ARIC Manuscript Proposal # 1125

PC Reviewed: _12/20/05	**Status: _____**	**Priority: ____**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Diabetes, obesity and insulin resistance as risk factors for incident hospitalized heart failure: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Obesity, DM, IR & Hrt Failure

2. Writing Group:

Writing group members:

Laura Loehr, Wayne Rosamond, Annie McNeill, Patricia Chang, Aaron Folsom, Lloyd Chambless, Gerardo Heiss

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

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3. Timeline:

Analysis to begin immediately, first draft by July, 2006

Rationale:

Heart failure is responsible for more hospitalizations than any other condition in those 65 and older. The temporal trend of heart failure (HF) indicates a steadily increasing population burden [1]. In addition, obesity and its associated conditions are rapidly increasing. Obesity and overweight as measured by BMI have been identified as risk factors for heart failure from the Framingham Heart Study and other studies [2, 3]. Framingham created a HF risk estimation formulas in which BMI was only included in the equation for women and not men [4]. Further support for the association of obesity with HF comes from echocardiographic studies in which obesity is an even stronger predictor of left ventricular mass, a known HF predictor, than hypertension [5]. BMI is the only ponderosity metric to date to be assessed as a HF risk factor in a large population based study; The importance of measures of central adiposity (such as waist circumference and waist-hip ratio) as compared to BMI has yet to be studied.

Type 2 diabetes, and even poor glycemic control amongst diabetics, is an established risk factor for HF [6, 7]. Diabetes is known to cause microvascular disease and has been theorized as one the processes by which it causes HF. Retinopathy, a microvascular disease, was found an independent predictor of heart failure in the Artherosclerosis Risk in Communities (ARIC) study [8]. Also, insulin resistance, a pre-diabetic state, was found to be predictive of HF and this relationship persisted even after adjustment for overt diabetes [9]. This finding, however, was from a selective cohort of elderly Swedish men and potentially not generalizable to other populations. Waist circumference and waist hip ratio are more highly correlated with insulin resistance than BMI.

The Artherosclerosis Risk in Communities (ARIC) study is a well-characterized biracial population-based cohort with 13 years of follow-up to date for incident hospitalized heart failure. This cohort is an excellent resource to explore the relationship between obesity, diabetes mellitus and insulin resistance as risk factors for the development of incident hospitalized heart failure. Many of the population-based studies to date have been in predominately white communities, whereas the ARIC cohort will allow potentially important insights into race and gender-specific associations.

References:

1. Masoudi, F.A., E.P. Havranek, and H.M. Krumholz, *The burden of chronic congestive heart failure in older persons: magnitude and implications for policy and research.* Heart Fail Rev., 2002. 7(1): p. 9-16.
2. Kenchaiah, S., et al., *Obesity and the risk of heart failure.* NEJM, 2002. 337(5): p. 305-13.
3. Murphy, N., et al., *Long-term cardiovascular consequences of obesity: 20-year follow-up of more than 15,000 middle-aged men and women (the Renfrew-Paisley study).* European Heart Journal, 2005: p. 1-11.
4. Kannel, W., et al., *Profile for estimating risk of heart failure.* Archives of Internal Medicine, 1999. 159: p. 1197-1204.
5. Drazner, M., et al., *Increased left ventricular mass is a risk factor for the development of a depressed left ventricular ejection fraction within five years: the Cardiovascular Health Study.* JACC, 2004. 43(12): p. 2207-15.
6. Bertoni, A.G., et al., *Heart Failure Prevalence, Incidence, and Mortality in the Elderly With Diabetes.* Diabetes Care, 2004. 27(3): p. 699-703.

7. Iribarren, C., et al., *Glycemic control and heart failure among adult patients with diabetes.* Circulation, 2001. 103: p. 2668-2673.
8. Wong, T.Y., et al., *Retinopathy and Risk of Congestive Heart Failure.* JAMA, 2005. 293(1): p. 63-69.
9. Ingelsson, E., et al., *Insulin resistance and risk of congestive heart failure.* JAMA, 2005. 294: p. 334-341.

5. Main Hypothesis/Study Questions:

a). Each of BMI, waist circumference and waist/hip ratio will be independently predictive of incident hospitalized heart failure, overall and across all race and gender groups. Waist/hip ratio will be a better predictor of incident hospitalized heart failure than BMI and waist circumference.

b). Diabetes and insulin resistance will be independently predictive of incident hospitalized heart failure, overall and across all race and gender groups. Interaction by race or sex will be explored using interaction terms in multivariate PH modeling.

c). These associations will be stronger in the post-MI related HF group than in the non-MI related HF group.

d). Obesity and insulin resistance are synergistic in their association with HF. Interaction by obesity and insulin resistance will be explored using interaction terms in a Cox PH model.

e) Methods for indirectly measuring insulin resistance (HOMA, QUICKI, McCauley index, insulin-to-glucose ratio, etc) will be compared as to their ability to predict HF. –

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

Exclusions:

Participants with prevalent heart failure at baseline, as defined by self-report use of heart failure medication ("yes" to the following visit 1 question: "Were any of the medications you took during the last two weeks for heart failure?) will be excluded (N= 131).

Other exclusions:

- Subjects not black or white
- Black subjects from Minnesota (so few)
- Fasting state (people use either >=8)
- Missing baseline data on any key variables
- For the IR analysis those with diabetes at baseline will be excluded

Data to be used are as follows:

Variables: From visit 1 – self-report use of HF medication, diabetes, measures of obesity (BMI, WC, WHR), hypertension, prevalent CHD, smoking, age, education, ecg variables, insulin, creatnine, glucose, race, and gender.

Anthropometric measures from visits 2-4.

Hospital discharge diagnosis codes and dates for heart failure from cohort eligibility forms (CEL), and death from HF as indicated by codes from death certificates and date of death. Through most recent year available.

MI-related HF to be defined by the occurrence of an MI, silent MI or procedure before the hospitalization for HF. Currently available as "in_02sp" (MI/FATCHD/SMI Procedure) and "futimea" (follow-up time for in_sp) from the events file for follow-up time through 2002. This will then be combined with those that have had previous CHD at baseline.

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)?
#554 Echocardiographic characteristics related to Diabetes Mellitus
#632 Insulin Resistance Syndrome and Echocardiographic Indices in African Americans
855 Retinal microvascular abnormalities and congestive heart failure
#927 Heart Failure Incidence and Survival: 13 Year Follow up of the ARIC cohort

There is no overlap for the first three proposals. Echocardiographic characteristic are related to HF but are not symptomatic HF, and retinal microvascular abnormalities are associated with diabetes and insulin resistance, but are not actual measures of insulin resistance. For the final proposal, #927, the first and senior authors are the same as for

this proposal. Proposal #927 will include the univariate relationship of obesity and diabetes with HF, but there will not be any multivariable modeling to further define this association.

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. primiarly 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.