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The Association of the QT Interval with Atrial Fibrillation and Stroke: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—Prolongation of the QT interval is associated with an increased risk of atrial fibrillation (AF) and stroke.

Objectives—The purpose of this analysis was to determine if atrial fibrillation (AF) explains the association between prolonged QT and stroke.

Methods—A total of 6,305 participants (mean age 62 ± 10 years; 54% women; 38% whites; 27% blacks; 23% Hispanics; 12% Chinese-Americans) from the Multi-Ethnic Study of Atherosclerosis (MESA) were included in this analysis. A linear scale was used to compute heart rate adjusted QT interval (QT_a). Prolonged QT_a was defined as 460 ms in women and 450 ms in men. Incident AF cases were identified using hospital discharge records and Medicare claims data.

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Vascular neurologists adjudicated stroke events by medical record review. Cox Regression was used to examine the association between prolonged QT_a and stroke with and without AF.

Results—A total of 216 (3.4%) of study participants had prolonged QT_a. Over a median follow-up of 8.5 years, 280 (4.4%) participants developed AF and 128 (2.0%) participants developed stroke. In a multivariable Cox regression analysis adjusted for socio-demographics, cardiovascular risk factors, and potential confounders, prolonged QT_a was associated with an increased risk of AF (HR=1.7, 95%CI=1.1, 2.6) and stroke (HR=2.3, 95%CI=1.3, 4.1). When AF was included as a time-dependent covariate, the association between prolonged QT_a and stroke was not substantively altered (HR=2.4, 95%CI=1.3, 4.3).

Conclusion—The increased risk of stroke in those with prolonged QT potentially is not explained by documented AF. Further research is needed to determine if subclinical AF cases explain the association between the QT interval and stroke.

Keywords

atrial fibrillation; stroke; long QT

INTRODUCTION

Several reports from population-based studies have shown that prolongation of the QT interval is independently associated with an increased risk of atrial fibrillation (AF) and stroke [1–5]. The association of prolonged QT with AF has been explained by abnormalities in myocardial repolarization and shared risk factors for both conditions [1,6]. Similar explanations have been provided for the increased risk of stroke in persons with prolonged QT [3].

Given the known stroke risk among individuals with prolonged QT and AF, the association between prolonged QT and stroke potentially is explained by AF [1,2,7–9]. However, evidence from population-based studies to support this hypothesis is lacking. Therefore, the purpose of this study was to examine the associations of the QT interval with AF and stroke in the Multi-Ethnic Study of Atherosclerosis (MESA), and to determine whether AF explains the association between the QT interval and stroke.

METHODS

Study Population

Details of MESA have been reported previously [10]. Briefly, between July 2000 and September 2002, 6,814 participants were recruited at 6 field centers: Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota. Study participants were required to be between 45 and 84 years and to have no history of clinically apparent cardiovascular disease at the time of study enrollment. However, participants with hypertension and hyperlipidemia were allowed to participate as long as these conditions did not result in clinically apparent cardiovascular disease. All MESA participants with baseline electrocardiogram data and follow-up data on AF and stroke were included in this study. Participants were excluded if they did not have

baseline electrocardiogram data, had evidence of AF at or before baseline, or were missing data regarding baseline characteristics and follow-up. Additionally, participants with evidence of major intra-ventricular delay (QRS duration ≥ 120 ms and/or complete left or right bundle branch block) which prolong the QT interval were excluded.

Baseline Characteristics

Participant characteristics recorded during the first MESA visit were used. Age, sex, race/ethnicity, income, and education were self-reported. Annual income was categorized into 3 levels ($< \$20,000$, $\$20,000$ – $\$49,999$ and $\geq \$50,000$). Similarly, education was categorized into “high school or less,” “some college,” and “college graduate or more.” Smoking was defined as current or former smoker. Blood samples were obtained after a 12-hour fast and measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, plasma glucose, and high-sensitivity C-reactive protein (hs-CRP) were used in this analysis. Diabetes was defined as a fasting glucose value ≥ 126 mg/dL or a history of diabetes medication use. After the participant rested for 5 minutes in a seated position, blood pressure was measured 3 separate times and the mean of the last 2 values was used. Aspirin, statin, antihypertensive, and lipid-lowering medication use were self-reported. The use of QT-prolonging medications was obtained using an inventory of current medications reported by each participant. Body mass index was computed as the weight in kilograms divided by the square of the height in meters. Left ventricular hypertrophy was defined by the Cornell criteria (R wave amplitude AV_L plus S wave amplitude $V_3 \geq 2.8$ mV for men and ≥ 2.0 mV for women) using baseline electrocardiogram data [11].

Prolonged QT

Guided by the current electrocardiogram interpretation recommendations, heart rate adjusted QT (QT_a) was computed from baseline electrocardiogram data using a linear regression model [12]. Specifically, the QT interval was regressed on heart rate [13]. Based on the β coefficient associated with heart rate, the following formula was derived to adjust for heart rate: $QT_a = QT + 2.38 * (\text{heart rate} - 60)$. Prolonged QT_a was defined as ≥ 460 ms for women and ≥ 450 ms for men [12]. Additionally, a sensitivity analysis was performed using Bazett's formula ($QT_c = QT / (60 / \text{heart rate})^{1/2}$).

Atrial Fibrillation

Follow-up phone calls to study participants every 9–12 months were used to identify hospitalizations. Medical records, including discharge diagnoses, were obtained for each hospitalization. Additionally, Medicare claims data were used to identify AF cases for participants 65 years or older enrolled in fee-for-service Medicare. Incident AF was defined by International Classification of Disease Ninth Revision codes 427.31 or 427.32.

Stroke

Study personnel identified possible stroke events and two vascular neurologists independently reviewed medical records for end-point classification and assignment of event dates. If the reviewing physicians disagreed on the event classification, differences were adjudicated. Stroke was classified as present or absent, and was defined by a rapid onset of

documented focal neurologic deficits lasting at least 24 hours or until death [10]. If symptoms were present for <24 hours, a clinically relevant lesion on brain imaging must have been present for stroke to be documented as present. Due to the small number of documented stroke events, ischemic and hemorrhagic strokes (intraparenchymal and subarachnoid) were grouped together.

Statistics

Categorical variables were reported as frequency and percentage while continuous variables were recorded as mean $\pm$ standard deviation. Statistical significance for categorical variables was tested using the chi-square method and the Wilcoxon rank-sum procedure for continuous variables. Kaplan-Meier estimates were used to compute cumulative incidence of AF and stroke by prolonged QT_a, and the differences in estimates were compared using the log-rank procedure [14]. Two separate Cox regression models were used to compute the hazard ratios (HR) and 95% confidence intervals (CI) for the association of prolonged QT_a (prolonged versus not prolonged) with AF and stroke. Also, the QT_a interval was examined as a continuous variable per 1-unit increase in standard deviation. In the model to examine the association of prolonged QT_a with AF, follow-up time was defined as the time between the initial electrocardiogram measurement until a diagnosis of AF, death, loss to follow-up, or end of follow-up. Similarly, in the model to examine the association of prolonged QT_a with stroke, follow-up time was defined as the time between initial electrocardiogram measurement until a diagnosis of stroke, death, loss to follow-up, or end of follow-up. Multivariable models were constructed with incremental adjustments as follows: Model 1 adjusted for age, sex, race/ethnicity, income, and education; Model 2 adjusted for Model 1 covariates plus smoking, systolic blood pressure, diabetes, body mass index, total cholesterol, HDL-cholesterol, aspirin, antihypertensive and lipid-lowering medication use, hs-CRP, left ventricular hypertrophy, and QT-prolonging medications. Using similar models, we also examined the association between prolonged QT_a and stroke with and without AF to explore the potential attenuation of AF on stroke among participants with prolonged QT_a by adjusting for AF as a time-dependent variable. The mediation proportion and its 95%CI was computed [15,16]. Sensitivity analyses including incident coronary heart disease and heart failure as time-dependent covariates were conducted to determine if these variables influenced the degree to which AF attenuated the relationship between prolonged QT_a and stroke. Although there were a small number of stroke events (n=128), ischemic strokes represented the majority (n=107, 84%) and a sensitivity analysis was performed examining the association of prolonged QT_a with ischemic strokes. Additionally, we used a restricted cubic spline model to examine the graphical relationship between QT_a and the risk for AF and stroke to assess the potential for a non-linear association and incorporated knots at the 5th, 50th, and 95th percentiles [17]. Statistical significance was defined as p<0.05. SAS® (Cary, NC USA) version 9.3 was used to conduct all analyses.

RESULTS

Of the 6,814 participants from the original MESA cohort, 58 participants had a diagnosis of AF before enrollment. The majority of these cases were detected by Medicare linkage and only 1 case was present in baseline electrocardiogram data. Of those that remained, 6

participants with missing follow-up data, 49 with missing QT data, 294 with QRS 120 ms, and 102 participants with either missing baseline characteristics or medication data also were excluded. A total of 6,305 study participants (mean age 62 ± 10 years; 54% women; 38% whites; 27% blacks; 23% Hispanics; 12% Chinese-Americans) were included in the final analysis.

A total of 216 (3.4%) of study participants had prolonged QT_a (median=466 ms; range=451, 520 ms). Baseline characteristics for study participants are shown in Table 1. Participants with prolonged QT_a were more likely to be older, and to have diabetes and left ventricular hypertrophy than participants without prolonged QT_a. Participants with prolonged QT_a also were more likely to have higher values for body mass index and systolic blood pressure than participants without prolonged QT_a. Additionally, these participants were more likely to use antihypertensive medications and aspirin.

Over a median follow-up of 8.5 years (interquartile range=7.7, 8.6), 280 (4.4%) participants developed AF and 128 (2.0%) participants developed stroke. The incidence of AF among participants with prolonged QT_a was 14.3 per 1000 person-years compared with 5.5 per 1000 person-years for participants without prolonged QT_a. Similarly, an increased incidence of stroke was observed for participants with prolonged QT_a (7.9 per 1000 person-years) compared with those without prolonged QT_a (2.5 per 1000 person-years). Unadjusted cumulative incidence curves for AF ($p<0.0001$) and stroke ($p<0.0001$) by prolonged QT_a are shown in Figure 1.

Table 2 shows the HRs for the association between prolonged QT_a and AF. In a multivariable Cox regression analysis, prolonged QT_a was associated with an increased risk of AF (HR=1.7, 95%CI=1.1, 2.6). Prolonged QT_a also was associated with an increased risk of stroke (HR=2.3, 95%CI=1.3, 4.1) (Table 3). Increasing QT_a was associated with both AF and stroke when modeled as a continuous variable (Table 3). Figure 2 shows the association between QT_a values and incident AF and incident stroke using a restricted cubic spline model. As shown, the risk for AF and stroke increased with increasing QT_a values.

When AF was included as a time-dependent covariate, the association between prolonged QT_a and stroke was not substantively altered (Table 3). The mediation proportion of AF was -0.052 (95%CI= -0.14, 0.032). The results were not changed when coronary heart disease (HR=2.4, 95%CI=1.3, 4.3) and heart failure (HR=2.5, 95%CI=1.4, 4.6) were included in the final model as time-dependent covariates, separately. A similar association was observed in a sensitivity analysis using QT_c (Table 3). Additionally, the association between prolonged QT_a and stroke was similar when limited to ischemic strokes (HR=2.6, 95%CI=1.4, 4.8) and the addition of AF did not materially alter this result (HR=2.7, 95%CI=1.4, 4.9).

DISCUSSION

In this study, we have shown that prolongation of the QT interval is associated with both AF and stroke in MESA. Additionally, prolonged QT was more strongly associated with stroke than with AF, and the increased risk of stroke among participants with prolonged QT was

unchanged when accounting for AF as a time-dependent covariate. These findings suggest that the increased risk of stroke with prolonged QT is not explained by documented AF.

The associations of prolonged QT with AF and stroke have been previously described [1–5]. One study using data from 3 large prospective cohort studies in the United States (Atherosclerosis Risk In Communities, Cardiovascular Health Study, Dynamics of Health, Aging, and Body Composition) and a report from Denmark have both shown that prolonged QT is associated with AF [1,2]. Similarly, the association of prolonged QT with stroke was confirmed from population-based studies among diabetics, the general Japanese population, and in an analysis from the REasons for Geographic And Racial Differences in Stroke Study [3–5]. Our results confirm both findings as similar associations were observed in MESA.

AF has been proposed to mediate the risk of stroke in those with prolonged QT due to the shared association of both AF and stroke with prolonged QT [1,2]. The association of prolonged QT with AF has been explained by aberrations in atrial and ventricular repolarization and long-standing exposure to shared risk factors for both prolonged QT and AF (e.g., hypertension, diabetes) [1,6]. Similar explanations exist for the association of prolonged QT with stroke [3]. Although our results support that prolonged QT is associated with both AF and stroke, they do not support that documented AF explains the increased risk of stroke associated with prolonged QT.

Recent reports have shown a higher prevalence of AF is detected by means of prolonged monitoring in patients with cryptogenic stroke [18,19]. The fact that prolonged QT was more strongly associated with stroke than with AF hints at the problem of detecting subclinical AF. This also possibly explains our findings that the increased stroke risk with prolonged QT is not completely explained by documented AF and further research is needed to determine if subclinical AF cases explain the association between the QT interval and stroke.

The risk of stroke among individuals with prolonged QT potentially is explained by poor cardiovascular risk factor profiles that currently are unable to be accounted for due to the dynamic nature of these conditions (e.g., progression of diabetes). This explanation would support the hypothesis that QT prolongation possibly is an indicator of subclinical cardiovascular disease and add strength to the argument that the association with stroke reflects the detection of at-risk individuals for future cardiovascular events. Additionally, the fact that participants from MESA had no evidence of clinical cardiovascular disease at study enrollment supports this claim.

Several methods to adjust for the QT interval have been described. A linear regression formula was used for QT correction rather than the traditional Bazett's formula due to its inability to adjust for heart rates that significantly deviate from 60 beats per minutes [12]. Similar results were obtained for both methods when examining the risk of stroke. However, a non-significant result was observed for AF using Bazett's correction. This likely is due to the fact that more cases were appropriately labeled as prolonged with the linear regression function for QT correction. Similar variation has been observed in previous studies depending on the correction technique used [1,3].

Our results should be interpreted in the context of certain limitations. AF was ascertained from hospitalization discharge records and inpatient Medicare claims data, and persons with non-permanent AF possibly were missed due to the time-dependent nature of certain cases (e.g., paroxysmal). However, we do not know of any reason to suggest that the resulting bias, if any, would have been differential in nature, rather than merely reducing effect estimates toward the null and diminishing the power to detect a statistically significant result. The QT interval is a dynamic measurement that varies between electrocardiogram tracings and potentially our results differ with subsequent recordings [12]. Additionally, we used pre-defined cut points for prolonged QT classification and results may vary with different cut points. However, the cut points used in this analysis have been proposed in recent guidelines [12]. Our findings also were unchanged when we modeled the QT interval as a continuous variable, suggesting that our results were not due to the choice of the cut points used. Furthermore, we acknowledge that residual confounding remains a possibility due to the observational nature of this study and limits the etiologic inference implied [20].

In conclusion, the present study confirms that prolongation of the QT interval is associated with AF and stroke. Additionally, our results suggest that documented AF does not explain the risk of stroke in persons with prolonged QT. Further research is needed to confirm our findings and also to determine if subclinical AF explains the association between the QT interval and stroke.

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Figure 1.

Unadjusted Cumulative Incidence of AF (A) and Stroke (B) by Prolonged QT_a*

The differences between unadjusted incidence curves for AF (log-rank $p < 0.0001$) and stroke (log-rank $p < 0.0001$) by prolonged QT_a were statistically significant.

*QT_a was computed with the following formula: $QT + 2.38 * (\text{heart rate} - 60)$.

AF=atrial fibrillation.

Figure 2.

Association of QT_a with AF (A) and Stroke (B).^{*†}

^{*}Each hazard ratio was computed from a restricted cubic spline model with a median QT_a value of 416 ms as the referent group and was adjusted for age, sex, and race/ethnicity. Dotted-lines represent the 95% confidence interval.

[†]QT_a was computed with the following formula: QT + 2.38*(heart rate-60).

AF=atrial fibrillation. ms=milliseconds

Table 1

Baseline Characteristics

Characteristic	Prolonged QT _a [†] (n=216)	No Prolonged QT _a [†] (n=6,089)	P-value [*]
Age, mean (SD), y	65 (10)	62 (10)	<0.0001
Male (%)	106 (49)	2,803 (46)	0.38
Race/ethnicity			
White (%)	84 (39)	2,296 (38)	
Black (%)	61 (28)	1,667 (27)	
Chinese-American (%)	26 (12)	750 (12)	
Hispanic (%)	45 (21)	1,376 (23)	0.93
Education			
High school or less (%)	83 (38)	2,218 (36)	
Some college (%)	57 (26)	1,730 (28)	
College or more (%)	76 (35)	2,141 (35)	0.77
Annual income			
< \$20,000 (%)	71 (33)	1,620 (27)	
\$20,000 to \$49,999 (%)	65 (30)	2,148 (35)	
\$50,000 (%)	80 (37)	2,321 (38)	0.095
Body mass index, mean (SD), kg/m ²	29 (6.1)	28 (5.5)	0.25
Current or former smoker (%)	109 (50)	3,000 (49)	0.73
Diabetes (%)	42 (19)	827 (14)	0.014
Systolic blood pressure, mean (SD), mm Hg	133 (27)	126 (21)	0.0003
Total cholesterol, mean (SD), mg/dL	193 (32)	195 (36)	0.58
HDL-cholesterol, mean (SD), mg/dL	51 (14)	51 (15)	0.80
Antihypertensive medication use (%)	119 (55)	2,162 (36)	<0.0001
Statin use (%)	39 (18)	881 (14)	0.14
Aspirin use (%)	72 (33)	1,404 (23)	0.0005
Lipid-lowering medication use (%)	41 (19)	963 (16)	0.21
hs-CRP, mean (SD), mg/L	4.2 (5.3)	3.8 (5.9)	0.29
Left ventricular hypertrophy (%)	14 (6.5)	203 (3.3)	0.013
QT prolonging medication use (%)	11 (5.1)	173 (2.8)	0.053

* Statistical significance for continuous data was tested using Wilcoxon rank-sum procedure and the chi-square method was used for categorical data.

[†]QT_a was computed with the following formula: QT + 2.38*(heart rate-60).

ECG=electrocardiogram; HDL=high-density lipoprotein; hs-CRP= high-sensitivity C-reactive protein; SD=standard deviation; y=years.

Table 2

Association of Prolonged QT with AF

	Events/No. at risk	Incidence Rate* (95%CI)	Model 1 [†] HR (95%CI)	P-value	Model 2 [‡] HR (95%CI)	P-value
QT _a ^δ						
No Prolonged QT _a	257/6,089	5.5 (4.9, 6.2)	1.0	-	1.0	-
Prolonged QT _a	23/216	14.3 (9.5, 21.5)	1.9 (1.2, 2.9)	0.0045	1.7 (1.1, 2.6)	0.0023
QT _a per 1-SD	280/6,305	5.8 (5.2, 6.5)	1.2 (1.1, 1.4)	0.0010	1.1 (1.02, 1.3)	0.022
QT _c ^{//}						
No Prolonged QT _c	262/6,073	5.6 (5.0, 6.4)	1.0	-	1.0	-
Prolonged QT _c	18/232	10.5 (6.6, 16.6)	1.6 (1.02, 2.7)	0.043	1.4 (0.89, 2.4)	0.13
QT _c per 1-SD	280/6,305	5.8 (5.2, 6.5)	1.2 (1.03, 1.3)	0.016	1.1 (0.97, 1.2)	0.13

* Incidence rates presented per 1000 person-years.

[†] Adjusted for age, sex, race/ethnicity, income, and education.

[‡] Adjusted for Model 1 covariates plus smoking status, systolic blood pressure, diabetes, body mass index, total cholesterol, HDL-cholesterol, aspirin, antihypertensive and lipid-lowering medication use, hs-CRP, left ventricular hypertrophy, and QT-prolonging medications.

^δ QT_a was computed with the following formula: $QT + 2.38 \times (\text{heart rate} - 60)$.

^{//} QT_c was computed using Bazett's formula.

AF=atrial fibrillation; CI=confidence interval; HDL=high-density lipoprotein; hs-CRP= high-sensitivity C-reactive protein; HR=hazard ratio; SD=standard deviation.

Table 3

Association of Prolonged QT with Risk of Stroke with and without Adjustment for AF.

	Events/No. at risk	Incidence Rate* (95%CI)	Model 1 [†] HR (95%CI)	P-value	Model 1 [†] with AF HR (95%CI)	P-value	Model 2 [‡] HR (95%CI)	P-value	Model 2 [‡] with AF HR (95%CI)	P-value
QT_a^δ										
No Prolonged QT _a	115/6,089	2.5 (2.0, 2.9)	1.0	-	1.0	-	1.0	-	1.0	-
Prolonged QT _a	13/216	7.9 (4.6, 13.7)	2.8 (1.6, 5.0)	0.0005	2.9 (1.6, 5.2)	0.0003	2.3 (1.3, 4.1)	0.0054	2.4 (1.3, 4.3)	0.0035
QT _a per 1-SD	128/6,305	2.6 (2.2, 3.1)	1.3 (1.1, 1.5)	0.0028	1.3 (1.1, 1.5)	0.0018	1.2 (1.01, 1.4)	0.036	1.2 (1.02, 1.4)	0.026
QT_c^{//}										
No Prolonged QT _c	115/6,073	2.5 (2.0, 2.9)	1.0	-	1.0	-	1.0	-	1.0	-
Prolonged QT _c	13/232	7.5 (4.3, 12.9)	2.9 (1.6, 5.1)	0.0003	2.9 (1.6, 5.2)	0.0003	2.4 (1.4, 4.3)	0.0028	2.5 (1.4, 4.5)	0.0021
QT _c per 1-SD	128/6,305	2.6 (2.2, 3.1)	1.5 (1.3, 1.8)	<0.0001	1.5 (1.3, 1.8)	<0.0001	1.4 (1.2, 1.6)	0.0003	1.4 (1.2, 1.7)	0.0002

* Incidence rates presented per 1000 person-years.

[†] Adjusted for age, sex, race/ethnicity, income, and education.[‡] Adjusted for Model 1 covariates plus smoking status, systolic blood pressure, diabetes, body mass index, total cholesterol, HDL-cholesterol, aspirin, antihypertensive and lipid-lowering medication use, hs-CRP, left ventricular hypertrophy, and QT-prolonging medications.^δ QT_a was computed with the following formula: QT + 2.38*(heart rate-60).^{//} QT_c was computed using Bazett's formula.

AF=atrial fibrillation; CI=confidence interval; HDL=high-density lipoprotein; hs-CRP= high-sensitivity C-reactive protein; HR=hazard ratio; SD=standard deviation.