

## ARIC Manuscript Proposal #2208

PC Reviewed: 9/10/13

Status: A

Priority: 2

SC Reviewed: \_\_\_\_\_

Status: \_\_\_\_\_

Priority: \_\_\_\_\_

**1.a. Full title:** Association between novel ECG metrics and sudden cardiac death

**1.b. Abbreviated title** (26 char): Mechanistic ECG risk markers and SCD

**Writing group:** Larisa G. Tereshchenko, Elsayed Z. Soliman, Nona Sotoodehnia, David S. Siscovick, Yiyi Zhang, Sunil Agarwal, Rajat Deo, Eliseo Guallar, Ronald D. Berger, Wendy S. Post, Dan Arking, Mark E. Josephson, Josef Coresh

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

**First author:**

Name: **Larisa G. Tereshchenko MD, PhD**

Address: Johns Hopkins Hospital

600 N Wolfe St., Carnegie 568

Baltimore, MD, 21287

Phone 410-502-2796; fax 410-614-8039. Cell 314-537-1361

Email: [lteresh1@jhmi.edu](mailto:lteresh1@jhmi.edu); [larisagt@gmail.com](mailto:larisagt@gmail.com)

**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).

Name: Dan Arking, PhD, Associate Professor of Medicine

Address: Johns Hopkins University School of Medicine

McKusick-Nathans Institute of Genetic Medicine

Johns Hopkins University School of Medicine

733 N. Broadway, Broadway Research Building, Room 447

Baltimore, MD 21205

(410) 502-4867 Office

(410) 614-8600 FAX

[arking@jhmi.edu](mailto:arking@jhmi.edu)

2. **Timeline:** Start – immediately after approval (expected, fall 2013). Manuscript submission expected: 2013-2015

**Rationale:**

Cardiovascular mortality and in particular, sudden cardiac death (SCD) is the leading cause of death in the adult US population. In about half of SCD cases, death is the first clinical manifestation of the coronary heart disease (CHD), and an estimated 80% of SCDs are associated with CHD. Arrhythmic SCD due to ventricular arrhythmia remains the most frequent

SCD. It is crucial to determine the population at risk of SCD. Yet risk factors of SCD early in the natural history of conditions predisposing SCD have not been fully identified, and SCD risk stratification strategy in the general population has not been developed.

The electrocardiogram (ECG) is an easily available, non-expensive, and non-invasive tool, which carries essential information on electrophysiological properties of the heart. Several ECG metrics (elevated resting heart rate, QTc, QRS duration, left ventricular hypertrophy and scar on ECG, left bundle branch block) predict SCD. However, traditional ECG markers identify advanced cardiac disease late in its natural history. Development of novel mechanistic ECG risk markers of SCD is needed.

Underlying functional electrophysiological substrate (interplay between source-sink mismatch, dispersion of refractoriness, increased sympathetic tone in the ventricles of the heart, cell-to-cell coupling) is critically important for SCD. We are developing novel 12-lead ECG mechanistic risk markers that assess (1) slow discontinued conduction and source-sink mismatch, (2) temporal repolarization lability, (3) dispersion of refractoriness, (4) increased sympathetic tone; (5) early repolarization, early and delayed afterdepolarizations; (6) early stages of structural heart disease (e.g. fibrosis and infiltrated fat).

In this proposal for papers we will explore association between each of tested ECG markers and SCD. Separate paper(s) will be prepared to describe associations with outcomes for each novel ECG parameter.

**Main hypothesis/Study questions:** We hypothesize that ECG parameters, that characterize (1) slow discontinued conduction and source-sink mismatch [e.g. fragmented and notched QRS], (2) temporal repolarization lability [e.g. TT' angle], (3) steepness of the dispersion of refractoriness [e.g. SAI QRST], (4) increased sympathetic tone [e.g. RR' angle]; (5) early repolarization, early and delayed afterdepolarizations [e.g. U-wave amplitude]; (6) early stages of structural heart disease, such as fibrosis and infiltrated fat [e.g. heterogeneity of depolarization metrics], are associated with sudden cardiac death (SCD).

**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).**

#### Methods

ECG signal was analyzed using customized Matlab (MathWorks, Inc, Natick, MA) software. The inverse Dower transformation was applied to construct orthogonal XYZ leads. ECG metrics will be measured by custom Matlab software.

All ARIC participants with good quality baseline digital 12-lead ECG in sinus rhythm will be eligible for inclusion in this analysis.

#### Statistical analyses plan.

1. Check distribution of tested marker and decide whether natural log (ln) transformation should be done (if distribution is non-normal).
2. Check if race and/or sex are significant predictors of tested marker in linear regression. If they are, develop sex-and/or-race-adjusted quintiles

3. Univariate and multivariate cross-sectional analysis of association with CHD, MI, HF.
4. Model ECG marker using 2 approaches
  - Quartiles or quintiles (depending the number of events)
  - Splines
5. Survival analysis. Run univariate Cox regression (or competing risk regression).
6. Run multivariate Cox (or competing risk model), adjusted for the following demographic and clinical confounders (known risk factors of CHD):
  - Model 1: by age, sex, race-center interaction term
  - Model 2: model 1 +diabetes, smoking, alcohol, leisure activity index, BMI, total cholesterol, HDL, systolic blood pressure, anti-hypertensive medications, triglycerides, lipid-lowering, QT-prolonging meds, albumin, creatinine.
  - In case if statistical power will allow, the following confounders could be added: potassium, magnesium, use of beta-blockers.
  - In case if statistical power would be smaller (< 170 SCDs), we will drop the following predictors in order: creatinine, cholmeds, replace 2 variables systolic blood pressure+anti-hypertensive meds by one variable hypertension; leisure activity, albumin)
  - Model 3: model 2 + ECG confounders (mean heart rate, QTc, QRS duration, QRS-T angle, other ECG parameters as needed).
7. Stratified analysis by baseline CHD status. Participants with history of MI, HF, CHD, and QRS  $\geq$  120ms will be analyzed separately; models will be adjusted in addition for history of MI, HF, CHD, use of beta-blockers.
8. Analysis stratified by sex and by race.

**7.a. Will the data be used for non-CVD analysis in this manuscript? \_\_\_ Yes  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  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.csc.unc.edu/ARIC/search.php> \_\_\_  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  No**

**11. b. If yes, is the proposal**

**A. primarily the result of an ancillary study (list number\* 2012.14)**

**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.csc.unc.edu/aric/forms/>

**12. 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.**