ARIC Manuscript Proposal #2476

PC Reviewed: 12/9/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Romhilt-Estes Point Score System and Risk of Mortality: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):

AF and MI risk

2. Writing Group:
Writing group members:

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

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3. Timeline:

The projected timeline for this manuscript is 6 months from the time of submitting the proposal to journal submission.

4. Rationale:

For the past half century, the electrocardiogram (ECG) has been used as a means of detecting the development of left ventricular hypertrophy (LVH) in the course of hypertension, valvular heart disease and other cardiovascular disorders. It has never been very good at this task, and most of the research over these years has been directed at improving its sensitivity and specificity in detecting LVH. In recent years, it has been recognized that the ECG features traditionally used to indicate hypertrophy also have the ability to predict an adverse course and death from the cardiovascular diseases causing hypertrophy. This ability is independent of the ability to predict left ventricular (LV) mass.

Many investigators have concluded that the electrical phenomena reflected in the ECG are not directly related to LV mass, and that further attempts to improve the prediction of LV mass from features of the ECG should be discontinued in favor of studies of its ability to predict the course and understand the physiology of the underlying cardiovascular diseases (1). This opinion is bolstered by the fact that echocardiography and MRI measure LV mass with much greater precision and reliability, and are now widely available.

In 1968, the lead author of this proposal (Harvey E Estes) developed a point score system for the diagnosis of LVH from the ECG (Romhilt-Estes Score). The Romhilt-Estes Score system utilized six features of the ECG, each of which had been previously reported as being altered with LVH (2). The six features involved all components of the ECG: the P wave (left atrial enlargement), the QRS complex (amplitude in limb and precordial leads, left axis deviation, QRS duration, intrinsicoid deflection), and the ST-T wave (ST and T wave altered in a direction opposite to QRS). This system became widely used internationally as the basis for the ECG diagnosis of LVH, but as automated interpretation programs became widely available, it has been replaced by LVH criteria which rely on amplitude of QRS alone or on a combination of QRS amplitude and duration. These newer LVH criteria are more easily adapted to automated reading, with little or no sacrifice in sensitivity in the “diagnosis” of LVH.

While this shift from a system utilizing all components of the ECG (the Romhilt-Estes score), to those primarily utilizing the amplitude and width of the QRS complex (Sokolow-Lyon criteria (4) and Cornell Index (5)) has had few if any negative effects with respect to the clinical identification of LVH, there is little information about these differing systems of LVH detection with respect to their prognostic ability. Therefore, we seek to validate and quantitate the predictive ability of each of the six components of the Romhilt-Estes score as a predictor of all-cause mortality. Since the components of the Romhilt-Estes score include elements with QRS amplitude and duration as separate components, we can also determine the independent prognostic ability of each of these components as prognostic indicators, simulating the Sokolow-Lyon criteria and the Cornell Index.

Establishing the usefulness of the Romhilt-Estes score as a predictor of a hard outcome such as death and showing that each component of the score may have different predicative ability will be further emphasize the growing paradigm shift in thinking of ECG-LVH as more of a prognostic marker rather than diagnostic tool, and will encourage further research aimed to modify the current ECG LVH criteria to be tailored towards prognosis rather than diagnosis.

5. Main Hypothesis/Study Questions:

This study aims to examine the association between Romhilt-Estes Point Score, overall as well as each of its component, with all-cause mortality.

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 population:

All ARIC participants with good quality baseline ECG data as well as mortality data during follow up. Non-white and non-black individuals will be excluded. Also, we will exclude participants with ECG conditions that interfere with appropriate interpretation or calculation of the Romhilt-Estes score. This includes major ventricular conduction defects (e.g. complete left bundle branch block) and atrial fibrillation.

Summary of variables of interest:

Covariates: Age, race, sex, education level, study site, body mass index, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, total cholesterol, HDL cholesterol, current smoker, estimated glomerular rate (eGFR), diabetes, and prior coronary heart disease (CHD) , stroke and heart failure.

Exposure variable (s): The components of the Romhilt-Estes score: the amplitude and duration of the negative portion of the P wave in V1 (left atrial enlargement), the QRS complex (amplitude in limb and precordial leads, left axis deviation, QRS duration, intrinsicoid deflection), and the ST-T wave (ST and T wave altered in a direction opposite to QRS).

Outcome: All-cause mortality

Brief Analysis:

Baseline Romhilt-Estes score will be calculated for all participants. Baseline characteristics of the analysis population will then be tabulated and compared by the level of the score as follows: Romhilt-Estes score=0, 1-3, 4, and >=5.

Age-adjusted incidence rates of all-cause mortality per 1000 person-years in each of the Romhilt-Estes score levels will be calculated, and Kaplan-Meir survival curves will be plotted to compare event-free survival curves across these levels.

Cox proportional hazards analysis will be used to examine the association between Romhilt-Estes score and all-cause mortality in a series of models with incremental adjustments as follows: model 1 adjusted for age, sex, race, study site, education level, and income; model 2 adjusted for model 1 covariates plus total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, body mass index, diabetes, use of antihypertensive medications, aspirin, statin, history of other cardiovascular disease (stroke, CHD, heart failure) and eGFR. In these models Romhilt-Estes score will be used in different ways, separately, as follows: 1) the risk of mortality will be calculated for each level of the score with score=0 as the reference group; 2) the risk of mortality will be calculated for each the components of the score (e.g. left atrial enlargement, left axis, QRS duration >=0.09 sec, intrinsicoid deflection in V5 or V6 ≥ 0.05 msec, ST/T abnormalities, QRS voltage criteria). Each component will be entered separately, as present/absent (1/0) in the model with absent value being the reference group. Interaction by sex and race will be examined in the final model. P value<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 __X__ 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.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.

References

1. L. Bacharova, E.H. Estes, L. Bang et al. The first statement of the Working Group on Electrocardiographic Diagnosis of Left Ventricular Hypertrophy J Electrocardiol, 43 (2010), p. 197
2. D.W. Romhilt, E. H. Estes. A point-score system for the ECG diagnosis of left ventricular hypertrophy. Am. Heart J.(1968) 75:752-758.
3. W. A. Carter, E. H. Estes. Electrocardiographic manifestations of ventricular hypertrophy; a computer study of ECG-anatomic correlations in 319 cases. Am. Heart J. (1964) 68:173- .
4. M. Sokolow, T. Lyon. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am. Heart J. (1949) 37: 161-186.
5. P. M. Okin, M. J. Roman, R. B. Devereux, P. Kligfield. Electrocardiographic identification of increased left ventricular mass by simple voltage-duration products. J. Am Coll Cardiol (1995) 25:417-423.