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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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 A1c (HbA1c), 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 subgroups (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 HbA1c 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 HbA1c, 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 A1c (HbA1c) 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 (HbA1c) 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 HbA1c 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\textsubscript{1c}
We measured hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) from ARIC visit 2 stored whole blood samples as part of ARIC Ancillary Study # 2003.5, “Glycemic Control (HbA\textsubscript{1c}) at Visit 2 as a Predictor of Coronary Heart Disease, Kidney Disease, and Incident Diabetes.” HbA\textsubscript{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\textsubscript{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\textsubscript{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 HbA1c and risk of stroke using different assumptions for the exposure, including categorization (e.g., tertiles, or clinically relevant cut-points such as HbA1c <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 HbA1c 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 HbA1c 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 HbA1c and incident stroke in persons without diabetes?).

**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 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
- 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]


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. primarily 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


(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.


