Monday, March 13, 2017

Dear Dr. Coresh, ARIC Publications Committee,

We thank you for the opportunity to revise and resubmit our proposal. Please find below, our response to the issues raised by the ARIC P&P committee:

**P&P:** MS 2547 by Estes et al. (including Dr. Elsayed) look at ECG and prediction. Can you provide us information about the overlap with this proposal?

**Response:** The purpose of MS# 2547 was to examine the association between one of the LVH criteria (Romhilt-Estes score) with CVD events without making any changes to the score or its components. On the other hand, the purpose of the current proposal is to develop *new ECG-LVH* with the sole purpose of prediction, unlike the currently available criteria. Developing new ECG-LVH criteria with sole purpose of prediction is in agreement with the call of the current AHA/ACCF/HRS ECG interpretation recommendations that suggested developing new LVH criteria with modified cut points for the purpose of prediction.

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Cardiology Section- Department of Medicine
ARIC Manuscript Proposal #2943r

1.a. Full Title: Prediction of Cardiovascular Disease Using Modified Electrocardiographic Left Ventricular Hypertrophy Criteria in the combined cohorts of ARIC and MESA studies

b. Abbreviated Title (Length 26 characters): ECG Prediction of CVD

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. [AOO]

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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 to begin after Publication Committee approval. Manuscript anticipated for initial P&P review 6 months after proposal approval.

4. **Rationale:**

Cardiovascular disease (CVD) remains the greatest killer of men and women in the United States. The burden of CVD is expected to increase significantly by 2030. In addition to the traditional CVD risk factors like age, diabetes, hypertension, obesity, smoking, hypercholesterolemia, and physical inactivity, left ventricular hypertrophy (LVH) is an important risk factor for CVD. Despite the known low sensitivity of ECG to detect LVH, presence of LVH on the resting electrocardiogram (ECG) has been shown to be strongly predictive of CVD. Due to the better performance of ECG LVH criteria to predict CVD than their ability to diagnose increased left ventricular mass, it has been suggested that risk stratification and identification of individuals at risk of CVD should be the most appropriate use for ECG-LVH criteria. However, currently there are no ECG-LVH criteria created specifically for prediction of CVD, and the currently used cut-off points for prediction are the same previously established cut-off points used for diagnosis of increased LV mass. Therefore, the current AHA/ACCF/HRS interpretation recommendations suggested developing new LVH criteria with modified cut points for the purpose of prediction. Notably, it has been shown that different criteria for ECG-LVH as well as different components of the same ECG LVH criteria have varying predictive abilities for different CVD outcomes. Consequently, we sought to take advantage of the availability of digital ECG data as well as the well-ascertained several types of CVD outcomes in the Atherosclerosis Risk in Communities (ARIC) study to develop new ECG criteria from different components of the established ECG-LVH criteria that best predict CVD outcomes.

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

1. Use components of the established ECG-LVH criteria to determine the most promising components that predict overall CVD outcomes (a composite of HF, CHD and stroke) and subsequently determine new LVH cut-off points/criteria for the prediction of overall CVD in the ARIC cohort.

2. Use components of the established ECG-LVH criteria to identify the most promising components that predict each of HF, CHD and stroke, separately, and create new LVH cut-off points/criteria for the prediction of each one of the outcomes in the ARIC cohort.

3. Validate the new cut-off points/criteria in the Multi-ethnic Study of Atherosclerosis (MESA) cohort (a separate proposal will be submitted to MESA).

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:* Prospective cohort study.

*Inclusion/Exclusion Criteria:* We will include all participants with good quality baseline electrocardiogram data and follow-up data. The following groups of participants will be excluded:

1) Participants with major ventricular conduction defects (i.e. QRS>=120 ms) including left bundle branch block and those who had an ICD or pacemaker placed.
2) Participants with a history of cardiovascular disease at the baseline examination.

Outcomes: CVD (a composite of HF, CHD and stroke), HF, CHD and stroke

ECG Variables: Single and combination ECG variables related to left ventricular electrical activity that have been previously reported as potential criteria for ECG-LVH will be considered. Provisionally, this list will include the ECG variables included in Table 1 of the AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram-Part V (Hancock et al; JACC 2009; 53(11):992-1002) 13. These variables include the components of the most commonly used ECG-LVH criteria such as Cornell voltage, Sokolow-Lyon, Romhilt-Estes, etc

- (R I–S I)+(S III–R III)
- R I+S III
- R I
- R aVL
- R aVF
- Q or S aVR
- S V1
- S V2
- S V1 + R V5
- S V2 + max R V5,6
- max S V1or 2 + max R V6
- S V2 + max R V4,5
- R V5
- R V6
- ΣQ,R,S aVF+V2+V6
- S V3+R aVL
- Total 12-lead voltage
- (R aVL+S V3)*QRS duration
- Total 12-lead voltage*QRS duration

In addition, for a separate analysis, all available digital ECG variables will be included.

Variables: Variables needed from the baseline study visit will include the following: Age, gender, race/ethnicity, body mass index, height, weight, income, education, systolic blood pressure, diastolic blood pressure, mean heart rate, treatment for hypertension, diabetes, treatment for diabetes, total cholesterol, HDL, LDL, statin use, aspirin use, tobacco use, alcohol use.

Statistics: Baseline characteristics for each cohort will be analyzed using descriptive statistics. Continuous variables will be presented as mean ± SD if normally distributed or median, Q1 and Q3 if the data do not follow a normal distribution. Categorical variables will be presented as number and % (percentage). Log transformation will be performed when necessary for variables with a skewed distribution. Comparison between participants with and without ECG-LVH, CVD, HF, CHD and stroke will be assessed using the Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables.

To determine the optimal cut off points for the prediction of the outcomes (overall CVD, HF, CHD and stroke), unadjusted and fully adjusted receiver operating characteristic (ROC) curve analysis will be conducted for each continuous ECG variable, separately14. Cut off points for each ECG-LVH variable that maximizes sensitivity and 1-specificity will be chosen based on the fully adjusted ROC curve analysis. The ECG-LVH variables will then be dichotomized based on the determined cut off points to create categorical variables.
In a multivariable Cox proportional hazard model, we will examine the association between each ECG-LVH variable using the derived categorical variables and overall CVD as well as each of the individual CVD outcomes (HF, stroke, CHD). Hazard ratios will be calculated for each component. To examine the predictive ability of the identified ECG-LVH variables, Harrell’s concordance (C-index) will be calculated for a fully adjusted model that includes relevant covariates and newly derived categorical ECG-LVH variables, separately.

In an exploratory analysis to possibly identify other ECG variables that are not among the components of the established ECG-LVH criteria, a second model that includes all digital ECG variables available in ARIC (about 500 variables) will be constructed and variable selection will be conducted using an elastic net regularization due to the large number of variables that will be included15.

For validation, data from MESA will be used to make quantitative and graphical evaluations of the discrimination and calibration of the ARIC-derived model.

In a sensitivity analysis, ethnic variations in the association of ECG-LVH with CVD events will be assessed by stratifying by race/ethnicity.

All analyses will be performed using JMP Pro 12 and SAS 9.4 (Cary NC). A p value less than 0.05 will be considered significant.

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)?

None.
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.cscce.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.cscce.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


