trial was stopped because of increased mortality in the intensive treatment group.[2,5]

The ACCORD Eye Study was designed to evaluate the effects of the 3 interventions on the development and progression of diabetic retinopathy in a subset of ACCORD study participants.[6] As previously reported, the main results of the ACCORD Eye Study were reductions in retinopathy progression in both the intensive glycemia and fenofibrate plus statin treatment groups, but not in the intensive blood pressure treatment group.[7] We examine components of the primary eye outcome, present additional prespecified and exploratory analyses of primary and secondary outcome measurements, and compare results between trials and in subgroups.

Methods

The ACCORD Study

The designs of the ACCORD study and the ACCORD Eye Study have been described elsewhere.[1,6] The ACCORD study was approved by the institutional review board of each clinical center. Briefly, the ACCORD study was a multicenter study with a total of 10 251 participants randomly assigned in equal numbers to 2 glycemia management treatment arms. The intensive treatment arm aimed to achieve and maintain glycated hemoglobin (HbA1c) level <6.0%. The standard treatment arm targeted an HbA1c range of 7.0% to 7.9%, with an expected median value of approximately 7.5%. Of these participants, 5518 with moderate dyslipidemia were randomly assigned in a double-masked fashion to placebo or fenofibrate, 160 mg daily, in addition to statin, aiming to decrease triglyceride levels and increase high-density lipoprotein cholesterol levels. Participants in both the placebo and fenofibrate groups also took simvastatin to lower low-density lipoprotein cholesterol levels. The other 4733 participants, who had systolic blood pressures of 130 to 180 mmHg, were simultaneously randomized to 1 of 2 hypertension management protocols. The intensive treatment arm targeted systolic blood pressure <120 mmHg, and the standard treatment arm targeted systolic blood pressure <140 mmHg. The primary outcome of the ACCORD trial was the composite end point of the time until the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

ACCORD Eye Study

The primary aim of the ACCORD Eye Study was to examine the effect of each of the 3 interventions on the development and progression of diabetic retinopathy. Participants who had proliferative diabetic retinopathy (PDR) previously treated with laser and vitrectomy were excluded from the ACCORD Eye Study, and all other ACCORD subjects at participating sites were eligible. The eye study protocol was reviewed by the institutional review board of each clinical center and the coordinating center, and signed informed consent was obtained from each participant.

The ACCORD Eye Study consisted of standardized eye examinations conducted by a study ophthalmologist or optometrist and color fundus photography of 7 standard stereoscopic fields, scheduled for baseline and year 4 of follow-up. The eye examinations included visual acuity measurement and dilated examination of the anterior segment and fundus. The fundus photographs were graded centrally by trained personnel who had no knowledge of the medical status or the treatment assignment of the participants. Baseline and year 4 photographs were graded independently of each other. For assessment of retinopathy progression, the Early Treatment Diabetic Retinopathy Study (ETDRS) diabetic retinopathy severity scale, which combines the severity levels from both eyes for each person, was used,[8] with minor modifications,[7] providing 17 steps from no diabetic retinopathy in either eye to high-risk PDR in both eyes. The ETDRS diabetic macular edema (DME) severity scale was used to assess development of and change in DME on stereoscopic fundus photographs of the macula.[9] This scale classifies individual eyes by combining the extent of retinal thickening within 1 disc diameter (DD) of the macular center with degree of thickening at the center. The scale has 10 steps, beginning with absence of retinal thickening and ending with ≥3 disc areas (DAs) (1 DA = 2.54 mm^2) of thickening within 1 DD (1 DD = 1.8 mm) of center and thickening at center ≥2 times that of "reference thickness," defined as the maximum thickness of normal retina 0.5 to 1.0 DD from center. Change in DME between baseline and year 4 was assessed in 1 eye of each patient, choosing the eye in the higher step on the scale at baseline or, if both eyes were in the same step at baseline, the eye in the higher step at year 4. An extension of the ETDRS grading system was used to assess change in estimated areas of hard exudates and retinal thickening within 2 DD of the macular center.[10] Estimates from right and left eyes were summed. The hard exudates scale has 10 steps extending from 0 to ≥0.5 DA, and the retinal thickening scale has 12 steps extending from 0 to ≥10 DAs. In addition, the entire ACCORD cohort had visual acuity measurements with ETDRS logarithmic visual acuity charts at the medical clinics at baseline and every 2 years. Questionnaires regarding ocular surgery, such as cataract surgery, vitrectomy, and laser photocoagulation, were administered at each annual study visit.

ACCORD Eye Study Measures of Outcome

The primary outcome of the ACCORD Eye Study was a composite of ≥3 steps of progression along the ETDRS diabetic retinopathy severity scale for persons or treatment of diabetic retinopathy with photocoagulation or vitrectomy in either eye. Secondary and exploratory outcomes included alternative definitions of progression, development of the primary outcome in retinopathy severity subgroups, development of retinopathy in participants free of it at baseline, change in photographic measures of macular edema, and change in visual acuity.

Statistical Methods

Descriptive statistics and proportions are presented. The comparison of proportions of participants reaching an outcome at 4 years between groups was made using logistic regression models with likelihood ratio tests. Covariates included clinical network and whether the participant had a previous cardiovascular event. Separate models were used for the glycemia, lipid, and blood pressure comparisons. For the glycemia comparison, we also included indicator variables for fenofibrate, intensive blood pressure treatment, and trial (blood pressure vs. lipid). For the lipid and blood pressure comparisons, we also included an indicator variable for intensive glycemia treatment. Tests for interactions also were made using likelihood ratio tests by adding the interactions to the appropriate model. No adjustment for multiplicity has been made in this article.

Results

From January 2001 to October 2005, 10 251 participants were recruited in the main ACCORD trial. From October 2003 to