

## ARIC Manuscript Proposal #2057

PC Reviewed: 1/9/13  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

### 1.a. Full Title:

The QT Interval and Risk of Incident Atrial Fibrillation

### b. Abbreviated Title (Length 26 characters):

The QT Interval and AF

## 2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal: MM

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**3. Timeline:**

This manuscript stems from our writing group's ancillary study #2011.11. When originally planning this manuscript/study, we submitted an ancillary study proposal instead of a manuscript proposal in the case that multiple manuscripts would be derived from it. However, this manuscript covers the majority of the content in the ancillary study proposal. Now, this manuscript is complete, has been reviewed & edited by co-authors, and is ready for ARIC publications' committee review. Please note: co-authors are aware of a competing manuscript from another group in submission to a journal – if possible, we therefore request an expedited review of this proposal.

**4. Rationale:**

Electrical abnormalities, particularly in atrial repolarization and refractoriness, are important in the pathogenesis of AF.<sup>1-6</sup> The QT interval obtained from the standard 12-lead ECG is a readily available, inexpensive, and rapid measure of ventricular repolarization. However, it is not known if this manifestation of ventricular repolarization can reflect clinically relevant atrial electrophysiology. Both ventricular and atrial refractoriness are determined by similar potassium and sodium currents,<sup>7</sup> suggesting that there is likely a within-person correlation between the two. Small studies of individuals with the inherited Short QT<sup>8</sup> and Long QT<sup>9</sup> Syndromes demonstrate an increased risk of AF among these rare individuals. A recent analysis of the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study found that a longer corrected QT interval (QTc) is associated with stroke, but the mechanism remains unknown.<sup>10</sup> As AF is one of the most common causes of stroke,<sup>11</sup> we sought to determine if a longer

QT interval might be an important predictor of incident AF in a large population-based study.

1. Marcus GM, Smith LM, Whiteman D, et al. Alcohol intake is significantly associated with atrial flutter in patients under 60 years of age and a shorter right atrial effective refractory period. *Pacing Clin Electrophysiol.* 2008;31(3):266-272.
2. Ravelli F, Allesie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated langendorff-perfused rabbit heart. *Circulation.* 1997;96(5):1686-1695.
3. Cosio FG, Palacios J, Vidal JM, Cocina EG, Gomez-Sanchez MA, Tamargo L. Electrophysiologic studies in atrial fibrillation. slow conduction of premature impulses: A possible manifestation of the background for reentry. *Am J Cardiol.* 1983;51(1):122-130.
4. Byrd GD, Prasad SM, Ripplinger CM, et al. Importance of geometry and refractory period in sustaining atrial fibrillation: Testing the critical mass hypothesis. *Circulation.* 2005;112(9 Suppl):I7-13.
5. Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. *Am Heart J.* 1964;67:200-220.
6. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart J.* 1959;58(1):59-70.
7. Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. *Physiol Rev.* 2005;85(4):1205-1253.
8. Gaita F, Giustetto C, Bianchi F, et al. Short QT syndrome: A familial cause of sudden death. *Circulation.* 2003;108(8):965-970.
9. Johnson JN, Tester DJ, Perry J, Salisbury BA, Reed CR, Ackerman MJ. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. *Heart Rhythm.* 2008;5(5):704-709.
10. Soliman EZ, Howard G, Cushman M, et al. Prolongation of QTc and risk of stroke: The REGARDS (REasons for geographic and racial differences in stroke) study. *J Am Coll Cardiol.* 2012;59(16):1460-1467.
11. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: A report from the american heart association. *Circulation.* 2012;125(1):e2-e220.

## 5. Main Hypothesis/Study Questions:

Hypothesis: The QT interval on the standard resting 12-lead electrocardiogram is associated with the risk of incident atrial fibrillation.

## 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).

Below is the abstract of this manuscript:

### Background

Abnormal atrial repolarization is important in the development of atrial fibrillation (AF), but no direct measurement is available in clinical medicine. We hypothesized that the QT interval, a marker of ventricular repolarization, could be used as a surrogate for atrial repolarization to predict incident AF.

### Methods

We examined a prolonged QT corrected by the Framingham formula ( $QT_{Fram}$ ) as a predictor of incident atrial fibrillation (AF) in the Atherosclerosis Risk in Communities (ARIC) study. The Cardiovascular Health Study (CHS) and Health, Aging, and Body Composition (Health ABC) study were used for validation. Secondary predictors included QT duration as a continuous variable, a short QT interval, and QT intervals corrected by other formulae.

### Results

Among 14,538 ARIC participants, a prolonged  $QT_{Fram}$  predicted a roughly two-fold increased risk of AF (hazard ratio [HR] 2.05, 95% confidence interval [CI] 1.42-2.96,  $p < 0.001$ ). No substantive attenuation was observed after adjustment for age, race, sex, study center, body mass index, hypertension, diabetes, coronary disease, and heart failure. The findings were validated in CHS and Health ABC and were similar across various QT correction methods. Also in ARIC, each 10-ms increase in  $QT_{Fram}$  was associated with an increased unadjusted (HR 1.14, 95% CI 1.10-1.17,  $p < 0.001$ ) and adjusted (HR 1.11, 95% CI 1.07-1.14,  $p < 0.001$ ) risk of AF. Findings regarding a short QT were inconsistent across cohorts.

### Conclusions

A prolonged QT interval is associated with an increased risk of incident AF.

**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.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)?**

MS#1737: AFib and sudden cardiac death

MS#1559: PR interval, P wave indices and AFib

We have been working with ARIC investigator Alvaro Alonso to avoid overlap with existing proposals.

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?**  Yes  No

Please note: Though the proposal for the analysis performed in this manuscript is outlined in ancillary study proposal #2011.11, this manuscript itself is based entirely off ARIC data and not ancillary study data.

**11.b. If yes, is the proposal**

A. primarily the result of an ancillary study ( )

B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)\* #2011.11)

\*ancillary studies are listed by number at <http://www.csc.c.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.**