

ARIC Manuscript Proposal #2747

PC Reviewed: 4/12/16
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

QRS-T Angle and Risk of Silent Myocardial Infarction: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):

QRST & myocardial infarction

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

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3. Timeline:

Start analyses: After Publication Committee approval.

Submission for publication: December 2016.

4. Rationale:

Heart disease still is the leading cause of death globally. In 2013, about 14% of total deaths in the United States were due to coronary heart disease, with over 660,000 new myocardial infarctions (MI) occurring every year as well as 160,000 accidentally discovered asymptomatic silent MIs (SMI) (1-3). In a recent analysis from the ARIC study (4), we showed that asymptomatic or silent MI, identified on a screening electrocardiogram (ECG), is as common as clinically manifested MIs (CMI); about 45% of the total number of MIs in the ARIC study between visit-1 to visit-4 was silent. These SMIs were associated with an increased risk of death in a magnitude comparable to that for myocardial infarctions with clinical manifestations. Looking for predictors of silent MI will help identify individuals at risk who may benefit from more frequent follow-up or more aggressive risk factor management.

ECG markers of abnormal repolarization have been repeatedly shown to be predictive of cardiovascular disease (CVD) events and mortality (5-9). Therefore, we hypothesized that abnormal spatial and frontal QRS-T angle, measures of abnormal ventricular repolarization as it relates to depolarization, will be associated with silent MI as it is for clinically manifest MI (CMI).

5. Main Study Hypothesis:

- Abnormal spatial and frontal QRS/T angles are predictive of both incident silent and clinically manifested MI in the Atherosclerosis Risk in Communities (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).

Sample Size

All ARIC participants with a good quality baseline ECG and at least one follow up visit with a good quality ECG. Participants with past history of CHD (including MI by ECG at baseline) or with ECG showing QRS duration ≥ 120 ms, artificial pacemaker, or Wolf Parkinson White Syndrome will be excluded.

Variables:

Outcomes:

- Incident SMI and CMI occurring between baseline and visit 4.
- Clinical MI will be defined as definite or probable adjudicated MI occurring in the period from ARIC visit 1 to ARIC visit 4.
- Silent MI will be defined as ECG evidence of MI based on Minnesota code (10) in the absence of clinically detected in the same period (ARIC visit 1 to ARIC visit 4).

Main exposure variables:

- Baseline frontal QRS/T angle will be defined as the absolute value of the difference between the frontal plane QRS axis and T axis adjusted to the minimal angle using $(360^\circ - \text{angle})$ for an angle $>180^\circ$ (6);
- Baseline spatial QRS/T angle will be defined as the angle between the mean QRS vector and the mean T vector as in previous ARIC publications (6);
- Values greater than the sex-specific 95th percentile values of abnormal frontal and spatial QRS/T angle will be considered abnormal.

Covariates (all at baseline)

Age, race, gender, body mass index, education, income, smoking status, hypertension, diabetes mellitus, use blood pressure lowering medications, use of cholesterol lowering medications, use of aspirin, HDL cholesterol, LDL cholesterol, total cholesterol, systolic blood pressure, diastolic blood pressure, aspirin, and serum creatinine.

Data analysis:

Frequency distributions of all variables will be inspected to rule out anomalies and outliers possibly due to measurement artifacts.

The incidence rates of SMI and CMI will be calculated and compared in those with and without abnormally widened frontal and spatial QRS/T angle.

Cox proportional hazards analysis will be used to examine the association between abnormal frontal and spatial QRST angle, separately, with SMI and CMI (vs. no MI) occurring from visit 1 to visit 4. Follow-up time will be defined as the time from the initial study visit until one of the following: CMI or SMI, loss to follow-up, death, or end visit 4. Models will be adjusted as follows: Model 1 adjusted for baseline demographics (age, sex and race), and Model 2 adjusted for variables in Model 1 plus study field center, body mass index, income, education, smoking status, systolic blood pressure, blood pressure lowering medications, diabetes mellitus, ratio of total cholesterol/high density lipoprotein cholesterol, use of cholesterol lowering medications, use of aspirin, family history of CHD and serum creatinine (all variables measured at baseline). Interactions by sex and race will be examined in Model 2. We will consider extending the analysis until ARIC visit-5 if the adjudicated MI events are available until ARIC visit-5 exam.

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

7.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.csc.unc.edu/ARIC/search.php> 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)?**

ARIC-MS#2075: Zhang ZM, Rautaharju PM, Prineas RJ, Rodriguez CJ, Loehr L, Rosamond W, Kitzman D, Couper D, Soliman EZ. Race and sex differences in the incidence and prognostic significance of silent myocardial infarction in the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2016 in press

ARIC-MS#1151: 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.

ARIC-MS#1919: 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;114:412-418.

- 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.csc.unc.edu/anic/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.csc.unc.edu/anic/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:

- 1- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics –2016 Update. A report from the American Heart Association. *Circulation* 2016;133:e255-e269.
- 2- Thygesen K, Alpert JS, White HD on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal Definition of Myocardial Infarction. *Circulation*. 2007;116:2634-2653
- 3- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD: the writing group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020–2035.
- 4- Zhang ZM, Rautaharju PM, Prineas RJ, Rodriguez CJ, Loehr L, Rosamond W, Kitzman D, Couper D, Soliman EZ. Race and sex differences in the incidence and prognostic significance of silent myocardial infarction in the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2016 in press
- 5- Kors JA, van Herpen G, Sittig AC, van Bommel JH. Reconstruction of the frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. *Eur Heart J* 1990;11:1083-1092
- 6- 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.
- 7- 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;114:412-418.
- 8- Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women. The Women’s Health Initiative. *Circulation* 2006;113:473-480.
- 9- Zhang ZM, Prineas RJ, Soliman EZ, Chris Baggett, Gerardo Heiss for the ARIC Research Group: Comparison of the Prognostic Significance of Serial Q/STT Changes by the Minnesota Code and Novacode in the Atherosclerosis Risk in Communities Study. *Eur J Prev Cardiol* 2012;19:1430-1436.
- 10- Prineas RJ, Crow RS, Zhang ZM. The Minnesota Code Manual of Electrocardiographic Findings (Second edition). Published by Springer-London, 2009.