1.a. Full Title: “Implementation of validated ECG measurements to identify non-ischemic ST segment patterns associated with an increased risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) cohort”

b. Abbreviated Title (Length 26 characters): Characterization of non-ischemic ST elevation and the association with risk of sudden cardiac death

2. Writing Group:
   Writing group members: Ashleigh Owen, MD, Nicholas M. Pajewski, PhD, Elsayed Soliman, MD, Lynne Wagenknecht DrPH, David Herrington, MD

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___AAO___

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3. **Timeline:**
Data analysis will begin once the manuscript proposal has been approved. I plan to complete the preliminary analysis for abstract submission to the American Heart Association 2013 Scientific Sessions (May 2013). I anticipate manuscript completion within 6 months of abstract completion (November 2013).

4. **Rationale:**
Worldwide sudden cardiac death claims more than seven million lives annually and over 200,000 people experience cardiac arrest in the United States each year.\(^2,8\) Unfortunately, less than half of the people who experience sudden cardiac death are identified as “high risk” using current prediction tools.\(^5,14\) Various electrocardiogram (ECG) morphologies have been investigated to improve risk prediction for the 50% of patients who despite being labeled “low risk” go on to experience sudden cardiac death. The risk associated with non-ischemic ST segment elevation, part of the criteria for defining early repolarization, has become a topic of research.

Early repolarization was first identified in the 1950s as a benign normal variant found primarily in young, healthy athletes. The classic definition of early repolarization used in clinical practice and reported on all computer-read ECG printouts includes ST segment elevation $\geq 2$ mm with an up sloping and concave shape, a prominent J wave (or more pronounced ST segment elevation is required), and a large, positive T wave.\(^10\) Early repolarization has a similar appearance to two other ECG patterns that are proven predictors of more devastating outcomes. One such morphology, the Brugada Pattern, is a variant of ST elevation that occurs in a structurally normal heart and is associated with a substantial increase in risk of sudden cardiac death.\(^1\)

Despite electrophysiologic similarities, for more than 50 years the non-ischemic pattern of ST elevation termed “early repolarization” has been classified as a benign normal variant. Klatsky, et al. confirmed the longstanding belief that early repolarization carries no risk of sudden cardiac death with a cross sectional analysis that reported people with early repolarization (defined as $\geq 1$ mm ST elevation in any lead) were not more likely to be hospitalized or to die (HR = 1.0; 95% CI: 0.9-1.2 and 0.8; 95% CI: 0.6 to 1.2 respectively).\(^6\)

In contrast to the conventional practice that early repolarization represents a benign normal variant, in 2008 Haissaguerre and colleagues reported that patients who have experienced idiopathic ventricular fibrillation were more likely to have early repolarization on their ECG when compared to control subjects who have not experienced ventricular fibrillation (31% vs. 5%, P<0.001).\(^3\) Early repolarization was defined in this study as the presence of QRS-ST junction elevation of at least 0.1 mV from baseline in the inferior or lateral leads.\(^3\) In 2009 Tikkanen, et al, published further evidence that early repolarization is not a normal variant.\(^13\) The study included participants from the general population over a 30 year period and reported that J-point elevation $>0.2$ mV in the inferior leads was associated with an elevated risk of death from cardiac causes (RR, 2.98; 95% CI, 1.85 to 4.92; P<0.001).\(^13\)
After review of all available literature, many in the research community have concluded that the risk of sudden cardiac death associated with non-ischemic ST segment variants remains unknown. The key to deciphering the results published from various studies is the acknowledgement that each investigator has implemented a different set of criteria for the determination of early repolarization on the ECG. Despite widespread use of the term “early repolarization” in current literature, the complete and most accurate criteria to determine early repolarization has not been studied.

The ARIC cohort has a collection of several digital ECGs for each study participant. The digital ECG provides a wide range of unique opportunities for research due to its ability to precisely measure various aspects of the ST segment at multiple time points and on each ECG lead. Implementation of computer based measurements and specific algorithms are a novel approach that has not been utilized as a tool for broad characterization of the ST segment.

This proposal is unique from prior studies as it does not limit analysis to a pre-defined set of criteria but instead uses all possible ST segment variables to first identify individual ECG patterns. The patterns identified in the primary analysis will then be studied to determine a specific level of risk for sudden cardiac death associated with each individual pattern. In addition to identifying phenotypic groups in order to estimate risk of sudden cardiac death, the cluster analysis will highlight the prominent features of each group and potentially provide insight into different electrophysiological mechanisms.

5. Specific Aims

In the ARIC population we intend to:

1. Determine the distribution of individual baseline ST segment variables overall, and in analyses stratified by age, sex and race/ethnicity.

   1.1 Examine follow-up ECG recordings to determine if the prevalence of each ST segment variable changes significantly over time.

2. Determine the association between individual baseline ST segment variables and risk of sudden cardiac death after adjustment for potential confounders.

   2.1 Examine the association between individual baseline ST segment variables and the risk of fatal and non-fatal coronary heart disease (CHD) events.

3. Identify sets or clusters of ST segment features that define separate ST segment phenotypes present in the ARIC cohort.

4. Determine the association between the ST segment clusters (identified in #3) and risk for sudden cardiac death, after adjustment for potential confounders.
We expect that the proposed unbiased approach to the definition of ST segment phenotypes based on all of the ST segment variables could create a new lexicon for describing non-ischemic ST elevation. This analysis may identify distinct subgroups with clinically important differences in risk for sudden cardiac death or other arrhythmic events.

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 design:** Longitudinal analysis involving the ARIC baseline exam as well as all incident sudden death events.

**Inclusion/exclusion:** All participants who have a digital ECG from the initial baseline exam (1987-1989) will be included in this study. Participants will be excluded if they do not have a baseline ECG or if their baseline ECG is of poor quality and cannot be accurately interpreted. Participants with baseline significant ST depression as identified by Minnesota ECG code will be excluded as this could represent significant coronary artery disease.

**Key variables of interest**

**ECG data:**
ARIC participants have had ECGs recorded at baseline and at four follow-up examinations. The baseline ECG recordings will be used to characterize each ECG variable in the main analysis. The follow-up ECG recordings will be used for a secondary analysis to establish whether or not the variables change significantly over time. Other variables that will be collected from the baseline exam of the ARIC cohort include age, sex, and ethnicity, smoking status, systolic blood pressure, and the presence of diabetes.

Key predictor variables from each digital ECG lead include:

1. QRS duration
2. Heart rate
3. PR
4. Middle of ST segment amplitude
5. End of ST segment amplitude
6. Amplitude at the point of 60 msec from the J point
7. STJ amplitude
8. Minimum amplitude from STJ, STM or STE
9. Maximum amplitude from STJ, STM or STE
10. R amplitude
11. R’ amplitude
12. S amplitude
13. S’ amplitude
14. T amplitude
15. T’ amplitude

A dataset for these variables (total number of variables = 147) will be prepared in collaboration with the ARIC ECG Center and Dr. Elsayed Soliman.

**Outcome variable:**
The primary outcome will be physician-adjudicated sudden cardiac death. In the ARIC cohort sudden cardiac death is defined as a sudden pulseless condition of cardiac origin in a previously stable individual. Secondary outcomes will include fatal and non-fatal CHD events. Outcome analysis will include events occurring between the baseline exam and the latest available adjudicated events. Censoring will occur at the time of an event, loss to follow-up, or at the time of the last follow-up.

**Brief Analysis Plan:**

*Specific Aim 1:* The distribution will be visually inspected and the mean, standard deviation and skewness will be determined for each ECG variable. Normalizing transformations will be performed if required for highly skewed variables. The mean values for each ECG variable will be compared across sex and ethnicity categories using T-tests or ANOVA. Simple linear regression will be used to evaluate the relationship between each ECG variable and age.

*Specific Aim 2:* A series of nested Cox proportional-hazards models will be developed to assess the association of each of the individual ECG variables and sudden cardiac death after adjustment for age, sex, race (model 1), and age, sex, race and additional covariates previously demonstrated to be associated with SCD in this cohort (model 2). Secondary analysis will include assessment of the association between individual ECG variables and fatal and non-fatal CHD events.

*Specific Aim 3:* “K means cluster analysis” is a classification technique to identify individual groups within a large collection of data points. No standard criterion exists to determine the exact number of groups (k) in which a large set of data should be divided. 12 Bayesian Information Criterion (also referred to as Schwarz Bayesian Criterion), which maximizes the log-likelihood of the model while also introducing a penalty term for each additional group, will be used to define separate ST segment phenotypic subsets with the optimal number of clusters.

*Specific Aim 4:* Cox proportional-hazards analysis will be used to assess the association between ST phenotype cluster assignment and risk of sudden cardiac death after adjustment for age, sex, race (model 1) and age, sex, race and other potential confounders (model 2). Risk of fatal and non-fatal CHD events will also be assessed for association with ST phenotype cluster assignment using Cox proportional-hazards analysis (secondary outcome).
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.csc.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 Manuscript Proposal # 1601 and ARIC Manuscript Proposal # 1557.
   Dr. Elsayed Soliman from the ARIC ECG Center represented the ECG expertise in these two papers and is a coauthor on our proposal.

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 Cited


