ARIC Manuscript Proposal #1942

PC Reviewed: 5/8/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: Cardiac structure and function in elderly African-Americans with heart failure with preserved ejection fraction

b. Abbreviated Title (Length 26 characters): HFpEF in Elderly African-Americans

2. Writing Group:
   Writing group members: Deepak K. Gupta, Amil M. Shah, Scott D. Solomon; 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. 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) predominantly affects the elderly, with over 80% of HF hospitalizations occurring in persons over 65 years of age.\(^1\) In this age group, African-Americans have the highest risk of HF hospitalization, approximately 1.5 times that of white Americans, and have higher rates of readmission.\(^2,\)\(^3\) While recent data suggests declining hospitalization rates for HF over the past decade, African American men had the lowest rate of decline.\(^4\) Additionally, among the elderly, population studies suggest that heart failure with preserved ejection fraction (HFpEF) accounts for the majority of cases HF and that those with HFpEF were more likely to be African American as compared to healthy and hypertensive subjects without HF.\(^5,\)\(^6\) These data suggest elderly African-Americans experience a disproportionately high burden of HF.

However, there is a paucity of data regarding clinical characteristics as well as cardiac structure and function in elderly African Americans at risk for or in those with HF. The Cardiovascular Health Study demonstrated increased left ventricular diastolic diameter, stroke volume, and cardiac output in those with HFpEF as compared to those with hypertension but without HF. These findings were ascribed to the high prevalence of extra-cardiac comorbidities, such as obesity, anemia, and chronic kidney disease that contribute to volume overload, but these results were not further stratified by race.\(^6\) Furthermore, this analysis was performed on echocardiograms obtained in the early 1990s and may not reflect characteristics of cardiac structure and function in a contemporary population of elderly patients with HFpEF.

The Atherosclerosis Risk in Communities (ARIC) study is well suited to address outstanding questions regarding cardiac structure and function among elderly African Americans with HF. As part of visit 5, ARIC participants are undergoing comprehensive, state of the art, transthoracic echocardiography offering a unique opportunity to understand that pathophysiology of cardiovascular disease. It is anticipated that approximately 1,000-1,500 African Americans will undergo echocardiography during this visit. Using this data, we aim to describe cardiac structure and function in elderly African Americans with prevalent HFpEF as compared to subjects with hypertension without HF and healthy controls.

5. **Main Hypothesis/Study Questions:** The primary objective is to define clinical characteristics as well as cardiac structure and function, and prognosis in African-American participants with HFpEF as compared to hypertensive participants without HF, and healthy controls.

   **Hypothesis 1.** The prevalence of clinical risk factors for heart failure differs between subjects with HFpEF and those with hypertension without HF; namely those with HFpEF will be older and have more comorbidities, such as hypertension, diabetes, obesity, anemia, and renal disease.
Hypothesis 2. Subjects with HFpEF will have increased left ventricular mass, more frequent diastolic dysfunction, larger left atrial size, but similar left ventricular end diastolic diameter, volumes, and cardiac output as compared to those without HF.

Hypothesis 3. Subjects with HFpEF will be at increased risk for all cause mortality as compared to those without HF.

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 during visit 5 (2011-2012). 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 with severe valvular heart disease will also be excluded.

Participants free from HF, risk factors for HF, cardiovascular medication use, and structural or functional cardiac abnormalities will be categorized as “healthy normals”. Prevalent heart failure will be defined as those with prevalent HF at visit 1 plus those with incident HF (as previously defined) up to visit 5. Participants with prevalent HF will also be stratified according to preserved (≥50%) or reduced (<50%) LVEF based upon the visit 5 echo. Those without HF, but with hypertension, will define the third group. Clinical characteristics as well as cardiac structure and function will be compared between these groups, based upon data variables collected at visit 5. Prognosis (all cause mortality) will also be assessed and compared between groups.

Clinical variables 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, c reactive protein; 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 χ² 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. 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 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.

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)?

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.csc.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.csc.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.

References


