ARIC Manuscript Proposal # 1024

PC Reviewed: _7_/_27_/04	**Status: __A__**	**Priority: __2__**
SC Reviewed: __07/27/04__	**Status: ___A_**	**Priority: ___2__**

1.a. Full Title: Glycemic Control (HbA1c) and Coronary Heart Disease Risk in Persons with and Without Diabetes: The Atherosclerosis Risk in Communities Study

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

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

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Ackowledgements: Joyce Jordahl; Lori Boland, MPH

3. Timeline: July 2004-December 2004

4. Rationale:

The purpose of this study is to investigate the relationship between glycemic control and coronary heart disease (CHD) in persons with and without diabetes. Hemoglobin A1c (HbA1c) reflects long-term glycemic control and is more stable compared to fasting glucose levels. In persons with diabetes, HbA1c is related to the development of microvascular disease and is at the center of the clinical management of hyperglycemia. Although there is evidence that HbA1c is also associated with cardiovascular outcomes in persons with diabetes (1), this relationship is controversial (2).

Non-diabetic individuals with impaired glucose tolerance or borderline hyperglycemia have an elevated risk of cardiovascular diseases (3;4). Indeed, it seems likely that if chronic hyperglycemia is important in the pathogenesis of coronary heart disease that any such relationship would extend to those individuals with elevated HbA1c levels, but without a diabetes diagnosis. In persons without diabetes, several recent studies have shown that HbA1c predicts cardiovascular disease events independently of known cardiovascular disease risk factors (5-7). However, previous prospective studies of cardiovascular events in non-diabetic populations have not included information on fasting glucose and thus could not exclude the

possibility that persons with undiagnosed diabetes remained in the study population. Two previous studies (8;9), including one in ARIC (8), have shown a relationship between HbA1c and atherosclerosis in persons without diabetes. In summary, chronic hyperglycemia has been hypothesized to play an important role in contributing to coronary heart disease in both diabetic and non-diabetic individuals, but there is little consensus in the literature about the extent to which glycemic control is related to heart disease risk.

5. Main Hypothesis/Study Questions:

We hypothesize that HbA1c will be independently associated with incident CHD in both diabetic and non-diabetic individuals.

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." The study population will consist of all incident CHD cases with follow-up through the year 2000 and the ARIC visit 2 CHD cohort random sample.

Case-cohort Visit 1 Exclusions:

- 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

Additional Visit 2 Exclusions:

- 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

Exposure: Hemoglobin A1c

We measured hemoglobin A1c (HbA1c) 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 CHD cases through 2000 and the visit 2 cohort random sample.

Outcome: Incident CHD

This manuscript will summarize the relationship between HbA1c and incident CHD events through the year 2000. We will conduct a case-cohort analysis using the visit 2 cohort random sample and all incident CHD cases (IN_01SP).

Other variables of interest

Covariates will include sociodemographic characteristics (age, sex, race, education), behavioral chacteristics (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

Weighted crude and adjusted means and proportions of variables of interest by CHD status will be calucated using the WADJPROP and WADJMEANS SAS macros. Adjusted hazard ratios and their 95% confidence intervals for the time to development of CHD 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). We will perform the analyses stratified by diabetes status.

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 to define this group is that it will result in a more conservative estimate of the true effect of HbA1c on CHD, 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, fasting glucose, glucose-lowering drugs (in diabetics), and diabetes duration will be explored. However, we do not anticipate including these factors in the final multivariable models as they are directly related to glycemic control and inclusion would result in over-adjustment.

Power

Power calculations using a fixed sample size of 290 persons with diabetes suggest that we will have 80% power to detect a relative risk estimate of 1.50 to 1.80 for HbA1c > 7% vs < 7% in the diabetic group. Based on a sample size of 1,253 non-diabetics, we will have 80% power to detect a relative risk estimate between 1.27 and 1.40 in for HbA1c $\geq$ 5% vs < 5% in this population.

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)?

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. 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 F, Powe N, Golden S. Glycosylated Hemoglobin and Cardiovascular Disease in Diabetes Mellitus: A Meta-Analysis of Observational Studies. Ann.Intern.Med . 2004.

2. Gerstein HC. Is glucose a continuous risk factor for cardiovascular mortality? Diabetes Care 1999;659-60.

3. Pickup JC, Williams G. Textbook of diabetes. Oxford: Blackwell Science, 1997.

4. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999;233-40.

5. Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC-Norfolk). BMJ 2001;15-8.

6. Park S, Barrett-Connor E, Wingard DL, Shan J, Edelstein S. GHb is a better predictor of cardiovascular disease than fasting or postchallenge plasma glucose in women without diabetes. The Rancho Bernardo Study. Diabetes Care 1996;450-6.

7. Blake GJ, Pradhan AD, Manson JE, Williams GR, Buring J, Ridker PM, Glynn RJ. Hemoglobin A1c Level and Future Cardiovascular Events Among Women. Archives of Internal Medicine 2004;757-61.

8. 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;1454-8.

9. Sasso FC, Carbonara O, Nasti R, Campana B, Marfella R, Torella M, Nappi G, Torella R, Cozzolino D. Glucose Metabolism and Coronary Heart Disease in Patients With Normal Glucose Tolerance. JAMA: The Journal of the American Medical Association 2004;1857-63.