ARIC Manuscript Proposal #3392

PC Reviewed: 5/14/19 **Status: _____** **Priority:2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Sex and Race Differences in Cardiac Structure and Function, and Heart Failure Risk in Late Life: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Race & sex, echo, and HF in elderly

2. Writing Group:
Writing group members: Alvin Chandra, Hicham Skali, Brian Claggett, Scott D. Solomon, Thomas Mosley, Kunihiro Matsushita, Dalane Kitzman, Jospeh Rossi, Stuart Russell, Suma Konety, Patricia Chang, Amil M Shah; Others welcome.

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

First author: **Alvin Chandra, MD**
Address: 75 Francis St
Boston, MA 02115

Phone: 617-525-3122 Fax: 617-582-6027
E-mail: achandra5@bwh.harvard.edu

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).

Name: **Amil M Shah, MD MPH**
Address: 75 Francis Street
Boston, MA 02115

Phone: 617-525-6733 Fax: 617-582-6027
E-mail: ashah11@rics.bwh.harvard.edu

3. Timeline:
Our analysis will start after this proposal is approved. We anticipate final manuscript completion in approximately 6 months after proposal approval.

4. Rationale:

The combination of an aging population and treatment advances for cardiovascular disease and other non-cardiovascular diseases have contributed to increasing incidence and prevalence of

heart failure (HF) in the United States.[1,2] However, the risk for HF has been reported to differ significantly by race and gender. Findings from MESA demonstrated higher risk of incident HF in black participants when compared to Hispanic, white, and Chinese American participants.[3] Blacks have also been shown to have higher incidence and worse prognosis of HF in younger age groups.[4,5,6] In the CARDIA study, of the 27 incident HF cases, 26 occurred in African American participants.

Among the 2 HF subtypes [heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF)], the lifetime risk for HFrEF was similar in blacks and non-blacks, whereas the lifetime risk for HFpEF was lower in blacks in a recent analysis of 2 cohort studies (CHS and MESA).[7] In HFrEF, the lifetime risk was higher in men compared to women, whereas in HFpEF, the lifetime risk was similar in both genders.[7] Sex-specific differences in heart failure risk factors have been reported. For example, diabetes and hypertension appear more strongly associated with HF incidence in women compared to men.[8,9] Previous results from ARIC have also demonstrated the importance of both sex and race. In that analysis of the cohort in largely mid-life, HF incidence rates in black women were more similar to those of black men and white men, while the risk for white women was significantly less.[10] More recently, data from the ARIC Surveillance study showed that HFrEF-related hospitalization was more common in men (both white and black) compared to women, and HFpEF-related hospitalization was more common in white women.[11]

The ACC/AHA HF staging system was developed to facilitate the detection and recognition of persons at heightened risk for clinical HF, such that preventative therapies could be instituted. This system defines stage A as asymptomatic persons with HF risk factors but without cardiac structural and functional abnormalities; stage B as asymptomatic persons with evidence of cardiac structural/functional abnormalities; and stage C as persons with current/prior signs and symptoms of HF (clinical HF).[12] A previous study from ARIC found that majority of ARIC participants in late life (at Visit 5) had either Stage A or B HF, and were at heightened risk for developing symptomatic HF.[13] Existing data suggested that sex and race significantly impact cardiac structure and function. Findings from CARDIA showed that black men had greater LV size and lower LV systolic and diastolic function when compared to black women and white men/women in a younger/middle-aged cohort.[14] A study from HyperGEN cohort found that black race was associated with increased LV mass and relative wall thickness in both sexes.[15] However, little data exist regarding sex and race-based differences in cardiac structure and function in late life, when HF risk is highest.

HF incidence and prevalence are highest in late life, with ≥80% of HF hospitalizations occur in persons above the age of 65 years.[16] However, despite their importance influence in early- and mid-life, race- and sex-based differences in HF risk factors, cardiac structure and function, and incident HF in late life are understudied.[17,18,**Error! Bookmark not defined.**] Our aim is to examine sex- and race-based differences in cardiac structure and function and HF risk in late-life.

5. Main Hypothesis/Study Questions:

We hypothesize that in an elderly cohort free of heart failure, male gender and black race will be associated with higher prevalence of established HF risk factors, higher prevalence pathological changes in cardiac structure and function, and higher future HF incidence.

We will address the following specific aims:

1. Quantify differences in HF risk factors (diabetes, hypertension, obesity, coronary disease, atrial fibrillation, and chronic kidney disease) between participant subgroups based on race and sex
2. Quantify differences in cardiac structure and function between participant subgroups based on race and sex
3. Compare the risk of incident adjudicated HF overall, and HF phenotype (HFrEF or HFpEF), between participant subgroups based on race and sex

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 and Inclusion/Exclusion Criteria:
Inclusion: Attended Visit 5
Exclusions: Prevalent HF at Visit 5 based on PREVDEFHF51 variable; absent echocardiographic data at Visit 5; race other than white or black at Visit 5

For Aims 1 and 2, we will perform a cross-sectional analysis of the association of race and gender with HF risk factors and echocardiographic measures at Visit 5. For Aim 3, we will perform time-to-event analysis for incident adjudicated HF (overall, HFrEF, and HFpEF) post-visit 5.

Key variables of interest:
1. Clinical characteristics (Visit 5): age, gender, race/ethnicity, ARIC center, systolic blood pressure, diastolic blood pressure, heart rate, history of coronary heart disease, atrial fibrillation, hypertension, diabetes, body mass index, eGFR, chronic kidney disease, smoking, education level, total combined family income, physical activity level

2. Echocardiographic variables (visit 5)
- LV structure: LV systolic and diastolic diameters and volumes, wall thickness, relative wall thickness, and left ventricular hypertrophy
- LV systolic function: ejection fraction, mitral annular systolic velocities, longitudinal strain, circumferential strain, radial strain
- LV diastolic function: E wave, septal and lateral, TDI E', E/e' ratio, LAVi

3. Adjudicated incident HF (overall, HFrEF, and HFpEF) and death

Data analysis:
Participants will be stratified by gender, and within each gender, they will be stratified by race. Clinical characteristics, laboratory variables, and echocardiographic measures of

LV structure, systolic function, and diastolic function will be described by each gender-race category, i.e. white men, black men, white women, and black women. Continuous variables will be shown as mean ± standard deviation if normally distributed. Categorical variables will be shown as proportions. For Aims 1 and 2, association of gender/race with clinical characteristics and echocardiographic measures of LV structure, systolic function, and diastolic function will be evaluated by comparing races within each gender category using t-test (continuous variables) and chi-square test (categorical variables). We will adjust the comparison of echocardiographic measures between groups for age using multivariable linear and logistic regression modeling, and then additionally adjust for HF risk factors differing significantly between groups. We will perform interaction testing between gender and the association of race with the characteristics mentioned above. To address Aim 3, parallel analyses will be performed for the endpoint of HF overall, HFpEF, and HFrEF using multivariable Cox proportional hazard models.

Limitations:
Attendance bias may limit the generalizability of our findings. We will attempt to mitigate this by performing sensitivity analyses with inverse probability of attrition weighting. The strong linkage between race and field center in ARIC makes center effects difficult to disentangle from 'race/ethnicity' effects. We will attempt to mitigate this by accounting for measures of socioeconomic status in multivariable models. We will also clearly state this limitation in the manuscript discussion section.

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 ICTDER 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 ____ 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)?

#927: Aaron Folsom, Paul Sorlie, Woody Chambless, Patricia Chang. Heart Failure Incidence and Survival: 13 Year Follow up of the ARIC Cohort

#2281: Kavita Sharma, Sunil K. Agarwal, Lisa Wruck, Patricia Chang, Amil Shah, Kunihiro Matsushita, Dalane Kitzman, Anita Deswal, Gerardo Heiss, Josef Coresh, Wayne Rosamond, Stuart Russell. Race and Gender Differences in Heart Failure with Preserved Ejection Fraction: Morbidity, Case Fatality, and their Determinants

#1942: Deepak K. Gupta, Amil M. Shah, Scott D. Solomon. Cardiac structure and function in elderly African-Americans with heart failure with preserved ejection fraction

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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