ARIC Manuscript Proposal # 1835

PC Reviewed: 8/32/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Subclinical Atherosclerosis, Glucose Status and Incident Heart Failure: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Atherosclerosis and HF

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. VE **[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**: Analyses will begin as soon as this manuscript proposal is approved.

4. **Rationale**:

Congestive heart failure (CHF) is one of the leading causes of morbidity and mortality[1-4] and its prevalence continues to rise in the United States despite the decline in cardiovascular disease (CVD) death rates.[2] In the Framingham Study, median survival from CHF is only 1.7 years for men and 3.2 years for women, with only 25% of men and 38% of women surviving 5 years. This mortality rate is 4-8 times that of the general population of the same age.[1]

Atherosclerosis plays a central role in the pathophysiology of coronary heart disease (CHD), which is believed to be the most common etiology for heart failure.[5] Recent work has associated greater carotid intima-media thickness (IMT) with alterations of myocardial strain parameters reflecting reduced systolic and diastolic myocardial functions, even after adjustment for established CHD risk factors.[6] Because asymptomatic left ventricular dysfunction is considered to be a subclinical marker of heart failure[7], carotid IMT associations with left ventricular function could represent an earlier marker of of myocardial dysfunction along the heart failure continuum. Whether these changes in LV function translate directly to heart failure in middle-aged adults remains uncertain. Also, little is known on the role of subclinical atherosclerosis in heart failure risk prediction. A better understanding of the role of atherosclerosis in the occurrence of heart failure could facilitate early detection of high-risk subjects for heart failure.

A few studies have examined the relationship between glucose categories and incident heart failure. Abnormal glucose metabolism status (impaired fasting glucose, IFG, and type 2 diabetes, T2DM) are strongly associated with increased left ventricular mass and wall thickness and lower end-diastolic volume, which are markers of heart failure.[8] Thrainsdottir et al – in a study involving 19,381 subjects aged 33-84 years – showed a strong association between heart failure and glucose status; heart failure was diagnosed in 3.2% of subjects with normal glucose tolerance (NGT), compared with 6.0% and 11.8% in subjects with IFG and T2DM, respectively[9]. In a sample of 9,591 individuals with T2DM, age- and sex-matched with a control group without diabetes, incident cases of CHF were observed in 7.7% of T2DM subjects free of CHF at baseline and in 3.4% of control subjects.[10] In the Strong Heart Study, subjects with T2DM were shown to have a 2.8-fold greater risk of CHF than those with NGT (95%CI: 2.0–3.8, $p<0.0001$), independently of established risk factors; no differences were observed between subjects with NGT and IFG.[11]

We propose to investigate the independent association of subclinical atherosclerosis (assessed using carotid IMT) with incident heart failure across categories of glucose metabolism among middle-aged whites and African-Americans (AA). The ARIC Study is a large cohort study of middle-aged individuals with over **1,282 HF cases,** and thus provides an excellent opportunity to explore this relationship.

5. Main Hypothesis/Study Questions:

1. Carotid IMT (visit 1) is associated with incident heart failure. This association is independent of established risk factors (age, male sex, hypertension, T2DM, LV hypertrophy, obesity, total cholesterol, smoking, CRP, IL-6, albuminuria) and CHD.
2. While the association of carotid IMT with incident heart failure will be present in all three categories of glucose metabolism (NGT, IFG, T2DM), it will be strongest for T2DM and weakest for persons with NGT (i.e., glucose status modifies the association between carotid IMT and HF).
3. Increased carotid IMT (change between visit 1 and visit 3) will be associated with incident heart failure, independently of established risk factors and CHD.

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).

Study design: we will perform a longitudinal analysis of data.

Main exposure: **baseline** carotid IMT and **change** in carotid IMT. Visit 1 measurement for carotid IMT will be considered as baseline for our analysis. Measurement of carotid IMT was done on approximately half of the cohort at visit 3 and a subset (less than half) of the cohort at visit 4. Because of the smaller number of carotid IMT measures at visit 4 (due to attrition and a lower response rate), we will estimate **change** in carotid IMT between visits 1 and 3.

Main outcome: our primary outcome will be incident HF, defined as the first occurrence of either i) a HF hospitalization which included an International Classification of Diseases, 9th revision, discharge code of 428 (428.0 to 428.9) in any position, or ii) a death certificate with a 428 (HF) or International Classification of Diseases, 10th revision, code I50 (HF) in any position. We will consider cases of incident HF from the baseline visit (visit 1) up till December 2009.

Covariates: additional variables required for analysis will include demographic factors (age, gender, race, study center, level of education), anthropometric data (waist circumference, BMI), laboratory measurements (blood glucose, LDL-cholesterol, HDL-cholesterol, triglycerides, C-reactive protein), comorbid conditions (T2DM, hypertension, prevalent CHD at visit 1 as well as incident CHD over the course of follow-up), smoking status (current, former or never), alcohol consumption status (current, former or never), and medication use (hypertensive, lipid-lowering). Finally, the estimated glomerular filtration rate (eGFR) will be calculated from age, sex, gender, and serum creatinine, using the re-expressed abbreviated MDRD Study equation[12] and will be incorporated as a covariate.

Inclusion/Exclusion: We will exclude from the study: i) prevalent cases of HF at baseline, either by self-reported current intake of HF medication (n = 83), or those with stage 3 or manifest HF by Gothenburg criteria (n = 699);[13-14] ii) participants with missing values of carotid IMT at baseline; and iii) participants with missing criteria needed to define prevalent HF (n = 289), and iv) participants with missing criteria needed to define glucose status.
Also, for analysis of **change** in carotid IMT, we will exclude participants with prevalent HF at visit 3, and all other participants with missing values of follow-up carotid IMT.
Finally, we will exclude races other than whites or blacks (n = 48).

Data analysis: The end of follow-up time for those without HF will be i) December 31, 2009, ii) date of last contact for those lost to follow-up, or iii) date of death, whichever occurred first. By December 2002 there were 1,282 cases of incident HF, so we will have sufficient power for our analyses.
Baseline characteristics (visit 1) for participants with and without HF will be compared using descriptive statistics. Data will be presented as mean ± standard deviation (SD) for continuous variables and number (percentage) for categorical variables. Where appropriate, log transformation will be performed for variables with a skewed distribution. Differences in baseline characteristics will be assessed using analysis of variance (for continuous variables) and chi-square test (for categorical variables).
Carotid IMT will be modeled as both a continuous and a categorical variable (in quartiles). For assessing the relationship between change in carotid IMT and HF, annual average change in carotid IMT will be categorized into quartiles. A Cox proportional hazards model will be used to estimate the relative hazards of incident heart failure as a function of carotid IMT; the relative hazards of the first and fourth quartiles will be compared.
A stratified Cox regression analysis with a time interaction term will be used to examine the association of carotid IMT with incident HF across glucose categories.
When **change** in carotid IMT is used as the exposure variable, we will exclude all prevalent HF cases present at visit 3 from our analysis. We will consider incident cases of HF from visit 3.
We will run these analyses for two groups of participants – those with complete data on carotid IMT (visits 1 through 3) and those with partial data (no measurement done at visit 3) on carotid IMT (using their carotid IMT values for visits 1 and 2) – and observe any trends.
We will perform a complete analysis for incident HF cases from baseline through 2009, and separate parallel analyses for adjudicated HF cases (beyond 2006) and non-adjudicated HF cases (prior to 2006) to observe any trends.
In order to obtain the most parsimonious regression model, we will perform a backward elimination procedure (while retaining age, gender and race in the model). Elimination will be based on p-values and likelihood ratio tests. The proportionality for hazards will be checked by visually examining the "-log(-log)" survival plots and time interaction terms. Cumulative hazards of HF will be illustrated in Nelson-Aelen plots and compared using the log-rank test.

Limitations: The main limitation of this project relates to misclassification of our outcome variable, incident HF. Before 2006, incident HF was not adjudicated by the HF MMCC. Moreover, information is only available for heart failure signs and symptoms (using the Gothenburg criteria), hospitalizations and deaths; echocardiographic data is lacking for this cohort. Also, the Gothenburg criteria used to exclude cases has a high specificity but only a moderate sensitivity[15]. In order to address this aim, we will perform separate analyses for adjudicated and non-adjudicated HF cases to observe any patterns. Also, data on outpatient cases of HF is not available; however, community surveillance reports of ARIC communities indicate that 74% of outpatient HF cases are hospitalized within 1.7 years[16].

7.a. Will the data be used for non-CVD analysis in this manuscript? **No**
b. N/A

8.a. Will the DNA data be used in this manuscript? **No**
8.b. N/A

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

There are no existing manuscript proposals that overlap

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)?

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 #922: Alcohol consumption and risk of congestive heart failure
MP #974: Change in carotid IMT is associated with Incident CHD and Incident Stroke
MP #1118: Kidney function as a Risk Factor for Heart Failure Hospitalization: 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) Study
MP #1164: Hemoglobin A1c as a Risk Factor for Heart Failure Hospitalization among Persons with Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study
MP #1197: Albuminuria as a Predictor of Incident Heart Failure Hospitalization and Mortality in the Atherosclerosis Risk in Communities (ARIC) Study
MP #1376: Optimal predictors of incident hospitalized heart failure: the ARIC cohort study
MP #1475: Hypertension, left ventricular hypertrophy, and risk of incident hospitalized heart failure: The ARIC study

MP #1806: The association between arterial stiffness and incident heart failure and microvascular disease – an analysis from the ARIC Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? No
11.b. N/A

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.

The authors understand and will comply.

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