ARIC Manuscript Proposal #2636

PC Reviewed: 10/13/15 Status: A Priority: 2
SC Reviewed: _________ Status: _____ Priority: ____

1.a. Full Title: Maintaining Normal Electrocardiogram as a Measure of Maintaining Cardiovascular Health: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Normal ECG and CV Risk

2. Writing Group:
Writing group members: Elsayed Z Soliman MD, MSc, MS; Zhu-Ming Zhang MD PhD; Larisa Tereshchenko MD, Lin Y Chen MD, Dan Arking PhD, Alvaro Alonso MD, PhD; Other Welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __ES__ [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:
The projected timeline for this manuscript is 6 months from the time of proposal approval to journal submission.
4. **Rationale:**

The resting 12-lead electrocardiogram (ECG) is the most accessible test for screening and detection of cardiovascular disease (CVD) (1). In addition to its role in assessment of prevalent CVD, ECG abnormalities have also been used to predict poor outcomes in different populations (2-13). The increased risk of poor outcomes associated with different abnormal ECG traits fundamentally means that normal ECG is associated with favorable outcomes. This is further supported by a meta-analysis involving 366,559 participants from 5 cohort studies showing that the concomitant presence of normal ECG and favorable cardiovascular risk profile is associated with lower risk of long-term mortality and greater longevity (14). These findings suggest that presence of normal ECG at any point of time could be an indication of good cardiovascular health. Whether maintaining normal ECG over time reflects maintaining cardiovascular health, and subsequently more favorable prognosis than presence of normal ECG at one time point is currently unknown.

Abnormal ECG could be triggered by a wide variety of diseases that are not limited to structural and functional abnormalities of the cardiac muscle, but also neurohormonal abnormalities and electrolyte imbalance. Although presence of abnormal ECG regardless of its cause has been associated with poor outcomes, the heterogeneity of the pathophysiological basis of abnormal ECG may require considering certain ECG abnormalities not others when it comes to accurate prediction of outcomes. This is unlike normal ECG which simply means no deleterious effect on the heart by any factor i.e. good cardiovascular health.

Assessment of cardiovascular health using an objective simple tool, such as the ECG, not only could help appropriately allocating resources to high risk groups without normal ECG but also could help assessing and monitoring the success of programs and interventions aimed to maintain cardiovascular health such as the AHA Life’s Simple 7 and the cardiovascular health metrics defining ideal CVD risk profile (15). Maintaining normal ECG in those following Life’s simple 7, for example, would be an indication that the program is doing what it is supposed to do.

5. **Main Hypothesis/Study Questions:**

Our hypothesis is that maintaining normal ECG status over time reflects maintaining good cardiovascular health. Therefore, among ARIC participants with normal ECG at baseline, maintaining normal ECG status during visit 2 to visit 4 is associated with less risk of CVD events after visit 4 compared to those who did not maintain their normal ECG status.

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 population:** All ARIC participants free of CVD at the time of visit 4 and with available ECG data in all of the first 4 ARIC visits (visits 1-4) as well as follow-up data after visit 4 will be included in this analysis. Non-white and non-black individuals will be excluded, as well as non-whites from the Minnesota and Washington sites.
Summary of variables of interest:

Exposure variables: Based on the presence of normal ECG in the first 4 ARIC visits as defined by Minnesota ECG Classification (16), the following three groups will be created: 1) Maintained normal ECG status defined as presence of normal ECG at baseline (visit 1) as well as in visits 2, 3 and 4; 2) Did not maintain normal ECG status defined as presence of normal ECG at baseline (visit 1) but abnormal ECG in visits 2, 3 and 4; 3) Inconsistent pattern defined as normal ECG at baseline (visit 1) and inconsistent normal pattern during visits 2 to 4.

Outcome: Composite CVD events (non-fatal CHD, stroke and heart failure events plus CVD death) occurring after visit 4 until 2010. Each outcome in the composite CVD will also be considered in separate analyses.

Covariates: Baseline (visit 1) age, race, sex, education level, study site, body mass index, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, total cholesterol, HDL cholesterol, smoking status, serum glucose, hypertension, diabetes, and physical activity. In additional analyses, the same variables but in visit 4 will be used.

Brief Analysis:

Baseline characteristics (visit 1) of the analysis population will be tabulated and compared by the status of maintaining normal ECG (maintained normal ECG status, did not maintain normal ECG status and inconsistent pattern).

Age-adjusted incidence rates of each of the outcomes per 1000 person-years in the study participants stratified by normal ECG status (maintained normal ECG status, did not maintain normal ECG status and inconsistent pattern) will be calculated, and Kaplan-Meir survival curves will be plotted to compare event-free survival curves across these levels starting from visit 4.

Cox proportional hazards analysis will be used to examine the association between maintaining normal ECG status (maintained normal ECG status, did not maintain normal ECG status and inconsistent pattern) with each of the outcomes. Not maintaining normal ECG status will be the reference group in the models. Models will be adjusted as follows: Model 1 adjusted for baseline (visit 1) age, sex, race, study site, education level, and income; and Model 2 adjusted for model 1 covariates plus body mass index, diabetes, hypertension, dyslipidemia, and smoking status.

Additional analysis will include: 1) Examining the association between the number of visits with normal ECG and each of the outcomes. Having ECG in only visit will be used as the reference group. The aim of this analysis is to examine the dose-response relationship between years with normal ECG and adverse outcomes. 2) Subgroup analysis stratified by age (>65 years vs. younger), sex, race and ideal levels of cardiovascular health metrics (15) (never smoking, body mass index <25 kg/m2, physical activity >150 min/week moderate, or >75 min/week vigorous, or >150 min/week moderate+vigorous, untreated total cholesterol <200 mg/dL, untreated blood pressure <120/<80 mmHg, and fasting blood glucose <100 mg/dL). Interactions will be examined in model 2; 3) limiting the follow up period to 10 years after ARIC visit 4. The aim of this sensitivity analysis is to examine the possibility of higher favorable associations of maintaining normal ECG in the short-term rather than the longer follow up; 4) Adjusting for participant characteristics at visit 4 instead of baseline. This is to take into account the
development of cardiovascular risk factors between visit 1 and visit 4. In all analyses, P
value<0.05 will be considered significant.

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   ___X___ No

8.a. Will the DNA data be used in this manuscript? ___
     Yes   ___X___
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   ___X___ No

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   ___X___ 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)?
    None.

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://publicaccess.nih.gov/submit_process_journals.htm shows you which journals
      automatically upload articles to Pubmed central.
References

6) Prineas RJ, Le A, Soliman EZ, Zhang ZM, Howard VJ, Ostchega Y, Howard G. US National Prevalence of Electrocardiographic Abnormalities in Black and White Middle Aged (45-64 Years) and Older ≥ 65 Years) Adults (From the Reasons For Geographical and Racial Differences In Stroke Study). Am J Cardiol. 2012;109:1223-1228
15) Lloyd-Jones DM, et al; American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: