

## ARIC Manuscript Proposal # 1164

PC Reviewed: 06 / 20 /06

Status: A

Priority: 2

SC Reviewed: 06/23/06

Status: A

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**1.a. Full Title:** Hemoglobin A1c as a Risk Factor for Heart Failure Hospitalization among Persons with Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study

**b. Abbreviated Title (Length 26 characters):** HbA1c and Heart Failure

### 2. Writing Group:

Writing group members: Antonio Pazin Filho, Anna Kottgen, Alain Bertoni, Stuart D. Russell, Elizabeth Selvin, Josef Coresh, Others welcome.

Invited: Wayne Rosamond,

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

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**3. Timeline:** Analysis to start immediately, first draft by September 2006

**4. Rationale:**

Heart failure (HF) has a prevalence of over 5 million in the U.S. population and a yearly incidence rate of more than 500,000. Data from the Framingham Study suggests that the lifetime risk of heart failure is 1 out of 5 for both genders (1). The disease burden of HF is magnified in individuals with diabetes, in whom incidence rates are two to five times greater than those in the general population.

In patients with type 2 diabetes previous prospective studies have shown an association between the degree of hyperglycaemia and an increased risk of microvascular complications, sensory neuropathy, myocardial infarction, stroke, macrovascular mortality, and all-cause mortality (2-6). Generally, these studies measured glycaemia as being either high or low or assessed glycaemia on a single occasion, whereas repeated measurements of glycaemia over time would be more informative.

Hemoglobin A1c (HbA1c) reflects long-term glycemic control, is more stable compared to fasting glucose levels, and tracks well in individuals over time, especially when compared with fasting glucose. In persons with diabetes, HbA1c is related to the development of micro- and macrovascular disease and is at the center of the clinical management of hyperglycemia.

A few studies have looked at the relationship between hemoglobin A1c and heart failure incidence (7;8). Nichols et al have studied averaged HbA1c over 6 year follow up on incident heart failure in a population of 8,231 patients, showing a 32% increased risk of HF for every 1-percentage point increase in HbA1c. Nevertheless, the averaged HbA1c in this study is highly problematic as a marker of long term glycemic control (7). Stratton et al studied the prospective relationship between updated mean HbA1c and incident heart failure in the United Kingdom Prospective Diabetes Study (UKPDS) population and demonstrated that each 1% reduction in updated HbA1c was associated with reductions in risk of 16% (8).

ARIC data can improve our understanding of the relationship between HbA1c and risk of heart failure, allowing for race specific analyses and focusing on a population based sample of diabetics.

## **5. Main Hypothesis/Study Questions:**

1. Poor glycemic control in diabetics will predict a higher incidence of hospitalized heart failure and deaths from HF.
2. The relationship above will be independent of other risk factors for heart failure including existing coronary heart disease, demographics, and coronary heart disease risk factors.

**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).**

We will conduct a prospective analysis of the incidence of heart failure hospitalizations and deaths among persons with diabetes using Visit 2 as baseline (the only visit for which HbA1c measurements are available). We use the same definition of hospitalized heart failure as manuscript proposal 927, where incident HF was defined either as death from HF in the first position on the death certificate or as the underlying cause of death, or as the first HF hospitalization, and was identified through review of county death certificates and local hospital discharge lists (HF as a discharge diagnosis). Hospitalizations were coded as heart failure (428) using the International Classification of Diseases Code, Ninth Revision (ICD-9), and deaths were coded as heart failure (428 and I50) using the ICD-9 and ICD-10. All cohort hospitalizations occurring by January 1, 2003, were included. Study participants with evidence of prevalent HF will be excluded from analyses. Prevalent HF is assumed if participants were either currently taking heart failure medication at visit 1 or 2 or if there was evidence of manifest heart failure stage 3 applying the Gothenburg criteria at visit 1 or 2, or if they developed a heart failure hospitalization prior to visit 2.

Glycemic control will be defined by HbA1c which was measured on all persons with diabetes (prevalent and incident cases) at Visit 2. HbA1c was measured on stored whole blood samples using a high performance liquid chromatography instrument (Tosoh Corporation, Tokyo, Japan) (9). HbA1c was also measured on a random sample of the cohort (and several case groups). These groups will be explored but we are concerned that power may be limited and therefore these analyses will either be excluded or be considered secondary analyses.

The primary analysis will include individuals with a history of coronary heart disease at baseline. However, given the critical importance of myocardial infarction in the development of heart failure, analyses will also be stratified by history of CHD at baseline (absent vs. present).

Potential confounding variables of interest include participant demographics (age, sex, and race-center), pre-existing disease (history of coronary heart disease and stroke, left ventricular hypertrophy, carotid atherosclerosis on ultrasound), coronary heart disease risk factors (blood pressure level and medications, cholesterol level and medications, smoking, body mass index, waist hip ratio, physical activity) and education. Use of cardiac medications before and after the onset of heart failure will be tabulated but is not the primary focus of this paper.

**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.csc.unc.edu/ARIC/search.php>**

Yes  No

Five proposals use HF as the primary outcome:

MP#927 – Heart Failure Incidence and Survival: 13 Year Follow up of the ARIC Cohort

MP#922 - Alcohol consumption and risk of congestive heart failure

MP#855 - Retinal Microvascular Abnormalities and Congestive Heart Failure

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)

Other proposals with some heart failure focus include:

MP#617 - Evaluation of International Classification of Diseases Codes to Identify Hospitalized Heart Attack Patients with Acute Congestive Heart Failure: The Atherosclerosis Risk in Communities Study

MP#328 - Analysis of the relationship between potassium and incidence of cardiovascular diseases

MP#1049 - Prevalence and Prognosis of Asymptomatic Left Ventricular Systolic Dysfunction (ALVSD) in African Americans: the ARIC study

**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)?**

Manuscript proposal #927 to investigate heart failure incidence and survival at 13 year follow up. We have contacted Drs. Chang, Folsom and Rosamond

