Published in final edited form as:

Heart Rhythm. 2016 February ; 13(2): 527–535. doi:10.1016/j.hrthm.2015.11.008.

Optimal QT Correction Formula in Sinus Tachycardia for Identifying Cardiovascular and Mortality Risk: Findings from the Penn Atrial Fibrillation Free Study

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Abstract

Background—QT interval measures cardiac repolarization, and prolongation is associated with adverse cardiovascular outcomes and death. The exponential Bazett correction formula overestimates QT interval during tachycardia.

Objective—We evaluated four methods of QT correction in individuals with sinus tachycardia for the development of coronary artery disease, heart failure and mortality.

Methods—The Penn Atrial Fibrillation Free Study (PAFF) is a large cohort of patients without AF. This study examined 6,723 PAFF patients without a history of HF and with baseline sinus rate 100 beats per minute. Medical records were queried for index clinical parameters, incident cardiovascular events, and all-cause mortality. QT was corrected by Bazett ($QT/RR^{0.5}$); Fridericia ($QT/RR^{0.33}$); Framingham ($QT + 0.154 \times (1000 - RR)$); and Hodges ($QT + 105 \times (1/RR - 1)$).

Results—Among 6,723 patients with median follow-up of 4.5 [1.9, 6.4] years, annualized cardiovascular event rate was 2.3% and annualized mortality rate was 2.2%. QT prolongation was diagnosed in 39% of the cohort by Bazett, 6.2% by Fridericia, 3.7% by Framingham, and 8.7% by Hodges. Only Hodges' formula was an independent risk marker for death across the range of QT values [HR highest tertile: 1.26, 95% CI (1.03–1.55)].

Conclusions—Although all correction formulas demonstrated an association between QT_c values and cardiovascular events, only the Hodges formula identified one-third of individuals with tachycardia that are at higher risk for all-cause mortality. Further, Bazett's correction overestimates the number of patients with a prolonged QT and was not associated with mortality.

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Conflicts of interest: None.

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Future work may validate these findings and result in changes to automated algorithms for QT interval assessment.

Keywords

tachycardia; QT Interval; mortality; cardiovascular disease

Introduction

Prolongation of the QT interval reflects abnormalities in cardiac repolarization and is a risk marker for ventricular arrhythmias, other adverse cardiovascular events including heart failure (HF) and coronary artery disease (CAD), and death in various populations.^{1–9} The repolarization time reflects the electrophysiologic properties of ion channels that are responsible for maintaining equilibrium in myocardial cells. In addition, repolarization is also a function of the underlying heart rate and decreases with a progressive rise in the ventricular rate. This response ensures that the myocardium remains completely excitable and avoids zones of heterogeneous conduction that could result in the induction of re-entrant arrhythmias. Assessment of the QT interval, therefore, requires correction for the heart rate in order to enable comparisons with standard, reference values.

Multiple correction formulas have been empirically developed in an attempt to provide a standard index for the duration of myocardial repolarization.^{10–16} The Bazett method, which multiplies the measured QT interval by the inverse square root of the RR interval,¹⁰ is most commonly used to derive the corrected QT interval in clinical practice. Since the Bazett formula utilizes an exponential term, it is believed to overestimate the QT interval during states of tachycardia.^{17–20} We sought to compare the prognostic significance of the various correction methods in states of tachycardia and hypothesized those formulas utilizing a linear term such as Hodges or Framingham will provide a more accurate assessment of cardiac repolarization and be a better marker of adverse risk than the traditional Bazett formula.¹⁸ Further, resting sinus tachycardia results from a multitude of disease processes and is independently associated with both heart failure and all-cause mortality.^{21–23} In a large cohort of patients with resting sinus tachycardia, we compared four different QT-correcting formulas and their association with incident cardiovascular events and all-cause mortality.

Methods

The Penn Atrial Fibrillation Free (PAFF) study is a large, multi-hospital cohort of patients from the University of Pennsylvania Health System (UPHS) that were free of atrial fibrillation (AF) or atrial flutter at the index visit. The index visit was defined as having both a clinical encounter with a practitioner within the University of Pennsylvania Health System and a standard twelve-lead electrocardiogram (ECG). Of the 91,274 patients that had an index electrocardiogram (ECG) between January 1, 2004 and December 31, 2009, 67,265 were eligible for the study (Figure 1). To ensure adequate longitudinal data, subjects with fewer than 30 days of clinical follow-up within the UPHS were excluded. We also excluded individuals with baseline AF, atrial flutter, or a history of heart failure given the known

alterations in repolarization currents that occur among patients with cardiac dysfunction.^{24–26} Our final analysis included the 6,723 subjects with sinus tachycardia on index ECG. This study was approved by the Institutional Review Board of the University of Pennsylvania.

Measurement of clinical parameters

Information about patient demographics, cardiovascular risk factors, laboratory values, and medications were extracted from electronic medical records and included a comprehensive set of clinical encounters. Clinical risk factors and diagnoses were assessed utilizing the International Classification of Diseases, version 9 (ICD-9) codes that were generated from emergency room visits, inpatient hospitalizations, outpatient encounters, and telephone encounters. These sources also provided data related to laboratory investigations and medications. In particular, we accessed Sunrise Clinical Manager (Eclipsys Corporation, Atlanta, GA), Epic (Verona, WI), Cerner (North Kansas City, MO), EmTrac (University of Pennsylvania, Philadelphia, PA), and Medview (University of Pennsylvania, Philadelphia, PA) (see Supplementary Materials). Race was self-reported by subjects. ICD-9 codes were assessed for the following conditions: heart failure; hypertension; coronary artery disease; valvular heart disease; diabetes; and chronic kidney disease (see Supplementary Materials for full listing of all ICD-9 codes). CAD was defined as either an ICD-9 code consistent with either acute myocardial infarction or chronic coronary heart disease or having evidence of prior myocardial infarction on the index ECG. Concordance between automated queries and manual chart review was confirmed in a subset of randomly chosen subjects (see Supplementary Materials).

ECG measures and assessment of the corrected QT interval

The MUSE Cardiology Information Manager (GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom) was queried to identify selected ECG data. ECGs are performed primarily using the MAC 5500 HD system, which utilizes GE Marquette 12SL ECG analysis programs, versions 231–239 (see Supplementary Materials). Left ventricular hypertrophy, left bundle branch block, or right bundle branch block was diagnosed by the over-reading cardiologist on index ECG. RR interval and QT interval measurements were performed by automated software (MUSE, GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom). In particular, the QT interval was measured as a global interval from the earliest depolarization in any lead to the latest offset of repolarization, which was defined as the T wave crossing back to baseline.²⁷

Four methods for QT correction were used: Bazett ($QT_{cBaz} = QT/RR^{0.5}$)¹⁰; Fridericia ($QT_{cFrid} = QT/RR^{0.33}$)^{11, 16}; Framingham ($QT_{cFram} = QT + 0.154 \cdot (1000 - RR)$)¹⁴; and Hodges ($QT_{cHodg} = QT + 105 \cdot (1/RR - 1)$)^{15, 28}. RR interval was in seconds for all formulas except for Framingham, where it was in milliseconds. QT prolongation was defined as a corrected QT interval that was ≥ 460 ms for women or ≥ 450 ms for men.²⁹

Ascertainment of Incident Outcomes

Patients were followed over the course of clinical care from the date of index visit to December 31, 2013. The outcomes of interest were ascertained via ICD-9 codes (see

Supplementary Materials) and included incident cardiovascular disease, which is defined as the development of either heart failure or CAD, and all-cause mortality.

Statistical analysis

We compared baseline characteristics among patients with QT prolongation versus a normal QT interval according to the Bazett's formula. Categorical variables are presented as frequencies and percentages, and continuous variables as mean $\pm$ standard deviation if normally distributed and median [interquartile range] if skewed. We calculated the corrected QT interval using the four different formula: Bazett, Fridericia, Framingham and Hodges. Using each correction method, we then estimated associations between the QT interval and incident cardiovascular disease and all-cause mortality using Cox proportional hazards models. Since we had already excluded individuals with a history of heart failure as part of our study design, the analysis assessing associations between the QT interval and incident cardiovascular disease required the additional exclusion of patients with any history of CAD. For the all-cause mortality analysis, we did not exclude individuals with CAD at study baseline.

Initially, we assessed associations by QT tertiles allowing the lowest tertile to serve as the reference category. Then we assessed associations by the presence of prolonged QT defined as 450 ms in men and 460 ms in women. Potential confounding variables in the multivariable model included age, gender, race, diabetes, hypertension. For the all-cause mortality endpoint, we added CAD as an additional confounding variable in the multivariable analysis. Finally, we assessed the risk of incident cardiovascular disease and all-cause mortality among individuals who were classified as having a prolonged, Bazett-corrected QT interval and normal QT_c according to one of the other formulas. All *P* values are 2-tailed, with *P* < 0.05 indicating statistical significance. Analyses were performed using SPSS version 20.0 (IBM Corporation, Armonk, New York, USA).

Results

In the PAFF study of 6,723 individuals with sinus tachycardia, women comprised 55% of the population. In addition, nearly half of all participants in our study were Black (Table 1). Compared to patients with a normal QT_c interval, which was calculated using the traditional Bazett criteria, patients with QT_c prolongation were more likely to be older and men. They were also more likely to have a history of hypertension, coronary artery disease, diabetes, and chronic kidney disease.

Calculation of the corrected QT interval with either one of the four equations resulted in a normal distribution; however, the mean QT_c and subsequent number of individuals diagnosed with a prolonged QT interval varied by each formula (Figures 2A and 2B). The mean $\pm$ standard deviation QT_c was 450 $\pm$ 36 ms by Bazett, 405 $\pm$ 33 ms by Fridericia, 400 $\pm$ 28 ms by Framingham, and 423 $\pm$ 27 ms by Hodges. A diagnosis of QT prolongation, defined as 450 ms in men and 460 ms in women, varied according to the criteria used: 2,593 (39%) patients had QT prolongation using Bazett's, 419 (6.2%) using Fridericia's, 246 (3.7%) using Framingham's, and 583 (8.7%) using Hodges' criteria.

After a median follow-up of 4.5 [interquartile range (IQR) 1.9, 6.4] years, there were 495 incident cardiovascular events (annualized rate 2.3%) and 629 deaths (annualized mortality rate 2.4%). Among the 4,891 patients in our cohort without any baseline history of coronary heart disease or heart failure, there was an increase in the rate of cardiovascular events across QT_c tertiles of all four correction formulas (Figure 3A). After multivariable adjustment, the highest QT_c tertile remained an independent risk marker for incident cardiovascular events using all four equations (Table 2A). The corrected QT interval calculated using the Hodges formula provided the largest gradient in risk. Specifically, the highest tertile was independently associated with a 65% higher incidence of cardiovascular disease.

In the full cohort of 6,723 patients, only the Hodges correction demonstrated an increase in mortality rates across tertiles (Figure 3B). The other three correcting formulas including Bazett, Framingham, and Fridericia demonstrated V-shaped mortality curves across the range of corrected QT intervals. Further, only the Hodges correction method resulted in a QT_c that was an independent risk marker for all-cause mortality (Table 2B). The highest tertile was comprised of over 2,200 patients that had a 26% higher risk of death compared to patients in the lowest tertile. None of the other three methods identified a higher risk population in either unadjusted or adjusted analyses.

When assessing risk in the minority of patients that met criteria for prolonged QT_c interval (defined as ≥450 ms in men or ≥460 ms in women), we detected independent associations between prolonged QT_c interval and cardiovascular events and mortality using all formulas (Tables 3A and 3B). The only exception was that a Bazett-corrected prolonged QT_c was not an independent marker of mortality risk compared to patients with a normal QT_c. Further, compared to the Fridericia, Hodges, and Framingham formulas, the Bazett's correction method identified more than 2,000 additional tachycardic patients (30% of the cohort) with prolonged QT_c. The majority of individuals with a prolonged, Bazett-corrected QT interval had a normal QT_c when assessed by one of the other formulas (Figure 4). Individuals who had a prolonged QT_c using Bazett's and a normal QT_c by either Fridericia's or Framingham's correction method continued to have a greater than 50% incidence of cardiovascular disease when compared to those with a normal QT_c according to both Bazett's and either Fridericia's or Framingham's. The subgroup of individuals with a prolonged Bazett QT_c and normal Hodges QT_c did not have a significantly increased risk of cardiovascular events when compared to the normal Bazett and Hodges QT_c. Additional classification of the prolonged, Bazett-corrected QT interval patients to a normal QT_c according to any of the 3 other formulas did not result in an increased risk of death.

Discussion

Our findings demonstrate that the Bazett method over-diagnoses prolonged QT_c by identifying nearly 40% of sinus tachycardia patients. Most of these individuals have prolonged QT interval by the Bazett's correction method only and did not have an increased risk of death compared to those with a normal QT interval. In addition, the Hodges formula displayed the steepest gradient in cardiovascular risk and was the only method that demonstrated an increase in all-cause mortality across the range of QT_c values. It identified

nearly one-third of the cohort patients that had a 26% higher and independent risk of death than those in the lowest tertile. Compared to the Hodges' correction method, the Bazett's formula demonstrated a similar increase in cardiovascular risk. However, none of the other formulas including Bazett, Fridericia or Framingham demonstrated a gradient in mortality risk across the entire range of QT intervals. The Fridericia and Framingham correction formulas identified only 5% of our cohort with prolonged QT interval and higher risk of death compared to the respective group of patients with normal QT_c. As a result, these formulas have limited ability to stratify risk across the range of QT_c.

Computerized ECG software, which utilizes Bazett's formula, often overestimates the corrected QT interval in patients with sinus tachycardia.^{17, 18} Approximately 2,000 patients in our study had a prolonged QT based on the Bazett formula only. These individuals did not have a higher risk of death compared to those with a normal QT and suggests that Bazett's has poor specificity in identifying a group of sinus tachycardia patients at higher risk for death. In addition, the Bazett formula did not provide any additional information on cardiovascular risk when used in conjunction with the Hodges' correction method. The Bazett correction for tachycardia was formulated based on empiric observations of the duration of systole and diastole at various heart rates in animal models and humans.¹⁰ However, the original investigation included just a limited number of subjects, and only three out of 42 male subjects and one out of 21 female subjects had resting tachycardia. Its hyperbolic association with heart rate makes the Bazett formula ill-suited for accurate measurement of the QT during tachycardia.^{29–33} Our study is one of the largest studies in patients with sinus tachycardia to demonstrate that the Bazett correction results in an overestimation of cardiac repolarization abnormalities that are not associated with an increased risk of death.

The corrected QT interval is clinically relevant only when it is a proven risk marker for adverse events. The various QT correction formulas differ in their ability to identify high-risk subgroups. Of all four formulas assessed, only the Hodges' method demonstrated an increase in risk of incident cardiovascular disease and death across the range of QT_c values. Both Fridericia and Framingham methods revealed V-shaped mortality curves suggesting a protective effect of the QT_c in the second tertile. This finding for all-cause death, however, is discordant with the higher risk of incident cardiovascular disease in this same tertile. Our findings also suggest that the Hodges' method was the only one that could simply stratify the approximately 2600 patients with a Bazett's prolonged QT_c into those at increased cardiovascular or mortality risk. As such, the QT_c-Hodges should be assessed routinely in patients with sinus tachycardia. In patients with a longer QT_c, avoidance of QT prolonging medicines or safeguarding against drug interactions that may increase the QT interval may be potential interventions that reduce the risk for arrhythmic complications.³⁴ Future work should also determine whether a wider spectrum of Hodges-corrected QT_c values, and not just the traditional long QT cutoffs, could be incorporated into clinical risk scores.

Several limitations of our study should be considered. We used automated software for measurement of QT. Though measurements were over-read by cardiologists, it is unclear how many of the automated QT measurements were modified after personal inspection. However, all measurements were made similarly across the large study population, which

diminishes the influence of errors in measurement. Also, long QT is associated with arrhythmic sudden cardiac death, and our primary endpoint was all-cause mortality. Our study design precluded a thorough evaluation and adjudication of the modes of death in the UPHS patient population. However, the strong correlations with incident cardiovascular disease suggest that the QT_c may also be a marker for other adverse pathways that result in non-arrhythmic complications. In addition, our study design utilized administrative data collection within a large healthcare network. As a result, we may not have collected information on all the potential confounders.

Conclusions

All 4 formulas demonstrated an increase in the risk of incident cardiovascular disease including both CAD and CHF in our cohort. The Hodges formula identified the steepest gradient across the range of QT_c values and identified up to one third of the cohort at risk for mortality. Further validation studies will be important to assess the routine use of the Hodges formula by automated computer algorithms especially among individuals with sinus tachycardia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by the F. Harlan Batrus Research Fund, the Murray and Susan Bloom Research Fund, and grant K23DK089118 from the National Institutes of Health (RD). The sponsors had no role in the study design, actual research, or manuscript preparation. The authors would like to thank the Penn Data Store for assistance in assembling the information used in this study. PJP and RD had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Abbreviations

AF	Atrial Fibrillation
PAFF	Penn Atrial Fibrillation Free
HF	Heart Failure
CAD	Coronary Artery Disease
UPHS	University of Pennsylvania Health System
ECG	Electrocardiogram
ICD-9	International Classification of Diseases, version 9

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Clinical Perspectives

Prolongation of the QT interval, which is a measure of cardiac repolarization, is associated with adverse cardiovascular events and death. The repolarization period is a function of the underlying heart rate and decreases as the ventricular rate rises. Several methods have been proposed for correcting the QT interval. However, limited studies have compared the corrected QT interval according to the different methods in patients with sinus tachycardia. In a large cohort of individuals with sinus tachycardia, we evaluated the corrected QT intervals from four different formulas (Bazett, Fridericia, Framingham, and Hodges) as a risk marker for incident cardiovascular events and death. The linear Hodges formula provided the best correlation with cardiovascular outcomes and all-cause mortality. In addition, the traditional Bazett-correction formula overestimated the QT_c and identified nearly half of all sinus tachycardia patients with a prolonged QT interval. Automated ECG reading algorithms that incorporate the Hodges formula during sinus tachycardia could offer a more accurate measurement of QT_c . This method may help to identify patients at higher risk for cardiovascular events or death.

Figure 1.
Design of the Penn Atrial Fibrillation Free (PAFF) Cohort.

Figure 2A

Figure 2B

Figure 2. Distribution of the Corrected QT Interval in Men (Figure 2A) and Women (Figure 2B). The vertical line at 450 ms in men and 460 ms in women demarcates the cutoff for long QT.

Figure 3A

Figure 3B

Figure 3. Corrected QT Intervals and Cardiovascular Event Rates (Figure 3A) and All-Cause Mortality Rates (Figure 3B). Figure 3A: The rate (% per year) of incident cardiovascular events is higher in tertile 3 compared to tertile 1 for all QT correction methods ($P<0.001$).

Figure 3B: Mortality rate is higher in tertile 3 compared to tertile 1 for the Hodges correction formula only ($P=0.001$; all other $P>0.05$).

Figure 4.

Cardiovascular event and mortality risk among individuals with a QT_c that was prolonged by the Bazett criteria only. The hazard ratio (HR) assesses the risk of death among individuals with prolonged QT interval by the Bazett correction method and a normal QT interval using the Hodges, Fridericia, or Framingham formulas compared to individuals with a normal QT interval by Bazett and either one of the other formulas. For the outcome of incident cardiovascular disease, the multivariable model adjusts for age, gender, race, diabetes, and hypertension. For the outcome of death, the multivariable model adjusts for these same variables plus coronary artery disease.

Table 1

Baseline characteristics of Individuals with Sinus Tachycardia from the PAFF cohort

Parameter	Total population	Prolonged QT _c *	Normal QT _c
No. of participants, n (%)	6,723 (100)	2,593 (39)	4,130 (61)
Age (years), median [IQR]	46 [31, 59]	50 [37, 62]	43 [28, 57]
Female, n (%)	3,769 (55)	1,257 (48)	2,512 (61)
Black, n (%)	3,211 (47)	1,154 (45)	2,057 (50)
Hypertension, n (%)	1,838 (27)	983 (40)	855 (21)
Coronary artery disease, n (%)	1,837 (27)	827 (32)	1010 (24)
Diabetes, n (%)	792 (12)	390 (15)	402 (9.7)
Valvular heart disease, n (%)	126 (2)	51 (2)	75 (2)
Chronic kidney disease, n (%)	256 (4)	127 (5)	129 (3)
Hemoglobin (mg/dl)±SD	12.2±2.5	12.3±2.5	12.1±2.5
ECG metrics			
Left ventricular hypertrophy, n (%)	453 (7)	200 (8)	253 (6)
Left bundle branch block, n (%)	87 (1)	56 (2)	31 (1)
Right bundle branch block, n (%)	447 (7)	302 (12)	145 (4)
Heart rate (beats/min) ±SD	114±13	113±12	114±14
QT (ms) ±SD	329±33	353±37	312±24
QT _c Bazett correction (ms) ±SD	450±36	483±31	430±20

* The QT_c was corrected using the Bazett's method, and a prolonged QT_c was defined as 450ms (males) or 460ms (females).

IQR, interquartile range; SD, standard deviation

Table 2A

Association between Corrected QT Interval and Incident Cardiovascular Disease

Cardiovascular event	QT _c interval	# events/# at risk	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
Bazett						
Tertile 1	<435 ms	142/1,696	1.00 (ref)		1.00 (ref)	
Tertile 2	435–460 ms	154/1,677	1.18 (0.94–1.48)	0.2	1.13 (0.90–1.42)	0.3
Tertile 3	>460 ms	200/1,518	1.78 (1.43–2.21)	<0.001	1.60 (1.28–1.99)	<0.001
Fridericia						
Tertile 1	<391 ms	139/1,677	1.00 (ref)		1.00 (ref)	
Tertile 2	391–415 ms	157/1,690	1.17 (0.93–1.47)	0.2	1.13 (0.90–1.42)	0.3
Tertile 3	>415 ms	199/1,524	1.70 (1.36–2.11)	<0.001	1.52 (1.22–1.90)	<0.001
Framingham						
Tertile 1	<389 ms	138/1,672	1.00 (ref)		1.00 (ref)	
Tertile 2	389–409 ms	158/1,692	1.17 (0.93–1.47)	0.2	1.15 (0.91–1.44)	0.2
Tertile 3	>409 ms	200/1,530	1.65 (1.33–2.06)	<0.001	1.49 (1.20–1.87)	<0.001
Hodges						
Tertile 1	<411 ms	143/1,721	1.00 (ref)		1.00 (ref)	
Tertile 2	411–429 ms	153/1,653	1.25 (0.99–1.57)	0.06	1.24 (0.99–1.57)	0.06
Tertile 3	>429 ms	198/1,507	1.82 (1.46–2.26)	<0.001	1.65 (1.33–2.06)	<0.001

* Adjusted for age, gender, race, diabetes and hypertension.

Table 2B

Association between Corrected QT Interval and Death

Cardiovascular event	QT _c interval	# events/# at risk	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
Bazett						
Tertile 1	<435 ms	211/2,239	1.00 (ref)		1.00 (ref)	
Tertile 2	435–460 ms	180/2,243	0.88 (0.71–1.08)	0.2	0.85 (0.69–1.04)	0.1
Tertile 3	>460 ms	238/2,236	1.17 (0.96–1.43)	0.1	1.07 (0.88–1.31)	0.5
Fridericia						
Tertile 1	<391 ms	223/2,241	1.00 (ref)		1.00 (ref)	
Tertile 2	391–415 ms	175/2,238	0.78 (0.63–0.96)	0.02	0.74 (0.60–0.91)	0.004
Tertile 3	>415 ms	231/2,240	1.07 (0.88–1.30)	0.5	0.98 (0.81, 1.19)	0.8
Framingham						
Tertile 1	<389 ms	228/2,242	1.00 (ref)		1.00 (ref)	
Tertile 2	389–409 ms	177/2,251	0.76 (0.62–0.94)	0.01	0.72 (0.59–0.89)	<0.01
Tertile 3	>409 ms	224/2,230	1.03 (0.85–1.25)	0.7	0.95 (0.81–1.16)	0.6
Hodges						
Tertile 1	<411 ms	177/2,236	1.00 (ref)		1.00 (ref)	
Tertile 2	411–429 ms	209/2,233	1.20 (0.97–1.48)	0.09	1.14 (0.93–1.41)	0.2
Tertile 3	>429 ms	242/2,238	1.38 (1.13–1.70)	0.002	1.26 (1.03–1.55)	0.03

* Adjusted for age, gender, race, diabetes, hypertension and coronary artery disease.

Table 3A

Association between Prolonged QT_c* and Incident Cardiovascular Disease

Cardiovascular event	# events/# at risk	Unadjusted HR (95% CI)	P value	Adjusted [†] HR (95% CI)	P value
Bazett					
Normal QT	267/3,120	1.00 (ref)		1.00 (ref)	
Prolonged QT _c	229/1,774	1.73 (1.45–2.07)	<0.001	1.38 (1.15–1.66)	<0.001
Fridericia					
Normal QT	437/4,635	1.00 (ref)		1.00 (ref)	
Prolonged QT _c	59/259	2.40 (1.82–3.18)	<0.001	1.78 (1.34–2.36)	<0.001
Framingham					
Normal QT	455/4,743	1.00 (ref)		1.00 (ref)	
Prolonged QT _c	41/151	2.74 (1.97–3.80)	<0.001	1.95 (1.40–2.72)	<0.001
Hodges					
Normal QT	418/4,524	1.00 (ref)		1.00 (ref)	
Prolonged QT _c	78/370	2.51 (1.96–3.21)	<0.001	1.86 (1.45–2.40)	<0.001

* The QT_c was corrected using the Bazett's method, and a prolonged QT_c was defined as 450ms (males) or 460ms (females).

[†] Adjusted for age, gender, race, diabetes and hypertension.

Table 3B

Association between Prolonged QT_c* and Death

All-cause mortality	# events/# at risk	Unadjusted HR (95% CI)	P value	Adjusted [†] HR (95% CI)	P value
Bazett					
Normal QT	354/4,130	1.00 (ref)		1.00 (ref)	
Prolonged QT _c	275/2,593	1.29 (1.09–1.53)	0.003	0.94 (0.79–1.11)	0.5
Fridericia					
Normal QT	563/6,304	1.00 (ref)		1.00 (ref)	
Prolonged QT _c	66/419	1.99 (1.52–2.62)	<0.001	1.59 (1.20–2.09)	<0.001
Framingham					
Normal QT	587/6,477	1.00 (ref)		1.00 (ref)	
Prolonged QT _c	42/246	2.20 (1.60–3.05)	<0.001	1.70 (1.22–2.37)	<0.001
Hodges					
Normal QT	541/6,140	1.00 (ref)		1.00 (ref)	
Prolonged QT _c	88/583	1.84 (1.45–2.35)	<0.001	1.50 (1.17–1.91)	<0.001

* The QT_c was corrected using the Bazett's method, and a prolonged QT_c was defined as 450ms (males) or 460ms (females).

[†] Adjusted for age, gender, race, diabetes, hypertension, and coronary artery disease.