ARIC Manuscript Proposal #1954

PC Reviewed: 7/10/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Left Ventricular Hypertrophy and Coronary Heart Disease Risk Reclassification by Race: The Atherosclerosis Risk in Communities (ARIC) Study**

b. Abbreviated Title (Length 26 characters): **LVH for CHD Risk Classification**

2. Writing Group:

Writing group members: Tochi M. Okwuosa, Elsayed Z. Soliman, Alvaro Alonso, Faye Lopez, Kim A. Williams, Keith C. Ferdinand

I, Tochi Okwuosa, confirm that all the coauthors have given their approval for this manuscript proposal. _T.O._ **[please confirm with your initials electronically or in writing]**

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3. Timeline: Start immediately after approval (expected June 2012). Submit manuscript by December 2012.

4. Rationale:

Cardiovascular disease (CVD) – the leading cause of morbidity and mortality in the United States (US) – is significantly more prevalent in black men and women compared with any other

racial/ethnic group within the US.[1] It is a major contributor to the reduced life expectancy observed in African-Americans.[2] Compared with any other race/ethnic group in the US, African-Americans have the highest incidence of stroke, heart failure, sudden death, and CVD in general – with an earlier age of onset.[3, 4] They also exhibit the highest overall prevalence of hypertension and out-of-hospital coronary deaths, with highest mortality rates from hypertension, heart failure, stroke and sudden cardiac death. The high rate of CVD and CHD observed in African-Americans appears to be out of proportion to risk burden, and various mechanisms have been proposed for this disparity.

Left ventricular hypertrophy (LVH), diagnosed using 12-lead ECG, robustly predicts CVD events (including myocardial infarction (MI), sudden death, stroke, congestive heart failure (CHF) and overall CVD mortality,[5-7] independent of traditional cardiovascular risk factors including hypertension, diabetes, smoking status and dyslipidemia.[5, 8] It is also a major independent predictor of cardiovascular mortality, and African-Americans are known to have higher left ventricular mass compared with whites.[9-11] LVH is more prevalent in blacks than whites,[10] and in African-Americans, LVH is an independent predictor of CHD/CVD survival,[8, 10, 12] and appears to be more important than multi-vessel CAD and left ventricular systolic dysfunction in predicting survival in this population.[10] Furthermore ECG-determined LVH regression is associated with lower cardiovascular morbidity and mortality, as well as lower overall mortality, independent of blood pressure-lowering and treatment modality in patients with essential hypertension.[13, 14] As such, LVH has been cited as a possible major player in black-white differential in CVD survival.

Appropriate risk prediction and prognostication – with the goal of prevention and management of CHD/CVD – is an important component in the determination of appropriate patient care. Conventional risk assessment tools have traditionally incorporated risk factors such as age, gender, diabetes, hypertension, smoking status and dyslipidemia; in addition to extent of CAD and systolic cardiac dysfunction in the prediction of CHD/CVD risk. While LVH has been determined as an important prognosticator of CHD/CVD outcomes beyond these traditional CV risk factors, it has not been incorporated into the usual risk prediction tools for CHD assessment. ECG-diagnosed LVH was incorporated into the Framingham risk prediction tool for stroke, but not that for CHD – despite a large effect of LVH on CHD risk prediction.[15-17] One reason that has been cited for not incorporating LVH into the CHD Framingham risk prediction tool is lack of a universal criteria for what constitutes ECG diagnosis of LVH. Nonetheless, the Framingham risk score has been shown to be equally effective as a risk prediction tool in blacks as in whites.[18] Whether LVH would improve this risk prediction in either or both racial groups is unknown.

Cardiac MRI is the current standard of reference for accurate and reproducible assessment of left ventricular mass.[19] Combined, the various ECG criteria for diagnosis of LVH have shown low sensitivity, but high specificity for diagnosis of magnetic resonance imaging (MRI)-defined LVH, particularly in African-Americans.[20] This means that ECG-diagnosed LVH has significant ability to rule in MRI-defined LVH.

Using the various developed criteria for LVH diagnosis by ECG, we propose to evaluate the ability of LVH to predict CHD outcomes beyond traditional cardiovascular risk factors in black, compared with white men and women. Findings from this study might provide further insight

into observed black-white differences in CVD outcomes, and might further support the incorporation of LVH into the general cardiovascular risk assessment tools. This is particularly essential clinically since ECG is a very inexpensive and accessible modality for assessment various aspects of CVD.

5. Main Hypothesis/Study Questions:

a. In terms of CHD events, a model based on traditional risk factors + LVH will correctly reclassify participants in the ARIC cohort beyond the model made up of traditional risk factors (based on the Framingham Risk Score [FRS]) only

b. The model based on traditional risk factors + LVH will correctly reclassify blacks more than whites

c. The performance of ECG-LVH criteria in the models will vary with some criteria being more predictive than others

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).

All ARIC participants with good quality baseline ECG data will be eligible for inclusion in this analysis. We willexcludeparticipants with prevalent CHD at baseline, ECG conditions that make measurment or interpretation of LVH inappropriate according to the current AHA/ACCF/HRS recomemdations[21] (left bundle branch block, pacemakers, Wolf-Parkinson-White (WPW) syndrome), those with missing covariates and those with race other than white or black.

Summary of variables of interest:

Demographic and clinical variables (Covariates)

- Age
- Race
- Sex
- Site
- Body mass index
- Systolic blood pressure
- Diastolic blood pressure
- Use of antihypertensive medication
- Total cholesterol
- HDL cholesterol
- Current smoker
- Diabetes
- Current drinker
- Prior CHD
- Prior stroke
- Prior heart failure
- Education level
- Family income

ECG variables (Exposure measurement)

In collaboration with the ARIC ECG reading center (represented in this proposal; EZ Soliman, PI of ARIC ECG Reading Center), LVH using the following criteria will be calculated:

- Sokolow-Lyon voltage (SV1 + RV5/V6 ≥3.5 mV and/or RaVL ≥1.1 mV)
- Gender-specific Cornell voltage (SV3 + RaVL N2.8 mV [for men] and >2.0 mV [for women])
- Romhilt-Estes point score (partition values ≥5 points and ≥4 points will be examined)
- Framingham ECG score (presence of a strain pattern and at least 1 of the following voltage criteria: RI + SIII ≥2.5 mV, SV1/V2 + RV5/V6 ≥3.5 mV, the S wave on the right precordial lead ≥2.5 mV, and the R wave on the left precordial lead ≥2.5 mV)
- Left ventricular strain (presence of isolated ST-T wave ischemic abnormalities as per Novacode 5.5 or 5.6)
- Perguia score (requires positivity of at least 1 of the following 3 criteria: SV3 + RaVL >2.4 mV [men] or >2.0 mV [women], left ventricular strain, or Romhilt-Estes score of ≥5)
- Minnesota code 3.1 (RV5/V6 >2.6 mV or RI/II/III/aVF >2 mV or RaVL >1.2 mV)
- Lewis index ([RI + SIII] − [RIII + SI] >1.7 mV)
- Framingham-adjusted Cornell voltage (men: [RaVL + SV3 + 0.0174*{age − 49} + 0.191*{body mass index (BMI) − 26.5}] ≥2.8 mV; women: [RaVL + SV3 + 0.0387*{age − 50} + 0.212*{BMI − 24.9}] ≥2.0 mV)
- Cornell voltage product ([RaVL + SV3]*QRS duration ≥243,600 μVms)
- Sokolow-Lyon voltage product ([SV1 + RV5/RV6]*QRS duration ≥371,000 μVms)
- Gubner and Ungerleider voltage (RI + SIII ≥2.2 mV)

Other ECG variables will include heart rate, QRS duration, and ECG-evidence of old myocardial infarction by the Minnesota Code criteria.

Outcome

- Incident CHD. This will include fatal and non-fatal CHD during ARIC follow-up defined as a definite/ probable MI, death from CHD, resuscitated cardiac arrest.
- Total (all cause) mortality.

Follow-up time will be the time from baseline until death, the first CHD event, loss to follow-up, or Dec. 31st 2009, whichever comes first.

Brief Analytic Plan:

ECG LVH will be determined within the ARIC cohort using various criteria. General linear models will be used to compare Baseline characteristics stratified by ECG LVH status (by any of the listed LVH criteria) will be compared by student's T-test for continuous variables, and chi-square tests for categorical variables. Results will also be stratified by race and sex (since sex and race differences have been well described). Cox proportional hazards models will be used to estimate *10 and 20 year* risks of events occurrence. Model 1 will employ the Framingham risk *factors/model,* while model 2 will add LVH using each set of criteria, separately, to model 1. The risk estimates will be categorized as <10%, 10 to less than 20%, and >20%, corresponding to low, intermediate and high risk respectively. The C-statistic will be used to assess the discrimination ability of each model (the ability of each model to predict who will and will not have events). Receive operator characteristics (ROC) curves will then constructed for each model and compared. The integrated discrimination index (IDI) – which measures the improvement in the average sensitivity of each model[22] – will be calculated for each model. Cross tabulations of risk categories based on both models, will then be performed to describe the number and percentage of participants who were reclassified appropriately (to a lower group for non-events, and a higher group for events) and inappropriately (to a lower group for events, and a higher group for non-events). Based on this, the net reclassification index (NRI) will be calculated as: ([number of events reclassified higher – number of events reclassified lower]/number of events) + ([number or events reclassified lower-number of events reclassified higher]/number of non-events). Kaplan-Meier 10-year and 20-year event rates will be calculated. All data will be assessed all together, stratified by race, and stratified by sex. Statistical significance will be set *a priori* at P <0.05.

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)?

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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