

Duration of the QT Interval and Total and Cardiovascular Mortality in Healthy Persons (The Framingham Heart Study Experience)

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The baseline electrocardiograms of 5,125 original subjects of the Framingham Heart Study were measured to examine the relation of the QT interval corrected for heart rate (QTc) to risk of total mortality, sudden cardiac death, and death due to coronary artery disease over a 30-year follow-up period. Quintiles of QTc (seconds) ≤ 0.36 , 0.36 to 0.38, 0.39 to 0.40, 0.41 to 0.43 and ≥ 0.44 were studied in relation to these outcomes. There were no significant differences in the risk of total mortality, sudden cardiac death or death due to coronary artery disease according to QTc. A similar lack of significant association between QTc and these 3 outcomes was observed among all persons studied and in the 2 sexes after using a multiple regression analysis to control for several potentially confounding characteristics including age, gender, cigarette smoking, serum total cholesterol, systolic systemic blood pressure and Framingham relative weight. The results of this study fail to demonstrate an association between baseline QTc and overall mortality, and deaths due to sudden cardiac events or coronary artery disease in a large population-based cohort of essentially healthy persons in whom pathologic forms of QTc prolongation are uncommon.

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Several conditions, including electrolyte imbalance, subarachnoid hemorrhage, mitral valve prolapse, selected drugs, and a congenital long QT syndrome have been associated with prolongation of the QT interval.¹⁻³ A prolonged QT interval has been associated with the occurrence of malignant ventricular arrhythmias during the hospital and postdischarge phase of acute myocardial infarction.⁴⁻⁷ QT interval prolongation has also been associated with sudden cardiac death and an adverse long-term survival in patients with previous myocardial infarction⁷⁻¹⁰ and in persons resuscitated from out-of-hospital ventricular fibrillation.¹¹ In 2 small studies of patients with acute myocardial infarction, a prolonged QTc was not associated with occurrence of either ventricular fibrillation¹² or serious ventricular arrhythmias.¹³ A number of methodologic concerns arise, however, in the interpretation of these clinical series and hospital-based studies. These concerns include small sample sizes, use of inappropriate comparison groups, failure to control for potentially confounding factors of etiologic or prognostic significance and relatively short-term follow-up of patients with varying degrees of QT prolongation. The purpose of the present study is to examine the association of QT interval duration, corrected for heart rate (QTc) as recorded on the baseline entry electrocardiographic examination, with total mortality, sudden cardiac death and coronary artery disease mortality among the original cohort of the Framingham Heart Study.

METHODS

Patient population: The population under study consisted of the original cohort of 5,209 persons of the Framingham Heart Study who were between the ages of 30 and 62 years at the time of entry into the study in 1948.^{14,15} The initial electrocardiogram of these persons was used to measure the duration of the QT interval, which was then adjusted for baseline heart rate (QTc) according to Bazett's formula.¹⁶ The RR interval immediately preceding the QT interval was used in this formula. The average of 2 to 3 QT intervals from the electrocardiographic lead with the longest QT interval was analyzed.

The electrocardiograms of persons with coronary artery disease at the time of the baseline examination were excluded from study consideration as were the electrocardiograms of persons taking medications (e.g., antiarrhythmic drugs or tricyclic antidepressants) that

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TABLE I Baseline Characteristics According to Heart Rate–Corrected QT Interval (QTc): Framingham Heart Study

	Duration of QTc (seconds)				
	<0.36 (n = 499)	0.36–0.38 (n = 1,079)	0.39–0.40 (n = 1,464)	0.41–0.43 (n = 1,804)	≥0.44 (n = 279)
Age (yrs)					
<40 (%)	35	36	30	25	16
40–49 (%)	35	33	36	36	39
≥50 (%)	30	31	34	39	45
Male (%)	69	61	44	37	18
Current cigarette smoker (%)	60	60	52	47	39
Total cholesterol (mean, mg/dl)	227	227	226	228	230
Systolic blood pressure (mean, mm Hg)	132	133	134	133	134
Diastolic blood pressure (mean, mm Hg)	80	80	81	80	81
Framingham relative weight (% of normal weight)	102	102	103	102	103

might have affected the duration of the QT interval. Persons with missing baseline electrocardiograms were also excluded from further consideration. After these exclusions, a total of 5,125 persons remained and comprised the population of the present report. The primary study end points were defined as the following: total mortality (deaths from all causes); sudden cardiac death (onset of death within 1 hour of the onset of symptoms suggestive of acute coronary disease); and death due to coronary artery disease (persons dying from myocardial infarction, angina pectoris, or coronary insufficiency including sudden and nonsudden coronary events).

Each of the QT and RR intervals was measured manually by trained readers with the aid of calipers and magnifying lens. Ongoing quality control checks of the electrocardiograms were performed. These checks consisted of a weekly blinded duplicate review of a random sample of all electrocardiograms read during that time period by each of the observers. A high degree of inter- as well as intraobserver agreement was found and any discrepancies noted were subsequently adjudicated and corrected. In addition, a sample (n = 480) of these baseline electrocardiograms was independently and blindly reread 5 times by one of the study investigators (EL). A high degree of correlation was observed between the multiply read samples and the singly read baseline measurements with regard to the mean RR, average QT and QTc intervals (p <0.001).

Data analysis: Differences in the distribution of selected baseline characteristics between persons classified according to selected QTc intervals were examined through the use of chi-square and analysis of variance tests for discrete and continuous variables, respectively. A life-table approach was used to examine the risk of selected long-term mortality outcomes in relation to baseline QTc.¹⁷ The log-rank test was used to assess the statistical significance of any observed overall differences in long-term outcome measures.¹⁸ A Cox regression analysis was used to examine the relation of baseline QTc to various long-term end points while simulta-

neously controlling for the effect of several potentially confounding prognostic factors.¹⁹

RESULTS

Significant baseline differences existed between the various comparison groups with regard to age, gender and cigarette smoking status (p <0.05) (Table I). Persons with the more prolonged QT intervals included a significantly greater proportion of older persons, females and nonsmokers. A prolonged QTc (≥0.44 second) was observed in 5.4% of the persons studied.

Sex-specific analyses were also performed to examine differences in the distribution of selected coronary risk factors as well as QTc among the 2 sexes. Significant differences existed between the sexes with regard to systolic and diastolic blood pressure, smoking status and QTc. Men had significantly higher systolic (134.0 vs 130.6 mm Hg) as well as diastolic (81.3 vs 78.6 mm Hg) blood pressure and included a significantly greater proportion of current cigarette smokers (65 vs 42%) (p <0.001). On the other hand, women had a significantly longer mean QTc (0.401 ± 0.027 vs 0.385 ± 0.029 second) and QTc interval distribution (p <0.05). Among the men, 15% had a baseline QTc of <0.36 second, 29% a QTc between 0.36 to 0.38 second, 29% between 0.39 to 0.40 second, 25% between 0.41 to 0.43 second and 2% a prolonged QTc of ≥0.44 second. Among the women the distribution of these QTcs was 5% (<0.36 second), 15% (0.36 to 0.38 second), 29% (0.39 to 0.40 second), 43% (0.41 to 0.43 second) and 7% (≥0.44 second), respectively.

The association of QTc interval and all-cause mortality, sudden cardiac death and mortality from coronary artery disease was examined. No relation existed between duration of QTc and total mortality (Figure 1). Although not statistically significant, the greatest risks of dying were seen at the 2 most extreme QTc intervals examined.

In examining the association of QTc to long-term risk of sudden death (Figure 2), there were no significant differences observed in the risk of sudden death

according to QTc. Trends toward an increased risk of sudden death were observed in persons with the shortest QTc (<0.36 second).

Similar to previously observed findings, there was no significant association observed between QTc and risk of dying from coronary artery disease in the cohort studied (Figure 3). Despite the lack of overall statistical significance, trends of increased death rates from coronary artery disease were seen in persons with the shortest baseline QTc.

A series of multiple regression analyses were then performed to examine the association of QTc to each of the 3 primary outcome measures while controlling for various potentially confounding demographic and coronary risk factor characteristics. The baseline variables adjusted for in these analyses included age, gender, cigarette smoking status, level of serum cholesterol, systolic blood pressure and Framingham relative weight. The results of these analyses confirmed previously observed univariate life-table findings, namely the absence of a significant association between duration of QTc and risk of total mortality, sudden cardiac death, and death due to coronary artery disease. The adjusted relative risks of these outcomes according to baseline QTc and accompanying 95% confidence intervals are listed in Table II.

Separate regression analyses for the 3 outcomes examined were also performed for the 2 sexes. The variables adjusted for in these analyses included age, cigarette smoking status, systolic and diastolic blood pressure, serum cholesterol level and Framingham relative weight. The results of these analyses were consistent with the previously observed summary findings of a significant lack of association between QTc and the selected outcomes examined. In both men and women, no significant association was seen between QTc interval and risk of either total mortality, sudden cardiac death and death due to coronary artery disease.

DISCUSSION

The results of this study suggest a lack of association between baseline QTc interval and overall mortality as well as mortality due to sudden cardiac events and coronary artery disease. The strengths of the present investi-

TABLE II Adjusted Relative Risk (RR) of Mortality from Selected Outcomes According to Duration of Heart Rate-Corrected QT Interval (QTc): Framingham Heart Study

QTc (seconds)	Adjusted RR of Mortality		
	Total*	Sudden Death	Coronary Artery Disease
<0.36†	1.0	1.0	1.0
0.36-0.38	0.80 (0.62, 1.04)‡	0.95 (0.57, 1.61)	0.96 (0.67, 1.40)
0.39-0.40	0.93 (0.72, 1.18)	1.15 (0.70, 1.89)	0.97 (0.68, 1.39)
0.41-0.43	0.93 (0.73, 1.19)	1.05 (0.63, 1.74)	0.97 (0.68, 1.39)
≥0.44	1.02 (0.70, 1.49)	1.31 (0.60, 2.86)	0.85 (0.48, 1.50)

* Adjusted risk of selected long-term outcome in relation to referent category.
† Referent category.
‡ 95% confidence intervals.

gation include a large study population consisting of essentially healthy men and women originally enrolled in the Framingham Heart Study, long-term (30 years) follow-up, and use of various analytic approaches to examine the association of QT interval duration with selected study end points. The limitations of the study are that only the baseline electrocardiogram of the study population was used in relation to subsequent risk of selected

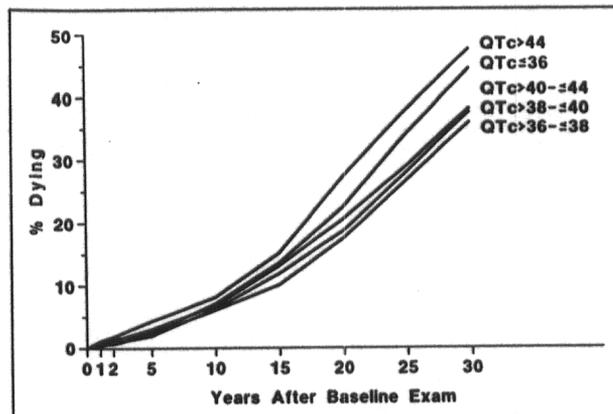


FIGURE 1. Cumulative risk of total mortality in the Framingham Heart Study.

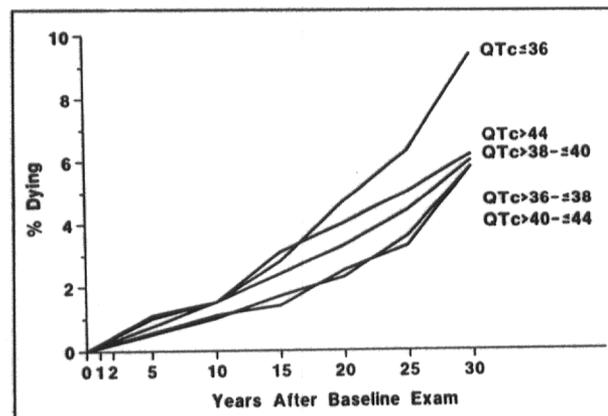


FIGURE 2. Cumulative risk of sudden death in the Framingham Heart Study.

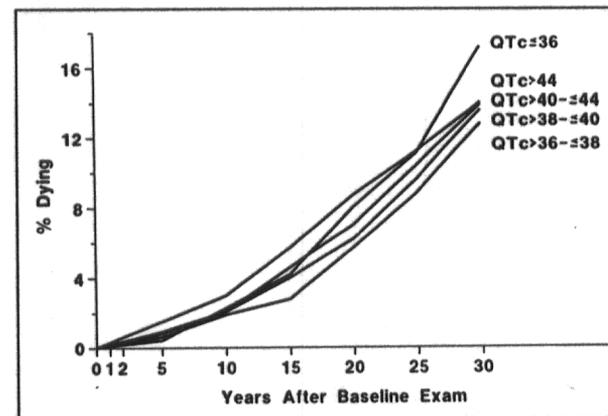


FIGURE 3. Cumulative risk of death from coronary artery disease in the Framingham Heart Study.

events and that changes in the QT interval may have occurred before the development of a cardiac event.

Previous studies examining the association of the QTc interval prolongation with risk of subsequent sudden or coronary death have primarily included patients with prior myocardial infarction,⁷⁻¹⁰ those with out-of-hospital ventricular fibrillation¹¹ and persons with angiographically confirmed coronary artery disease.²⁰ Additional observational studies have examined the relation between prolongation of QTc interval and occurrence of serious ventricular arrhythmias in patients with acute myocardial infarction.⁴⁻⁷ The consensus of these and other studies in patients with acute ischemic heart disease^{21,22} is that increases in the duration of the QTc interval are frequently observed in patients during acute myocardial ischemia; increases in the length of the QTc are associated with an increased risk of sudden or coronary death in hospital survivors of myocardial infarction and in those resuscitated from out-of-hospital cardiac arrest. Measurement of the QTc interval in patients with documented coronary artery disease may, therefore, be of prognostic importance and of use in designing therapeutic interventions for such patients. The results of the present study suggest, however, a lack of association between QTc duration and risk of selected mortality outcomes in a large cohort of essentially healthy persons.

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