ARIC Manuscript Proposal #1921

PC Reviewed: 3/20/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Frequency and Correlates of Heart Failure Stages in the Community

b. Abbreviated Title (Length 26 characters): **HF Stages in the Community**

2. Writing Group:

Writing group members: Deepak K. Gupta, Amil M. Shah, Laura Loehr, Patty Chang, Kunihiro Matsushita, Dalane Kitzman, Suma Konety, Gerardo Heiss, Hanyu Ni, Carla Sueta, Ervin Fox, Alain Bertoni, OTHERS WELCOME, Scott D. Solomon

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

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3. Timeline: Analysis will begin following proposal approval. Anticipating completion of echocardiography of the ARIC Visit 5 cohort in 2013, a manuscript will be completed within 6 months of that date.

4. Rationale:

Heart failure (HF) is a major public health problem affecting 5.7 million Americans, with >550,000 new cases per year (1). Moreover, the individual lifetime risk for HF after 40 years of age is approximately 20% in both men and women (2). HF predominantly affects the elderly, with over 80% of HF hospitalizations occurring in persons over 65 years of age (1). The observation that the risk of HF increases with aging highlights the progressive course of this disease, starting with the accumulation of risk factors, proceeding through asymptomatic cardiac dysfunction, and culminating in the onset of HF symptoms. Once HF occurs, morbidity and mortality are high causing nearly 57,000 deaths annually (1). Consequently, the American College of Cardiology (ACC) and American Heart Association (AHA) introduced a staging system that incorporates the factors contributing to the development of HF (3). Notably, the ACC/AHA HF staging model emphasizes identification of these asymptomatic patients at risk without (stage A) or with (stage B) evidence of cardiac structural and functional abnormalities to facilitate preventive measures prior to progression to symptomatic HF (stages C [current or prior symptoms of HF] and D [refractory symptoms despite optimal medical therapy or specialized cardiac support).

Despite recognition of the progressive course of HF and increasing focus on preventive strategies, the aging population and high frequency of risk factors, is an ominous combination portending a surge in the HF epidemic. Moreover, approximately half of HF cases occur in the setting of preserved left ventricular ejection fraction (HFpEF), a syndrome for which there is currently no proven therapies to improve survival (4-6). Furthermore, within the aging population, women and African Americans are critically understudied populations that carry a sizeable portion of the HF burden. Therefore, enumerating the prevalence of stages of HF and understanding differences in cardiac structure and function through the spectrum of HF stages are unmet needs. In particular, understanding how risk factors, cardiac structure and function vary between gender and race groups will significantly contribute to clarifying the pathophysiology driving HF progression in these populations.

The Atherosclerosis Risk in Communities (ARIC) study began in 1987 and enrolled nearly 16,000 middle aged (44-66 years) individuals in four communities in the U.S., approximately 30% of whom are African American. Participants are now in their seventh to ninth decades of life, a period of life during which the prevalence of HF increases dramatically. Approximately 9,000 participants are expected to attend Visit 5 and will undergo comprehensive state of the art transthoracic echocardiography. ARIC therefore presents a unique opportunity to investigate risk factors and cardiac structure and function across the spectrum of HF (stages A, B, C, and D) and whether they vary in understudied populations, including women and African Americans.

5. Main Hypothesis/Study Questions: The primary objective of this study is to describe the ARIC cohort according to stages of HF, stratified by gender and race, and compare clinical, cardiac structure and function, and biomarker data between these groups. To meet this goal, we have the following specific aims:

1. Describe the frequency of stage A HF, stage B HF, and stage C HF (HFpEF and Heart Failure with reduced ejection fraction [HFrEF]) in the community setting and how these frequencies vary by gender and race.
2. Define the clinical, vascular (pulse wave velocity), and biomarker (NT-proBNP, high sensitivity troponin) correlates of the HF stages and whether these relationships vary by gender and race.
3. Determine the impact of including novel markers of cardiac dysfunction, such as echocardiographic measures of diastolic function, systolic strain and strain rate from speckle tracking, as well as NT-proBNP and high sensitivity troponin, on the classification of participants into the ACC/AHA HF stages.

Future Directions/Studies

1. The cross sectional study proposed here will provide the foundation for a longitudinal analysis evaluating the association between stages of HF and outcomes (death, incident HF, and recurrent HF events), which will be submitted as a separate manuscript proposal.

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).

This will be a cross sectional study of ARIC cohort participants who undergo echocardiography during visit 5 (2011-2013). To be included in the analysis participants must have undergone echocardiography with acceptable image quality for analysis. Patients with missing echocardiographic data, heart failure status, or data regarding risk factors for HF will be excluded.

Participants will be categorized according to the ACC/AHA heart failure guidelines into Stages A, B, C, or D (Figure 1). Subjects free from HF, risk factors for HF, and structural or functional cardiac abnormalities will be categorized as "normal". Prevalent heart failure (Stage C) will be defined as those with prevalent HF at visit 1 plus those with incident HF (as previously defined) up to visit 5 (7,8). Participants with prevalent HF will also be stratified according to preserved (≥50%) or reduced (<50%) LVEF based upon the visit 5 echo. The categories of HF stage will be further stratified by gender and race. Clinical characteristics, echocardiographic cardiac structure and function, and biomarkers will be compared between these groups.

Clinical variables (collected at visit 5) to be evaluated include:

age, gender, duration of prevalent HF, cardiac and HF risk factors, such as hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, coronary heart disease, stroke/TIA, peripheral arterial disease, atrial fibrillation/flutter, chronic kidney disease, anemia, COPD, asthma, and alcohol use; electrocardiographic left ventricular hypertrophy and QRS duration; heart rate, blood pressure (systolic, diastolic, mean arterial, and pulse pressure), height, weight, body mass index, body surface area, creatinine, WBC count, hemoglobin, red cell distribution width, glucose, lipids, brain natriuretic peptide, high sensitivity troponin T; pulse wave velocity; and pulmonary function tests.

Echocardiographic variables to be evaluated include:

Cardiac structure: left ventricular (LV) size, LV wall thickness, LV mass, LV geometry, left atrial size and volumes, aortic root dimension, valvular disease, and right ventricular size.

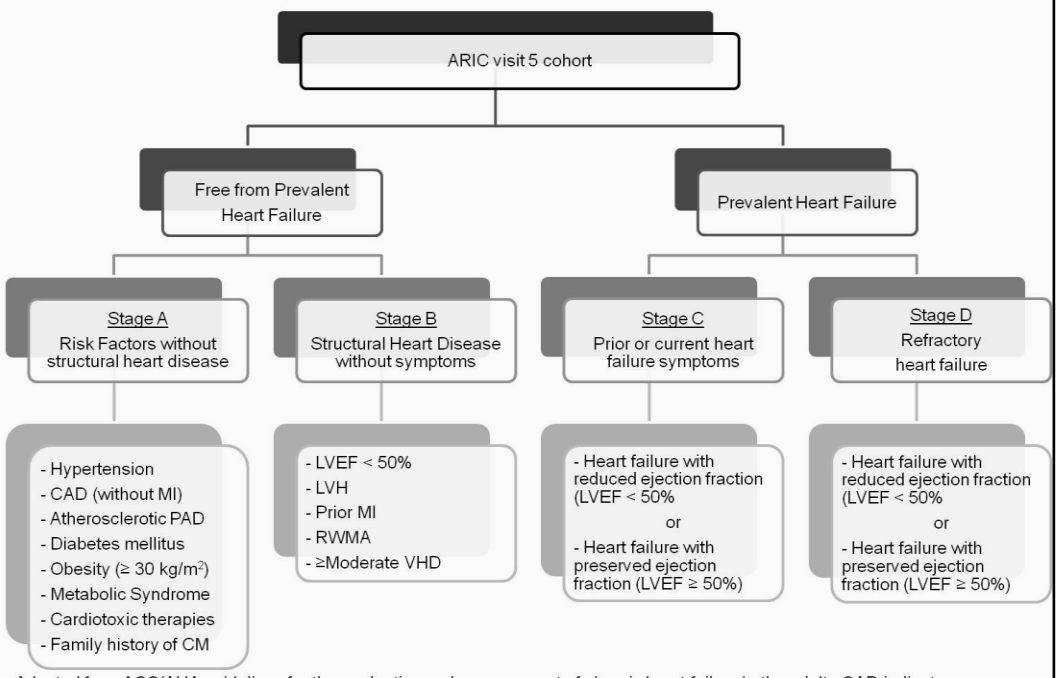
Cardiac function: LV ejection fraction, right ventricular fractional area change, Doppler mitral inflow E and A wave peak velocities, E/A ratio, deceleration time, tissue Doppler systolic and diastolic indices at both the mitral and tricuspid annulus, as well as LV myocardial mechanics from speckle tracking imaging.

Noninvasive hemodynamics: stroke volume, cardiac output, LV filling pressures, pulmonary vascular resistance, and pulmonary artery pressures.

Categorical variables will be compared via $\chi 2$ or Fischer exact test, while continuous data will be compared between groups via Wilcoxon Rank Sum or Kruskal-Wallis tests. P values < 0.05 will be considered significant. Univariable and multivariable linear or logistic regression analysis will be used to assess associations between categories of participants and echocardiographic characteristics. Adjustments for differences in clinical characteristics (based upon P <0.05 and/or clinically important covariates) will be performed. Similar analyses will be repeated after including novel markers of cardiac dysfunction (eg. Diastolic dysfunction, strain and strain rate, NT-proBNP, and troponin) into defining stage B.

Limitations include that this is a cross sectional analysis using data collected at visit 5. Moreover, as the visit 5 echocardiogram will not be performed concurrently with a HF event, the preserved versus reduced distinction will not reflect EF status at the time of HF diagnosis. The use of ICD-9 coding for defining prevalent HF limits our analysis to those participants who have had a prior hospitalization for HF. However, it has previously been demonstrated that the majority of participants with incident HF events as outpatients eventually become hospitalized with HF and would thus be captured in the ICD-9 based approach. Furthermore, the ACC/AHA staging system for HF includes prior symptoms of HF as stage C. Thus, a hospitalization with an ICD-9 discharge code for HF would account for participants with prior HF, even if the primary discharge diagnosis for a given hospitalization was not HF. Finally, those with advanced or symptomatic HF may choose not attend visit 5 resulting in a selection bias for our study. This may limit our ability to differentiate Stage C and D HF, in which case we may need to combine these two groups for the analysis. Those who do not attend visit 5 will be evaluated for differences with regards to age, gender, center, and prevalent coronary heart disease, stroke, and heart failure as compared to those who do attend visit 5 in attempt to identify any systematic biases that may confound our results.

Figure 1. Algorithm for ACC-AHA staging of heart failure in ARIC.



Adapted from ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult. CAD indicates coronary artery disease; MI, myocardial infarction; PAD, peripheral arterial disease; CM, cardiomyopathy; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; RWMA, regional wall motion abnormality; VHD, valvular heart disease.

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 _X__ 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 __X__ 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)?

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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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