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The QT Interval and Risk of Incident Atrial Fibrillation

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Abstract

BACKGROUND—Abnormal atrial repolarization is important in the development of atrial fibrillation (AF), but no direct measurement is available in clinical medicine.

OBJECTIVE—To determine whether the QT interval, a marker of ventricular repolarization, could be used to predict incident AF.

METHODS—We examined a prolonged QT corrected by the Framingham formula (QT_{Fram}) as a predictor of incident 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.

Keywords

atrial fibrillation; epidemiology; risk; QT interval; electrocardiography; ECG

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice.¹ Major population-based studies have focused on AF risk factors that are most closely related to hemodynamic and atrial substrate abnormalities, such as hypertension, heart failure, and left atrial enlargement.^{1–4} However, computer modeling, animal models, and small human studies make it clear that electrical abnormalities, particularly in atrial repolarization and refractoriness, are also important in the pathogenesis of AF.^{5–10}

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 several of the same potassium and sodium currents,¹¹ suggesting that there is likely a within-person correlation between the two. Of interest, small studies of individuals with the inherited Short QT¹² and Long QT^{13,14} Syndromes suggest an increased risk of AF among these rare individuals with monogenically-mediated abnormalities in myocardial repolarization. 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.¹⁵ A recent analysis of a large administrative database demonstrated a J-shaped association between QTc and AF among patients referred for an ECG.¹⁶ We sought to determine if a longer QT interval might be an important predictor of

incident AF in well characterized, population-based cohort studies free of selection bias for ECG referral.

METHODS

We assessed the relationship between QT interval length and risk of incident AF in the Atherosclerosis Risk in Communities (ARIC) cohort, a prospective population-based cohort study. Because biological plausibility supports both longer or shorter atrial repolarization as risk factors for AF (suggesting that a longer or shorter QT interval could be important), we validated our findings in two independent prospective cohort studies, the Cardiovascular Health Study (CHS) and the Health, Aging, and Body Composition (Health ABC) study.

Recruitment, characterization, and outcome ascertainment of ARIC, CHS, and Health ABC have been described in detail previously.^{18–20} ARIC was selected as the primary cohort because it represents a relatively young and healthy population, limiting the roles of atrial fibrosis and structural heart disease and therefore potentially optimally uncovering innate electrophysiological abnormalities as the cause of AF. Each cohort's research protocol was approved by its respective institutional review board, and all participants provided written informed consent. Brief descriptions of each are provided below:

ARIC

Between 1987–1989, 15,792 adults aged 45–64 years sampled from four US communities (northwest suburbs of Minneapolis, MN; Washington County, MD; Jackson, MS; Forsyth County, NC) underwent a comprehensive baseline assessment. Subsequent contact included annual phone interviews and three repeat examinations spaced approximately three years apart.¹⁸ Standard resting 12-lead ECGs were performed at each visit. All measurements were digitally recorded, and a globally-averaged QT interval was generated from the earliest QRS onset and T-wave offset using all leads. All ECG waveforms were verified by visual inspection.²¹ Prevalent AF was identified from the baseline ECG, and incident AF was identified from study visit ECGs, hospital discharge diagnoses, and death certificates.²² Self-reported medication use in the 2 weeks prior to study entry was recorded. Methods of ascertaining baseline hypertension (HTN), coronary heart disease (CHD), congestive heart failure (CHF), and diabetes (DM) for each cohort are described in Supplementary Appendix Table 1.

CHS

From 1989–1990, 5,201 adults aged 65 years and older were recruited from the Medicare eligibility lists of four US counties (Forsyth, NC; Sacramento, CA; Washington, MD; Alleghany, PA), and an additional 687 African-Americans were recruited from 1992–1993.¹⁹ Participants underwent a comprehensive baseline examination and were followed by alternating semiannual phone calls and clinic visits until 1999 and phone calls every six months thereafter. Resting 12-lead ECGs were recorded using MAC PC ECG Machines (Marquette Electronics) and processed using the GE Marquette 12-SL program.¹⁹ This program measured the QT interval from a median QRS-T complex derived from all leads.²³ ECG waveforms were measured automatically after visual inspection for errors and quality. Prevalent AF was identified from the baseline ECG,²⁴ and incident AF was identified by study visit ECGs or hospital discharge diagnosis codes supplemented with Medicare inpatient claims data. Participants were asked to provide containers of all medications used in the 2 weeks prior to the baseline home interview.²⁵

Health ABC

Between 1997–1998, 3,075 adults aged 70–79 years were sampled from two US regions (Pittsburgh, PA; Memphis, TN). Participants underwent a comprehensive baseline exam and were followed thereafter with semi-annual alternating phone calls and clinic visits.²⁰ Baseline ECGs were analyzed at the ECG core laboratory at Saint Louis University Medical Center (St Louis, Missouri). ECGs were coded using the Minnesota Coding system and were visually inspected for accuracy.²⁶ Analysts measured the QT interval from the start of the QRS complex to the T-wave offset in three beats in lead II, and an average duration was generated. Prevalent AF was identified from the baseline ECG or from Medicare claims data. Incident AF was identified from the year 4 visit ECG, hospital discharge diagnoses, or Medicare claims data provided through the National Center for Health Statistics' Medicare claims linkage. Participants provided medications used in the previous two weeks at the year 1 visit.

QT Interval Ascertainment

We excluded participants with known prevalent AF, QRS duration ≥ 120 ms, left ventricular hypertrophy (LVH), ventricular pre-excitation, Vaughan-Williams Class I or III antiarrhythmic drug use, artificial pacing, or extremes of QT interval duration (>600 or <200 ms) at baseline. We corrected the QT interval using the Framingham, Fridericia, Hodge and Bazett formulae (Supplementary Appendix Table 2). We used the Framingham formula for primary analyses, a linear correction method that is recommended by American Heart Association/American College of Cardiology/Heart Rhythm Society consensus and previously used in population-based studies.^{15,27} Our primary predictor was an abnormally long Framingham-corrected QT interval (QT_{Fram}), defined as ≥ 460 ms in women and ≥ 450 ms in men.²⁷ Secondary predictors included abnormally long QT intervals corrected by the other formulae, QT_{Fram} as a continuous variable, and abnormally short corrected QT intervals (defined as ≤ 390 ms).²⁷ Incident AF was the primary outcome.

Statistical Analyses

Normally distributed continuous variables are presented as means \pm SD, and variables that were not normally distributed are presented as medians and interquartile ranges (IQR). Hazard ratios (HR) and 95% confidence intervals (CI) for the association between QTc interval and incident AF were obtained using Cox proportional hazards models. In CHS and Health ABC, QTc as a continuous variable was not consistently amenable to analysis using Cox proportional hazards models due to non-linear response, as assessed by restricted cubic splines. Covariates in multivariable models included age, race, sex, body mass index (kg/m^2), study center, HTN, CHF, CHD, and DM. Race was analyzed as white versus non-white. Sex and race-specific effects of our primary predictor (a prolonged QT_{Fram}) were examined using stratified analyses and statistical tests for interaction. Missing values were excluded from analyses. All analyses were performed using Stata Version 12 (College Station, TX).

RESULTS

After the exclusion criteria were applied, our final study cohorts included 14,538 participants in ARIC, 4,745 in CHS, and 2,396 in Health ABC (Table 1).

Individuals with a prolonged QT_{Fram} had an increased risk of developing AF in all three cohorts (Figure 1). The association persisted after multivariable adjustment for potential confounders (Figure 2). Similar statistically significant findings also persisted in ARIC and Health ABC regardless of the method of QT interval correction (Table 2). Although the point estimates consistently demonstrated a positive association, statistical significance was

not achieved in adjusted analysis using the Hodge correction in CHS. Stratified analyses according to sex and race did not significantly change the association between a prolonged QTc and risk of AF; there was no evidence for an interaction between either sex or race and prolonged QTc.

Examining the corrected QT interval as a continuous variable in ARIC, every 10-ms increase in QT_{Fram} was associated with an increased risk of AF, both prior to (HR 1.14, 95%CI 1.10–1.17, p<0.001) and after adjustment (HR 1.11, 95%CI 1.07–1.14, p<0.001).

Findings were consistent across correction methods used. Findings regarding a short QT were inconsistent by method of QT interval correction and across cohorts (Table 3).

DISCUSSION

We found that individuals with a prolonged QT_{Fram} had an increased risk of AF. This association was consistent across three prospective, population-based cohorts and remained significant after adjustment for traditional AF risk factors. Our data also support a continuous association between a longer QT and increased risk of AF. These findings suggest that ventricular repolarization represents a new and easily identifiable marker of AF risk that may provide insights into the pathophysiology of this arrhythmia.

Recent evidence has demonstrated an increased risk of AF in individuals with Long QT Syndrome (LQTS).^{13,14} While this rare syndrome is estimated to affect only 0.05% of the general population,^{28,29} the prevalence of a long QTc interval in our cohorts was substantially higher at 1–9%. Therefore, it is unlikely our methods simply detected those with an occult diagnosis of the LQTS—indeed, the larger prevalence observed suggests that a phenomenon clinically relevant to the general population is present. A longer QT interval may directly reflect a greater propensity to AF as a manifestation of aberrations in refractoriness paralleled in the atrium and ventricle. For example, LQTS patients with prolonged cardiomyocyte refractoriness exhibit polymorphic atrial tachycardia with an undulating P-wave axis that has been termed “atrial torsades de pointes,”³⁰ a state known to degenerate into AF.³¹ An alternative explanation may be related to enhanced activity of the late sodium current: increased late sodium entry into cardiomyocytes manifests on the 12-lead ECG by prolonging the QT interval^{32,33} and, by increasing intracellular calcium and triggered automaticity, may promote AF.^{34,35}

Investigators in the REGARDS study demonstrated that individuals with a prolonged QT had an increased risk of stroke independent of traditional risk factors, but no clear explanation was provided.¹⁵ Our finding that a prolonged QT increases the risk of AF provides a potential explanation. Subsequent analyses to determine if AF mediates the association between the QT interval and stroke may prove fruitful.

More recently, Nielson et al. provided an important analysis of nearly 300,000 patients from the greater region of Copenhagen referred for an ECG.¹⁶ Using covariates and incident outcome data derived from Danish registries, they demonstrated a J-shaped association between QTc (using both Framingham and Bazett corrections) and AF. These findings compliment ours nicely, and our data address several limitations inherent to that study. First, all participants in our three population-based cohort studies underwent 12 lead ECGs, thereby avoiding any potential referral bias that may have been present in the Copenhagen study. Second, because we were able to leverage the in-person data that was prospectively collected as part of these cohort studies, we were able to adjust for important baseline covariates such as body mass index and hypertension. Finally, our cohorts were enriched for African Americans, extending these findings beyond a Northern European population. It is unclear whether the relationship between a prolonged QTc and AF is genetic, due to an

environmental exposure, or is a manifestation of AF-associated comorbidities. Because our findings persisted after multivariable adjustment, we suspect this represents a process independent of previously identified risk factors for AF, such as HTN and CHF. Future examination of longitudinal cohorts that include younger individuals may be useful in determining if a longer QTc present in childhood or young adulthood predicts long-term AF risk. Additional future studies may also demonstrate whether AF patients with a longer QT represent a clinically-distinct AF subtype that is more or less amenable to certain therapies. For example, AF that arises due to a diffuse electrical abnormality may theoretically be less responsive to ablation procedures or antiarrhythmic drugs that prolong refractoriness.

Of note, individuals with the inherited Short QT Syndrome may have increased rates of AF,¹² a finding consistent with the notion that a shorter atrial effective refractory period may facilitate reentry and the presumed multiple wavelets that may sustain AF.^{5–10} We observed inconsistent findings regarding a short corrected QT interval and incident AF. These findings are clearly more complex and difficult to interpret than our consistent observations regarding a long QT interval, but they may provide a source of valuable future investigation to better understand differing mechanisms of AF between diverse populations.

Various methods to adjust the QT interval for heart rate exist. The Bazett formula is the most frequently employed method in clinical practice, but it is inaccurate at faster and slower rates.²⁷ Based on the AHA/ACCF/HRS consensus guidelines, we adjusted the QT interval using the Framingham formula, a linear correction method in which the adjusted QT is less dependent on heart rate.²⁷ This was also the primary correction formula in the REGARDS study. It is important to note that our findings regarding a prolonged QT were robust and consistent across correction methods.

Study Limitations

While medication use was rigorously obtained in each cohort, it remains possible that participants on Class I or III antiarrhythmic drugs were incompletely ascertained. Similarly, although AF diagnoses were identified from serial ECGs and hospitalizations, it is likely that some AF was not detected. We thus cannot exclude the possibility that some under-ascertained AF patients treated with undocumented antiarrhythmic drugs contributed to our results—however, given our consistent findings across three different cohorts, we believe this to be unlikely. Although measurement error in assessing the QT interval is possible, we would not expect it to be differentially present in those who later did and did not develop AF. Additionally, the 3 cohorts demonstrating consistent results represented two separate ECG core labs. Finally, it is possible that individuals with a longer QT are more aggressively monitored and therefore are more likely to have asymptomatic AF identified. However, this would not appear to sufficiently explain our finding that a continuous measure of QT predicted a progressively increased risk of AF.

Conclusions

We found that a longer QT interval is associated with an increased risk of incident AF. As a readily available measurement on the routine 12-lead ECG, the QT interval may therefore provide a widely applicable novel predictor of incident AF. Individuals with AF who have a prolonged QT may also represent a distinct subtype of AF patients with abnormal repolarization, and future investigation can determine if identification of this subtype is useful in selecting particular therapeutic strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AF	atrial fibrillation
ECG	electrocardiogram
QT_c	corrected QT interval
REGARDS	Reasons for Geographic and Racial Differences in Stroke
ARIC	Atherosclerosis Risk in Communities
CHS	Cardiovascular Health Study
Health ABC	Health, Aging, and Body Composition
HTN	hypertension
CHD	coronary heart disease
CHF	congestive heart failure
DM	diabetes mellitus
LVH	left ventricular hypertrophy
QT_{Fram}	QT corrected by Framingham formula
QT_{Frđ}	QT corrected by Fridericia formula
QT_B	QT corrected by Bazett formula
QT_H	QT corrected by Hodge formula
IQR	interquartile range
HR	hazard ratio
CI	confidence interval

LQTS Long QT Syndrome

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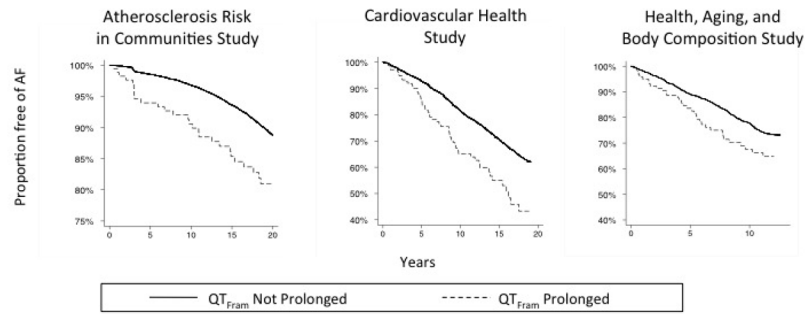


Figure 1. Kaplan-Meier curves for incident atrial fibrillation in Atherosclerosis Risk in Communities (ARIC) study, Cardiovascular Health Study (CHS), and Health, Aging, and Body Composition (Health ABC) study participants with and without a prolonged corrected QT interval

AF = atrial fibrillation. QT_{Fram} = QT interval corrected by Framingham formula.

Differences in proportions with and without AF are compared using log-rank tests.

Individuals with a prolonged QT_{Fram} had a significantly increased risk of AF in ARIC ($p < 0.001$), CHS ($p < 0.001$) and Health ABC ($p = 0.02$), compared to those without.

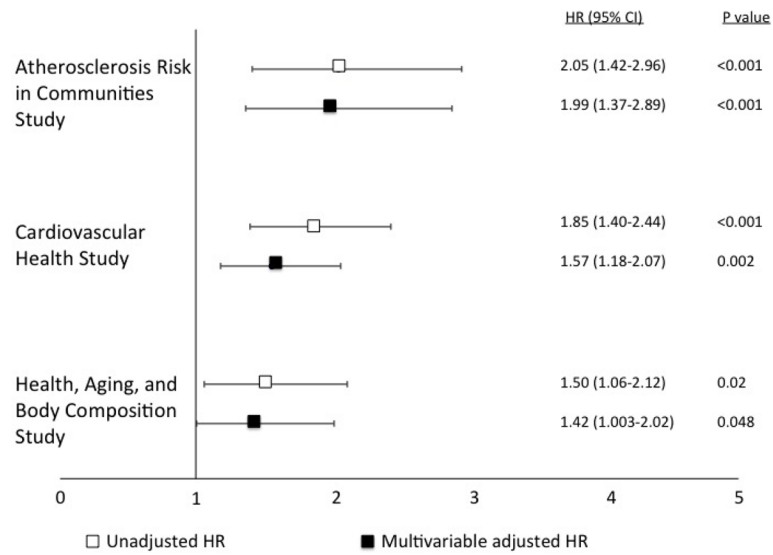


Figure 2. Hazard ratios (HR) and 95% confidence intervals (CI) for risk of atrial fibrillation for individuals with prolonged QT intervals corrected by the Framingham formula
 Multivariable models are adjusted for age, race, sex, body mass index, study center, hypertension, diabetes, coronary heart disease, and congestive heart failure. The vertical axis represents a HR of 1. Error bars denote 95% confidence intervals.

Table 1

Participants' baseline characteristics

Variable	Atherosclerosis Risk in Communities Study (n=14,538)	Cardiovascular Health Study (n=4,745)	Health, Aging, and Body Composition Study (n=2,396)
Age, in years	54 ± 5.7	72 ± 5.5	74 ± 2.8
Female	8,115 (56%)	2,809 (59%)	1,274 (53%)
Body mass index, in kg/m ²	28 ± 5.4	27 ± 4.8	27 ± 4.8
Race			
White	10,739 (74%)	4,996 (84%)	1,428 (60%)
Black	3,754 (26%)	718 (15%)	968 (40%)
Asian	32 (0.2%)	4 (0.1%)	0 (0%)
American Indian/Alaskan Native	13 (0.1%)	9 (0.2%)	0 (0%)
Other	0 (0%)	18 (0.4%)	0 (0%)
Hypertension	4,875 (34%)	2,682 (57%)	1,389 (58%)
Diabetes	1,660 (12%)	693 (15%)	345 (14%)
Coronary heart disease	607 (4.2%)	791 (17%)	466 (19%)
Congestive heart failure	626 (4.4%)	124 (2.6%)	64 (2.7%)
QT (uncorrected), in ms	399 ± 30	409 ± 34	412 ± 33
QT _{Fram} (Framingham), in ms	410 ± 16	416 ± 18	420 ± 21
QT _{Frd} (Fridericia), in ms	410 ± 17	416 ± 19	421 ± 22
QT _B (Bazett), in ms	416 ± 17	420 ± 19	426 ± 23
QT _H (Hodge), in ms	410 ± 18	417 ± 21	421 ± 22
Long QT _{Fram}	174 (1.2%)	144 (3.0%)	118 (4.9%)
Short QT _{Fram}	996 (6.9%)	177 (3.7%)	91 (3.8%)
Follow-up, in years	19.7 (17.1–20.7)	14.0 (8.7–18.2)	7.0 (3.8–9.8)
Incident atrial fibrillation	1,470 (10%)	1,271 (27%)	562 (23%)

Values are reported as mean ± standard deviation, median (interquartile range), or number (percent).

Table 2

Hazard ratios and 95% confidence intervals for risk of atrial fibrillation among individuals with an abnormally long QT interval corrected by Bazett, Fridericia, and Hodge formulae.

	Atherosclerosis Risk in Communities Study		Cardiovascular Health Study		Health, Aging, and Body Composition Study	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Bazett						
HR	2.07	1.56	1.45	1.29	1.38	1.30
95% CI	1.62–2.64	1.22–2.01	1.13–1.86	1.01–1.66	1.06–1.78	1.002–1.69
P value	<0.001	<0.001	0.003	0.045	0.02	0.048
Fridericia						
HR	1.94	1.82	1.79	1.48	1.63	1.57
95% CI	1.39–2.72	1.29–2.57	1.40–2.32	1.15–1.91	1.18–2.24	1.14–2.18
P value	<0.001	0.001	<0.001	0.003	0.003	0.006
Hodge						
HR	1.92	1.67	1.51	1.22	1.70	1.58
95% CI	1.44–2.57	1.24–2.25	1.20–1.89	0.97–1.54	1.27–2.27	1.18–2.12
P value	<0.001	0.001	<0.001	0.09	<0.001	0.002

* Adjusted for age, race, sex, body mass index, study center, hypertension, diabetes, heart failure, and coronary heart disease.

HR = hazard ratio. CI = confidence interval.

Table 3

Hazard ratios and 95% confidence intervals for risk of atrial fibrillation among individuals with an abnormally short corrected QT interval

	Atherosclerosis Risk in Communities Study		Cardiovascular Health Study		Health, Aging, and Body Composition Study	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Framingham						
HR	0.79	0.84	1.06	1.09	1.34	1.37
95% CI	0.63-0.99	0.66-1.06	0.79-1.42	0.81-1.47	0.91-1.99	0.92-2.04
P value	0.039	0.14	0.71	0.57	0.14	0.12
Bazett						
HR	0.68	0.83	0.80	0.83	1.07	1.11
95% CI	0.48-0.95	0.59-1.18	0.49-1.28	0.46-1.35	0.63-1.82	0.65-1.89
P value	0.02	0.31	0.35	0.46	0.79	0.70
Fridericia						
HR	0.75	0.76	1.05	1.11	1.01	1.08
95% CI	0.61-0.91	0.61-0.94	0.81-1.35	0.86-1.44	0.67-1.52	0.71-1.63
P value	0.004	0.01	0.74	0.42	0.97	0.72
Hodge						
HR	0.75	0.79	1.13	1.18	0.95	1.02
95% CI	0.62-0.91	0.65-0.97	0.89-1.44	0.94-1.51	0.63-1.43	0.67-1.54
P value	0.003	0.02	0.30	0.16	0.80	0.93

* Adjusted for age, race, sex, body mass index, study center, hypertension, diabetes, heart failure, and coronary heart disease.

HR = hazard ratio. CI = confidence interval.