1.a. Full Title:
The progression of electrocardiographic parameters and the risk of sudden cardiac death

b. Abbreviated Title (Length 26 characters):
Progression of electrocardiographic parameters and SCD

2. Writing Group:

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _YZ_ [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 will begin as soon as data is available. The manuscript will be complete by Dec 2011.

4. Rationale
Several electrocardiographic (ECG) parameters, such as heart rate, QT interval, and QRS interval duration, have been shown to be predictive of total, cardiovascular, and sudden cardiac death (SCD).\textsuperscript{1-12} This includes a recent analysis from the combined ARIC and CHS cohorts.\textsuperscript{13} However, all of these studies have only used a single (baseline) ECG from which the ECG variables of interest were examined for their predictive ability. It is largely unexplored: 1) how these parameters change over time; 2) whether their progression trajectories are also predictive of increased risk of SCD; and 3) whether longitudinal information on ECG parameters would add additional predictive value to the baseline ECGs. The availability of digital ECG data in all of the 4 previous ARIC exam visits provides a unique opportunity to answer these research questions.

5. Main Hypothesis/Study Questions
The purpose of this analysis is to evaluate the changes of ECG parameters over time, as well as the associations between their progression trajectories and SCD, fatal and non-fatal CHD events and total mortality. We will focus on three well established prognostic markers (heart rate, heart rate corrected-QT duration, QRS duration), but will also explore other ECG markers in an exploratory fashion.

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)
Primary outcome will be sudden cardiac death (SCD). In ARIC, adjudicated definite SCD was defined as a sudden pulseless condition of cardiac origin in a previously stable individual. Possible SCD was defined as death occurring <24hrs from a stable condition for unwitnessed events without other evidence indicating instantaneous death. Only definite sudden death cases will be used in this analysis. Other outcomes which will be also tested are: total mortality, fatal and non-fatal coronary heart disease (CHD) events.

Exposure of interest will be ECG parameters (primarily heart rate, heart rate corrected-QT interval duration, and QRS duration), and their progression trajectories over time.
The analysis will use visit 1, 2, 3, and 4 ARIC data. Included will be all ARIC participants in whom ECG measurements from baseline (visit 1) and at least one follow-up visit are available, so that the progression trajectory can be analyzed. Participants with major conduction defects will be excluded to allow for an appropriate examination of the ECG parameters. For the analysis of fatal and non-fatal CHD event, we will also exclude participants with a history of coronary disease at baseline.

For the primary analysis, we will first assess the trajectory of heart rate, QT, and QRS progression over time using multilevel models for change. More precisely, we will model each ECG parameter for subject $i$ and visit $j$ recorded at time $t_{ij}$ as:

$$ ECG \text{ Parameter}_{ij} = b_{0i} + b_{1i}t_{ij} + f(t_{ij}) + Z_i \beta + \epsilon_{ij} $$

where “ECG parameter” represents heart rate, QT, or QRS, respectively; $b_{0i}$ and $b_{1i}$ are the subject specific random intercept and slope of the deviations from the population average; $f(t_{ij})$ represents time-varying covariates or covariates that have interactions with time; $Z_i$ represents the vector for time-fixed covariates; and $\epsilon_{ij}$ is the residual variability. We will then use $b_{0i}$ and $b_{1i}$ as predictors in the Cox proportional hazards models for mortality endpoints. Potential interactions between $b_{0i}$ and $b_{1i}$ will also be assessed. In this analysis, we will use all available ECG data for each participant prior to the development of an outcome event.

The fully adjusted model will likely include age, race, sex, study site, BMI, smoking, alcohol, education, total cholesterol, HDL, systolic blood pressure, use of antihypertensive meds, diabetes, history of myocardial infarction, history of heart failure, creatinine-based eGFR, and use of medications that potentially affects the ECG. As a secondary analysis, we will use time-dependent Cox-proportional hazards models in which ECG and other variables are treated as time dependent exposures and updated at each visit, using the same covariates and potential confounders as in the previous analysis. To assess whether adding longitudinal information on ECGs improves risk prediction beyond baseline ECGs, we will calculate the net reclassification improvement (NRI), as well as compare c-statistics of models that only include the baseline ECG parameters and models that further include longitudinal ECGs.

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)?

No study has looked at the longitudinal change in ECG parameters. The most related ARIC proposal is: MS#1557 (Soliman EZ, previously Prineas R): “Electrocardiographic and clinical predictors separating atherosclerotic sudden cardiac death from incident coronary heart disease.” The lead author of this paper (Soliman EZ) is on the author’s list.

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/

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.

References


