

## ARIC MANUSCRIPT PROPOSAL #705

PC Received: 01/06/00

Status: Approved

Priority: 1

SC Reviewed: \_\_\_\_\_

Status: Approved

Priority: 1

**1a. Full Title:** Atherosclerosis and diabetic retinopathy. The Atherosclerosis Risk in Communities Study

**1b. Title (26 char):** Atherosclerosis/diabetic retinopathy

### **2. Writing Group**

(Lead person listed first) Klein R, Moss SE, Sharrett R, Wong T, Brancati F, Couper D.

Electronic mail address of lead author: kleinr@epi.opth.wisc.edu

### **3. Timeline:**

Analyses will include data from all participants with diabetes evaluated in the study for both generalized narrowing of retinal arterioles using the image processor protocol and other signs of retinal vascular disease using the light box protocol. The analysis plan will include initial analyses of data in February 2000 through June 2000 and writing of manuscript between July 2000 and December 2000.

### **4. Rationale:**

Diabetic retinopathy is an important cause of loss of vision in the United States. While the natural history of this complication has been well described its pathogenesis is less certain. Recent data from epidemiologic studies and clinical trials have shown that hyperglycemia is associated with an increased risk of the incidence and progression of diabetic retinopathy in persons with diabetes. As a result of these findings, guidelines were developed that recommended that good glycemic control (glycosylated hemoglobin A<sub>1c</sub> of <8.0%) be maintained to minimize microvascular complications. However, despite intensive insulin treatment and good glycemic control in Type 1 patients in the Diabetes Control and Complications Trial (DCCT), diabetic retinopathy progressed in about 14% over a 9-year period. In persons with Type 2 diabetes, despite good glycemic control (HbA<sub>1c</sub> of <7.0%, retinopathy progressed in 31% over a ten-year period.

For this reason it has important to identify other modifiable risk factors that might contribute to the pathogenesis of diabetic retinopathy. Two such factors, hypertension and dyslipidemia independent of glycemia, have been shown to be associated with an increased risk of developing retinopathy in some studies. In a randomized controlled clinical trial in persons with Type 2 diabetes, the United Kingdom Diabetes Prospective Study (UKPDS), control of

hypertension, independent of glycemia, was shown to significantly reduce the progression of diabetic retinopathy and visual loss.

It is not known whether persons with signs of subclinical (internal and common carotid intima-medial wall thickening and plaque) and clinical atherosclerotic vascular disease (coronary heart disease and stroke) have a higher frequency of retinopathy compared to those without these signs. Furthermore, it is not known whether diabetic persons with hypertension and signs of retinal arteriolar disease (e.g., focal and generalized narrowing and arterio-venous nicking) have a higher frequency of retinopathy compared to diabetic hypertensive persons without these signs.

Inflammation and endothelial dysfunction have been hypothesized in the pathogenesis of atherosclerotic vascular disease in persons with impaired glucose tolerance and type 2 diabetes. In the ARIC cohort, these factors were found to be associated with retinal arterio-venous nicking, independent of hypertension. There are no population-based data regarding the association of presence of signs of systemic inflammatory processes or of endothelial dysfunction and retinopathy in people with type 2 diabetes, independent of hypertension.

## 5. **Main Hypotheses:**

- (1) After controlling for the duration of diabetes, hyperglycemia, dyslipidemia and hypertension are associated with the presence and severity of diabetic retinopathy;
- (2) After controlling for hyperglycemia and duration of diabetes and other factors associated with retinopathy, diabetic persons with hypertension and generalized and focal arteriolar narrowing and A/V nicking are more likely to have signs of retinopathy present compared to diabetic persons with hypertension present without these microvascular signs;
- (3) After controlling for hyperglycemia, duration of diabetes, and hypertension (if associated with retinopathy), diabetic persons with signs of subclinical and clinical carotid atherosclerotic vascular disease are more likely to have signs of retinopathy present compared to diabetic persons without atherosclerotic vascular disease present;
- (4) After controlling for hyperglycemia, duration of diabetes and other factors associated with retinopathy, diabetic persons with inflammatory factor levels (e.g., white blood count, platelets, fibrinogen, albumin (lower levels), and smoking) will be associated with retinopathy; and
- (5) After controlling for hyperglycemia, duration of diabetes and other factors associated with diabetic retinopathy, levels of indicators of endothelial dysfunction (elevated vWF and Factor VIII levels) will be associated with retinopathy.

## 6. **Data (variables, time frame, source, inclusions, exclusions):**

Light box variables: focal narrowing on disc, focal narrowing of arterioles, sheathing of arterioles, A/V crossing changes, generalized narrowing, number of microaneurysms, number of retinal hemorrhages, type of retinal hemorrhage, hemorrhage/microaneurysms, hard exudate,

soft exudate, IRMA, venous beading, macular edema, papillary swelling, proliferative diabetic retinopathy, diabetic retinal severity level. Image processor variables: CRAE, branch CRAE, CRVE, CRAE/CRVE, branch CRAE/CRVE, number of arterioles, number of venules, trunk/branch ratio. Nonocular variables: age, sex, race, diabetes status, age at diagnosis of diabetes, duration of diabetes (age at Visit 3 examination- age at diagnosis), fasting blood sugar (at all visits); glycosylated hemoglobin (collected on the a subsample);

For all the following would like values from all visits when available; when not please specify): blood pressure, hypertension status (controlled/uncontrolled), hypertension medications, EKG information of LVH, body weight, BMI, smoking status and cigarette pack-years smoked , past and current alcohol consumption usual ethanol intake, serum lipids(total cholesterol, LDL, HDL, total triglycerides, Lp(a), Apo A1 and B), carotid intimal medial wall thickness and plaque, ankle/arm blood pressure index, serum albumin, microalbuminuria, white blood cell and platelet count, hematocrit, von Willebrand antigen, Factor VIII, family history of cardiovascular disease/coronary heart disease, prevalent coronary heart disease (history, ECG, myocardial infarction history), stroke, and popliteal IMT and plaque.