ARIC Manuscript Proposal #1930

PC Reviewed: 4/17/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Echocardiographic measures of cardiac structure and function and the risk of Atrial Fibrillation in Blacks: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Echocardiogram and AF in Blacks

2. Writing Group:
Writing group members: Wobo Bekwelem, Suma Konety, Scott Solomon, Elsayed Soliman, Laura Loehr, Jeffrey R. Misialek, Faye L. Lopez, Ervin R. Fox, Thomas H. Mosley, Alvaro Alonso

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __WB___ **[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: Following approval of this manuscript by the ARIC Publications Committee this work will lead to manuscript within 6 months (likely by July 2012).

4. Rationale:

Atrial Fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and its prevalence in the population is increasing (1-3). Multiple risk factors have been associated with AF including hypertension, age, and underlying structural and functional cardiac abnormalities such as heart failure, chamber dilatation, diastolic dysfunction, and valvular problems (4-6). Although blacks have a higher prevalence than Caucasians of most AF risk factors (7,8), they are thought to be at lower risk for developing AF (2,11). Echocardiography is a useful modality in evaluating underlying structural and functional heart disease, and several studies have examined the link between various echocardiographic markers of cardiac structure and function, and AF in Caucasians (9,10). To our knowledge, however, no study has examined this association in a large cohort with long term follow up among blacks. Our analyses will be the first to systematically assess echocardiographic parameters predicting AF in blacks, and attempt to identify factors contributing to this disconnect between prevalence of risk factors and AF incidence in this population.

The availability of echocardiograms at visit 3 for members of the Jackson cohort (all black), will allow us to examine, using echocardiography, which measures of cardiac structure and function are associated with development of AF in blacks, what the magnitude and direction of this association is, and how it might explain the possible lower incidence of AF in this population.

5. Main Hypothesis/Study Questions:

We hypothesize that echocardiographic measures of cardiac structure and function are associated independently with incident atrial fibrillation (AF) in Blacks.
As a secondary hypothesis, we propose that addition of ECG measures of increased LA size (p-wave indices) and ECG-LVH (Cornell voltage), to echocardiographic parameters will improve prediction of AF.

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).

Design:

This study will assess the association between echocardiographic parameters and the incidence of AF using a longitudinal data analysis approach. Data will be obtained from the visit 3 exam on Blacks in the Jackson cohort who have echocardiographic measures available. For this analysis, we will exclude individuals with prevalent AF at visit 3, and those missing variables in any of the covariates.

Endpoint:

The main outcome variable is time to AF from visit 3 through 2008. Incident AF will be defined by ECGs in visit 4 or ICD9CM code 427.31 or 427.32 in any hospitalization after visit 3 (11,12).
In preliminary analyses, there are approximately 180 new AF events from visit 3 through the end of 2008 among eligible Jackson participants, which will provide adequate power to detect moderate to strong associations.

Exposures:

A. Visit 3 echocardiographic parameters, including the following

1. Left Ventricular systolic Function
   - Ejection Fraction (LVEF) - qualitative
2. Left Ventricular size
   - Left Ventricular Internal Diameter M-Mode (diastole),
3. LV Mass
   - Left Ventricular Mass Index (g/m),
4. Left Atrial size:
   - left atrial diameter (M-mode parasternal long-axis)
5. Transmitral Doppler Velocity Patterns/ LV diastolic function
   - Late inflow Doppler mitral valve velocity time integral (A wave VTI)
   - Early inflow Doppler mitral valve velocity time integral (E wave VTI)

B. Visit 3 ECG parameters, including the following

1. ECG measures of increased LA size (p-wave indices) – yes/no
2. ECG-LVH (Cornell voltage) – yes/no

Main covariates:

We will calculate the individual predicted risk of AF using the recently developed he CHARGE AF risk score, which will be calculated from the following covariates measured at visit 3: Age, height, weight, current smoking, Systolic blood pressure, diastolic blood pressure, anti-hypertensive medications, diabetes, prevalent heart failure, and prevalent myocardial infarction. {Reference: Alonso et al; A simple model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium – submitted}. This predicted risk will be used as an adjustment covariate in all analyses.

Other variables that will be considered as potential confounders include: education, lipids (LDLc, HDLc), sport index, anti-hyperlipidemic medications, digoxin. Incident HF and incident MI will be considered in additional analyses as potential mediators.

Analysis:

We will use Cox proportional hazards with time to AF as the main outcome variable. Echocardiographic parameters will be modeled as a continuous variable and as quintiles. Non-linear associations will be explored with restricted cubic splines. In an initial model, we will adjust for age and sex. A second model will additionally adjust for the CHARGE-AF risk score. A third model will additionally adjust for other potential confounders measured at visit 3, if relevant (see above). In a final model, we will additionally adjust

for incident HF and MI as time-dependent covariates to assess potential mediation. We will determine whether echocardiographic measures improve the predictive ability of the CHARGE AF risk score measuring improvement in C-statistic and calculating the Net Reclassification Improvement.

In a sensitivity analysis, we will exclude cases of AF occurring in the first 2 years after baseline (visit 3), to avoid including possible prevalent AF cases as new incident cases. Interactions between echocardiographic parameters and sex will be examined. We will also examine interactions between these parameters and hypertension (a major risk factor for AF).

Finally, as a secondary analysis, we will compare the predictive ability of ECG measures of increased LA size (p-wave indices) and ECG-LVH (Cornell voltage), with those of echocardiography, and determine whether ECG measures have predictive value beyond that provided by echocardiographic measures.

Limitations:
NT-proBNP, TSH and eGFR, markers of HF, thyroid dysfunction and renal disease respectively, which are recognized risk factors for AF were not measured at visit 3, hence we are unable to adjust for them.

References:

1. Majeed A, Moser K, Carroll K. Trends in the prevalence and management of atrial fibrillation in general practice in England and Wales, 1994-1998: analysis of data from the general practice research database. *Heart.* 2001;86:284-288.

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11. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J.* 2009;158(1):111-117.

12. Chamberlain AM, Agarwal SK, Ambrose M, Folsom AR, Soliman EZ, Alonso A. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J.* 2010;159(5):850-856.

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

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)?

Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2009;158(1):111-117.

Chamberlain AM, Agarwal SK, Ambrose M, Folsom AR, Soliman EZ, Alonso A. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J*. 2010;159(5):850-856.

MP1537: Fox E, et al. Echocardiographic predictors of incident CHF and cardiovascular events in AFrican Americans.

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

_X_ A. primarily the result of an ancillary study (list number* 2008.12)

___ 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.