ARIC Manuscript Proposal # 3165

PC Reviewed: 5/8/18 **Status: _____** **Priority: 2**

SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Short-term repeatability of electrocardiographic indices

b. Abbreviated Title (Length 26 characters): Repeatability of ECG indices

2. Writing Group:

Writing group members: Michelle Meyer, Elsayed Z Soliman, Zhu-ming Zhang, Dominique Drager, Adam Moskovitz, Aaron Folsom, Alvaro Alonso

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MM__ **[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**: Analysis is to start as soon as approval is obtained. We plan to complete the manuscript within one year from data analysis.

4. **Rationale**: We propose to estimate the short-term repeatability of selected electrocardiographic (ECG) indices derived from a 12-lead ECG, some established and frequently used and others novel. We will focus on "established" measures of ECG left ventricular hypertrophy (LVH),[1-4] including a novel index,[5] that represent preclinical cardiovascular disease and predict the risk for cardiovascular disease and mortality. Additionally, we will include two novel ECG repolarization

markers[6-13] that studies are using extensively because of their strong associations with CHD, mortality, and sudden death in different populations. In each case, the short-term repeatability of these indices is not well documented in the literature. The setting of the proposed analyses is the Atherosclerosis Risk in Communities (ARIC) ECG Repeatability Study (Ancillary Study #2002.5). All ECG readings, inclusive of the indices to be included in the proposed analyses, were derived at the Epidemiological Cardiology Research Center (EPICARE).

Indices to be included:

a. "Established" indicators of left ventricular hypertrophy (both binary and on a continuous scale[2, 14]): Cornell voltage (CV); Cornell voltage product (CVP); Sokolow-Lyon (SL); Sokolow-Lyon Product (SLP).

b. A novel indicator of left ventricular hypertrophy: A new ECG LVH index by Peguero et al. (JACC, 2017)[5] that reportedly has a better diagnostic performance compared to traditional ECG-LVH criteria.

c. Two novel repolarization measures: The two measures are the spatial QRS-T angle,[6, 7, 9-12] frontal QRS-T angle,[8, 13] and T-axis.[13]

The ARIC ECG Repeatability Study will allow enable an evaluation of short-term repeatability of the above indices. This will contribute new information to the literature to help guide the interpretation and reporting of these measures and in the design of studies that rely in such ECG indices.

5. Main Hypothesis/Study Questions:

1. Estimate the repeatability of ECG indices of LVH and repolarization markers.
2. Calculate the minimal detectable change in each index for use in epidemiological studies.
3. Examine the use of repeated measurements for detecting changes in each of these indices in a clinical trial setting.

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 methodological limitations or challenges if present).

Study design: The Repeatability Study included 63 healthy participants 45-64 years old recruited from Chapel Hill, NC, that had similar characteristics to the ARIC study cohort at baseline with respect to age, gender and race. Participants were free of diabetes, hypertension, emphysema, chronic obstructive pulmonary disease, congestive heart failure, renal disease, a pacemaker, and were not taking class I or III antiarrhythmics. Participants were asked to avoid intense physical activity, smoking, eating, or drinking alcoholic beverages for 10 hours before the visits. Each participant underwent two standardized visits between 7:30 to 11:30 am one to two weeks apart at the General Clinical Research Center at UNC hospitals between July and October 2001. Two standard 12-lead ECG recordings were taken after participants rested for 15 minutes in the supine position at the initial

visit (ECG1, ECG2) and then another set two weeks later (ECG3, ECG4). The ECG recordings were obtained by four trained technicians that followed the ECG protocol used in ARIC. The ECG recordings were taken using Kendall QTrace 5400 Ag/AgCl electrodes (Ludlow Co., Chicopee, MA) and digitized using the MAC PC Personal Cardiograph (Marquette Electronics, Inc., Jupiter, FL). The images were sent to the Epidemiology Cardiology Research (EPICARE) Center in Winston-Salem, NC, for processing.

Outcomes: Repeatability estimates of ECG indices, as noted below.

The indices addressed in these analyses are listed above. When applicable, each index is included as a continuous variable and a binary variable. The Cornell voltage traditional cut-off point for women is 2000, although a threshold of 2200 is now used (both cut points will be used in these analyses). The traditional cut-off point is mentioned as CV_LVH2, which also impacts LVH by the Cornell voltage product (CVP_LVH2). Sokolow-Lyon and Cornell may be used as one variable; its repeatability also will be assessed.

The spatial QRST-angle used to be derived from vectorcardiograms, but algorithms are now available to measure QRST-angle from the 12-lead ECG. The frontal QRS-T angle is a simpler index proposed by EPICARE researchers that is derived from the QRS axis and T axis, i.e., measures typically available on the printout of the 12-lead ECG. Thus, the analyses will estimate the repeatability of spatial QRS-T angle and frontal QRS-T angle, as well as T-axis which is a component of the QRS-T angle and has been shown to be predictive of cardiac outcomes.

A sample of the publications using frontal and spatial QRST-angle[6-13] and the papers in which T axis was used[13] are cited below. This list of repolarization markers is not exhaustive.

Inclusions: The 63 participants from the ECG repeatability ancillary study.

Exclusions: Participants lacking ECGs or whose ECG is unreadable.

Statistical Analysis:

We will present summary statistics for each ECG measurement as means and standard deviations (SD). Indices with a skewed distribution will be expressed as medians and inter-quartile ranges, and will be log transformed for the analysis.

We will also calculate:

1. The average difference between measurements within visit: [(ECG 2-ECG1) + (ECG4-ECG3)]/2
2. The average difference between visit: [(ECG 3-ECG1) + (ECG4-ECG2)]/2
3. The absolute difference between measurements (ECG 2-ECG1, ECG4-ECG3 and ECG 3-ECG1, ECG4-ECG2)

A nested random-effects analysis of variance model will be used to estimate the between-participant, between-visit and within-visit variance. We will calculate the intra-class correlation

coefficient (ICC) by dividing the between-participant variance by the total variance to estimate the reproducibility of the indices: Estimate variance between-participant (σ^2_p), between-visit (σ^2_{bv}), and within-visit (σ^2_{wv}), where $Y_{ijk}=\mu + P_i + V_j (Pi) +\varepsilon_{ijk}$

- Y_{ijk} = value at j^{th} visit of i^{th} participant
- μ = intercept
- P_i = i^{th} participant
- $V_j(P_i)$ = j^{th} visit nested within i^{th} participant
- ε_{ijk} = random error

Assume P_i, $V_j(P_i)$ and ε_{ijk} are independent and ~$N(0,\sigma^2)$, to calculate the intraclass correlation coefficient (ICC): ICC = $\frac{\sigma^2_p}{\sigma^2_{Total}} = \frac{\sigma^2_p}{\sigma^2_p+\sigma^2_{bv}+\sigma^2_{wv}}$

Standard error of measurement (SEM): SEM = $\sqrt{(\sigma^2_{bv}+\sigma^2_{wv})}$

For categorical variables, we will use Kappa (K) to evaluate agreement within- and between-visit: $K = P_o – P_e/1-P_e$

To examine the implications of these measurement properties for study design and data interpretation we will estimate informative changes in each ECG index based on the variance and sample size for one- and two-sample study designs. For a one-sample study, we will calculate the minimal detectable change (MDC; with 95% confidence) between two time points for an individual that reflects true change above that of measurement error, [MDC95 = SEM*√2*1.96]. For a two-sample study design, we will calculate the minimal detectable difference (MDD) between two measurements as MDD = $[(\sqrt{2}*\sigma 2total)/N]*(t_{\alpha(df)}+t_{\beta(df)})$. We also calculated the MDD as a percent of the grand mean.

Sensitivity analyses: In a sensitivity analyses, we will investigate whether excluding participants who on pharmacologic therapies including β-blockers, cardiac glycosides, calcium-channel blockers, and antiarrhythmics affects the repeatability estimates.

Limitations:

ECG measurements are available at only two time points (initial visit and 1 week later) thus these analysis are limited to short term repeatability. The study was conducted on volunteer participants selected to be similar to the ARIC Cohort.

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)?

The most related manuscripts are based on ECG measures from the ECG Repeatability Study.

Manuscript Proposal # 894 Repeatability of Heart Rate Variability Measures: The ECG Repeatability Study (published)

Manuscript Proposal # 897 Repeatability of the Spatial T Wave Axis Deviation Measures: The ECG Repeatability Study (published)

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* _AS #2002.5_)

___ 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/

This study will use ECG data obtained from the ancillary study: AS #2002.5 ECG Repeatability Study (ReECG) Heiss, G

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. Rautaharju PM and Soliman EZ. Electrocardiographic left ventricular hypertrophy and the risk of adverse cardiovascular events: a critical appraisal. *Journal of electrocardiology*. 2014;47:649-54.
2. Bang CN, Soliman EZ, Simpson LM, Davis BR, Devereux RB and Okin PM. Electrocardiographic Left Ventricular Hypertrophy Predicts Cardiovascular Morbidity and Mortality in Hypertensive Patients: The ALLHAT Study. *American journal of hypertension*. 2017;30:914-922.
3. Bacharova L, Chen H, Estes EH, Mateasik A, Bluemke DA, Lima JA, Burke GL and Soliman EZ. Determinants of discrepancies in detection and comparison of the prognostic significance of left ventricular hypertrophy by electrocardiogram and cardiac magnetic resonance imaging. *The American journal of cardiology*. 2015;115:515-22.
4. Okin PM, Hille DA, Kjeldsen SE and Devereux RB. Combining ECG Criteria for Left Ventricular Hypertrophy Improves Risk Prediction in Patients With Hypertension. *Journal of the American Heart Association*. 2017;6.
5. Peguero JG, Lo Presti S, Perez J, Issa O, Brenes JC and Tolentino A. Electrocardiographic Criteria for the Diagnosis of Left Ventricular Hypertrophy. *Journal of the American College of Cardiology*. 2017;69:1694-1703.
6. Dawood FZ, Khan F, Roediger MP, Zhang ZM, Swaminathan S, Klinker H, Hoy J, Lundgren JD, Neaton JD and Soliman EZ. Electrocardiographic spatial QRS-T angle and incident cardiovascular disease in HIV-infected patients (from the Strategies for the Management of Antiretroviral Therapy [SMART] study). *The American journal of cardiology*. 2013;111:118-24.
7. Dawood FZ, Roediger MP, Grandits G, Miller D, Fisher M, Zhang ZM, Hodder S, Hoy JF, Lundgren JD, Neaton JD and Soliman EZ. Determinants of developing widened spatial QRS-T angle in HIV-infected individuals: results from the Strategies for Management of Antiretroviral Therapy [SMART] Study. *Journal of electrocardiology*. 2014;47:264-71.
8. Jogu HR, O'Neal WT, Broughton ST, Shah AJ, Zhang ZM and Soliman EZ. Frontal QRS-T Angle and the Risk of Atrial Fibrillation in the Elderly. *Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc*. 2017;22.
9. Zhang ZM, Prineas RJ, Case D, Soliman EZ and Rautaharju PM. Comparison of the prognostic significance of the electrocardiographic QRS/T angles in predicting incident coronary heart disease

and total mortality (from the atherosclerosis risk in communities study). *The American journal of cardiology*. 2007;100:844-9.
10. Zhang ZM, Rautaharju PM, Prineas RJ, Loehr L, Rosamond W and Soliman EZ. Usefulness of electrocardiographic QRS/T angles with versus without bundle branch blocks to predict heart failure (from the Atherosclerosis Risk in Communities Study). *The American journal of cardiology*. 2014;114:412-8.
11. Zhang ZM, Rautaharju PM, Prineas RJ, Tereshchenko L and Soliman EZ. Electrocardiographic QRS-T angle and the risk of incident silent myocardial infarction in the Atherosclerosis Risk in Communities study. *Journal of electrocardiology*. 2017;50:661-666.
12. Zhang ZM, Rautaharju PM, Prineas RJ, Whitsel EA, Tereshchenko L and Soliman EZ. A wide QRS/T angle in bundle branch blocks is associated with increased risk for coronary heart disease and all-cause mortality in the Atherosclerosis Risk in Communities (ARIC) Study. *Journal of electrocardiology*. 2015;48:672-7.
13. Shah AJ, Vaccarino V, Janssens AC, Flanders WD, Kundu S, Veledar E, Wilson PW and Soliman EZ. An Electrocardiogram-Based Risk Equation for Incident Cardiovascular Disease From the National Health and Nutrition Examination Survey. *JAMA cardiology*. 2016;1:779-786.
14. Soliman EZ, Byington RP, Bigger JT, Evans G, Okin PM, Goff DC, Jr. and Chen H. Effect of Intensive Blood Pressure Lowering on Left Ventricular Hypertrophy in Patients With Diabetes Mellitus: Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial. *Hypertension (Dallas, Tex : 1979)*. 2015;66:1123-9.