ARIC Manuscript Proposal #2361

PC Reviewed: 5/13/14  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title:

Relationship between changes in electrocardiographic traits over time, echocardiographic measures of cardiac structure and function, and cardiovascular outcomes in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):

ECG changes and outcome.

2. Writing Group:

Writing group members:


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

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3. **Timeline:**
   Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.

4. **Rationale:**
   Several electrocardiographic (ECG) traits, such as interval duration and measures of chamber hypertrophy, can predict cardiovascular events and mortality in patients with or without prevalent cardiovascular disease (1-8). In patients with established heart failure and reduced ejection fraction, ECG interval traits such as QRS width can differentiate individuals with higher versus lower risk profiles as well as those who may benefit from cardiac resynchronization therapy (9). To date, relatively little is known about the extent to which longitudinal changes in ECG traits are related to clinically important outcomes (6). Furthermore, the extent to which temporal changes in ECG traits are associated with abnormalities in cardiac structure and function, prior to the development of overt cardiovascular disease, has not been fully elucidated. It is possible that patterns of longitudinal change in ECG traits may be related to both subclinical cardiac disease and also cardiovascular outcomes – and that significant associations of longitudinal ECG changes with cardiovascular events are mediated by subclinical abnormalities in cardiac structure and function.

   The Atherosclerosis Risk in Communities (ARIC) study, which comprises multi-ethnic participants with different degrees of cardiovascular disease followed for over 25 years, is well-suited to investigate the relationships between temporal changes ECG traits, the echocardiographic manifestation of abnormalities in cardiac structure function, and the eventual development of adverse cardiovascular outcomes. Therefore, we aim to investigate how ECG traits change over time and the extent to which longitudinal change in ECG traits are associated with echocardiographic abnormalities in cardiac structure and function as well as the development of adverse cardiovascular outcomes.

5. **Main Hypothesis/Study Questions**
   Our main hypothesis is that longitudinal changes in ECG traits are associated with both subclinical cardiac disease as well as the overt development of adverse cardiovascular events, particularly heart failure (HF).

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).**

   This will be a longitudinal study of ARIC cohort participants, beginning at visit 1, when participants were aged 44-66 years.

   **Study Sample**
   The study sample will include individuals who have attended and undergone electrocardiography during at least in 2 different ARIC visits. For analyses of the relationship between temporal change in ECG traits and echocardiographic abnormalities, the study sample will include participants who underwent echocardiography at visit 5.
Exclusion Criteria
1) Missing basic covariate data for determination of standard cardiovascular risk factors (e.g. body mass index, blood pressure, diabetes data, prevalent CVD data, smoking status, alcohol status, total cholesterol), defined according to standard ARIC definitions.
2) Use of antiarrhythmic drugs, identified with the Medi-Span Therapeutic Classification system (codes = 350000, 350500, 351000, 352000, 353000, 354000, and 355000) at the time of ECG.
3) Wolf Parkinson White/preexcitation on ECG, identified using the Minnesota Coding System for ECG, using codes 6-4-1 or 6-4-2.
4) Paced rhythm, identified using the Minnesota Coding System for ECG, using code 6-8.
5) Prevalent CVD at the time of electrocardiography (CHD, HF, stroke) for analyses of incident CVD events.

Electrocardiographic traits
ECG traits to be studied will include PR, QRS, QT interval durations as well as QRS amplitude.

Echocardiographic traits
The association between changes in ECG traits from the preceding visit and abnormalities of cardiac structure and function will be made. Echocardiographic measurements of cardiac structure and function include: LV mass, LV end diastolic volume, indexed LA volume, LVEF, global longitudinal strain, lateral E’, S’, E:E’, RV areas and fractional area change.

Clinical outcome variables
1) Incident heart failure (HF) and other cardiovascular disease, including incident coronary heart disease (CHD) and stroke
2) All-cause mortality

Statistical analyses
All analysis will be performed using STATA v13 (StataCorp, College Station, Texas).

Relationship between trajectories of change in ECG traits and echocardiographic measures of cardiac structure and function
Longitudinal regression analyses will be used to examine the associations of change in ECG traits leading up through 5 and echocardiographic measures of cardiac structure and function at visit 5 (e.g. LV mass, E’, longitudinal strain). Multivariable analyses will adjust for age, sex, race, and traditional cardiovascular risk factors (time-updated covariates) including: body mass index, blood pressure measures, use of antihypertensive medications, diabetes mellitus, lipid levels, and smoking status.

Prognostic importance of longitudinal change in ECG traits, echocardiographic traits, and outcomes
We will use multivariable-adjusted regression analyses to examine the association of change in ECG traits (considered longitudinally as well as time-averaged measures, or the slope of change from earliest to latest value divided by the time interval between measures) with incident HF and other CVD outcomes as well as all-cause mortality. In analyses of the HF outcome, additional adjustment will be performed for interim development of coronary heart disease (specifically, interval hard CHD events). After assessing for accumulation of an adequate number of events for
each outcome for analyses, we will perform formal tests of mediation to examine the degree to which any significant association between ECG traits and outcomes are modified by the presence vs. absence of cardiac structural or functional abnormalities detected by echocardiography. Also to be performed at a later date, we will also use Cox proportional hazards models to assess the separate and joint contributions of change in ECG traits and measures of cardiac structure and function with risk for incident HF and other CVD events. These analyses will be performed using multivariable models adjusting for traditional cardiovascular risk factors (listed above) in addition to prior myocardial infarction and prevalent valve disease.

In secondary analyses, we will use multiplicative terms to assess for effect modification by age, sex, and race and perform stratified analyses if indicated.

A two-sided p-value of <0.05 will be considered statistically significant.

Limitations and challenges
Absence of echocardiography at the time of participants’ enrollment in ARIC precludes concurrent investigations of longitudinal change in echocardiographic traits.

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.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)?

1) Zhu-ming Zhang, Pentti Rautaharju, Ronald J Prineas, Laura Loehr, Wayne Rosamond, Elsayed Z Soliman. Prognostic Significance of Bundle Branch Blocks as Independent
Predictors of Incident Heart Failure in the Atherosclerosis Risk in Communities Study (ARIC). MS Proposal #1919.


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.cscn.unc.edu/aric/forms/

12.a. 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.

12.b. 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.cscn.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:


