ARIC Manuscript Proposal #1891

PC Reviewed: 1/10/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Phenotypic profile of heart failure with preserved ejection fraction in African Americans: risk factors, cardiac structure and function, and prognosis.

b. Abbreviated Title (Length 26 characters): HFpEF in blacks

2. Writing Group:

Writing group members: Deepak K. Gupta, Davide Castagno, Madoka Takeuchi, Amil M. Shah, Scott D. Solomon; Ervin Fox; Ken Butler; Tom Mosley; Others welcome.

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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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: Analysis will begin following proposal approval with the aim of completing analysis and submitting an abstract to the 2012 American Heart Association

Annual Meeting (deadline June 2012). The subsequent aim will be to complete a manuscript within 6 months of proposal approval.

4. Rationale:

African Americans have increased prevalence of cardiovascular risk factors, higher incidence rates of heart failure (HF), and worse prognosis compared to white patients.[1-7] Nevertheless, most epidemiologic studies of HF, including the Framingham Heart Study and Olmsted County, Minnesota, have enrolled predominantly white participants.[8,9] Consequently, HF in blacks remains relatively unexplored. In particular, the phenotypic profile of black patients with heart failure and preserved ejection fraction (HFpEF) compared to heart failure with reduced ejection fraction (HFrEF) and those without HF is not well understood. Therefore, we aim to clarify the relationships between risk factors, cardiac structure and function, and prognosis in blacks with HF.

The relative importance of cardiovascular risk factors for the development of heart failure may differ between blacks and whites. While coronary artery disease (CAD) is considered a leading etiology for heart failure, it appears to play a lesser role in blacks.[4] This is despite a higher prevalence of cardiovascular risk factors, namely hypertension, diabetes, smoking, obesity, and renal dysfunction.[6, 10-12] This pattern of risk factors aligns with the description of the "typical" HFpEF patient identified in predominantly white cohorts. However, among blacks these clinical characteristics have also been associated with left ventricular systolic dysfunction and lower ejection fraction.[6, 10, 11] Thus, the relationship between clinical risk factors and cardiac structure and function in blacks with HF remains unclear.

Left ventricular hypertrophy (LVH) is highly prevalent among the general African American population and is related to hypertension, diabetes, and obesity.[13-15] In addition, eccentric and concentric patterns of hypertrophy have been related to systolic and diastolic dysfunction, respectively.[13] However, the type and extent of cardiac remodeling in black patients with HF, especially as stratified according to HFpEF vs. HFrEF, has not been well described.

The distinction between HFpEF and HFrEF among African Americans carries prognostic and therapeutic importance. The Studies of Left Ventricular Dysfunction (SOLVD) trial demonstrated that black patients with mild to moderate left ventricular systolic dysfunction may have a worse prognosis than white patients and respond to medications (i.e. enalapril) differently.[7, 16] Building upon these findings, the African American Heart Failure Trial (AA-HeFT) specifically evaluated black patients with HFrEF and demonstrated a survival benefit of fixed dose combination hydralazine-nitrates.[17] In contrast, no therapies to date have been demonstrated to confer a survival benefit in patients with HFpEF. Thus, clarifying the relationships between clinical risk factors, cardiac structure and function, and prognosis in black patients with HF, and in particular HFpEF, remains an unmet need.

The Atherosclerosis Risk in Communities (ARIC) study is well suited to address outstanding and unresolved questions regarding HF in black patients as the Jackson, MS site specifically enrolled an African American cohort. 2,445 of the Jackson participants underwent echocardiography during visit 3. Using this data, we aim to describe the phenotypic profile of black patients with prevalent HFpEF as compared to subjects with

HFrEF and matched non HF controls. This will be the first analysis in ARIC to specifically evaluate HFpEF and address a gap in our knowledge of HF in black patients.

5. Main Hypothesis/Study Questions: The primary objective is to define clinical risk factors, cardiac structure and function, and prognosis in black patients with HFpEF as compared to HFrEF, and matched controls free from HF.

Hypothesis 1. The prevalence of clinical risk factors for heart failure differs between subjects with HFpEF and HFrEF; namely those with HFpEF will be older and have more comorbidities, such as hypertension, diabetes, anemia, and renal disease, but less coronary heart disease, compared to those with HFrEF.

Hypothesis 2. Subjects with HFpEF will have increased left ventricular mass, more frequent diastolic dysfunction, and larger left atrial size than matched controls, while left ventricular geometry will differ between those with HFpEF (concentric hypertrophy) and HFrEF (eccentric hypertrophy).

Hypothesis 3. Subjects with HFpEF will be at increased risk for all cause mortality, cardiovascular death, and hospitalization compared to matched controls, but lower risk for these outcomes compared to those with HFrEF.

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 African American cohort participants who underwent echocardiography (1993-1996) at the Jackson, MS center during visit 3. To be included in the analysis participants must have undergone echocardiography at visit 3 and have data available (end diastolic diameter and end systolic diameter) to calculate a left ventricular ejection fraction via Teicholz method. Jackson participants with prevalent heart failure at visit 3 will be identified as those with prevalent heart failure at visit 1 plus those with incident heart failure between visit 1 and the visit 3 date. Patients with missing echocardiographic data and/or heart failure status will be excluded. Participants with severe valvular heart disease will also be excluded. From Jackson participants with echocardiographic data available and without prevalent heart failure, age, gender, ± comorbidity matched controls will be identified.

Participants will be dichotomized according to prevalent HF status. Those with prevalent heart failure will then be stratified according to preserved (≥50%) or reduced (<50%) LVEF based upon the visit 3 echo. From the remaining cohort without prevalent heart failure, matched controls will then be identified as 1) At risk: age, gender, and comorbidity matched subjects, and 2) Normal: age and gender matched subjects free from cardiovascular disease and risk factors.

Clinical characteristics, echocardiographic cardiac structure and function, and outcomes will be compared between these groups, based upon data variables collected at visit 3. In particular, clinical variables to be evaluated include: age, gender, comorbidities, such as hypertension, diabetes, dyslipidemia, smoking status, coronary heart disease, stroke/tia, peripheral arterial disease, atrial fibrillation/flutter, obesity, 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, waist to hip ratio; creatinine (imputed from values obtained at visits 1, 2, and/or 4), WBC count, hemoglobin, red cell distribution width, glucose, and lipids; vascular stiffness by carotid ultrasound from visit 2; and pulmonary function tests from visit 2. Echocardiographic variables to be evaluated include: left atrial size, left ventricular (LV) size, aortic root dimension, LV fractional shortening and ejection fraction, valvular disease, regional wall motion abnormalities, mitral annular calcification, aortic valve fibrosis, LV wall thickness, LV mass, LV geometry, LV stroke volume and cardiac output, Doppler mitral inflow E and A wave peak velocities, and E/A ratio. Outcomes of interest include all cause mortality, cardiovascular hospitalizations, and cardiovascular death through December 31, 2008.

Categorical variables will be compared via $\chi 2$ or Fischer exact test, while continuous data will be compared between groups via Mann-U Whitney test. P values < 0.05 will be considered significant. Univariable and multivariable 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. Finally, Kaplan Meier survival analysis and Cox proportional hazard models will be used to assess the relationship between heart failure status and outcomes. Statistical comparisons will be made via the log rank test.

Limitations include that this is a cross sectional analysis using data collected at visit 3 which may not fully reflect clinical status at the time of the echocardiogram. Furthermore, creatinine, carotid stiffness, and pulmonary function tests were not measured at visit 3, therefore imputed values from visits 1, 2, and/or 4 will be used. Echocardiographic data is based upon M-mode, 2 dimensional, and blood flow Doppler measurements. Thus, ejection fraction and grading of diastolic function will not be assessed using current American Society of Echocardiography recommendations. Nevertheless, Teicholz' method for LVEF has previously been validated and transmitral E and A wave velocities and the E/A ratio to describe diastolic function have been previously published from ARIC.[18] We will not be able to assess overall prevalence of HFpEF vs. HFrEF as not all patients with prevalent HF at visit 1 or incident HF by visit 3 have echocardiographic data available. Finally, as the visit 3 echocardiogram was not performed concurrently with the HF event, the preserved versus reduced distinction will not reflect EF status at the time of HF diagnosis.

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 ____ 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

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 ____ 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)?

Tom Mosley, Alan Penman, Herman Taylor, Patricia Chang, Ervin Fox, Peter Johnson, Charles Moore , Saul Blecker, Cameron Guild, Sunil Agarwal, Tandaw Samdarshi. Echocardiographic Predictors of Incident CHF and Cardiovascular Events in African Americans. Manuscript proposal #1537 July 14, 2009.

Blecker S, Matsushita K, Fox E, Russell SD, Miller ER, 3rd, Taylor H, Brancati F, Coresh J. Left ventricular dysfunction as a risk factor for cardiovascular and noncardiovascular hospitalizations in African Americans. *Am Heart J*. 2010;160:488-495

Fox ER, Han H, Taylor HA, Walls UC, Samdarshi T, Skelton TN, Pan J, Arnett D. The prognostic value of the mitral diastolic filling velocity ratio for all-cause mortality and cardiovascular morbidity in African Americans: The Atherosclerotic Risks in Communities (ARIC) study. *Am Heart J*. 2006;152:749-755.

Fox ER, Taylor J, Taylor H, Han H, Samdarshi T, Arnett D, Myerson M. Left ventricular geometric patterns in the Jackson cohort of the Atherosclerotic Risk in Communities (ARIC) study: Clinical correlates and influences on systolic and diastolic dysfunction. *Am Heart J*. 2007;153:238-244.

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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