Rationale, Design, and Methods of the Action to Control Cardiovascular Risk in Diabetes Eye Study (ACCORD-EYE)

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Diabetic retinopathy (DR) is a major microvascular complication of diabetes mellitus. The Action to Control Cardiovascular Risk in Diabetes Eye Study (ACCORD-EYE), a prospective study of a subset of patients in the randomized controlled clinical ACCORD trial, is being conducted at enrollment and after 4 years of follow-up to assess the progression of DR with standardized comprehensive eye exams and fundus photography of 7 standard stereoscopic fields. This study aims to assess the effects of the ACCORD medical treatment strategies of tight control of glycemia and blood pressure and management of dyslipidemia on the course of DR in patients with type 2 diabetes. Photographs will be evaluated at a centralized location using the modified Early Treatment Diabetic Retinopathy Study (ETDRS) classification. The primary outcome of ACCORD-EYE, which will measure the development and progression of DR, is a composite of (1) progression of DR (≥3 steps on the ETDRS scale), (2) photocoagulation for DR, or (3) vitrectomy for DR. Specifically, the following questions will be addressed: (1) Does a therapeutic strategy targeting a glycosylated hemoglobin (HbA_{1c}) level <6.0% reduce development and progression of DR more than one targeting an HbA_{1c} level of 7.0%–7.9% (target median level, 7.5%)? (2) In the context of good glycemic control, does a strategy using a fibrate to increase high-density lipoprotein cholesterol and lower triglyceride levels and a statin to maintain the level of low-density lipoprotein (LDL) cholesterol at <2.59 mmol/L (100 mg/dL) reduce development and progression of DR compared with one using placebo and a statin to treat LDL cholesterol? (3) In the context of good glycemic control, does a strategy targeting a systolic blood pressure level <120 mm Hg reduce development and progression of DR compared with one targeting a level <140 mm Hg? Secondary outcome variables include various levels of loss of visual acuity at 4 years versus baseline, cataract extraction, and the development or progression of diabetic macular edema. Methods to measure DR progression have been incorporated into ACCORD, and complete baseline data have been collected on 3,537 participants. These data will provide valuable information regarding the effects of medical treatment on the prevention and progression of DR. **(Am J Cardiol 2007;99[suppl]:103i–111i)**

Diabetic retinopathy (DR), a major microvascular complication of diabetes mellitus, is a leading cause of blindness in adults aged <65 years in the United States.[1] One of the most important risk factors associated with the development of DR is poor glycemic control, as reflected by increasing glycosylated hemoglobin (HbA_{1c}).[2–9] The results of randomized controlled clinical trials of the effect of glycemic control on DR support the association found in observational studies.[10–13]

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Elevated blood pressure is also known to be an important contributing factor to the progression of DR. A randomized controlled clinical trial of tight versus conventional blood pressure control has also demonstrated the beneficial effects of blood pressure treatment on DR.[14]

Elevated serum cholesterol levels have been implicated in population-based and prospective studies as a risk factor for the development of DR as well as visual loss.[15,16] However, there has never been a randomized controlled intervention trial with sufficient power to evaluate the effect of dyslipidemia treatment on DR. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study offers a unique opportunity to evaluate the effects of treatment for dyslipidemia and the role of the medical treatment of all 3 risk factors in the progression of DR, as their effects on cardiovascular outcomes are being measured. Details regarding the overall design and methods for the ACCORD trial are found elsewhere in this supplement[17] and are briefly summarized below.

Glycemic Control and Eye Disease: Type 1 Diabetes

The results of the Diabetes Control and Complications Trial (DCCT), a randomized controlled clinical trial of glycemic control in patients with type 1 diabetes, demonstrated that intensive glycemic control reduced the risk for the development and progression of DR compared with conventional glycemic control.[10] After 3 years of intensive treatment to reduce glucose levels, in patients without retinopathy, the development of any retinopathy was reduced by 75%, although not prevented completely, over the 9-year course of the study. The benefit of strict glucose control was also evident in patients with existing mild-to-moderate nonproliferative retinopathy (a 50% reduction in the rate of progression of retinopathy compared with controls). Beyond 3.5 years of follow-up, the risk for progression was 5 times lower in the former intensive insulin treatment group than in the former conventional treatment group.

The durability of the beneficial effects of tight glycemic control were demonstrated in the follow-up study of the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study.[11] After the completion of the DCCT, 95% of the study patients were enrolled in EDIC and were all encouraged to achieve strict control of blood glucose. By 5 years of follow-up, the mean HbA_{1c} level of the former intensive-treatment group was not statistically significantly different from the former conventional-treatment group. However, the beneficial effects of tight glycemic control persisted for the former intensive-treatment group. The further progression of DR for the first 4 years of EDIC was 66%–77% less in the former intensive-treatment group than in the former conventional-treatment group. The benefit persisted over 7 years, despite the narrowing of the separation of the mean HbA_{1c} between the 2 treatment groups. It appears to take more time for improvements in glycemic control to negate the effects of previous prolonged hyperglycemia, but once the biologic effects of prolonged improved control are manifest, the benefits are long lasting. Furthermore, the total glycemic exposure of a patient (ie, degree and duration) determines the degree of retinopathy observed at any given time.[18]

Glycemic Control and Eye Disease: Type 2 Diabetes

Evidence regarding the effects of controlling hyperglycemia in patients with type 2 diabetes comes from observational data as well as randomized clinical trials. Definitive results were seen in the United Kingdom Prospective Diabetes Study (UKPDS),[12,13] a randomized controlled clinical trial of blood glucose control in 3,867 patients with newly diagnosed type 2 diabetes. Intensive blood glucose control by either sulfonylureas or insulin decreased the risk for microvascular complications but not the risk for macrovascular disease. There were no adverse effects of the individual drugs on cardiovascular outcomes. In this study, there was a 29% reduction in the need for retinal photocoagulation in the group with intensive glycemic therapy compared with those with conventional treatment (relative risk, 0.71; 95% confidence interval, 0.53–0.96; $p = 0.003$).

The pathogenesis of DR is likely to be similar in types 1 and 2 diabetes. The microvascular complications appear to follow a similar course in the Early Treatment Diabetic Retinopathy Study (ETDRS), in which participants with types 1 and 2 diabetes were enrolled. No differences were seen in the progression of DR by diabetes type.

Blood Pressure Control and Eye Disease

Also in the UKPDS, 1,148 patients with diabetes and hypertension were randomly assigned to antihypertensive treatment.[14] Additional analyses from this nested trial of antihypertensive medications (captopril, an angiotensin-converting enzyme [ACE] inhibitor, or atenolol, a β-blocker) showed that tight blood pressure control achieved a clinically important reduction in the risk for deaths related to diabetes and the progression of DR. There was a 34% reduction in the risk for the progression of retinopathy from the baseline by ≥ 2 steps by a median of 7.5 years ($p = 0.004$) and a 47% reduced risk for decreased vision by 3 lines on the ETDRS chart ($p = 0.004$).[19] There was no difference in the progression of retinopathy or the final visual acuity in those patients treated with an ACE inhibitor compared with those treated with a β-blocker.

Dyslipidemia and Eye Disease

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a population-based study, and the ETDRS found that elevated levels of serum cholesterol were associated with increased severity of retinal hard exudates, which are discrete, irregular yellowish clumps found in the deeper layers of the retina.[15,16] Their presence is often accompanied by macular edema. Independent of the accompanying macular edema, the severity of retinal hard exudates at baseline was associated with decreased visual acuity in the ETDRS. The severity of retinal hard exudates was also a significant risk factor for moderate visual loss (≥15 letter loss) during the course of the study. In addition, the strongest risk factor for the development of subretinal fibrosis, a cause of severe vision loss, in ETDRS patients with diabetic macular edema was the presence of severe hard exudates.[20] Elevated serum triglyceride levels were also associated with a greater risk for developing high-risk proliferative DR in the ETDRS patients.[18] In the Epidemiology of Diabetic Complications Study, elevated triglycerides, as well as elevated low-density lipoprotein (LDL) cholesterol were found to be associated with proliferative DR.[21] In the ETDRS, the results showed an increased risk for the progression of DR in those participants with elevated triglycerides and decreased high-density lipoprotein (HDL) cholesterol.[18] Although these are observational findings, the data are compelling enough to consider lowering triglycerides and/or increasing HDL in patients with DR to reduce the risk for vision loss. In addition to reducing the risk for cardiovascular disease (CVD), reducing the risk for vision loss may be another motivating factor for patients to treat their dyslipidemia.

Summary of the Design of the Action to Control Cardiovascular Risk in Diabetes Trial

The design of the ACCORD trial is described in detail elsewhere in this supplement.[17] In brief, ACCORD is a randomized controlled clinical trial with 3 components, determining the effects of lowering blood glucose, lowering blood pressure, and using fibrates to lower serum triglycerides and increase serum HDL cholesterol levels (on a background of treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors [statins]) on CVD in patients with type 2 diabetes. A total of 10,251 participants were randomly assigned in equal proportions to 2 glycemic management treatment arms. The intensive treatment arm aims to achieve and maintain an HbA_{1c} level <6.0%. The standard treatment arm targets an HbA_{1c} range of 7.0%–7.9%, with an expected median value of approximately 7.5%. Of these participants, 4,733 were simultaneously randomized to 1 of 2 hypertension management protocols. The intensive treatment group targets a systolic blood pressure <120 mm Hg, and the standard treatment group targets a systolic blood pressure <140 mm Hg. In addition, the remaining 5,518 ACCORD participants were randomly assigned in a double-masked fashion to either a placebo or fenofibrate for the reduction of triglyceride levels and increase in HDL cholesterol levels, after LDL cholesterol has been lowered with statin therapy to target levels of ≤2.59 mmol/L (100 mg/dL) in the 2 groups.

The primary end point of the ACCORD trial is the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Microvascular complications are assessed as secondary outcomes of ACCORD. The main microvascular outcome of the ACCORD trial is the primary outcome of the ACCORD Eye Study (ACCORD-EYE). Thus, the ACCORD trial offers the opportunity to answer important questions regarding DR in patients with type 2 diabetes who are at great risk for CVD events over the ensuing 4 years.

Aims of the Action to Control Cardiovascular Risk in Diabetes Eye Study

The primary outcome of ACCORD-EYE is the progression of DR of ≥3 steps on the ETDRS scale or progression to proliferative DR that requires photocoagulation and/or vitrectomy.

The primary questions are as follows:

1. Will targeting HbA_{1c} to <6.0% reduce the development and progression of DR compared with maintaining HbA_{1c} in the range of 7.0%–7.9%, with an expected median of approximately 7.5%?
2. In patients with type 2 diabetes whose LDL cholesterol levels have been reduced appropriately by statin therapy, will the addition of fibrate therapy to reduce triglyceride levels and increase HDL cholesterol levels decrease the development and progression of DR?
3. Will targeting the systolic blood pressure level to <120 mm Hg reduce the development and progression of DR compared with maintaining systolic blood pressure at <140 mm Hg?

Secondary outcomes variables include the following:

1. Change in visual acuity at 4 years compared with baseline:
   a. Moderate vision loss or loss of ≥3 lines on the log minimum angle of resolution visual acuity charts
   b. Legal blindness: 20/160 or worse at 4 years
   c. Severe vision loss: 5/200 at 4 years
2. Rates of cataract extraction
3. Rates of photocoagulation and/or vitrectomy
4. The development or progression of macular edema

Secondary questions for ACCORD-EYE are as follows:

1. Is baseline DR a risk factor for CVD events independent of other cardiovascular risk factors?

2. Will the treatment effects of glycemic, blood pressure, and lipid control on DR parallel the effects on cardiovascular risk?
3. What are the effects of other cardiovascular risk factors, such as smoking and elevated body mass index, on DR?

The 3 subgroup questions for the glycemia intervention are to determine whether the effects of glycemic control on the primary outcome are the same across baseline levels of HbA_{1c}, whether the effects of glycemic control on the primary outcome are independent of effects due to the blood pressure and lipid interventions, and whether the effects of glycemic control on the primary outcome are independent of baseline retinal status.

The 3 subgroup questions for the lipid intervention are to determine whether the benefits of fibrate (in the context of desirable levels of LDL cholesterol and good glycemic control) are (1) equal across levels of LDL cholesterol measured before the initiation of fibrate therapy, (2) equal across HDL cholesterol levels measured before the initiation of fibrate therapy, and (3) equal across triglyceride levels measured before the initiation of fibrate therapy.

The consistency of the effects for the glycemia, lipids, and blood pressure interventions will also be examined in subgroups defined by sex, age, race or ethnicity, and the presence of clinical CVD at baseline (ie, primary and secondary prevention participants), diabetes duration, smoking, body mass index, and the presence or absence of the other interventions.

Action to Control Cardiovascular Risk in Diabetes Eye Study Design

The vanguard phase of ACCORD began in early 2001, the main trial phase began in February 2003, and ACCORD-EYE was officially added in March 2003, with the first participant visit in October 2003. ACCORD recruitment ended in October 2005. Participants who have had proliferative DR treated with laser and or/vitrectomy at baseline are excluded from ACCORD-EYE, while all other ACCORD participants recruited after the initiation of ACCORD-EYE are eligible. The exclusion criteria were assessed by the ACCORD clinics during the baseline histories and on recruitment to ACCORD-EYE. The institutional review boards of all the clinical sites, each clinical center network (CCN), and the Coordinating Center approved the protocol, and all participants signed the informed consent for ACCORD-EYE. A total of 4,036 participants were recruited (ie, agreed to have extensive eye examinations) from 4,716 eligible ACCORD-randomized participants (86%). Of these, complete baseline data were obtained on 3,537 participants (88% of those recruited).

The progression of DR is evaluated in this subset of the ACCORD cohort by 2 standardized eye examinations conducted by an ophthalmologist or optometrist, along with fundus photography of 7 standard stereoscopic fields at baseline and year 4. The eye examination includes visual acuity measurement, examination of the anterior segments, and fundus evaluation after dilation. These data and the 7 stereoscopic fundus photographs are gathered at the Fundus Photograph Reading Center, located at the University of Wisconsin (Madison, WI). The photographs are graded by trained personnel masked to the treatment assignments of the participants. The Fundus Photograph Reading Center has been involved in previous major trials of DR and has been instrumental in developing the measurement of DR by the ETDRS scale, which is now used in a number of clinical trials of DR,[22] including ACCORD-EYE.

Sample-Size Considerations

All 77 clinical centers from all 7 CCNs are encouraged to participate in ACCORD-EYE. In addition, the entire cohort of 10,251 ACCORD participants has visual acuity assessment at baseline, years 2, 4, and 6, and at year 8 or the study closeout visit performed at each clinical center using a standardized protocol of visual acuity assessment with a logarithmic visual acuity chart (the ETDRS chart). Information regarding laser photocoagulation, cataract surgery, and vitrectomy are collected at each annual visit on all ACCORD participants. The information on the visual function and ocular histories collected on the entire ACCORD cohort will also be used to determine the effects of the medical treatments on visual function.

In the ACCORD-EYE protocol, it was established that a target of 4,065 participants would be recruited from the ACCORD randomized participants. With a sample of this size, ACCORD-EYE would have the following:

- 88% power to detect a 15% treatment effect of intensive glycemic control compared with standard glycemic control on the primary outcome of the progression of retinopathy
- 91% power to detect a 20% treatment effect of lipid control through LDL cholesterol lowering and a fibrate compared with lipid control using LDL cholesterol lowering alone on the primary outcome
- 80% power to detect a 20% treatment effect of intensive blood pressure control compared with standard blood pressure control on the primary outcome

At the end of recruitment, 3,537 participants were recruited and completed the baseline eye examination and photographs. Of these 3,537, 1,947 were in the lipid trial and 1,590 were in the blood pressure trial. This 13% shortfall in sample size (from the original target of 4,065 participants) still provides 84% power for the glycemia eye question, 85% for the lipid question, and 77% power for the blood pressure question.

The population event rate was based on the WESDR, which

showed a 38.4% 4-year rate of the progression of retinopathy in type 2 diabetes. We assumed that this is the incidence rate in participants who receive the less intensive glycemic control and either the less intensive blood pressure control or the statin-only lipid control. The UKPDS found a relative risk of 0.83 for 6-year incidence of DR for newly diagnosed patients with type 2 diabetes with intensive glycemic control compared with conventional therapy, on the basis of progression rates of 23.0% for the intensive group and 27.8% for the conventional group. This corresponds to a 4-year relative risk of 0.819. Our assumption of a 15% treatment effect for glycemia is close to this and is conservative. There may be insufficient power for our secondary questions and end points, but we will examine the data for trends.

Statistical Methods

For the primary questions listed previously, separate models will be used to test the primary comparison associated with each intervention. The main comparisons of the intervention groups with respect to the development and progression of DR over the 4 years between eye examinations will be based on logistic regression incorporating adjustment for important design factors, with primary analysis focusing on the effects of glycemic control, lipid treatment, and blood pressure control. As a supplementary analysis, we will use a Cox proportional-hazards survival model to account for the likely slight variability in follow-up times using the same models described as for logistic regression. Although a patient scale will be used to take into account data from both eyes, other models using generalized estimating equations that use the data on both eyes will also be used as supplementary analyses.

The glycemia hypothesis will be tested in all randomized participants who participate in the DR portion of the trial. The model to be fit will contain separate indicator variables that identify participants (1) in the blood pressure trial, (2) in the blood pressure trial and randomized to the intensive blood pressure intervention, (3) in the lipid trial, (4) in the lipid trial and randomized to fibrate plus active drug, and (5) randomized to intensive glycemic control. In addition to these variables, indicator variables will be included that identify (6) secondary prevention participants and (7) CCNs. Our reasoning for including term 6 is that secondary prevention participants should have higher event rates than primary prevention participants. Likewise, term 7 will be included because CCNs contain very different types of participants, who may have different event rates. For example, US Department of Veterans Affairs (VA) clinics will consist primarily of men. The main comparison in this model will be based on the χ^2 statistic from a likelihood ratio test obtained from logistic regression models with or without term 5. The lipid hypothesis will be tested in all randomized ACCORD-EYE participants who participate in the lipid arm of the trial. The model to be fit will contain terms 4, 5, 6 and 7. This hypothesis will be tested using a likelihood ratio test for models with or without term 4. The blood pressure hypothesis will be tested in all randomized ACCORD-EYE participants who participate in the blood pressure arm of the trial. The model to be fit will contain terms 2, 5, 6, and 7. This hypothesis will be tested using a likelihood ratio test for models with or without term 2.

Estimates of DR incidence will be obtained for the intervention and control groups for each main comparison, and confidence intervals for these rates will be calculated. An unadjusted analysis will also be performed, and we will make comparisons among the 8 cells of the double 2×2 factorial design. It is recognized that there will be participants who are examined at baseline who will be lost to follow-up or will die before their follow-up examinations are conducted. To examine the effect of these missing data on our analysis, we will look for systematic differences between participants who were and were not seen at follow-up. This comparison of those who do and do not return for their follow-up eye examinations will focus on baseline characteristics but may also include follow-up data from other scheduled ACCORD visits as appropriate. In secondary analyses, we will also attempt to model the impact of the missing data.

Conclusion

DR is an important microvascular abnormality of diabetes and is also one of the leading causes of blindness in the United States.[23] Future projections suggest that DR will increase markedly with increased longevity and increase in diabetes.[23] ACCORD-EYE provides a unique opportunity to evaluate the effects of the combination of 3 medical risk factors on the progression of DR. This is the first time that the effects of the treatment of dyslipidemia on DR will be assessed with a controlled clinical trial, lowering triglycerides and increasing HDL cholesterol while maintaining LDL cholesterol at optimal levels.

There were challenges in launching a substudy after recruitment for the main trial had started. At the rapid rate at which the enrollment into the main study was occurring, it was difficult to achieve the target enrollment of 4,065 participants. The certification of the nearly 70 fundus photographers in an efficient manner was another hurdle. Because the changes in grading of the fundus photographs over the follow-up period are the primary outcome, it was imperative to have a standardized protocol with excellent technique from the study photographers. ACCORD-EYE met most of these goals, with 87% of the target population enrolled.

As baseline eye examinations were completed, clinical reports of the association of diabetic macular edema with the treatment of an oral hypoglycemic agent, rosiglitazone, emerged.[24–26] It became apparent that the ACCORD-EYE data would be the study to most likely reveal interesting and clinically meaningful data on this association. Cross-sectional and prospective evaluations will be valuable in this assessment.

In summary, ACCORD-EYE will determine the rates of progression of retinopathy in high-risk patients with type 2

diabetes and will assess the effects of the intensive control of glycemia and blood pressure and the comprehensive management of dyslipidemia on the progression of DR. It will also provide opportunities to address other important questions regarding DR and associated factors in this important study of type 2 diabetes.

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