ARIC Manuscript Proposal # 1761

PC Reviewed: 3/8/11 Status: A Priority: 2
SC Reviewed: _________ Status: _____ Priority: ____

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

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

2. Writing Group:
 Writing group members:

Pentti Rautaharju, Elsayed Z Soliman, Zhu-Ming Zhang, Anna M. Kucharska-Newton,
Joel Xue, Ian Rowlandson, Wayne Rosamond

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]

First author:
Name: Pentti Rautaharju MD, PhD
Address: 737 Vista Meadows Dr.
Weston, FL 33327
Phone: 984-385-5622 Fax: 984-385-5622
E-mail: pentti.rautaharju@gmail.com

ARIC author to be contacted if there are questions about the manuscript and the first author
does not respond or cannot be located (this must be an ARIC investigator).
Name: Elsayed Z Soliman, MD, MSc, MS
Address: EPICARE/ Department of Epidemiology and Prevention
Division of Public Health Sciences
Wake Forest University School of Medicine
2000 W. First Street/Suite 505
Winston-Salem, NC 27104
Phone: (336)716-8632 Fax: (336) 716-0834
E-mail: esoliman@wfubmc.edu

3. Timeline: Start: Immediately after approval (March 2011, Expected)
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 incident heart failure, 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 mechanism 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 heart failure. In incident heart failure the myocardial region repolarizing first is not shifted. On the other hand, in acute coronary syndrome, the shift in location of the region repolarized first appears to be the mechanism of increased initial QRS|T angle.

Specifically regarding increased risk of incident HF, widened initial QRS|T angle reflecting deviant transmural repolarization has been postulated to induce dyssynchrony of left ventricular relaxation leading to diastolic heart failure (6). In canine heart models, the transmural relaxation time gradient had a nearly perfect correlation with the transmural repolarization time gradient (r=0.99). The authors concluded that their findings may have significance not only in the diagnosis and but also in the management of ventricular diastolic dysfunction.

The usefulness of ECG estimates of regional repolarization times and action potential durations as prognostic markers for incident heart failure 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 incident heart failure 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 incident heart failure after adjustment for demographic, clinical and other known ECG predictors of incident heart failure.
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 heart failure, 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:

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<thead>
<tr>
<th>Demographic and clinical variables</th>
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<tbody>
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<td>• Age</td>
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<td>• Sex</td>
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<td>• Race</td>
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<td>• Site</td>
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<tr>
<td>• Body mass index</td>
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<td>• Waist circumference</td>
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<td>• Cigarette smoking</td>
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<td>• Alcohol intake, moderate and heavy</td>
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<tr>
<td>• Diabetes</td>
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<tr>
<td>• Ratio of Total to HDL cholesterol</td>
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<td>• Systolic blood pressure</td>
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<td>• Diastolic blood pressure</td>
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<td>• Use of antihypertensive medication</td>
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<td>• Prior CHD</td>
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<td>• Prior stroke</td>
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<td>• Prior heart failure</td>
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<tr>
<th>ECG variables</th>
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<td>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:</td>
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<td>o Epicardial action potential duration (APDepi) = epicardial repolarization time (RTepi) – Epicardial excitation time (ETepi), where RTepi = QTpa, rate-adjusted QTpeak interval and ETepi = QRp, the interval from QRSonset to Peak of the global R wave, approximated by QTp interval in lead V6.</td>
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<tr>
<td>o Intramural action potential (APDmid) = mid-repolarization time (RTmid) – mid-excitation time =</td>
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QTpa + Tp-Txd, where Txd is the inflection point at the global T wave downstroke.

- Terminal action potential = QTa - QRSdur, where QTa is the rate-adjusted QT interval (determined only if terminal repolarization sequence is congruent with terminal ES.

- Initial $\theta(QRS|T)_{init}$, maximum $\theta(QRS|T)_{max}$ and terminal $\theta(QRS|T)_{ter}$ rate-adjusted spatial QRS|T angle, defined as follows: rate-adjusted spatial QRS|T angle during the initial 3 quintiles excitation and repolarization periods of time-normalized global QRS and T; spatial angle between maximal QRS and T vectors; used to approximate $\theta(QRS|T)_{init}$; 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 heart failure during ARIC follow-up using hospital discharge codes

Brief analysis:

The association between each of the QT subintervals and QRS|T angle (listed above) with incident heart failure 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 and QRS|T angle with incident heart failure (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 2\textsuperscript{nd} 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 heart failure; 2) examining the value of combining different QT subintervals and QRS|T angle variables together for a better prediction of heart failure.

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](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)?

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.cscb.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