ARIC Manuscript Proposal #1245

PC Reviewed: 4/10/07 Status: _A___ Priority: __2__
SC Reviewed: ____ Status: ____ Priority: ____

1.
a. Full Title: Glycemic Control (HbA1c) and Incident Chronic Kidney Disease in Diabetes: The Atherosclerosis Risk in Communities Study

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

2. Writing Group:
Writing group members: Elizabeth Selvin PhD, MPH; Michael W. Steffes MD, PhD; Josef Coresh MD, PhD; Brad Astor PhD, MPH.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _LB_ **[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 June 2007

4. Rationale:
The purpose of this study is to investigate the relationship between glycemic control and incident chronic kidney disease (CKD) in persons with diabetes. Hemoglobin A1c (HbA1c) reflects long-term glycemic control, is more stable compared to fasting glucose levels and is often used in managing the care of diabetic individuals. We seek to examine the independent association between HbA1c and CKD among individuals and evaluate the consistency of this association among those with and without albuminuria and/or retinopathy.

More than 19 million US adults, about 11% of the adult population, have chronic kidney disease (CKD), defined by decreased kidney function (glomerular filtration rate (GRF)) or urinary albumin excretion.[1] CKD is associated with an increased risk of cardiovascular disease (CVD) mortality and morbidity [2-6], coronary artery disease (CAD) [7], all-cause mortality and adverse cardiovascular events in high risk populations, and with CVD death and incident MI in the general population.[8]

Individuals with CKD, compared to healthy controls, have impaired vascular function, greater arterial stiffness and endothelial dysfunction,[2] and are predisposed to atherosclerosis, arteriosclerosis, cardiomyopathy, and remodeling of the large arteries.[6]

As a major risk factor for CVD, [5, 6, 9] the National Kidney Foundation, and the American Heart Association placed individuals with CKD in the highest risk group for intervention. [4]

Diabetes is a leading cause of kidney failure in the U.S., accounting for more than 40% of all incident ESRD cases. [10] Albuminuria and retinopathy are two hallmarks of diabetic nephropathy, and are thought to indicate microvascular disease.

Albuminuria is a strong risk factor for kidney disease progression in both diabetic and non-diabetic individuals.[11, 12, 12] Both albuminuria and estimated GFR have been shown to be independent risk factors for cardiovascular events even after stratifying by albuminuric status.[13]

In persons with diabetes, HbA1c is related to the development of microvascular disease and is at the center of the clinical management of hyperglycemia. Previous studies in ARIC have found HbA1c levels to be associated with increased risk of incident ischemic stroke[14] and coronary heart disease in both diabetic and non-diabetic participants.[15]

While randomized studies have shown that poor glycemic control increases the incidence of kidney failure among diabetics, the continuous relationship between HbA1c levels and incidence of milder CKD among diabetics has not been well studied. It is unknown, for example, whether moderately elevated HbA1c levels predict a decline in kidney function in the absence of detectable microvascular disease, as evidenced by albuminuria and/or retinopathy.

5. Main Hypothesis/Study Questions:

We hypothesize that HbA1c is independently and positively associated with incident CKD in individuals with diabetes, even within the currently recommended general levels of glycemic control and even among those without albuminuria or retinopathy.

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

<u>Data Source and Study population</u>

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 participants with prevalent diabetes as of Visit 2 (with follow-up through the year 2002).

<u>Defining Diabetes</u>

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 (hypoglycemic medication or insulin) for diabetes.

Visit 2 Exclusions:

- Subject not seen at Visit 2
- Race not African American or White
- Prevalent CKD or estimated glomerular filtration rate (GFR) <60 at baseline
- Incident CKD between Visit 1 and Visit 2
- HbA1c missing at Visit 2
- Serum creatinine missing at Visit 2 or Visit 4
- Free of diabetes at Visit 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 individuals with diabetes, all post-Visit 2 incident CKD cases through 2000 and the Visit 2 cohort random sample.

Outcome: Incident CKD

Incident CKD was defined as an estimated glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2 at Visit 4 or a kidney disease related hospitalization. GFR was estimated from calibrated serum creatinine using the simplified Modification of Diet in Renal Disease equation developed at the Cleveland Clinic: estimated GFR = 186.3 x (serum creatinine [mg/dL]$^{1.154}$) x (age$^{0.203}$) x (0.742 if female) x (1.21 if African American). [16]

Other variables:

Urinary Albumin Excretion:

Urinary albumin excretion was measured at ARIC visit 4 as the ratio of albumin to creatinine. We will be conducting subgroup analyses on individuals who were also present for these measures.

Retinopathy:

Retinopathy level was scored at ARIC visit 3. We will be conducting subgroup analyses on individuals who were also present for these measures.

Covariates of interest

Covariates will include baseline estimated GFR, sociodemographic characteristics (age, race, gender), smoking status, body mass index, CHD prevalence, blood pressure (including blood pressure-lowering medications) and lipid parameters (HDL cholesterol, LDL cholesterol, triglycerides).

Data Analysis

Adjusted hazard ratios and their 95% confidence intervals for the time to development of CKD will be computed. In the cohort analysis, a standard Cox proportional hazards model will be used to compare hazards by HbA1c quartile. We will repeat the analyses to assess risk using a continuous measure of HbA1c and stratify by HbA1c quartile to evaluate nonlinear associations of glycemic control.

Among individuals who were present at subsequent visits, and for whom retinography was gradeable and urinary albumin measured, we will repeat analyses to assess risk of HbA1c as we stratify by various risk groups (those with albuminuria and retinopathy; those without either; those with one or the other).

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:

Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW. Glycemic control and coronary heart disease risk in persons with and without diabetes. Arch Intern Med 2005; 165:1910-16.

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.

References

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3. Lepor NE. Impact of chronic kidney disease and diabetes on percutaneous coronary intervention outcomes. *Rev Cardiovasc Med*. 2006;7 Suppl 4:S38-48.

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13. Stuveling EM, Bakker SJ, Hillege HL, et al. C-reactive protein modifies the relationship between blood pressure and microalbuminuria. *Hypertension*. 2004;43:791-796.

14. Selvin E, Coresh J, Shahar E, Zhang L, Steffes M, Sharrett AR. Glycaemia (haemoglobin A1c) and incident ischaemic stroke: The atherosclerosis risk in communities (ARIC) study. *Lancet Neurol*. 2005;4:821-826.

15. Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW. Glycemic control and coronary heart disease risk in persons with and without diabetes: The atherosclerosis risk in communities study. *Arch Intern Med*. 2005;165:1910-1916.

16. Astor BC, Coresh J, Heiss G, Pettitt D, Sarnak MJ. Kidney function and anemia as risk factors for coronary heart disease and mortality: The atherosclerosis risk in communities (ARIC) study. *Am Heart J*. 2006;151:492-500.