

ARIC Manuscript Proposal # 964

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Status: A

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SC Reviewed: 10/08/03

Status: A

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1.a. Full Title: Diabetes, Retinopathy and Risk Of Ischemic Stroke

b. Abbreviated Title (Length 26 characters): Diabetes, Retinopathy and Stroke

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

The intent of this analysis is to investigate the prospective association of the diabetic retinopathy and risk of incident ischemic stroke. Initial analyses and writing will take place between December 2003 and March 2004, final analysis between March 2004 and June 2004, and final writing and manuscript submission between July 2004 and October 2004.

4. Rationale:

The incidence of stroke, particularly ischemic stroke, is increased two to three fold in persons with diabetes.¹⁻⁴ Improved prevention of stroke in persons with diabetes requires a greater understanding of its pathogenic mechanisms and identification of new risk factors.⁵ Hypertension, the presence of coronary heart disease and peripheral vascular disease have all been identified as risk factors for stroke in these persons.⁶⁻¹⁰ Autopsy studies have further indicated that diabetic strokes are the result of occlusion of small deep penetrating arteries in the brain (cerebral microvascular disease).¹¹⁻¹³ In contrast, the contribution of carotid artery disease (macrovascular disease) to the pathogenesis and risk of stroke in diabetic persons appears to be less important.⁶⁻⁸

Diabetic retinopathy, a common microvascular complication in people, has long been hypothesized to predict stroke. However, although there have been several studies that have linked diabetic retinopathy with increased all-cause and cardiovascular mortality,¹⁴⁻¹⁶ there have been relatively few studies that have directly examined whether retinopathy predicts incident stroke or stroke-specific mortality.^{17,18} In a retrospective case-control study (56 cases and 56 age and sex matched controls), persons with diabetes who had an ischemic stroke were more likely to have retinopathy (odds ratio 4.0, 95% confidence interval, 1.0 to 14.5), after adjustment for blood pressure, smoking, random glucose and use of insulin.¹⁷ However, this study was limited by a small sample size and the use of medical records to define the presence of retinopathy.

Two large prospective studies have shown inconsistent results. In the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), the presence of proliferative retinopathy, as quantified from retinal photographs, was associated incident stroke, with an age-adjusted relative risk of 2.9 (95% confidence interval, 1.2-6.8) in older-onset diabetic persons taking insulin, and a relative risk of 6.0 (95% CI, 1.1-32.6) for persons not taking insulin.¹⁹ Proliferative retinopathy was also associated with increased stroke mortality (relative risk 1.9, 95% confidence interval, 1.0-3.4), after controlling for age, sex, duration of diabetes, glycosylated hemoglobin levels, and other factors.²⁰ However, the WESDR found no association between mild and moderate levels of non-proliferative retinopathy with either stroke or stroke mortality. The United Kingdom Prospective Diabetes Study (UKPDS) identified several risk factors for stroke developing over an 8-year period in more than 3,000 Type II diabetics, but retinopathy, as graded from retinal photographs, was not a significant risk factor for stroke.²¹

In the ARIC study, our previous cross-sectional analysis showed that level of diabetic retinopathy was not associated with prevalent stroke, after controlling for age, duration of diabetes, glucose and other risk factors in multivariable models.²² However, in the general ARIC population, we found an association between retinopathy (defined as microaneurysms, retinal hemorrhages, soft exudates and other lesions) and the 3-year incidence of stroke (relative risk of 2.6, 95% CI, 1.6, 4.2), controlling for the effects of blood pressure, cigarette smoking and other stroke risk factors.²³

The purpose of our current study is to examine prospectively the relationship of diabetes, retinopathy and the 6-year incidence of ischemic stroke in the ARIC cohort. We will examine the association of diabetic retinopathy and risk of stroke in people with diabetes, controlling for known stroke risk factors (e.g., blood pressure, carotid artery disease) and factors related to diabetes severity (e.g., duration of diabetes, fasting glucose). We will also examine whether the presence of retinal microvascular disease increases the risk of ischemic stroke associated with diabetes status. Results of the study will shed further insights into the contribution of microvascular disease to risk of ischemic stroke in people with diabetes, a key hypothesis of diabetic strokes.

Preliminary analysis

There are approximately 60 incident ischemic strokes among diabetics (from Visit 3 to Dec 2000). It is anticipated that there will be additional incident cases when analysis commences

		No at risk	No (%) incident ischemic stroke (up to Dec 2000)	P-value
No diabetes	No retinopathy	8458	110 (1.3)	<0.001
	Retinopathy	426	15 (3.5)	
Diabetes	No retinopathy	1133	33 (2.9)	<0.001
	Retinopathy	293	27 (9.2)	

5. Main Hypothesis/Study Questions:

- (1) Hypothesis 1: In persons with diabetes, the presence and level of retinopathy (mild, moderate, severe) is associated with a higher incidence of ischemic stroke, independent of age, gender, race, blood pressure, carotid artery disease, fasting glucose, duration of diabetes, and other risk factors. This analysis will be confined to people with diabetes in the ARIC study (n=1,400)
- (2) Hypothesis 2: In the general population, the presence of retinal microvascular disease (retinopathy, and retinal arteriolar disease) increases the risk of ischemic stroke

associated with diabetes status, independent of other stroke risk factors (i.e. interaction between diabetes and retinal microvascular disease on risk of stroke). This analysis will be examine participants in the entire ARIC study (n=10,000)

6. Data (variables, time window, source, inclusions/exclusions):

- (1) Diabetic retinopathy variables. Diabetic retinopathy presence and severity score. Macular edema and hard exudates.
- (2) Retinal arteriolar variables. Focal retinal microvascular changes (arteriovenous nicking, focal arteriolar narrowing, retinal hemorrhage, type of hemorrhage, microaneurysms and soft exudates). Generalized arteriolar narrowing (retinal arteriole-to-venule ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent).
- (3) Incident ischemic stroke and follow-up time
- (4) Covariates: age, sex, race, center, diabetes, hypertension, systolic and diastolic blood pressure, fasting glucose, fasting insulin, lipids, hemostatic and inflammatory markers (von Willebrand factor, factor VIIIc, fibrinogen, WBC), cigarette smoking, alcohol consumption, body mass index
- (5) Exclusion criteria: From participants at ARIC visit 3 (n=12,887), exclude persons whose race is not black/white, with ungradeable retinal photographs or missing retinal variables at visit 3 and prevalent stroke up to visit 3.

7.a. Will the data be used for non-CVD analysis in this manuscript? ☐ Yes ☒ No

b. If Yes, is the author aware that the file ICTDER01 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ☐ Yes ☐ No
(This file ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ☐ Yes ☒ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☐ Yes ☐ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://bios.unc.edu/units/csc/ARIC/stdy/studymem.html>
☒ Yes ☐ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

1. Klein R, Sharrett AR, Klein BE, Moss SE, Folsom AR, Wong TY, Brancati FL, Hubbard LD, Couper D; ARIC Group. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes : the atherosclerosis risk in communities study. Ophthalmology. 2002 ;109:1225-34.

2. Wong TY, Klein R, Couper DJ, Cooper LS, Shahar E, Hubbard LD, Wofford MR, Sharrett AR. Retinal microvascular abnormalities and incident clinical strokes. The Atherosclerosis Risk in the Communities Study. *Lancet* 2001; 358: 1134-40

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16. Klein R, Moss SE, Klein BEK, DeMets DL. Relation of ocular and systemic factors to survival in diabetes. *Arch Intern Med*. 1989;149:266-272.
17. Pettiti DB, Bhatt H. Retinopathy as a risk factor for nonembolic stroke in diabetic subjects. *Stroke*. 1995;26:593-6.
18. Iino K, Yoshinari M, Kaku K, et al. Prospective study of asymmetric retinopathy as a predictor of brain infarction in diabetes mellitus. *Diabetes Care*. 1993;16:1405-6.
19. Klein R, Klein BE, Moss SE. Epidemiology of proliferative diabetic retinopathy. *Diabetes Care*. 1992;15:1875-91.
20. Klein R, Klein BE, Moss SE, Cruickshanks KJ. Association of ocular disease and mortality in a diabetic population. *Arch Ophthalmol*. 1999;117:1487-95.
21. Davis TM, Millns H, Stratton IM, Holman RR, Turner RC. Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 29. *Arch Intern Med* 1999;159:1097-103
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23. Wong TY, Klein R, Couper DJ, et al Retinal microvascular abnormalities and incident clinical strokes. The Atherosclerosis Risk in the Communities Study. *Lancet* 2001; 358: 1134-40.