ARIC Manuscript Proposal #2685

1.a. **Full Title**: Refining the Romhilt-Estes LVH Score for better prediction of CVD Risk: the Atherosclerosis Risk in Communities (ARIC) Population

b. **Abbreviated Title (Length 26 characters)**: Redefining the R-E Score

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

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3. **Timeline**:
The projected time line for this manuscript is 6 months from the time of approval of the proposal by the ARIC P and P Committee.
4. **Rationale:**

We have recently demonstrated that the Romhilt-Estes (R-E) Score, originally designed for the diagnosis of left ventricular hypertrophy (LVH), is predictive of all-cause mortality and incident cardiovascular disease (1, 2). We have also shown that the six ECG components of the R-E Score differ in their ability to predict heart failure, coronary heart disease and stroke (2). These differences suggest that each of the R-E Score components is an electrical biomarker for a different underlying pathologic state. The potential importance of these observations lies in the fact that these ECG “biomarkers” could become a simple, noninvasive, objective, and relatively inexpensive method for detection of these basic pathophysiologic states, perhaps at a stage that would allow therapeutic intervention and avoidance of permanent cardiovascular damage and/or death. However, the current R-E score has significant flaws as a risk predictor. Its threshold values were originally selected for prediction of LVH, based on a study of heart weight and wall thickness in sequential autopsied hearts from a single Veterans Administration Hospital. Therefore, as the next phase of investigating R-E, we sought to refine and maximize the R-E Score, by recalibration of its threshold cut-points and score weights with the aim of increasing the sensitivity and specificity in its new use as a CVD risk predictive tool.

5. **Main Hypothesis/Study Questions:** The aims of this study are:
1) To redefine the threshold values for each of the six ECG components of the R-E score, by selecting the optimum value for prediction of CVD (a composite of heart failure, coronary heart disease, and stroke)
2) To examine the current weighting of the six ECG abnormalities which comprise the elements of the score, by comparing an unweighted version of the score with a system of weighting based on the beta coefficient of each component.

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 methodology limitations or challenges if present).**

**Study population:**
All ARIC participants free of CVD at baseline and with good quality baseline ECG data as well as CVD (heart failure, coronary heart disease and stroke) 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, 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:** Incident cardiovascular disease, defined as fatal and non-fatal cardiovascular events (coronary heart disease, stroke, and heart failure).

**Brief Analysis:**
The best threshold for each ECG component will be selected by considering the following three methods: (1) Youden index, which maximizes the sum of sensitivity and specificity; (2) Liu index, which maximizes the product of sensitivity and specificity; (3) the nearest to (0,1) method, which finds the cut-point on the ROC curve with perfect sensitivity and specificity. Each cut-point will be bootstrapped (500 replications) to estimate confidence intervals. The composite outcome “incident cardiovascular disease” will serve as an outcome. Since the major strength of the R-E score is in its simplicity, we will chose the best performing of two approaches for score development: (1) an unweighted risk score will be developed by combining together the six abnormal ECG components of the score; and (2) a weighted risk score in which each component contribution will be weighted by the rounded relative beta-coefficient. The best performing score will be selected as a new risk prediction tool, based on the optimal outpoints, validated by the experience of the ARIC population over a twenty year span of years.

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.cscu.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)?
ARIC MS # 2476-Estes: The Romhilt-Estes score and its components predict all-cause mortality in the general population.
ARIC MS #2547-Estes: Individual components of the Romhilt-Estes left ventricular hypertrophy score differ in their prediction of cardiovascular events

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.cscn.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.cscn.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