ARIC Manuscript Proposal # 1067

PC Reviewed: _03/11/05	**Status: __A__**	**Priority: __2__**
SC Reviewed: _03/14/05__	**Status: __A__**	**Priority: __2__**

1.a. Full Title: Glycemic Control and Risk of Ischemic Stroke: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Glycemic Control and Stroke

2. Writing Group:

Writing group members: Elizabeth Selvin, PhD, MPH; Josef Coresh, MD, PhD; Eyal Shahar, MD, MPH; Lin Zhang, MD, PhD; Michael Steffes, MD, PhD; Richey Sharrett, MD, DrPH; others welcome.

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Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Same as lead author.

3. Timeline: Data have already been collected; we expect to complete the manuscript by July 2005.

4. Rationale:

Chronic hyperglycemia, most accurately measured with hemoglobin A_{1c} (HbA_{1c}), has been hypothesized to contribute to cardiovascular disease in persons with (1;2) and without diabetes (3-5), although this relationship remains controversial. Persons with diabetes have an elevated risk of stroke (6;7), but it is unclear whether chronic hyperglycemia contributes to the development of cerebrovascular disease.

While the United Kingdom Prospective Diabetes Study (UKPDS) reported the effect of intensive versus conventional glucose control on different cardiovascular disease outcomes (8), no clinical trials have specifically addressed whether tight glucose control

reduces the risk of stroke. The UKPDS showed a significant reduction in microvascular disease (RR 0.75, 95% CI 0.60 to 0.93) and a borderline significant reduction in myocardial infarction (RR 0.84, 95% CI 0.71 to 1.00). However, there was no significant difference in risk of stroke comparing the intensive versus conventional treatment arms (RR 1.11, 95% CI 0.81 to 1.51). The UKPDS was not designed specifically to assess the relation between glycemic control and macrovascular disease and may have had insufficient power to detect moderate risk differences within cardiovascular disease sub-groups (e.g., stroke). Although epidemiologic re-analyses of UKPDS data suggest that intensive glycemic control reduces stroke incidence (2), there have been few epidemiologic studies which have investigated this hypothesis (9;10). Importantly, these prior studies did not comprehensively adjust for known cardiovascular risk factors. We have previously shown that HbA_{1c} predicts incident coronary heart disease [MS #1024] and is cross-sectionally related to atherosclerosis [MS #1025]. Nonetheless, previous studies have shown that risk factors for stroke may differ from those for coronary disease, with, for example, a greater contribution from hypertension and little or no contribution from elevated cholesterol levels.

The present study proposes to test the hypothesis that glycemic control, as measured by HbA_{1c}, is related to incident ischemic stroke in persons with and without diabetes after adjustment for known cardiovascular risk factors. To test this hypothesis, we will conduct a case-cohort study in persons without diabetes and a cohort study in persons with diabetes.

5. Main Hypothesis/Study Questions:

Is hemoglobin A_{1c} (HbA_{1c}) associated with incident ischemic stroke in persons with and without diabetes independently of other known cardiovascular disease risk factors?

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

Data Source and Study population

This manuscript will be based on an analysis of data from ARIC Ancillary Study # 2003.5, "Glycemic Control (HbA_{1c}) as Visit 2 as a Predictor of Coronary Heart Disease, Kidney Disease, and Incident Diabetes." Baseline for this study will be the second ARIC visit (the only visit for which HbA_{1c} data are available). The study population will consist of all incident ischemic stroke cases with follow-up through the year 2000 and the ARIC visit 2 cohort random sample ("Table 4"). Analyses will be conducted separately in populations of persons with diabetes (cohort analysis of *all* persons with diabetes by Visit 2) and without diabetes (Visit 2 case-cohort analysis).

Case-cohort Exclusions (analysis in non-diabetic population):

- Prevalent or missing CHD history at Visit 1
- TIA/stroke history at Visit 1
- Race not African American or White
- African American at Minnesota and Washington Co. field centers
- Subject not seen at Visit 2
- Self-reported stroke/TIA history at Visit 2
- Incident CHD between Visit 1 and Visit 2

- Incident stroke between Visit 1 and Visit 2
- Diabetes by Visit 2
- Missing covariates of interest

Cohort Exclusions (analysis in diabetic population, full visit 2 cohort of diabetics):
- Prevalent or missing CHD history at Visit 1
- TIA/stroke history at Visit 1
- Race not African American or White
- African American at Minnesota and Washington Co. field centers
- Subject not seen at Visit 2
- Self-reported stroke/TIA history at Visit 2
- Incident CHD between Visit 1 and Visit 2
- Incident stroke between Visit 1 and Visit 2
- African American at Minnesota and Washington Co. field centers
- Subject not seen at Visit 2
- No diabetes by Visit 2
- Missing covariates of interest

Exposure: Hemoglobin A_{1c}

We measured hemoglobin A_{1c} (HbA_{1c}) from ARIC visit 2 stored whole blood samples as part of ARIC Ancillary Study # 2003.5, "Glycemic Control (HbA_{1c}) at Visit 2 as a Predictor of Coronary Heart Disease, Kidney Disease, and Incident Diabetes." HbA_{1c} data are available for over 5,400 ARIC participants, including all post-Visit 2 incident stroke cases through 2000 and the visit 2 cohort random sample.

Outcome: Incident ischemic stroke

This manuscript will summarize the relationship between HbA_{1c} and incident ischemic stroke through the year 2000 (IN01ISC).

Other variables of interest

Covariates will include sociodemographic characteristics (age, sex, race, education), behavioral characteristics (smoking, physical activity, alcohol consumption), anthropometry (body mass index, waist-hip ratio), blood pressure (including blood pressure-lowering medications), and lipid parameters (HDL cholesterol, LDL cholesterol, triglycerides).

Data Analysis

For the case-cohort analysis (non-diabetics), weighted crude and adjusted means and proportions of variables of interest by stroke status will be calculated using the WADJPROP and WADJMEANS SAS macros (modified for use with SAS 9.1). Adjusted hazard ratios for HbA_{1c} and stroke risk and their 95% confidence intervals will be computed using a weighted Cox proportional hazards model, accounting for the ARIC visit 2 weighted case-cohort sampling design using the Barlow SAS V8 macro (BARLOWV8).

For the cohort analysis (diabetics), we will calculate crude and adjusted means and proportions of variables of interest by stroke status. We will use a Cox proportional hazards model to generate hazard ratios and their 95% confidence intervals adjusting for covariates of interest.

In multivariable models, we will examine the nature of the relationship between HbA_{1c} and risk of stroke using different assumptions for the exposure, including categorization (e.g., tertiles, or clinically relevant cut-points such as HbA_{1c} <7, 7-9, >9%), linear models, and spline models (to explore evidence of non-linearity, e.g. recursive cubic spline).

Defining Diabetes

Persons will be classified as diabetic on the basis of a fasting glucose greater than or equal to 126 mg/dL, a non-fasting glucose greater than or equal to 200 mg/dL, a self-reported physician diagnosis, or treatment for diabetes at either the first or second ARIC examination. Reliance on this sensitive definition of diabetes is important to exclude the possibility that any observed association in the non-diabetic group is being driven by persons with undiagnosed diabetes. In persons with diabetes, the rationale for using a definition of disease with inherently low specificity is that it will result in a more conservative estimate of the true effect of HbA_{1c} on stroke, if any, in persons with diabetes.

Other Factors Influencing Glycemic Control: Insulin, Diabetes Medication Use, Diabetes Duration, and Fasting Glucose Level

The relationships between HbA_{1c} and fasting insulin (available from Visit 1 only), fasting glucose, glucose-lowering drugs (in diabetics), and diabetes duration (available from Visit 3 only) will be explored. We will also assess whether controlling for diabetes as a time-dependent variable in the population of non-diabetics attenuates any observed association (i.e., does development of diabetes explain any observed association between HbA_{1c} and incident stroke in persons without diabetes?).

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

b. If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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 __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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://www.cscc.unc.edu/ARIC/search.php

____X__ 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)?

Selvin E, et al. Long-term stability of hemoglobin A_{1c} (HbA_{1c}) measurements from frozen whole blood samples stored over a decade, in press, *Diabetic Medicine*. [MS #1011]

Selvin E, et al. Glycemic control (HbA_{1c}) and coronary heart disease risk in persons with and without diabetes: The Atherosclerosis Risk in Communities Study, under review. [MS #1024]

Vitelli LL, Shahar E, Heiss G, McGovern PG, Brancati FL, Eckfeldt JH, Folsom AR. Glycosylated hemoglobin level and carotid intimal-medial thickening in nondiabetic individuals. The Atherosclerosis Risk in Communities Study. Diabetes Care 1997;20:1454-8.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* _#2003.5__)

___ B. primiarly based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

Reference List

(1) Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; 141(6):421-431.

(2) Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; 321(7258):405-412.

(3) Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC-Norfolk). *BMJ* 2001; 322(7277):15-18.

(4) Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med* 2004; 141(6):413-420.

(5) Levitan EB, Song Y, Ford ES, Liu S. Is Nondiabetic Hyperglycemia a Risk Factor for Cardiovascular Disease?: A Meta-analysis of Prospective Studies. *Archives of Internal Medicine* 2004; 164(19):2147-2155.

(6) Almdal T, Scharling H, Jensen JS, Vestergaard H. The Independent Effect of Type 2 Diabetes Mellitus on Ischemic Heart Disease, Stroke, and Death: A Population-Based Study of 13 000 Men and Women With 20 Years of Follow-up. *Archives of Internal Medicine* 2004; 164(13):1422-1426.

(7) Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Archives of Internal Medicine* 1991; 151(6):1141-1147.

(8) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352(9131):837-853.

(9) Lehto S, Ronnemaa T, Pyorala K, Laakso M. Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes. *Stroke* 1996; 27(1):63-68.

(10) Moss SE, Klein R, Klein BE, Meuer SM. The association of glycemia and cause-specific mortality in a diabetic population. *Arch Intern Med* 1994; 154(21):2473-2479.