1.a. Full Title: Heart failure diagnostic schemes in hospitalized patients and follow up outcomes: The Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:
   Writing group members: Wayne Rosamond
                        Sunil K. Agarwal
                        Patricia Chang
                        Gerardo Heiss
                        Others from HF committee are welcome

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

First/ARIC/ author
   Name: Wayne Rosamond
   137 E. Franklin Street, Suite 203,
   Chapel Hill, NC, 27514
   Phone: 919-962-3230 Fax: 919-966-9800
   E-mail: wayne_rosamond@unc.edu

3. Timeline:
   Following approval of this manuscript by the ARIC Publications Committee this work will lead to manuscript(s) within 15 months.

4. Rationale:
   Heart Failure (HF) is a major public health problem in the US [1]; while it has grim prognosis (30% mortality at one year)[2], its treatment cost exceeds those for both coronary artery disease and cancer combined and requires about 5.4% of the total US health care cost [3].

HF is a clinical syndrome, a result of complex pathological processes that culminate in the failure of the heart to circulate blood at normal pressure. The ACC/AHA advocate for the use of appropriate symptoms and signs, when present plus objective evidence and response to treatment when in doubt[4]. As unrecognized ventricular dysfunction and HF are frequent among individuals with common conditions, many of which with
manifestations such as chronic obstructive pulmonary disease (COPD), signs and symptoms of HF though sensitive have low specificity [5]. This problem is accentuated due to their high prevalence in the elderly, the obese and in women[6]. There is some evidence of physician misdiagnosis when patients are assessed using objective criteria[7]. Furthermore, there is no standard definition of diastolic dysfunction. It is mostly a diagnosis of exclusion of systolic heart failure (ejection fraction >30%) in the presence of symptoms of cardiac congestion[8]. Importantly, population based studies have found that at least half of the individuals with LV dysfunction on echocardiograph have never been diagnosed as having heart failure[9, 10].

In addition to understanding how closely the various classification schemes match with physician adjudicated classification ([11] and ARIC ms. #1331), it will be useful to understand the prognostic information provided by these classifications. In an only published report for hospitalized HF patients by Kim J et al, the discriminatory value for mortality rates didn’t differ appreciably between abbreviated Framingham, Framingham, Boston, Killip, and Duke classification schemes despite their high discordance in classification [12]. However, in community settings Boston criteria was found to have both better construct validity and prognostic discrimination than Framingham, Boston, and Gothenburg studies and of the European Society of Cardiology criteria (Di Bari, 2004 #57). Also, Cardiovascular Health Study (CHS) investigators compared the prognosis of HF events classified using Framingham and CHS criteria and reported worse prognosis in the concordant group (Schellenbaum, 2004 #130). The CHS investigators also compared prognosis of hospital discharge codes with CHS criteria and reported mortality rates in decreasing order for the following classification schemes: concordant, hospital discharge codes, and CHS criteria (Schellenbaum, 2006 #1053). In summary, there is no large study comparing mortality or rehospitalization rates by several classification schemes and adjudicated HF.

ARIC surveillance collects data various elements allowing a computer aided classification of a hospitalization (with possible HF) as HF vs. no HF using several available risk scores. ARIC ms. Proposal #1331 compares ARIC criteria with Framingham, Boston, Gothenburg and NHANES criteria and ICD9 code groups for HF. In this study, we will compare the mortality and hospital readmission rate for computerized classification using various classification, and ARIC classification. Also, whether there is an difference in prognosis by each classification in the strata of ejection fraction and BNP will be examined.

5. Main Hypothesis/Study Questions:

1. Compare the mortality rates for various classification of heart failure?
   - Evaluate if prognosis by each classification differ by ejection fraction and BNP levels category.
   - Examine mortality at 30 days, 6 months and a year.

2. Compare the CVD-specific mortality rates for various classification scores of heart failure?
   - Evaluate if prognosis by each classification differ by ejection fraction and BNP levels category.
   - Examine mortality at 30 days, 6 months and a year.
3. Compare the hospital readmission rates (overall and heart failure specific) for various classification scores for the ARIC cohort participants.

4. Evaluate the prognostic information carried by various signs, symptoms, and comorbidities used for computerized classification of HF events.

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).

The Coordinating Center will release a closed cohort file (including all deaths through 2007) by early 2010. A computer classification for data ARIC Surveillance 2005-2006 (n=3851) has been done. Also, ARIC classification using ARIC criteria is almost complete for year 2005 and about to be completed for 2006.

Mortality rates at one month, six months, and one year will be reported for each classification scheme including ARIC classification. Rates stratified by various cut-offs of ejection fraction (>=50, 50> to <=35, and <35), and BNP (>100, 100-400, >400) will be done. Survival analysis using Cox regression models will be similarly done to model percentiles of time to death and time to readmission for the cohort (repeated events, with robust variance adjustment). We understand that the power for stratified analysis may be limited due to missing information on ejection fraction or biomarkers.

Lastly, an prognostic values of variables used in the computerized classification schemes will be done using survival analysis methods.

This manuscript is not supposed to inform about whether one classification is better than other, as comparison for mortality/hospital readmission rates may indicate severity of heart failure or comorbidities and not whether heart failure was present. However, the estimates will be important to understand if the range of mortality rates among HF patients seen in the literature is due to classification criteria.

7.a. Will the data be used for non-CVD analysis in this manuscript? No

8.a. Will the DNA data be used in this manuscript? 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.csecc.unc.edu/ARIC/search.php
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#1331 Comparison of Hospitalized Heart Failure Diagnostic Criteria

Other proposals looking at risk factors of HF:
MP#922 Alcohol consumption and risk of congestive heart failure
MP#890B Plasma Fatty Acid Composition and Incidence of Heart Failure in Middle Aged Adults
MP#1118 Kidney Function as a Risk Factor for Incident Heart Failure
MP#1125 Diabetes, obesity and insulin resistance as risk factors for incident hospitalized HF
MP#1144 The Obesity Paradox in Heart Failure.
MP#1160 Life Course Socioeconomic Exposures and Heart Failure.
MP#1164 Hemoglobin A1c as a Risk Factor for HF Hospitalization among Persons with Diabetes.
MP#1197 Albuminuria as a Predictor of Incident Heart Failure Hospitalization and Mortality.
MP#1232 ECG Abnormalities Preceding Heart Failure: Estimation and Prediction
MP#1276 Exhaustion and risk for congestive heart failure.
MP#1342 The preventable burden of heart failure due to obesity and hypertension.
MP#1377 Relationship between pulmonary disease, lung function and incident hospitalized heart failure

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _____ Yes _____ 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.