1.a. Full Title: Racial differences in left atrial structure and function: the ARIC Study

b. Abbreviated Title (Length 26 characters): Left atrium and race

2. Writing Group:
   Writing group members: Deepak K. Gupta, Amil M. Shah, Susan Cheng, Hicham Skali, Brian Claggett, Cameron Guild, Kenneth R Butler, Eric Boerwinkle, Alvaro Alonso, Elsayed Z Soliman, Others Welcome, Bernard Gersh, 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 with the aim of completing analysis and a manuscript within 6 months of data becoming available.

4. Rationale:

Atrial fibrillation (AF) is the most common cardiac arrhythmia, is increasing in prevalence, and predominantly affects older individuals such that the estimated lifetime risk for the
development of AF approaches 1/6 (1). However, these data were derived from predominantly Caucasian cohorts and previous reports suggest a differential risk and prevalence of AF according to race, such that AF may be less common in African-Americans as compared to Caucasian Americans (2-11). This may occur despite a higher burden of cardiovascular risk factors and metabolic syndrome in African Americans (12-14). In addition, a lower incidence of AF has been observed in African-American participants in ARIC despite more frequent ECG markers of atrial abnormalities (15). While this may in part be related to ascertainment bias and the sensitivity of measures to detect AF particularly among African Americans in the community (16-18), racial differences in the incidence of AF have also been noted in the post-cardiac surgery period during which diagnosis of AF should be more uniform and complete (19-22).

There has been significant interest in trying to understand the underlying explanations for the differential risk for AF according to race. In particular, attention has been given to genetic variations that may contribute to AF (23-28). For example, a chromosome 4q25 variant (rs2200733) has been associated with a higher risk for AF and among African-Americans this allele was more commonly present in those with AF, as compared to those without AF (29). In addition to single gene/locus polymorphisms, patterns of ancestry identified through genetic admixture mapping may in part explain the susceptibility to AF, such that increasing European ancestry was significantly and independently associated with an increased risk of AF (30). Recently a genome-wide association study identified novel variants for AF in African-Americans, but did not find that the admixture of European ancestry explained the decreased AF susceptibility in African-Americans (31). Together these findings suggest a genetic component to AF risk, which may not be fully explained by genetic ancestry alone.

While much attention has been given to genetic variants that may explain the differential AF risk according to race, the data regarding racial differences in cardiac structure and function that may contribute to AF susceptibility are limited. As larger left atrial (LA) size and volumes are associated with increased risks of AF, a few groups have reported on LA size in relation to race with some suggesting that LA size is smaller among African-Americans (32,33). However, the representation of African-Americans in each of these studies was relatively low. Furthermore, whether genetic variants related to AF risk or percent European ancestry are related to contemporary measures of LA structure and function are unknown.

The Atherosclerosis Risk in Communities study is uniquely poised to address racial differences in LA structure and function and assess the relationship to genetic variation. During ARIC visit 5 (2011-2013) approximately 6,500 elderly participants (~25% African-American) underwent comprehensive 12-lead ECG and transthoracic echocardiography. Furthermore, most ARIC participants had blood collected at visit 1 with subsequent genotyping performed on these samples. Therefore ARIC offers an unmatched opportunity to phenotype LA structure and function in an elderly population at greatest risk for AF and pair this with existing genomic data.

5. **Main Hypothesis/Study Questions:**

   **Main Objectives:**

   1) To describe racial differences in ECG measures of atrial size.

   *Hypothesis: Atrial abnormalities, as measured by ECG, are significantly more common in African-Americans as compared to Caucasians.*

   2) To describe racial differences in echocardiographic measures of LA structure and function according to race.
Hypothesis: LA size (diameters and volumes) are significantly larger in Caucasians than in African-Americans.

3) To describe the relationships between ECG and echocardiographic measures of LA size and function according to race.
   Hypothesis: The association between ECG and echocardiographic measures of LA structure and function is modified by race, such that the relationship is more highly correlated in Caucasians than African-Americans.

4) To describe the relationships between genetic ancestry and/or previously described variants associated with AF and ECG and echocardiographic measures of LA structure and function.
   Hypothesis: European ancestry and genetic polymorphisms associated with AF are significantly associated with larger LA.

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 at visit 5.

Study population
To be included in the analysis the participant must have undergone electrocardiography and echocardiography during ARIC visit 5 (2011-2013) with available technically adequate measurements of atrial structure on ECG and echocardiography.

Exclusion criteria include:
- Self reported race other than Caucasian (white) or African-American (black)
- Prevalent or missing AF status at visit 5, including those in AF at the time of echocardiography, those with AF on ECG.
- History of prior stroke (as these participants may have had unrecognized atrial fibrillation or atrial flutter)
- Paced atrial and/or ventricular rhythms
- Uninterpretable ECG and/or echocardiographic
- Missing covariate data (age, gender, BMI, height, weight, diabetes, hypertension, prevalent CHD, prevalent HF, smoking status, alcohol status, systolic BP, diastolic BP, glucose, creatinine, hemoglobin)
- Moderate or severe mitral regurgitation or stenosis.

Primary Independent Variables
  Self reported race
  Percent European ancestry (from admixture mapping)
  Specific genetic polymorphisms previously reported to be related to AF
    Chromosome 4q25: rs2200733, rs4631108, rs6843082, rs10033464; rs6817105
    Chromosome 16q22: rs2106261, rs4845396, rs7293343
    Chromosome 1q21: rs13376333, rs16971547; rs6666258
Chromosome 1q24: rs3903239
Chromosome 7q31: rs3807989
Chromosome 14q23: rs1152591
Chromosome 9q22: rs1152591; rs10821415
Chromosome 15q24: rs7164883
Chromosome 10q22: rs10824026

Covariates
Defined according to standard ARIC visit 5 definitions and include, but are not limited to:
Clinical characteristics: age, sex, field center, hypertension, use of antihypertensive medications, diabetes mellitus, CHD, HF, alcohol use, smoking status, body mass index, heart rate, blood pressure, hemoglobin, creatinine, and eGFR.
ECG parameters: QRS voltage, left ventricular hypertrophy
Echo parameters: left ventricular (LV) size and volumes, LV ejection fraction, valvular disease, LV wall thickness, LV mass, LV geometry, LV stroke volume and cardiac output, Doppler mitral inflow E and A wave peak velocities, E/A ratio, mitral annular tissue Doppler e’ and a’ velocities, as well as E/e’

Primary dependent variables
ECG: P wave amplitude, P wave duration, P wave terminal force, P wave area, and PR duration.
Echocardiography: LA diameter (anterior-posterior), LA length (apical 4 and 2 chamber views), and LA volumes

Statistical analyses:
Within each sex strata, summary statistics for clinical, ECG, and echocardiographic characteristics will be reported as counts (%) or medians (inter-quartile ranges), as appropriate. Categorical variables will be compared via χ² or Fischer exact test, while continuous data will be compared between race via Wilcoxon rank sum test. Differences in ECG and echocardiographic parameters will also be assessed in adjusted analyses to control for demographic and clinical characteristics that may also be related to atrial structure and function, including but not limited to age, gender, height, history of hypertension, anti-hypertensive medication use, CHD, HF, diabetes mellitus, alcohol use, smoking status, heart rate, blood pressure, BMI, eGFR, and hemoglobin. The relationships between ECG and echocardiographic measures of LA structure and function will be assessed using Spearman rank correlation, stratified by race. Univariate and multivariate linear regression will be performed to assess the relationships between clinical and genetic characteristics and atrial structure and function determined by ECG and echocardiography. Prior to entry into linear regression models, the distribution of continuous variables will be assessed, with appropriate transformations as needed. The association between ECG and echo measures of LA structure will also be assessed as categorical variables using previously defined cut off values, e.g. ECG P wave terminal force > 4 mV, P wave duration > 120 msec, PR > 200 ms, etc, and Echo LA AP diameter > 4cm, LAVI > 29ml/m², etc. P values < 0.05 will be considered significant. We will assess for effect modification on the relationship between race and LA structure and function by prevalent cardiovascular disease (CHD or HF). We will also evaluate for the effect of a history of AF, but not being in AF at the time of
echocardiography or ECG at visit 5 in a sensitivity analysis. We will also perform a sensitivity analyses excluding participants with a QRS duration $\geq 120$ msec.

**Limitations**

Comprehensive transthoracic echocardiography was only performed in Caucasians and African-Americans at visit 5 and therefore we will not be able to assess associations with change in LA structure and function. While adjusted analyses will be performed there may be residual confounding with regards to unmeasured factors that contribute to LA structure and function. Race was determined by self report. Genetic admixture mapping may not completely inform ancestry and in ARIC race is linked to geographic locations of participant recruitment. The findings of associations between race and atrial structure and function would not alone explain the observation of a lower incidence and prevalence of AF in African-Americans as compared to Caucasians.

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?  _X__ Yes  ____ 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”?  _X__ 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](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)?

MS Proposal #1351:
MS Proposal #1389:

MS Proposal # 1396


MS Proposal #1628

MS Proposal #1156

MS Proposal #1453

MS Proposal # 1559

MS Proposal #2105

- The main difference between this proposal and MS Proposal #2105 is that the current proposal excludes participants with prevalent AF and will assess for racial differences in atrial structure and function. MS Proposal #2105 has the primary objective of identifying factors that may be associated with AF in participants with normal LA size.
11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  

____X__ Yes    ____ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* ____________)

_x_  B. primarily based on ARIC data with ancillary data playing a minor role  
(usually control variables; list number(s)* __2004.10________  __________)

*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:


32. Manolio TA, Gottdiener JS, Tsang TS, Gardin JM. Left atrial dimensions determined by M-mode echocardiography in black and white older (> or =65 years) adults (The Cardiovascular Health Study). Am J Cardiol 2002;90:983-7.