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The QT Interval Is Associated With Incident Cardiovascular Events

The MESA Study

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ABSTRACT

BACKGROUND Prolonged heart rate–corrected QT interval on electrocardiograms (ECGs) is associated with increased risk of myocardial infarction and cardiovascular disease (CVD)–related deaths in patients with prevalent coronary heart disease.

OBJECTIVES This study sought to examine the prognostic association between the baseline QT interval and incident cardiovascular events in individuals without prior known CVD.

METHODS The corrected baseline 12-lead ECG QT interval duration (QT_{corr}) was determined by adjustment for age, sex, race/ethnicity, and RR interval duration in 6,273 participants in MESA (Multi-Ethnic Study of Atherosclerosis). Cox proportional hazards models adjusting for demographic and clinical risk factors were used to examine the association of baseline QT_{corr} with incident cardiovascular events.

RESULTS The mean age at enrollment was 61.7 ± 10 years, and 53.4% of participants were women. Cardiovascular events occurred in 291 participants over a mean follow-up of 8.0 ± 1.7 years. Each 10-ms increase in the baseline QT_{corr} was associated with incident heart failure (hazard ratio [HR]: 1.25; 95% CI: 1.14 to 1.37), CVD events (HR: 1.12; 95% CI: 1.05 to 1.20), and stroke (HR: 1.19; 95% CI: 1.07 to 1.32) after adjustment for CVD risk factors and potential confounders. There was no evidence of interaction with sex or ethnicity.

CONCLUSIONS The QT interval was associated with incident cardiovascular events in middle-aged and older adults without prior CVD. (J Am Coll Cardiol 2014;64:2111–9) © 2014 by the American College of Cardiology Foundation.

Prolongation of the QT interval is associated with functional re-entry, torsade de pointes, and sudden death (1). Aside from its direct association with arrhythmia and sudden death, QT interval prolongation, perhaps through other mediating factors, is associated with mortality in high-risk individuals (2–5) and in the general population (6–11). Prolongation of the QT interval is also associated with incident stroke (7). However, the association of QT interval duration with incident cardiovascular events in healthy individuals has not been investigated. Increased catecholamine levels prolong the QT

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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease
CVD = cardiovascular disease
ECG = electrocardiogram
HF = heart failure
MI = myocardial infarction
PVD = peripheral vascular disease

interval in healthy individuals and are associated with the development of atherosclerosis (12–14) and may therefore be mediators of any association between the QT interval and incident cardiovascular events. We sought to examine the association between baseline QT interval and incident cardiovascular events in MESA (Multi-Ethnic Study of Atherosclerosis).

METHODS

STUDY PARTICIPANTS. Inclusion criteria and methods of the MESA study were previously described (15). In brief, between July 2000 and August 2002, 6,814 individuals aged 45 to 84 years and free of clinically apparent cardiovascular disease (CVD) were recruited from 6 U.S. areas: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. A full list of participating MESA investigators and institutions can be found at the MESA study website (16).

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We excluded participants who were taking antiarrhythmic medications or medications that might prolong the QT interval (n = 205), and participants with QRS duration ≥120 ms (n = 336). The final sample size was 6,273.

The study complies with the Declaration of Helsinki, and the institutional review boards at all participating centers approved the study. All participants gave written informed consent.

RISK FACTOR MEASURES. Standardized questionnaires were used to obtain information about self-reported race/ethnicity, smoking history, and medication use for high blood pressure, high cholesterol levels, and diabetes. Participant height and weight were measured, and body mass index (kg/m^2) was calculated. Resting blood pressure was measured 3 times with participants in the seated position with an automated oscillometric sphygmomanometer (Critikon, GE Healthcare, Waukesha, Wisconsin). The average of the last 2 measurements was used for analysis. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and glucose levels were measured from blood samples obtained after a 12-h fast. Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald equation (17). Diabetes was defined as fasting glucose ≥126 mg/dl or use of hypoglycemic medications.

ELECTROCARDIOGRAM ANALYSIS OF QT INTERVAL DURATION. Standard 12-lead electrocardiograms (ECGs) were digitally acquired using a MAC 1200 electrocardiograph (GE Healthcare, Milwaukee, Wisconsin) at 10 mm/mV calibration and speed of 25 mm/s. ECG reading was performed centrally at the Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine (Winston Salem, North Carolina). All ECGs were initially inspected visually for technical errors and inadequate quality and then automatically processed with the Marquette 12-SL program 2001 version (GE Healthcare). A global single measure of QT interval was defined as the time duration between the earliest QRS onset to the latest T-wave offset (end) in the 12 ECG leads. We corrected the QT interval according to the American Heart Association, American College of Cardiology, and Heart Rhythm Society recommendations for the standardization and interpretation of the ECG using a linear regression function for adjustment for covariates (method fully described in the Statistical Methods section) (18).

ADJUDICATION OF EVENTS. The follow-up was 8.0 ± 1.7 years. In addition to 4 follow-up MESA study examinations, participants were contacted by telephone every 12 months regarding interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. Self-reported diagnoses were confirmed by review of death certificates and medical records for hospitalizations and outpatient cardiovascular diagnoses. A detailed description of events and the process of adjudication can be found at the MESA website (16). Two physicians from the MESA study events committee independently reviewed all medical records for endpoint classification using prespecified criteria. An incident cardiovascular event was defined as a composite of adjudicated myocardial infarction (MI), resuscitated cardiac arrest, coronary heart disease–related death, stroke, or stroke-related death. The specific incidences of stroke, MI, peripheral vascular disease (PVD), and heart failure (HF) were also determined.

STATISTICAL METHODS. We used a linear regression method to adjust the QT interval for age, ethnicity, sex, and the RR interval using model residuals (19). Specifically, we set up a linear regression model with QT interval as the dependent variable and age (continuous), ethnicity (white, African American, Chinese American, and Hispanic), sex (female or male), and RR interval as independent variables. The RR interval was analyzed using restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles to allow a more flexible and nonlinear relationship between the QT and RR intervals. Model residuals represent the component of QT interval duration that is not explained by the independent

variables. Because the average of the residuals is 0, we rescaled the residuals by adding the mean QT interval of the overall study population to calculate the final corrected QT interval (QT_{corr}). Sensitivity analyses were also performed with the Bazett heart rate-corrected QT interval (QT_b) (20) and the Framingham QT correction formula (QT_{fr}) (21).

Baseline characteristics were compared according to the QT_{corr} distribution (categorized at <5th, 5th to <50th, 50th to <95th, and 95th and above percentiles) and by clinical thresholds for short QT_b (≤390 ms) or QT_b prolongation (≥460 ms) (18), using analysis of variance or Student *t* test for continuous variables and chi-square tests for categorical variables. Kaplan-Meier survival curves were plotted after stratification of participants by QT_{corr} percentiles and compared by means of the log-rank test. Cox proportional hazards models were used to evaluate the association between baseline QT_{corr} and incident cardiovascular events. The following models were used: model 1, unadjusted; model 2, adjusted for age (continuous), ethnicity (white, African American, Chinese American, and Hispanic), and sex (female or male); and model 3, further adjusted for antihypertensive medication use (yes or no); systolic blood pressure (continuous); cigarette smoking (never, former, current); diabetes (yes or no); family history of ischemic heart disease (yes or no); LDL (continuous); HDL (continuous); QRS duration (continuous); aspirin use (yes or no); statin use (yes or no); body mass index (continuous); and education (<12 years, completed high school to bachelor's degree, graduate education). Models including magnetic resonance imaging (MRI)-derived left ventricular mass (antihypertensive medication use and systolic blood pressure omitted due to strong collinearity) were used in the subset of participants with MRI data to examine a potential mediating effect by left ventricular mass for the association of QT_{corr} with cardiovascular outcomes. For detailed analyses of the dose-response relationship of the QT_{corr} with incident cardiovascular events, we modeled QT_{corr} with restricted

TABLE 1 Baseline Characteristics for All Patients and After Stratification by QT_{corr} Percentiles

	Total	QT_{corr} <5th (300–383 ms)	QT_{corr} 5th to <50th (384–409 ms)	QT_{corr} ≥50th to <95th (410–440 ms)	QT_{corr} ≥95th (441–503 ms)	p Value
Age, yrs	61.7 ± 10.14	61.8 ± 10.8	61.7 ± 10.2	61.8 ± 10.0	61.3 ± 9.9	0.877
Female	53.4	42.9	56.1	52.0	52.7	<0.001
Race						0.241
White	38.3	32.1	39.0	38.5	36.2	
African American	27.5	34.5	26.5	27.3	30.0	
Chinese American	12.0	11.8	12.0	12.2	10.8	
Hispanic	22.2	21.6	22.5	22.0	23.0	
Hypertension	43.8	32.4	38.5	47.3	56.5	<0.001
Antihypertensive medications	36.0	32.4	31.7	38.1	46.5	<0.001
Systolic blood pressure, mm Hg	126.3 ± 21.45	122.4 ± 21.17	123.8 ± 20.40	127.9 ± 21.43	132.1 ± 23.91	<0.001
Heart rate, beats/min	63.1 ± 9.59	59.4 ± 9.93	63.7 ± 9.19	62.7 ± 9.58	63.6 ± 10.62	<0.001
Diabetes	11.1	10.5	10.5	10.6	15.5	0.007
Family history of heart disease	42.6	40.9	43.2	42.4	41.7	0.811
Current smoking	13.1	12.2	12.4	12.5	18.7	0.001
QRS duration, ms	91.4 ± 9.66	88.4 ± 9.54	90.1 ± 9.49	92.7 ± 9.43	92.9 ± 10.25	<0.001
QT duration, ms	410.7 ± 30.25	383.3 ± 24.55	397.8 ± 23.87	422.1 ± 26.53	429.2 ± 38.07	<0.001
QT_b duration, ms	417.2 ± 20.61	377.5 ± 13.95	406.5 ± 11.33	427.5 ± 13.24	437.2 ± 27.35	<0.001
QT_{corr} duration, ms	410.7 ± 17.79	374.1 ± 9.38	399.6 ± 6.89	421.3 ± 8.08	451.2 ± 10.93	<0.001
QT_{fr} duration, ms	414.8 ± 18.9	377.4 ± 11.2	403.9 ± 9.1	425.3 ± 10.4	433.9 ± 25.7	<0.001
Height, cm	166.2 ± 10.04	166.7 ± 10.13	165.9 ± 10.0	166.7 ± 10.0	165.2 ± 10.31	<0.001
Weight, lbs	172.8 ± 38.16	163.8 ± 35.16	169.9 ± 37.31	176.0 ± 38.14	176.2 ± 41.28	<0.001
Body mass index, kg/m^2	28.3 ± 5.47	26.63 ± 4.75	27.9 ± 5.37	28.7 ± 5.43	29.2 ± 6.07	<0.001
Low-density lipoprotein cholesterol, mg/dl	117.6 ± 31.43	115.23 ± 33.05	117.8 ± 31.28	117.7 ± 31.26	116.9 ± 31.96	0.532
High-density lipoprotein cholesterol, mg/dl	51.1 ± 14.81	52.4 ± 16.38	51.4 ± 14.96	50.5 ± 14.46	51.1 ± 14.79	0.054
Aspirin	31.0	31.1	30.9	31.2	30.0	0.932
Statins	14.4	15.2	14.8	14.1	14.1	0.866
Education (graduate)	17.8	21.3	18.5	17.7	13.5	<0.001

Values are mean ± SD or %.

QT_b = QT interval corrected using Bazett formula; QT_{corr} = QT interval corrected for RR interval, race, age and sex; QT_{fr} = QT interval corrected using the Framingham formula.

TABLE 2 Association of Baseline QT_{corr} Interval With Incident CVD Events

	Model 1*				Model 2†				Model 3‡			
Event	Number of Events/Number at Risk§	Hazard Ratio (per 10 ms)	95% CI	p Value	Number of Events/Number at Risk§	Hazard Ratio (per 10 ms)	95% CI	p Value	Number of Events/Number at Risk§	Hazard Ratio (per 10 ms)	95% CI	p Value
Stroke	109/5,913	1.22	1.11–1.35	<0.001	109/5,913	1.21	1.10–1.34	<0.001	102/5,441	1.19	1.07–1.32	0.001
MI	145/5,913	1.11	1.01–1.21	0.022	145/5,913	1.10	1.01–1.20	0.031	129/5,441	1.10	0.99–1.21	0.055
HF	146/5,913	1.30	1.19–1.41	<0.001	146/5,913	1.29	1.19–1.39	<0.001	128/5,441	1.25	1.14–1.37	<0.001
PVD	63/5,913	1.19	1.04–1.35	0.01	63/5,913	1.18	1.04–1.34	0.012	52/5,441	1.16	0.99–1.35	0.054
CHD	187/5,913	1.08	1.00–1.17	0.044	187/5,913	1.08	1.00–1.16	0.064	167/5,441	1.08	1.00–1.18	0.065
CVD‖	291/5,913	1.13	1.06–1.20	<0.001	291/5,913	1.12	1.06–1.20	<0.001	264/5,441	1.12	1.05–1.20	0.001

*Model 1 was unadjusted. †Model 2 was adjusted for age, ethnicity, and sex. ‡Model 3 was adjusted for model 2 plus traditional risk factors (antihypertensive medication use, systolic blood pressure, current smoking, diabetes, family history of ischemic heart disease, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol) and QRS duration, aspirin use, statin use, body mass index, and education. §The number at risk varies for each model, depending upon participant follow-up and missing data. ‖CVD includes MI, resuscitated cardiac arrest, coronary heart disease death, stroke, and stroke death.

CHD = coronary heart disease; CVD = cardiovascular disease; HF = heart failure; MI = myocardial infarction; PVD = peripheral vascular disease; other abbreviation as in Table 1.

quadratic splines with knots at the 1st, 10th, and 99th percentiles of the QT_{corr} distribution to provide a description of the dose-response relationship. In spline analyses, we used the 50th percentile of the QT_{corr} distribution as the reference value (median). Finally, we examined the interaction of QT_{corr} with ethnicity and sex in its association with outcome using multiplicative interaction terms as well as using stratified analyses by sex and ethnicity. Comparisons of C statistics between Framingham Heart Study (FHS) risk scores (22–24) and FHS risk scores modified by the addition of 1 point for QT_{corr} ≥95th percentile (440.3 ms) for their association with incident CVD, HF, and stroke were performed. A 2-tailed p value <0.05 was considered statistically significant. Statistical analyses were performed using STATA statistical software version 12.0 (STATA Corp., LP, College Station, Texas).

RESULTS

The average age of study participants was 61.7 ± 10.1 years, and 53.4% of study participants were female. The average QT_{corr}, QT_b, and QT_{fr} were 410.7 ± 27.8, 417.2 ± 20.6, and 414.8 ± 18.9, respectively. **Table 1** summarizes the baseline characteristics by QT_{corr} distribution (stratified at <5th, 5th to <50th, 50th to <95th, and 95th and above percentiles). A summary of baseline characteristics by clinical thresholds for short QT_b at ≤390 ms, or QT_b prolongation at ≥460 ms can be found in Online Table 1.

Table 2 presents the unadjusted and adjusted associations of baseline QT_{corr} with incident CVD events over the follow-up period. In fully adjusted models, each 10-ms increase in the baseline QT_{corr} was positively associated with incident HF (hazard ratio [HR]: 1.25; 95% CI: 1.14 to 1.37; p < 0.001), CVD (HR: 1.12; 95% CI: 1.05 to 1.20; p < 0.001), and stroke (HR: 1.19; 95% CI: 1.07 to 1.32; p < 0.001). Positive trends for association were also noted between baseline QT_{corr} and MI (HR: 1.10; 95% CI: 0.99 to 1.21; p = 0.055), PVD (HR: 1.16; 95% CI: 0.99 to 1.35; p = 0.054), and coronary heart disease (CHD; HR: 1.08; 95% CI: 1.00 to 1.18; p = 0.065). Kaplan-Meier analyses revealed that participants with QT_{corr} intervals in the highest 5th percentile had increased risks of HF, CVD, and stroke (Online Figures 1 to 3). Consistent results were observed with the spline regression models, in which the risk of HF, CVD, and stroke events progressively increased with increasing QT_{corr} intervals (**Figures 1 to 3**).

In sensitivity analyses, each 10-ms increase in the QT_b was also positively associated with incident HF (HR: 1.27; 95% CI: 1.18 to 1.38; p < 0.001), CVD (HR: 1.15; 95% CI: 1.08 to 1.22; p < 0.001), and stroke (HR: 1.20; 95% CI: 1.10 to 1.33; p < 0.001) in fully adjusted models. Similarly, each 10-ms increase in the QT_{fr} was also positively associated with incident HF (HR: 1.23; 95% CI: 1.12 to 1.34; p < 0.001), CVD (HR: 1.11; 95% CI: 1.04 to 1.19; p = 0.002), and stroke (HR: 1.17; 95% CI: 1.06 to 1.30; p = 0.003) in fully adjusted models.

The baseline QT_{corr} had a weak positive association with left ventricular mass (Spearman rho 0.072; p < 0.001). Despite reduced power, the baseline QT_{corr} interval remained associated with incident HF (HR: 1.25; 95% CI: 1.00 to 1.55; p = 0.051) and CVD (HR: 1.20; 95% CI: 1.04 to 1.37; p = 0.010) after adjustment for left ventricular mass and other potential confounders in the subset of participants with MRI data (Online Table 2). After adjustment for left ventricular mass in this small subset of participants, positive trends for association were also noted between baseline QT_{corr} and stroke (HR: 1.21; 95% CI: 0.99 to 1.48; p = 0.061), MI (HR: 1.17; 95%

CI: 0.98 to 1.40; p = 0.087), PVD (HR: 1.23; 95% CI: 0.95 to 1.59; p = 0.114), and CHD (HR: 1.17; 95% CI: 0.98 to 1.40; p = 0.087).

C statistics for FHS risk scores modified with QT_{corr} were higher than FHS risk scores for their association with HF (0.735 vs. 0.724; p < 0.001), CVD (0.732 vs. 0.730; p = 0.119). and stroke (0.712 vs. 0.708; p = 0.024).

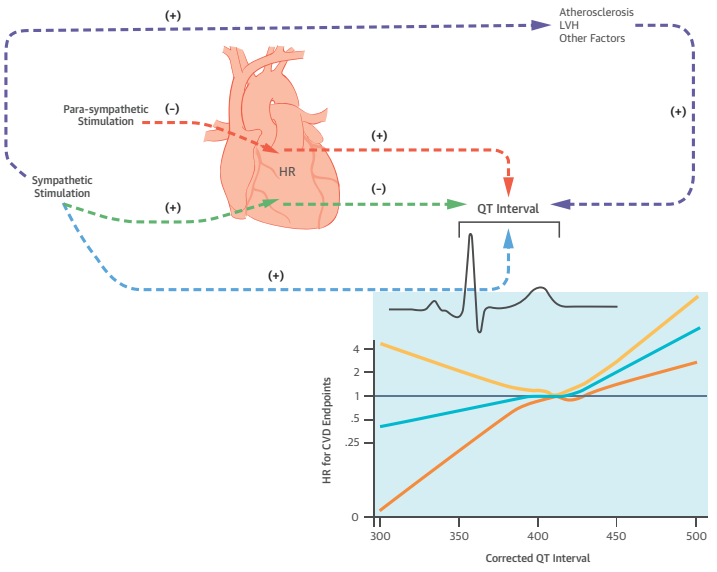
There was no evidence of multiplicative interaction with sex in the association of QT_{corr} with HF (HR for interaction: 0.97; 95% CI: 0.82 to 1.15; p = 0.725), CVD (HR for interaction: 1.07; 95% CI: 0.93 to 1.21; p = 0.342), or stroke (HR for interaction: 1.09; 95% CI: 0.89 to 1.33; p = 0.414). There was also no evidence of multiplicative interaction with ethnicity in the association of QT_{corr} with HF (HR for interaction: 1.00; 95% CI: 0.99 to 1.01; p = 0.834), CVD (HR for interaction: 1.00; 95% CI: 0.99 to 1.00; p = 0.388), or stroke (HR for interaction: 0.99; 95% CI: 0.99 to 1.01; p = 0.934). When stratified by sex and ethnicity, the association between QT_{corr} and HF, CVD, and stroke was similar among the subgroups (**Figure 4**).

DISCUSSION

In this study, we reported an independent positive association between the baseline QT_{corr} interval and cardiac and vascular events in middle-aged participants without prior CVD. Importantly, the association was not limited to a specific sex or ethnicity.

Individuals with prolonged ventricular repolarization, reflected on the surface ECG by prolongation of the QT interval, are predisposed to ventricular fibrillation and sudden death. Such an association is most evident in the setting of genetic abnormalities of potassium and sodium channels within cell membranes (25), as well as with comorbidities such as severe electrolyte imbalance, central nervous system injury, and MI (26,27). Acquired prolongation of the QT_{corr} interval due to antiarrhythmic, antibiotic, antihistaminic, or psychotropic drugs is also associated with ventricular arrhythmia and sudden death when the QT interval exceeds 500 ms (28). In addition, several studies of participants with and without prior CVD have found a positive association between the baseline QT interval and incident cardiovascular mortality (8,10,19,29-31) and cardiovascular morbidity, including a composite of atherosclerotic disease, angina, and cardiomyopathy in a general population sample (32) and coronary events in participants with hypertension (5). However, the results have been inconsistent, and negative studies of the association between the baseline QT interval and cardiovascular mortality (33) and coronary events (34) have also been published. A systematic review of 7 large prospective cohort studies reported that prolongation of the QT interval in patients with established CVD was associated with increased risk for total mortality, cardiovascular mortality, and sudden death; however, among individuals without baseline CVD, the QT interval was not associated with these outcomes (11). In contrast, another meta-analysis of 6 studies, with participants free of CVD at baseline, found a positive association between the QT interval and mortality (35).

Recently, Soliman et al. (7) reported a strong association between the QT interval and incident stroke



Beinart, R. et al. J Am Coll Cardiol. 2014; 64(20):2111-9.

CENTRAL ILLUSTRATION Sympathetic and Parasympathetic Stimuli, the QT Interval, and CVD Events

There is a complex interaction between the central nervous system sympathetic and parasympathetic stimuli and cardiac conduction intervals. By increasing the heart rate, sympathetic stimulation **(green arrows)** can secondarily decrease the QT interval. In contrast, by decreasing the heart rate, parasympathetic stimulation can increase the QT interval **(orange arrows)**. Autonomic stimuli also exert direct effects upon the QT interval. Increased catecholamine levels typically result in QT interval prolongation in healthy individuals **(light blue arrow)**. Additionally, high sympathetic tone is associated with the development of atherosclerosis with potential secondary effects upon cardiac repolarization and the QT interval **(purple arrows)**. Left ventricular mass is also positively associated with high sympathetic tone and the QT interval **(purple arrows)**. In this study, we observed positive associations between baseline-corrected QT intervals and risks of incident stroke, heart failure, and cardiovascular disease (CVD) events in a cohort of middle-aged participants free of CVD at baseline. Prolongation of the QT interval as a surrogate of elevated sympathetic tone and autonomic imbalance may explain its association with cardiovascular events. However, the QT interval may be associated with other factors, which may mediate its association with cardiovascular events. The **arrows** are provided to note associations and do not imply causality. HR = hazard ratio; LVH = left ventricular hypertrophy.

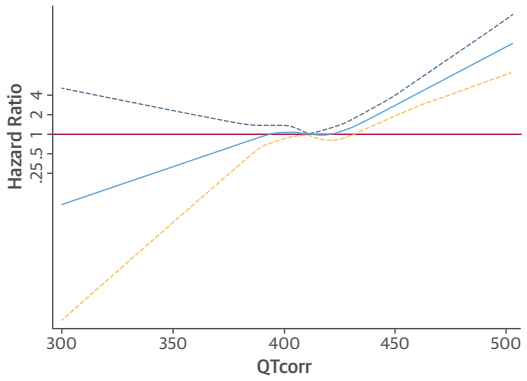


FIGURE 1 HRs for HF as a Function of the QT Interval

The **blue line** indicates multivariable-adjusted hazard ratios (HRs) for heart failure (HF) as a function of corrected QT interval (QT_{corr}) using restricted quadratic splines. The **dashed lines** delineate the upper and lower 95% CI. The **horizontal red line** indicates an HR of 1.00. The model was adjusted for age, ethnicity, sex, antihypertensive medication use, systolic blood pressure, cigarette smoking, diabetes, family history of ischemic heart disease, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, QRS duration, aspirin use, statin use, body mass index, and education.

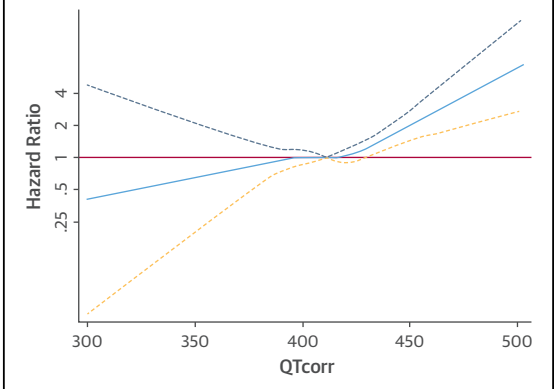


FIGURE 2 HRs for CVD as a Function of the QT Interval

The **blue line** indicates multivariable-adjusted HRs for cardiovascular disease (CVD) endpoints as a function of QT_{corr} using restricted quadratic splines. The **dashed lines** delineate the upper and lower 95% CI. The **horizontal red line** indicates an HR of 1.00. Adjustment factors and other abbreviations in Figure 1.

among 27,411 participants in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. The results of the REGARDS study are in full agreement with our findings. Our study differs from the REGARDS study in that the baseline prevalence of CVD in the REGARDS study was 17% among all participants and 43% among those with prolonged QT. Additionally, the REGARDS study was designed to investigate the causes of regional and racial disparities in stroke mortality, oversampling African Americans and residents of the southeastern region of the United States.

Several studies support an association between the QT interval and cardiovascular events in healthy individuals. Dekker et al. (6) reported an association between prolonged QT_b (>420 ms) and the combined endpoint of MI and CHD death compared with men with QT_b <385 ms in the Zutphen study cohort that included 851 middle-aged men without previous MI. In another study, Dekker et al. (9) noted an association between QT_{corr} and CHD, CVD mortality, and total mortality in the ARIC (Atherosclerosis Risk in Communities) cohort, which included middle-aged men and women without prior MI or coronary revascularization. In contrast to our results, the risk in the ARIC study was attenuated by ethnicity and was higher in African Americans. Our study builds upon prior reports in healthy individuals by the use of the regression-derived QT_{corr} variable with simultaneous adjustment for age, ethnicity, sex, and heart rate and by exclusion of participants with QRS ≥120 ms and those on QT-prolonging medications.

The QT interval varies as a function of sympathetic and parasympathetic tone (**Central Illustration**). Increased catecholamine levels induce QT interval prolongation in healthy individuals (12–14). Additionally, high sympathetic tone is associated with the

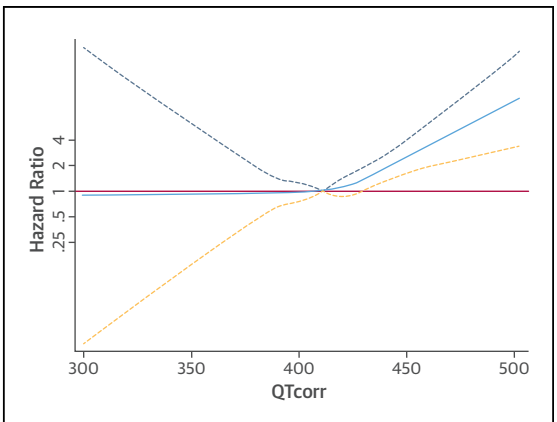


FIGURE 3 HRs for Stroke as a Function of the QT Interval

The **blue line** indicates multivariable-adjusted HRs for stroke as a function of QT_{corr} using restricted quadratic splines. The **dashed lines** delineate the upper and lower 95% CI. The **horizontal red line** indicates an HR of 1.00. Adjustment factors and other abbreviations as in Figure 1.

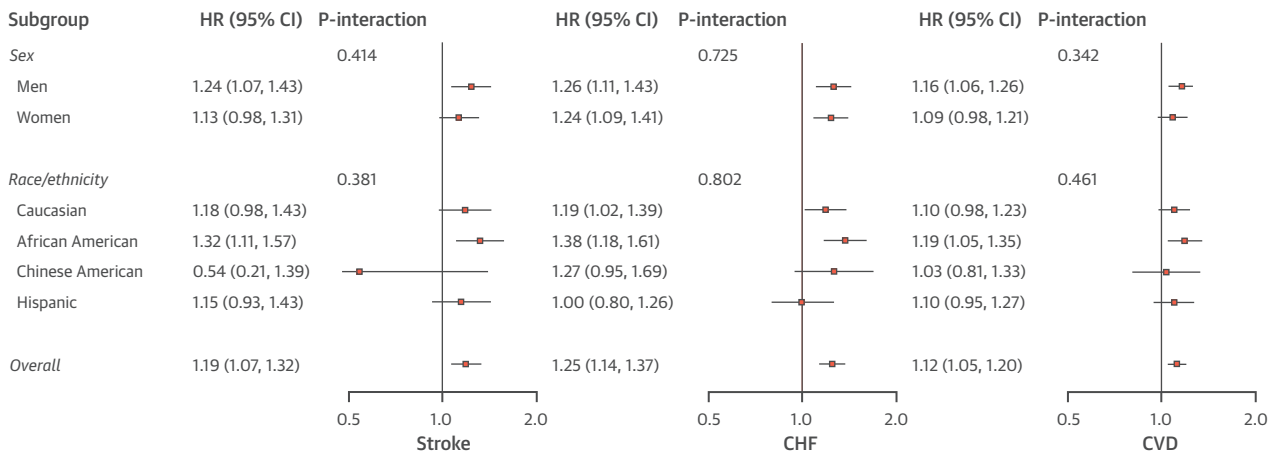


FIGURE 4 Forest Plot of HRs for HF, CVD, and Stroke After Stratification by Sex and Ethnicity

The forest plot summarizes multivariable-adjusted HRs for HF, CVD, and stroke. Models were adjusted for age, ethnicity (if not stratified by ethnicity), sex (if not stratified by sex), antihypertensive medication use, systolic blood pressure, cigarette smoking, diabetes, family history of ischemic heart disease, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, QRS duration, aspirin use, statin use, body mass index, and education. There were no significant differences among the subgroups and no evidence for interaction. CHF = congestive heart failure; other abbreviations as in Figures 1 and 2.

development of atherosclerosis (12–14). More than 3 decades ago, Pauletto et al. (36) proposed several mechanisms that may mediate the association of high sympathetic tone with atherosclerosis. First, elevated arterial pressure in the setting of high sympathetic tone may lead to arteriolar remodeling and alteration of flow with upstream impact on the large arteries. Secondly, epinephrine and norepinephrine appear to exert direct atherogenic effects, regardless of arterial pressure (37–41). Thirdly, the atherogenic effects of catecholamines may be mediated through platelet activation and subsequent platelet-derived growth factor up-regulation or platelet deposition at the arterial intima (42). Thus, prolongation of the QT interval as a surrogate of elevated sympathetic tone may explain its association with cardiovascular events. The association between QT_{corr} and incident HF may also be partially mediated by an association of QT_{corr} and left ventricular mass. However, despite the reduced sample size in the cohort of MESA participants with MRI data, the association of QT_{corr} with incident HF was preserved after adjustment for left ventricular mass. Nevertheless, QT prolongation may be associated with other factors, which may mediate its association with cardiovascular events. Our study did not investigate the mechanism, and the results simply point to an association. Finally, the association of QT_{corr} with incident cardiovascular events does not imply that the QT_{corr} should be used as an index for risk stratification in the clinical setting. Nevertheless, the C statistics for FHS risk scores modified with the QT_{corr} were higher than those for FHS risk scores for identification of cardiovascular events.

STUDY LIMITATIONS. We examined the association of only a single QT interval measurement at baseline with incident HF, CVD, and stroke events. Also, our findings represent a selected population enrolled from 6 different U.S. areas and may not be generalizable to all populations. However, the inclusion of 4 different ethnicities in the MESA cohort is a significant strength that improves the applicability of the data to various patient groups.

CONCLUSIONS

This analysis demonstrated positive associations between baseline-corrected QT intervals and risks of incident stroke, HF, and CVD events in a cohort of middle-aged participants free of CVD at baseline.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Prolongation of the corrected QT interval on the electrocardiogram is associated with an elevated risk of arrhythmic and sudden death, as well as incident stroke, heart failure, and ischemic cardiovascular events in patients with and without ischemic heart disease, including otherwise healthy individuals, regardless of sex or ethnicity.

TRANSLATIONAL OUTLOOK: Future studies should evaluate the discriminative value of adding the QT interval to existing risk assessment tools.

REFERENCES

1. Straus SM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. J Am Coll Cardiol 2006;47:362–7.

2. Williams ES, Thomas KL, Broderick S, et al. Race and gender variation in the QT interval and its association with mortality in patients with coronary artery disease: results from the Duke Databank for Cardiovascular Disease (DDCD). Am Heart J 2012;164:434–41.

3. Peters RW, Byington RP, Barker A, et al. Prognostic value of prolonged ventricular repolarization following myocardial infarction: the BHAT experience. The BHAT Study Group. J Clin Epidemiol 1990;43:167–72.

4. Naas AA, Davidson NC, Thompson C, et al. QT and QTc dispersion are accurate predictors of cardiac death in newly diagnosed non-insulin dependent diabetes: cohort study. BMJ 1998;316:745–6.

5. Schillaci G, Pirro M, Ronti T, et al. Prognostic impact of prolonged ventricular repolarization in hypertension. Arch Intern Med 2006;166:909–13.

6. Dekker JM, Schouten EG, Klootwijk P, et al. Association between QT interval and coronary heart disease in middle-aged and elderly men. The Zutphen Study. Circulation 1994;90:779–85.

7. 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;59:1460–7.

8. Noseworthy PA, Peloso GM, Hwang SJ, et al. QT interval and long-term mortality risk in the Framingham Heart Study. Ann Noninvasive Electrocardiol 2012;17:340–8.

9. Dekker JM, Crow RS, Hannan PJ, et al. Heart rate-corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: the ARIC study. J Am Coll Cardiol 2004;43:565–71.

10. Schouten EG, Dekker JM, Meppelink P, et al. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. Circulation 1991;84:1516–23.

11. Montanez A, Ruskin JN, Hebert PR, et al. Prolonged QTc interval and risks of total and cardiovascular mortality and sudden death in the general population: a review and qualitative overview of the prospective cohort studies. Arch Intern Med 2004;164:943–8.

12. Baumert M, Lambert GW, Dawood T, et al. QT interval variability and cardiac norepinephrine spillover in patients with depression and panic disorder. Am J Physiol Heart Circ Physiol 2008;295:H962–8.

13. Kaufman ES, Gorodeski EZ, Dettmer MM, et al. Use of autonomic maneuvers to probe phenotype/genotype discordance in congenital long QT syndrome. Am J Cardiol 2005;96:1425–30.

14. Vyas H, Hejlik J, Ackerman MJ. Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT response. Circulation 2006;113:1385–92.

15. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.

16. MESA Website. Available at: http://www.mesa-nhlbi.org. Accessed September 3, 2014.

17. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.

18. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol 2009;53:982–91.

19. Zhang Y, Post WS, Dalal D, et al. QT-interval duration and mortality rate: results from the Third National Health and Nutrition Examination Survey. Arch Intern Med 2011;171:1727–33.

20. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353–67.

21. Sagie A, Larson MG, Goldberg RJ, et al. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). Am J Cardiol 1992;70:797–801.

22. D'Agostino RB Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–53.

23. D'Agostino RB, Wolf PA, Belanger AJ, et al. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. Stroke 1994;25:40–3.

24. Kannel WB, D'Agostino RB, Silbershatz H, et al. Profile for estimating risk of heart failure. Arch Intern Med 1999;159:1197–204.

25. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003;348:1866–74.

26. Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978;57:1074–7.

27. Moss AJ. Prolonged QT-interval syndromes. JAMA 1986;256:2985–7.

28. Bednar MM, Harrigan EP, Anziano RJ, et al. The QT interval. Prog Cardiovasc Dis 2001;43:1–45.

29. de Bruyne MC, Hoes AW, Kors JA, et al. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. Eur Heart J 1999;20:278–84.

30. Algra A, Tijssen JG, Roelandt JR, et al. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. Circulation 1991;83:1888–94.

31. Karjalainen J, Reunanen A, Ristola P, et al. QT interval as a cardiac risk factor in a middle aged population. Heart 1997;77:543–8.

32. Elming H, Holm E, Jun L, et al. The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. Eur Heart J 1998;19:1391–400.

33. Goldberg RJ, Bengtson J, Chen ZY, et al. Duration of the QT interval and total and cardiovascular mortality in healthy persons (the Framingham Heart Study experience). Am J Cardiol 1991;67:55–8.

34. Crow RS, Hannan PJ, Folsom AR. Prognostic significance of corrected QT and corrected JT interval for incident coronary heart disease in a general population sample stratified by presence or absence of wide QRS complex: the ARIC study with 13 years of follow-up. Circulation 2003;108:1985–9.

35. Zhang Y, Post WS, Blasco-Colmenares E, et al. Electrocardiographic QT interval and mortality: a meta-analysis. Epidemiology 2011;22:660–70.

36. Pauletto P, Scannapieco G, Pessina AC. Sympathetic drive and vascular damage in hypertension and atherosclerosis. Hypertension 1991;17:III75–81.

37. Ostlund-Lindqvist AM, Lindqvist P, Brautigam J, et al. Effect of metoprolol on diet-induced atherosclerosis in rabbits. Arteriosclerosis 1988;8:40–5.

38. Lindqvist P, Olsson G, Nordborg C, et al. Atherosclerosis in rabbits identified as high and low responders to an atherogenic diet and the effect of treatment with a beta 1-blocker. Atherosclerosis 1988;72:163–72.

39. Kaplan JR, Manuck SB, Clarkson TB, et al. Social stress and atherosclerosis in normocholesterolemic monkeys. Science 1983;220:733–5.

40. Kaplan JR, Manuck SB, Adams MR, et al. Inhibition of coronary atherosclerosis by propranolol in behaviorally predisposed monkeys fed an atherogenic diet. Circulation 1987;76:1364–72.

41. Pettersson K, Bejne B, Bjork H, et al. Experimental sympathetic activation causes endothelial injury in the rabbit thoracic aorta via beta 1-adrenoceptor activation. Circ Res 1990;67:1027–34.

42. Armstrong ML, Peterson RE, Hoak JC, et al. Arterial platelet accumulation in experimental hypercholesterolemia. Atherosclerosis 1980;36:89–100.

KEY WORDS cardiovascular disease, coronary heart disease, heart failure, myocardial infarction, QT interval, stroke

APPENDIX For supplemental figures and tables, please see the online version of this article.