1.a. Full Title: Non-Diabetic Glycemia (HbA1c) and Incident Chronic Kidney Disease: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Glycemic control and CKD

2. Writing Group:
   Writing group members: Brad Astor, Lori Bash, Elizabeth Selvin, Michael W. Steffes, Josef Coresh, others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **BA** [please confirm with your initials electronically or in writing]

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3. Timeline: a draft of the manuscript is expected to be available July 2007

4. Rationale: The purpose of this study is to investigate the relationship between glycemic control and incident chronic kidney disease (CKD) in persons without diabetes. More than 19 million US adults, about 11% of the adult population, have chronic kidney disease (CKD), according to estimates from NHANES 1999-2000. Subjects who develop even modest degrees of kidney dysfunction are at increased risk of coronary artery disease (CAD) and cardiovascular mortality. As a major risk factor for CVD, individuals with CKD have been placed in the highest risk group in CVD treatment guidelines.

   Diabetes and hypertension are the leading causes of kidney failure in the US. Among individuals with diabetes, strict glycemic control, as measured by hemoglobin A1c (HbA1c), can reduce the progression of kidney disease. HbA1c reflects long-term glycemic control, is more stable than fasting glucose levels and is often used in managing the care of diabetic individuals. The role of HbA1c level within the normal range as a
predictor of development of chronic kidney disease, however, has not been explored among non-diabetic individuals in the general population.

5. Main Hypothesis/Study Questions:
We hypothesize that HbA1c is independently associated with incident CKD, even within the normal glycemic range, in individuals without diabetes.

6. Data (variables, time window, source, inclusions/exclusions):
Data Source and Study population
This manuscript will be based on data from ARIC Ancillary Study # 2003.5, “Glycemic Control (HbA1c) at Visit 2 as a Predictor of Coronary Heart Disease, Kidney Disease, and Incident Diabetes.” The study population will consist of all incident CKD cases, free of diabetes at Visits 1 and 2 with follow-up through the year 2000, and those free of diabetes at Visits 1 and 2 among the ARIC Visit 2 cohort random sample. Exclusion criteria for the ancillary study will necessarily apply to this analysis. Exclusions include:
- Diabetes at Visit 1 or 2
- Prevalent or missing CHD history at Visit 1 or 2
- TIA/stroke history at Visit 1 or 2
- Prevalent CKD: estimated glomerular filtration rate (GFR) <60 ml/min/1.73m² at Visit 1 or 2

Exposure: Hemoglobin A1c
Hemoglobin A1c (HbA1c) was measured from ARIC Visit 2 stored whole blood samples as part of ARIC Ancillary Study # 2003.5, “Glycemic Control (HbA1c) at Visit 2 as a Predictor of Coronary Heart Disease, Kidney Disease, and Incident Diabetes.” HbA1c data are available for over 5,400 ARIC participants, including all post-Visit 2 incident CKD cases through 2000 and the Visit 2 cohort random sample (a total of 1,013 participants without diabetes at Visit 2).

Defining Diabetes
Persons will be classified as diabetic on the basis of a fasting glucose ≥126 mg/dL, a non-fasting glucose ≥200 mg/dL, a self-reported physician diagnosis, or treatment (hypoglycemic medication or insulin) for diabetes at Visit 1 or 2. Only participants free of diabetes at both Visits 1 and 2 will be included.

Outcome: Incident CKD
We will perform a case-cohort analysis using the Visit 2 cohort random sample and all eligible incident CKD cases through 2000. Incident CKD is defined as an estimated GFR <60 ml/min/1.73m² at Visit 4, a kidney disease-related hospitalization, diagnosis or treatment for end-stage renal disease, or kidney disease-related death. GFR will be estimated from calibrated serum creatinine using the simplified Modification of Diet in Renal Disease.7

Other variables of interest
Covariates will include sociodemographic characteristics (age, race, gender), smoking status, body mass index, blood pressure (including blood pressure-lowering medications) and lipid parameters (HDL cholesterol, LDL cholesterol, triglycerides) at Visit 2.
Data Analysis

Adjusted hazard ratios and their 95% confidence intervals for the time to development of CKD will be computed by category of HbA1c at Visit 2. Weighted Cox proportional hazards models, using the Barlow SAS V8 macro (BARLOWV8), will be used to account for the weighted case-cohort sampling design. We will repeat the analyses to assess risk using a continuous measure of HbA1c and use HbA1c categories to evaluate nonlinear associations. Participant follow-up time will be censored at the time of death due to other causes. Additional models will censor follow-up at Visit 3 or 4 if the participant is classified as diabetic at these visits.

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)?
MS# 1024:
MS# 1245:
   Glycemic Control (HbA1c) and Incident Chronic Kidney Disease in Diabetes: The Atherosclerosis Risk in Communities Study, Lead: Lori Bash

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. Agreed
Reference List


