ARIC Manuscript Proposal #2198

1. a. Full Title: Clockwise and counterclockwise rotation of QRS transitional zone and cardiovascular disease incidence: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): QRS transitional zone & CVD

2. Writing Group:
Writing group members:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _SP_ [please confirm with your initials electronically or in writing]

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3. Timeline:
Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:
Electrocardiograms (ECG) have been useful for diagnosing several heart conditions such as cardiac arrhythmia, 1-3 cardiac ischemia, 4 and structural changes like left ventricular hypertrophy (LVH). 5 Also, several ECG parameters (e.g., bundle branch block, frontal QRS-T angle, QT interval, and LVH) predict cardiovascular disease (CVD) morbidity and mortality. 6-10

In this context, a recently published study from Japan, reported clockwise and counterclockwise rotation of QRS transitional zone (the lead where the dominant QRS wave changes from S to R) in 12-lead ECG was significantly associated with high and low risk of cardiovascular mortality, respectively. 11 Since clockwise and counterclockwise rotation is commonly found in the general population, these observations may have broad clinical implications but are yet to be confirmed in other racial/ethnic groups or regions. Thus, the main objective to this study is to investigate possible prognostic values of clockwise and counterclockwise rotation of QRS transitional zone in 12-lead ECG for incident cardiovascular events including non-fatal cases in whites and blacks from the ARIC Study.

5. Main Hypothesis/Study Questions:
Aim 1: We will assess whether clockwise and counterclockwise rotations of QRS transitional zone in 12-lead ECG are associated with future cardiovascular events.

Aim 2: Once the prognostic values of these rotations are confirmed, we will evaluate the frequency of newly developed clockwise and counterclockwise rotations over 25 years of follow-up.

Aim 3: We will also determine the baseline characteristics of those individuals who developed these rotations during follow-up.

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).

Inclusions:
All black and white ARIC participants with data on QRS transitional zone rotation of ECG

Exclusions:
Ethnicity other than black or white
Individuals without data on QRS transitional zone rotation
Participants with history of coronary heart disease (CHD), heart failure (HF), or stroke

Exposures:
Clockwise (determined as Minnesota Code [MC] 9-4-2: a transition zone at V4 or leftward of V4) or counterclockwise (MC 9-4-1: a transition zone at V3 or rightward of V3) rotation of QRS transitional zone in ECG 12 Thus, MC defines normal rotation as
ECG coded neither as 9-4-1 nor as 9-4-2. Normal rotation will be defined as dominant S in V3 and dominant R in V4.

Outcomes:
CHD: a hospitalized myocardial infarction, fatal CHD, cardiac procedure
HF: the first HF hospitalization coded 428 according to the ICD-9 or death from HF (coded 428 for ICD-9 and I50 for ICD-10)
Stroke: definite and possible incident stroke (ischemic and hemorrhagic)
All-cause mortality

Other variables of interest and covariates:
Socio-demographics: age, race/center, gender, education
Physical information: blood pressure, body mass index, other ECG parameters (mild Q-wave abnormality (MC 1-3), frontal plane QRS axis deviations (MC 2-1, 2-2, 2-3), high R wave (MC 3-1 to 3-4), ST depression (MC 4-1 to 4-4), T-wave abnormality (MC 5-1 to 5-5), combination of high R plus either ST depression or T abnormality, first- or second-degree atrioventricular block (MC 6-2 or 6-3), intraventricular conduction disturbances (bundle-branch block) other than left bundle-branch block (MC 7-2-1 to 7-8), ventricular premature beats (MC 8-1-2), AF (MC 8-3), sinus tachycardia (MC 8-7), sinus bradycardia (MC 8-8), low QRS voltage (MC 9-1), ST elevation (MC 9-2), tall P wave (MC 9-3-1), and long P wave (MC 9-3-2))
Lifestyle: smoking status and alcohol habit
Comorbidities: hypertension, diabetes, dyslipidemia

Statistical analysis plan:
The primary analysis will use Cox proportional hazards models to quantify the association between clockwise/counterclockwise rotation of ECG QRS transitional zone at visit 1 and incident CVD as well as all-cause mortality. Rotation of ECG would be treated as nominal variable in the models, with normal rotation as a reference. We will adjust for the covariates listed above. We will repeat the analysis using ECG data at visits 2, 3, and 4 and also treating clockwise/counterclockwise rotation as time-varying variable.

We will implement four models for the adjustment for covariates. Model 1 will be crude. Covariates in model 2 would be demographic variables such as age, gender, race, and education level. Model 3 would further include other established risk factors: cigarette smoking (never [reference], past, and current smoker), alcohol drinking (never [reference], past, and current drinker), hypertension, diabetes mellitus, and total and high-density lipoprotein cholesterol levels, and body mass index. Model 4 would additionally adjust for minor and major ECG abnormalities (e.g., mild Q-wave abnormality, frontal plane QRS axis deviations, combination of high R [MC 3-1 to 3-4] plus either ST depression or T abnormality, first or second degree atrioventricular block, ventricular premature beats, AF, sinus tachycardia, sinus bradycardia, low QRS voltage, ST elevation, tall P wave, and long P wave). The interaction of clockwise/counterclockwise rotation with demographic and clinical factors will be assessed using likelihood ratio test comparing models with and without their interaction terms.
We will subsequently quantify the incidence of newly developed QRS rotation at follow-up visits (normal QRS rotation at visit 1 but clockwise/counterclockwise rotation at later visits) and identify baseline characteristics (among covariates mentioned above) related to incident clockwise/counterclockwise rotation using logistic and Cox regression models.

Limitations:
Our results may not be generalizable to individuals younger than 45 years or racial/ethnic groups other than whites or blacks. As with any observational study, we will not be able to rule out the possibility of residual confounding.

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 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  ____ 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.uc.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)?
There are no proposals focusing on clockwise and counterclockwise rotations as exposures for cardiovascular risk

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* __________)
   ___ 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.cscb.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.cscb.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.
Reference

7. Israel Gotsman et al. Usefulness of Electrocardiographic Frontal QRS-T Angle to Predict Increased Morbidity and Mortality in Patients With Chronic Heart Failure. Am J Cardiol 2013;111:1452e1459
9. Pentti M. Rautaharju et al Am J Cardiol 2013;112:843e849