ARIC Manuscript Proposal # 1488

PC Reviewed: 03/17/08	**Status: _A__**	**Priority: _2_**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association of hemoglobin A1c with incident heart failure among persons without diabetes: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): HbA1c & HF in non-diabetes

2. Writing Group:

Writing group members:
Kunihiro Matsushita, MD, PhD; Antonio Pazin Filho, MD, PhD; Alain Bertoni, MD, Patricia P. Chang MD, MHS; Josef Coresh, MD, PhD; Elizabeth Selvin, PhD, MPH; others welcome.

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:

Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Heart failure (HF) is an emerging public health problem with approximately 6 million prevalent cases and almost 700,000 new cases occurring annually in the US (1). In 2009, medical expenditures related to HF in the US are estimated to reach $37 billion (1).

Diabetes mellitus is one of the most important risk factors for HF (2). Hemoglobin A1c (HbA1c) is a central measure of glucose control in the clinical management of diabetes and reflects endogenous glucose levels over the previous 2–3 months (3). Previous studies in individuals with diabetes have suggested that elevated HbA1c levels are associated with an independent risk of hospitalization or death due to HF (2, 4-7).

In contrast, little is known about the association between glycemic status and the risk of HF among persons without diabetes. Two studies investigating this topic showed that fasting blood glucose concentrations were significantly associated with incident HF among patients with diabetes but not among persons without diabetes (8, 9). To the best of our knowledge, no previous study has investigated the association between HbA1c and the risk of HF in a population without diabetes.

We will investigate a possible relationship between HbA1c and the incidence of HF in persons without diabetes who participated in the ARIC Study. Specifically, we will assess the presence of an association and evaluate whether this association is linear or non-continuous (exhibits a threshold effect) among persons without diagnosed or undiagnosed diabetes. This analysis should provide insights into the hypothesized "cardiotoxicity" of hyperglycemia, a controversial topic (10).

5. Main Hypothesis/Study Questions:

Hypothesis 1: Elevated HbA1c levels will be associated with incident HF in a non-diabetic population.

Hypothesis 1a: The relationship above will be independent of traditional risk factors for HF.

Hypothesis 1b: The relationship above will be present in both categories of participants with and without prevalent coronary heart disease.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Inclusions:

All black and white ARIC subjects with data of HbA1c at visit 2 (the only visit for which HbA1c data are available)

Exclusions:

Ethnicity other than black or white

Individuals without data of HbA1c or incident HF

Prevalent diabetes cases

Prevalent diabetes at visit 2 will be defined as a fasting glucose level of ≥7.0 mmol/l (≥126 mg/dl; reported minimum of 8 h of fasting prior to visit), a non-fasting glucose level of ≥11 mmol/l (≥200 mg/dl), a self-reported physician diagnosis of diabetes or medical treatment for diabetes at either visit 1 or visit 2 (6).

Prevalent HF cases

Prevalent HF will be assumed if there is evidence of manifest HF stage 3, applying the Gothenburg criteria that require the presence of specific cardiac and pulmonary symptoms as well as medical treatment of HF at either visit 1 or visit 2 (11-13).

Exposure: HbA1c

HbA1c was measured on stored whole blood samples using a high performance liquid chromatography instrument (Tosoh Corporation, Tokyo, Japan) on all participants with available stored whole blood visit 2 (N=14,069) (14). Thus, we will treat visit 2 as the baseline for this study.

Outcome:

Incident HF: the first HF hospitalization coded 428 according to the International Classification of Diseases Code, Ninth Revision (ICD-9) or death from HF (coded 428 for ICD-9 and I50 for ICD-10) (6, 15). All cohort hospitalizations and deaths that occurred before January 1, 2006 (or most recent data available), will be included.

Other variables of interest and covariates:

Sociodemographics: age, race/center,, gender, education, income
Physical information: blood pressure, body mass index, kidney function (estimated glomerular filtration rate), presence/absence of left ventricular hypertrophy by electrocardiogram and carotid atherosclerosis by ultrasound
Lifestyle: smoking status and alcohol habit
Comorbidities: hypertension, dyslipidemia, history of coronary heart disease

Statistical Analysis Plan:

The primary analysis will use Cox proportional hazards models to quantify the association between HbA1c and incident HF. HbA1c will be treated as categorical (quartiles) and continuous variables respectively in the models. We will adjust for the covariates listed above.

We will repeat the analysis after stratifying the study sample by gender, race, and presence/absence of coronary heart disease, hypertension, obesity, or left ventricular hypertrophy.

We will conduct three sensitivity analyses. Firstly, since coronary events can act as a competing endpoint of HF, we will conduct the same analysis among participants who did not have prevalent coronary heart disease at baseline (visit 2) and did not experience a coronary event during follow-up. Secondly, we will analyze a subsample of participants who did not have incident diabetes during the first 6 years of follow-up (between visit 2 and visit 4). Finally, we will run our models on those participants who were not taking any medication at baseline, since many medications can potentially induce under- or over-estimation of the association between glucose status and incident HF.

Limitations:

As with any observational study, we will not be able to rule out the possibility of residual

confounding. A single measurement of HbA1c is an additional limitation. One study showed that updated average HbA1c may predict future HF better than a single baseline HbA1c in patients with diabetes (7). In non-diabetic populations, however, a single HbA1c measurement is quite reliable (16-18).

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 ICTDER03 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 ICTDER03 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 ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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)?
The most related proposal is MP#1164 titled "Hemoglobin A1c as a Risk Factor for Heart Failure Hospitalization among Persons with Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study", which focused on the same association as the current proposal in population with diabetes (6). The first author and the corresponding author are also involved in the current proposal. Other related proposals are listed below.

Proposals using HF as the primary outcome
MP#855: Retinal Microvascular Abnormalities and Congestive Heart Failure

MP#890B: Plasma Fatty Acid Composition and Incidence of Heart Failure in Middle Aged Adults: The Atherosclerosis Risk in Communities (ARIC) Study
MP#922: Alcohol consumption and risk of congestive heart failure
MP#927: Heart Failure Incidence and Survival: 13 Year Follow up of the ARIC Cohort
MP#1118: Kidney Function as a Risk Factor for Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study
MP#1125: Diabetes, obesity and insulin resistance as risk factors for incident hospitalized heart failure: The Atherosclerosis Risk in Communities (ARIC)
MP#1144r: The Obesity Paradox in Heart Failure
MP#1145: Electrocardiographic Predictors of Incident Heart Failure
MP#1160r: Life Course Socioeconomic Exposures and Heart Failure in the Atherosclerosis Risk in Communities (ARIC) Study
MP#1182: Diet and the risk of congestive heart failure in the Atherosclerosis Risk in Communities Study (ARIC)
MP#1197: Albuminuria as a Predictor of Incident Heart Failure Hospitalization and Mortality in the Atherosclerosis Risk in Communities (ARIC) Study
MP#1232: ECG Abnormalities Preceding Heart Failure: Estimation and Prediction in the Atherosclerosis Risk in Communities (ARIC) Study
MP#1265r: Common Allele on Chromosome 9p21 and Risk of Heart Failure, Stroke, and Atherosclerosis in The Atherosclerosis Risk in Communities (ARIC) Study
MP#1276: Exhaustion and risk for congestive heart failure: The Atherosclerosis Risk in Communities (ARIC) Study
MP#1324: Neighborhood and Individual Socioeconomic Status and Heart Failure Rehospitalization: ARIC Cohort
MP#1342: The preventable burden of heart failure due to obesity and hypertension: the Atherosclerosis Risk in Communities (ARIC) study
MP#1352: The association of orthostatic hypotension with incident heart failure
MP#1376: Optimal predictors of incident hospitalized heart failure: the ARIC cohort study
MP#1377: Relationship between pulmonary disease, lung function and incident hospitalized heart failure: The Atherosclerosis risk in communities (ARIC) study
MP#1392: The association of genome-wide genetic variation with incident heart failure in adults of European and African ancestry: the CHARGE Consortium

<u>Other proposals focusing on the association between HbA1c and cardiovascular disease</u>
MP#1024: Glycemic Control (HbA1c) and Coronary Heart Disease Risk in Persons with and Without Diabetes: The Atherosclerosis Risk in Communities Study
MP#1056r: Hemoglobin A1c (HbA1c) and Peripheral Arterial Disease in Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study
MP#1067: Glycemic Control and Risk of Ischemic Stroke: The Atherosclerosis Risk in Communities (ARIC) Study

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)
___ 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. **Selvin E, Marinopoulos S, Berkenblit G, et al.** Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med*. 2004;141(6):421-31.
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15. **Kottgen A, Russell SD, Loehr LR, et al.** Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol*. 2007;18(4):1307-15.
16. **Meigs JB, Nathan DM, Cupples LA, Wilson PW, Singer DE.** Tracking of glycated hemoglobin in the original cohort of the Framingham Heart Study. *J Clin Epidemiol*. 1996;49(4):411-7.
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18. **Lacher DA, Hughes JP, Carroll MD.** Estimate of biological variation of laboratory analytes based on the Third National Health and Nutrition Examination Survey. *Clin Chem*. 2005;51(2):450-452.