

ARIC Manuscript Proposal # 1760

PC Reviewed: 3/8/11
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: QT subintervals and QRS|T angle as independent predictors of incident coronary heart disease and total mortality in the ARIC study.

b. Abbreviated Title (Length 26 characters): QT and QRS|T angle subintervals and risk of coronary heart disease and total mortality

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

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3. Timeline: Start: Immediately after approval (expected, March 2011); MS submission: Oct 2011

4. Rationale:

Abnormally wide electrocardiographic QRS|T angle between the mean QRS and T vectors in women was documented to be associated with fatal and non-fatal coronary heart disease, coronary heart disease (CHD) and all-cause mortality in reports from WHI (1,2) and with incident CHD and all-cause mortality in men and women in ARIC study (3). Recent data from a large group of patients with acute coronary syndrome have revealed that progressively increasing deviation of the *initial* repolarization and excitation sequences is the primary pathophysiological mechanisms accounting for ischemia-induced widening of the rate-adjusted QRS|T angle (4). Abnormally wide initial QRS|T angle was observed to be related to a shift of the initial repolarization location from the epicardial site normally repolarized earliest. In another recent development, a new repolarization model developed by the first author of this manuscript proposal (5) has enabled determination of ECG estimates of regional repolarization times, and related QT subintervals, including epicardial, terminal and mid repolarization times. In addition, availability of the estimates of excitation times corresponding to epicardial, mid and terminal repolarization times makes it possible to derive ECG estimates for regional action potential durations.

There appear adequately grounds to postulate that different repolarization parameters, especially, widened initial QRS|T angle, may be involved in the evolution of incident CHD. In acute coronary syndrome, the shift in location of the region repolarized first appears to be the mechanism of increased initial QRS|T angle. The usefulness of ECG estimates of regional repolarization times and action potential durations as prognostic markers for incident fatal and non-fatal CHD has not been evaluated before. Therefore, we sought to examine the prognostic significance of a number of ECG estimates of regional repolarization times, and related QT subintervals, including epicardial, terminal and mid repolarization time for the prediction of coronary heart disease and total mortality in the ARIC study. The digital nature of the ECG signal in ARIC which enables calculation of the regional repolarization times is a unique opportunity to fulfill our aims.

5. Main Hypothesis/Study Questions:

ECG estimates of regional repolarization times and action potential durations are associated with excess risk of CHD and total mortality after adjustment for demographic, clinical and other known ECG predictors of CHD.

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).

All ARIC participants with good quality baseline ECG data as well as information on heart failure during ARIC follow-up will be eligible for inclusion in this analysis. Participants with baseline history of CHD, atrial fibrillation/flutter, advanced AV block or any ECG condition that may result in secondary changes in ventricular repolarization

(such as complete LBBB, RBBB, ventricular preexcitation (WPW), pacemakers, etc..) will be excluded.

Summary of variable of interest:

Demographic and clinical variables

- Age
- Sex
- Race
- Site
- Body mass index
- Waist circumference
- Cigarette smoking
- Alcohol intake, moderate and heavy
- Diabetes
- Ratio of Total to HDL cholesterol
- Systolic blood pressure
- Diastolic blood pressure
- Use of antihypertensive medication
- Prior CHD
- Prior stroke
- Prior heart failure

ECG variables

- In collaboration with the ARIC ECG reading center (represented in this proposal), the following QT subintervals and QRS|T angle (predictor variables) will be calculated from the ARIC baseline ECGs:
 - Epicardial action potential duration (APD_{epi}) = epicardial repolarization time (RT_{epi}) – Epicardial excitation time (ET_{epi}), where RT_{epi} = QT_{pa}, rate-adjusted QT_{peak} interval and ET_{epi} = QR_p, the interval from QRS onset to Peak of the global R wave, approximated by QT_p interval in lead V6.
 - Intramural action potential (APD_{mid}) = mid-repolarization time (RT_{mid}) – mid-excitation time = QT_{pa} + Tp - T_{xd}, where T_{xd} is the inflection point at the global T wave downstroke.
 - Terminal action potential = QT_a - QRS_{dur}, where QT_a is the rate-adjusted QT interval (determined only if terminal repolarization sequence is congruent with terminal ES).
 - Initial ($\theta(\text{QRS|T})_{\text{init}}$), maximum ($\theta(\text{QRS|T})_{\text{max}}$) and terminal $\theta(\text{QRS|T})_{\text{ter}}$ rate-adjusted spatial QRS|T angle, defined as follows: rate-adjusted

spatial QRS|T angle during the initial 3 quintiles of excitation and repolarization periods of time-normalized global QRS and T; spatial angle between maximal QRS and T vectors; used to approximate $\theta(\text{QRS|T})_{\text{init}}$; rate-adjusted QRS|T angle between terminal QRS and T vectors during the last quintile of excitation and repolarization periods.

- Other ECG variables will include heart rate, left ventricular hypertrophy and the amplitudes/duration of different parts of the ECG waveforms in each of the 12 ECG leads.

Outcome

- Incident CHD. This will include fatal and non-fatal CHD during ARIC follow-up defined as a definite/ probable MI or definite death from CHD.
- Total (all cause) mortality.

Brief analysis:

The association between each of the QT subintervals and QRS|T angle (listed above) with incident CHD and total mortality will be considered, separately, in a set of incremental Cox proportional hazards models as follows: 1) Unadjusted, 2) adjusted for age, sex, and race (demographic model); 3) further adjustment for common heart failure risk factors (systolic blood pressure, current smoking, diabetes, left ventricular hypertrophy, prior cardiovascular disease), 4) Further adjustment for ECG variables that might have impacted the measurement of QTc (such as QRS duration) or may confound the association between QT subintervals or QRS|T angle with our outcome variables (such as presence of other major ECG abnormalities as defined by Minnesota code or use of QT-prolonging drugs such as antiarrhythmics and antidepressants).

In all models, QT subintervals and QRS|T angle variables will be used as tertiles (the 2nd tertile will be the reference value)

Other analyses will include: 1) examining interactions between sex and race (separately) with each of the QT subintervals and QRS|T angle for prediction of incident coronary

heart disease and total mortality (separately); 2) examining the value of combining different QT subintervals and QRS|T angle variables together for a better prediction of coronary heart disease.

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.cscce.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)?

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/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

1. 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.
2. Rautaharju, PM, Kooperberg C, Larson JC, LaCroix, A. Electrocardiographic Predictors of Incident Congestive Heart Failure and All-cause Mortality in Postmenopausal Women. The Women's Health Initiative. *Circulation* 2006;113:481-489.
3. Rautaharju PM, Prineas RJ, Wood J, Zhang Z-M, Crow R, Heiss G. Electrocardiographic predictors of new-onset heart failure in men and women free of coronary heart disease (from the Atherosclerosis in Communities [ARIC] Study). *Am J Cardiol* 2007;100:1437-1441.
4. Rautaharju PM, Zhou SH, Gregg RS, Selvester RH. The mechanism of spatial QRS-T angle widening in acute coronary syndrome patients: distinct differences by gender, phase of repolarization and presence versus absence of diagnostic ST elevation. Submitted.
5. Rautaharju PM, Zhou SH, Gregg RS, Selvester RH. Electrocardiographic Estimates of Action Potential Durations and Transmural Repolarization Time Gradients in Normal Subjects and in Acute Coronary Syndrome Patients – Profound Differences by Gender and by Presence versus Absence of Diagnostic ST Elevation. In press, *J Electrocardiol* 2011