ARIC Manuscript Proposal #2390

PC Reviewed: 7/8/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Electrocardiographic QRS/T angles in the Setting of Bundle Branch Blocks and Risk of Fatal and Non-fatal Coronary Heart Disease and All-cause Mortality in the Atherosclerosis Risk in Communities (ARIC) Study

1.B. Abbreviated Title (Length 26 characters):
Bundle Blocks and QRS/T angle

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. ZMZ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Start analyses: upon receipt of data from the coordinating centre
Submission for publication: June 2015

4. Rationale:

Abnormal electrocardiographic (ECG) repolarization markers such as wide spatial and frontal QRS-T angle have been repeatedly shown to be predictive of cardiovascular disease (CVD) events.[1-13] However, these previous studies excluded participants with bundle branch blocks (BBBs) or were conducted only in women.[12-13] Hence, there is a paucity of information on the prognostic significance of repolarization abnormalities in the setting of BBBs. Our recent data on predictors of heart failure from the ARIC study[14] shown that concomitant presence of BBB and widened QRS/T angle carries a much higher risk of heart failure than either predictor alone. These findings suggest that repolarization abnormalities in the setting of BBB should not be considered benign consequence of BBB. Therefore, we sought to evaluate the prognostic significance for the QRS/T angle and other ECG measures of abnormal repolarization for the prediction of coronary heart disease (CHD) and all-cause mortality in individuals with and without BBB.

5. Main Hypothesis/Study Questions:

<u>This study aims to</u>:

To examine the risk of CHD events and all-cause mortality associated with QRS/T angle in the presence of different BBB categories in men and women in the ARIC study

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).

<u>Sample Size</u>

All ARIC participants with good quality baseline ECG data as well as information on relevant risk factor variables and outcome variables of CHD events (fatal and non-fatal) and all-cause mortality during ARIC follow-up will be eligible for inclusion in this analysis. Participants with artificial pacemaker, or Wolf Parkinson White Syndrome will be excluded.

<u>The Variables:</u>

<u>ECG variables needed to fulfill the aim of the study will be:</u>

Complete Minnesota codes[15-16] for all ECGs at baseline and follow up visits, which will include:

- Complete left bundle branch block (MC-7.1)
- Complete right bundle branch block (MC-7.2)
- Combination of RBBB and left anterior fascicular block (MC-7.8)
- Indetermined type of ventricular conduction delay with QRS $\geq$ 120ms (MC-7.4).
- Myocardical infarction by ECG (ECG-MI) -- MC 1-1, MC 1-2, or MC 1-3 with MC 4-1/4-2 or MC 5-1/5-2.
- Myocardial ischemia (MC4-1/4-2).
- Frontal QRS axis and frontal T axis, QRS/T angles (spatial and frontal)
- Presence of arrhythmias including atrial fibrillation and ventricular/supraventricular ectopic complexes.

Non-ECG variables:

Non-ECG variables include demographic and clinical data, and outcome measures as follow:

(1) Age, race, gender, body mass index, education, smoking status, alcohol use, hypertension, diabetes mellitus, history of cardiovascular disease, family history of coronary heart disease, HDL cholesterol, LDL cholesterol, triglycerides, total cholesterol, systolic blood pressure, diastolic blood pressure, baseline fasting blood glucose.

(2) The outcomes include updated incident fatal and non-fatal CHD event and all-cause mortality confirmed by the endpoints committee. (update to the end of 2010)

Data Analysis:

First, frequency distributions of all ECG and non-ECG variables will be inspected to rule out anomalies and outliers possibly due to measurement artifacts.

Cox regression analysis will be used to examine the risk of CHD events and all-cause mortality, separately with each pattern of BBB (LBBB, RBBB, and IVCD) and QRS/T angles separately and in combination (i.e. concomitant presence of QRS/T angles and BBB).

Models will be initially adjusted for demographic (age, gender, race), then further adjusted for clinical characteristics (which are the variables mentioned as non-ECG variables above). Interaction by gender, race, and history of CVD will be examined and models will be stratified accordingly.

The proportional hazards assumption will be checked graphically for each of the candidate variables. All analyses will be performed with the SAS software, version 9.3.

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)?

1. Zhang ZM, Prineas RJ, Case D, Soliman EZ, Rautaharju PM for the ARIC Research Group: Comparison of the prognostic significance of the electrocardiographic QRS/Tangles in predicting incident coronary heart disease and total mortality (from the atherosclerosis risk in communities study). *Am J Cardiol* 2007; 100:844-849

2. Zhang ZM, Rautaharju PM, Prineas RJ, Loehr L, Rosamond W, Soliman EZ. Usefulness of Electrocardiographic QRS/T Angles With Versus Without Bundle Branch Blocks to Predict Heart Failure (from the Atherosclerosis Risk in Communities Study). Am J Cardiol. 2014 DOI:10.1016/j.amjcard.2014.05.011.

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:

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4 Rautaharju PM, Zhang ZM, Haisty WK, Prineas RJ, Kucharska-Newton AM, Rosamond W, Soliman EZ. Electrocardiographic Predictors of Incident Heart Failure in Men and Women Free from Manifest Cardiovascular Disease in the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Cardiol* 2013;112(6):843-849.

5 Zhang ZM, Prineas RJ, Case D, Soliman EZ, Rautaharju PM for the ARIC Research Group: Comparison of the prognostic significance of the electrocardiographic QRS/Tangles in predicting incident coronary heart disease and total mortality (from the atherosclerosis risk in communities study). *Am J Cardiol* 2007; 100:844-849

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13 Zhang ZM, Rautaharju PM, Soliman ES, Manson JE, Martin LW, Perez M, Vitolins M, Prineas RJ. Different Patterns of Bundle Branch Blocks and the Risk of Incident Heart Failure in the Women's Health Initiative (WHI) Study. *Circ Heart Fail* 2013;6:655-661.

14 Zhang ZM, Rautaharju PM, Prineas RJ, Loehr L, Rosamond W, Soliman EZ. Usefulness of Electrocardiographic QRS/T Angles With Versus Without Bundle Branch Blocks to Predict Heart Failure (from the Atherosclerosis Risk in Communities Study). Am J Cardiol. 2014 DOI:10.1016/j.amjcard.2014.05.011.

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