

ARIC Manuscript Proposal #2834

PC Reviewed: 09/13/16
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Priority: 2
Priority: _____

1.a. Full Title: The Association between QT Interval Components and Sudden Cardiac Death: The Atherosclerosis Risk In Communities Study

b. Abbreviated Title (Length 26 characters): QT interval and sudden cardiac death

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. [WO]

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3. Timeline: Analysis to begin after Publication Committee approval. Manuscript anticipated for initial P&P review 6 months after proposal approval.

4. Rationale:

Several reports have demonstrated that prolonged QT interval, a maker of ventricular repolarization, is associated with sudden cardiac death (SCD).^{1,2} The QT-interval encompasses phases 0-3 of the ventricular cardiac action potential and hence involves both depolarizing and repolarizing currents.³ Therefore, the precise component(s) within the QT interval responsible for its association with SCD remains unknown. Refining the current understanding of the association between the QT interval and SCD to know whether it is triggered mainly by ventricular depolarization or repolarization could help guide the development of novel treatment strategies and facilitate more effective identification of individuals at risk of developing SCD. Accordingly, we sought to compare the associations of the different components of the QT-interval with the risk of SCD in the Atherosclerosis Risk In Communities (ARIC) study.

5. Main Hypothesis/Study Questions:

To examine the association of between 5 individual components of the QT interval (intrinsicoid R-wave duration, R-peak to R-end duration, ST segment duration, T-onset to T-peak, and T-peak to T-end duration) with SCD in ARIC.

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).

Design: Prospective cohort study.

Inclusion/Exclusion Criteria: We will include all participants with good quality baseline electrocardiogram data and follow-up data. The following groups of participants will be excluded: 1) participants with major ventricular conduction abnormalities (e.g. complete left or right bundle branch blocks), pacemakers, Wolf-Parkinson–White Syndrome, QRS duration ≥ 120 ms or with extremes of absolute QT interval duration (>600 or <200 ms); 2) the few ARIC participants with race other than black or white; 3) participants with history of cardiovascular disease; 4) participants who reported the use of class I or III antiarrhythmic drug use at baseline.

Outcomes: The outcome of interest will be SCD.

ECG Variables: Baseline electrocardiogram data will be used to compute the QT interval and its components (The ECG Reading Center has already created these variables). When used as continuous variables, we will adjust for heart rate. Prolonged components will be defined as values greater than the sex-specific 95th percentile for each measurement.

Variables: Other variables needed from the baseline study visit will include the following: socio-demographics (age, sex, race, income, education, and study site), cardiovascular disease risk factors (systolic blood pressure, HDL cholesterol, total cholesterol, body mass index, smoking,

diabetes), and baseline medication use (blood pressure lowering drugs, statins and other lipid-lowering therapies, and aspirin).

Statistics: Baseline characteristics will be compared between those who developed vs. those who did not develop SCD using Chi-square test for categorical values and Student's t-test for continuous variables. Time-to-event analyses using Cox regression will be used to examine the association between each of the QT interval components with SCD. QT interval components initially will be treated as continuous variables (the hazard ratios will be computed per 1-standard deviation increase in each component) where the median value among the 12 individuals leads will be utilized. We also will examine the QT interval components as categorical variables using the sex-specific 95th percentile to define prolonged measures. Heart rate will be included as a covariate in all models in order to adjust for the association between the QT interval and heart rate. Sensitivity analyses using lead V5 in isolation will be also performed. Cox regression analyses simultaneously adjusting for the different components of the QT-interval will also be performed using the same covariates. Models will be constructed as follows: Model 1 adjusted for age, sex, race, heart rate, income, and education; Model 2 adjusted for Model 1 covariates plus smoking, systolic blood pressure, diabetes, body mass index, total cholesterol, HDL cholesterol, antihypertensive medication use, lipid-lowering medication use, and aspirin use. We also will examine the graphical dose-response relationship of each component with SCD using a restricted cubic spline model with knots incorporated at the 5th, 22.5th, 50th, 77.5th, and 95th percentiles, separately.⁴ An additional analysis will be performed to determine if any of the QT interval components explain the relationship between the QT interval and SCD by including each QT interval component in a model that examines the overall association between the QT interval and SCD.

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.unc.edu/ARIC/search.php> Yes No

