REVIEW ARTICLE

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

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Background: In certain subgroups of patients, prolongation of the QTc interval may increase total and cardiovascular mortality due to life-threatening ventricular arrhythmias and sudden death. Nonetheless, whether modest prolongation of the QTc interval in the general population has clinical importance remains unclear.

Methods: We conducted a literature search from 1990 forward to identify all published prospective cohort studies evaluating the association between prolonged QTc interval and risks of total and cardiovascular mortality as well as sudden death. We reviewed each of the studies individually and then conducted a qualitative overview.

Results: The 7 prospective cohort studies identified included 36 031 individuals. There were 2677 (8.7%) individuals with prolonged QTc interval, defined as 440 milliseconds or greater. Whereas 1 study reported no association between prolonged QTc interval and mortality (relative risk, 1.02; 95% confidence interval, 0.70-1.49), the other 6 reported inconsistent associations overall as well as across subgroups defined by various characteristics including age, sex, and comorbidities. The reported associations for both cardiovascular mortality and sudden death were also inconsistent. In the overview, the only consistent findings were for the subgroup of patients with prior cardiovascular disease, in which relative risks ranged from 1.1 to 3.8 for total mortality, from 1.2 to 8.0 for cardiovascular mortality, and from 1.0 to 2.1 for sudden death. Further, in individuals without prior cardiovascular disease, associations were either absent or greatly attenuated; specifically, relative risks ranged from 0.9 to 1.6 for total mortality, from 1.2 to 1.7 for cardiovascular mortality, and from 1.3 to 2.4 for sudden death.

Conclusions: There was no consistent evidence for increased risks of total or cardiovascular mortality or of sudden death, except perhaps for patients with prior cardiovascular disease. In the general population, if QTc interval prolongation is associated with any increase in mortality, that risk is likely to be small and difficult to detect reliably.

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THE QT INTERVAL ON THE surface electrocardiogram (ECG) represents the time from onset of ventricular depolarization (onset of the Q wave) to completion of repolarization (end of the T wave).[1] Since the QT interval varies with heart rate, several methods, most commonly the Bazzett formula,[2] are used to yield a corrected measure (QTc). Abnormalities of repolarization are associated with a specific ventricular arrhythmia—torsade de pointes—that may trigger ventricular fibrillation and sudden death.

The QTc interval can be prolonged because of genetic abnormalities of the potassium or sodium channels of the cardiac cells, resulting in intrinsic repolarization disturbances associated with fatal ventricular arrhythmias. Patients with congenital long QT syndrome present with dizziness, syncopes, or seizures, but cardiac arrest or sudden death may be the first symptom in as many as 13% of untreated patients.[3]

The QTc interval may also be prolonged because of drug use (eg, antiarrhythmic, antihistaminic, psychotropic, and antibiotic medications), electrolyte abnormalities (eg, hypokalemia and hypomagnesemia), and central nervous system injury. In the absence of other repolarization abnormalities, the risk of torsade de pointes and sudden death remains until the acquired condition is corrected or the responsible medications are discontinued. However, torsade de pointes is rarely associated with QTc intervals less than 500 milliseconds.[4]

Thus, a prolonged QTc interval increases mortality in certain subgroups of the general population. However, the clinical significance of a prolonged QTc inter-

val and whether it is associated with increased total or cardiovascular mortality in the general population is unclear. To address this issue we performed a qualitative overview of the 7 published prospective cohort studies of QTc interval and risks of cardiovascular morbidity, total and cardiovascular mortality, and sudden death in the general population.[5-11]

METHODS

We conducted a literature search from 1990 forward to identify all published prospective cohort studies evaluating the association between prolonged QTc interval and risks of total and cardiovascular mortality as well as sudden death. We reviewed each of the studies individually and then conducted a qualitative overview.

RESULTS

PROSPECTIVE COHORT STUDIES

In most studies, a prolonged QTc interval was defined as 440 milliseconds or greater. In contrast, the QTc interval of the reference group was not consistent, ranging from 360 to 440 milliseconds (**Table 1**). In general, data relate a single measurement of QTc interval based on a single ECG to clinical outcomes observed during succeeding years of follow-up.

The Framingham Study

In the Framingham study,[5] the association between prolonged QTc interval and risks of total mortality, sudden death, and coronary mortality at 30 years of follow-up was examined for 5125 (98%) of the 5209 original cohort members. Individuals with cardiovascular disease at baseline or those taking medications known to prolong the QTc interval were excluded (n=84). Subjects were between 30 and 62 years of age at initiation of the study. A single surface ECG measurement yielded a mean (SD) QTc interval of 385 (29) milliseconds for men and 401 (27) milliseconds for women. Subjects were subdivided according to quintiles based on QTc interval. The quintile of shortest duration was less than 360 milliseconds and the quintile of longest duration was 440 milliseconds or greater (279 individuals in the latter group).

There were no statistically significant differences in rates of total mortality, sudden death, or coronary mortality among groups. The lack of association persisted in separate analyses of men and women as well as in analyses that controlled for potential confounders including age, sex, smoking, blood cholesterol, systolic blood pressure, and relative weight (Table 1).

The Amsterdam Study

In the Amsterdam study[6] the association between baseline QTc interval with total, cardiovascular, or coronary mortality at 15 and 28 years of follow-up was examined. The cohort consisted of 3060 volunteers aged 40 to 65 years and subgroups included men (n=1564), women (n=1496), and apparently healthy individuals (n=2741). These volunteers were categorized into 3 groups by QTc interval values of less than 420 milliseconds, 420 to 440 milliseconds, and greater than 440 milliseconds (115 individuals in the latter group).

There were significant associations between QTc interval duration and total mortality at 15 years of follow-up for both men and women in the group with a QTc interval greater than 440 milliseconds compared with those with a QTc interval less than 420 milliseconds. However, at 28 years of follow-up, no overall association was observed. In subgroup analyses, men but not women had associations between QTc interval duration and mortality (Table 1).

The Rotterdam QT Project

In the Rotterdam QT project,[7] 6693 consecutive patients underwent a 24-hour ambulatory ECG to examine the association between QTc interval and sudden death. Of these, 245 died suddenly. The QTc interval was determined using a 12-lead ECG in the individuals who died suddenly (paradoxically, not all patients who experienced sudden death actually died) as well as in a random sample of 467 patients from the study cohort. Study participants whose ECG showed intraventricular conduction defects (ie, a wide QRS interval) were excluded from the analysis. A total of 1233 individuals had a QTc interval of 440 milliseconds or greater.

At 2 years of follow-up, there was a significant, approximately 2-fold increase in risk of sudden death in participants with a QTc interval of 440 milliseconds or greater compared with those with a QTc interval of less than 440 milliseconds. When subgroups with and without evidence of left ventricular dysfunction at baseline (ie, a clinical history of heart failure or ejection fraction <40%) were analyzed separately, the observed association was confined to individuals without evidence of left ventricular dysfunction (Table 1).

The Zutphen Study

The Zutphen Study[8] examined whether QT interval duration was associated with risks of coronary mortality, myocardial infarction, or sudden death in 877 middle-aged men (40-60 years old) followed up for 25 years and 835 elderly men (65-85 years old) followed up for 5 years. In this study men with a prior history of myocardial infarction were excluded. The elderly cohort comprised 555 survivors from the middle-aged cohort and an additional sample of men drawn from the same birth cohort without prior cardiovascular disease. Participants were categorized into 3 groups by QTc interval values of less than 385 milliseconds, 385 to 420 milliseconds, and greater than 420 milliseconds (356 individuals in the latter group).

The subjects with cardiovascular disease at the 25th year of follow-up had a significantly longer mean (SD) QTc interval (425 [39] milliseconds) than those without cardiovascular disease (402 [30] milliseconds). Men with a QTc interval greater than 420 milliseconds in both the middle-aged and the elderly cohort had higher risk of coronary mortality. There were no significant associations between QTc interval duration and risk of myo-

Table 1. Association of QTc Interval Prolongation and Risk of Mortality in Prospective Cohort Studies

Study	Population Size	Follow-up, y	QTc, Range, ms	Relative Risk Compared With the Reference QTc*				
				CV Morbidity	Total Mortality	CV Mortality	Coronary Mortality	Sudden Death
Framingham[5]	5125	30	<360†		1.0		1.0	1.0
			360-380		0.80 (0.62-1.04)		0.96 (0.67-1.4)	0.95 (0.57-1.61)
			390-400		0.93 (0.72-1.18)		0.97 (0.68-1.39)	1.15 (0.70-1.89)
			410-430		0.93 (0.73-1.19)		0.97 (0.68-1.39)	1.05 (0.63-1.74)
			≥440		1.02 (0.70-1.49)		0.85 (0.48-1.5)	1.31 (0.60-2.86)
Amsterdam[6]	3060	15	<420†		1.0 M and W	1.0 M and W	1.0 M and W	
			420-440		1.5 M, 1.7 W	1.6 M, 1.5 W	1.8 M, 1.0 W	
			>440		1.7 M, 1.6 W	1.8 M, 1.4 W	2.1 M, 1.0 W	
		28	<420†		1.0 M and W	1.0 M and W	1.0 M and W	
			420-440		1.1 M, 1.3 W	1.2 M, 1.3 W	1.4 M, 1.4 W	
			>440		1.3 M, 1.1 W	1.4 M, 1.2 W	1.5 M, 1.1 W	
No CV disease at baseline	2741	15	<420†		1.0 M and W	1.0 M and W	1.0 M and W	
			420-440		1.7 M, 1.6 W	1.9 M, 1.3 W	2.4 M, 0.3 W	
			>440		1.5 M, 1.6 W	1.2 M, 1.7 W	1.0 M, 0.9 W	
		28	<420†		1.0 M and W	1.0 M and W	1.0 M and W	
			420-440		1.2 M, 1.3 W	1.3 M, 1.3 W	1.5 M, 1.4 W	
			>440		1.4 M, 1.1 W	1.4 M, 1.2 W	1.2 M, 1.3 W	
Rotterdam QT Project[7]	6693	2	<440†					1.0
			≥440					2.1 (1.4-3.1)
LVD			≥440					1.0 (0.5-1.9)
No LVD			≥440					2.3 (1.4-3.9)
Age ≤60 y			≥440					2.4 (1.0-6.9)
Age >60 y			≥440					1.8 (1.0-3.3)
Men			≥440					3.3 (1.9-6.9)
Women			≥440					1.7 (0.7-4.0)
Previous MI			≥440					2.0 (1.0-4.7)
No previous MI			≥440					2.4 (1.2-4.8)
Zutphen[8]	1712							
Middle-aged men (40-60 y)	877	25	<385†	1.0			1.0	1.0
			385-420	1.4 (0.8-2.3)			4.0 (1.2-13.4)	1.6 (0.5-5.1)
			≥420	1.3 (0.7-2.5)			4.4 (1.2-16.4)	1.4 (0.3-5.7)
Elderly men (65-85 y)	835	5	<385†	1.0			1.0	1.0
			385-420	1.3 (0.5-3.4)			1.3 (0.5-3.3)	1.7 (0.5-5.1)
			≥420	2.4 (0.9-6.1)			3.0 (1.2-7.3)	3.0 (1.0-8.9)

(continued)

cardial infarction except for elderly men in the extreme QTc interval prolongation category. For sudden death, there was a significant 3-fold increase in risk in those in the most extreme category of QTc interval prolongation in the elderly men but not in the middle-aged men (Table 1).

The Finnish Study

The Finnish Study[9] examined whether a nomogram-corrected QT interval (QT_{Nc}) was associated with risks of total, cardiovascular, or coronary mortality, as well as sudden death, in a middle-aged population. The length of follow-up was 23 years for total, cardiovascular, and coronary mortality and 13 years for sudden death. The study population comprised 10717 individuals (5598 men and 5119 women) between 30 and 59 years of age at study entry. Subgroup analyses of healthy individuals and individuals with cardiovascular disease at baseline were performed. There were 381 individuals with a QT_{Nc} prolonged by more than 10%.

In the subgroup of men, there were associations between prolonged QT_{Nc} interval and total, cardiovascular, and coronary mortality. The associations in men with cardiovascular disease at baseline were stronger than those observed in the overall population. In women, there was no evidence of an association between QT_{Nc} interval duration and total, cardiovascular, and coronary mortality; however, in women with previous cardiovascular disease, although the risks were not significant, the pattern appeared to be similar to that of men. For sudden death, the number of cases was too small to provide meaningful data (Table 1).

The Danish Study

The Danish Study[10] examined whether QTc interval duration is associated with total and cardiovascular mortality and cardiovascular events (fatal and nonfatal). The length of follow-up was 13 years for total mortality and 11 years for cardiovascular mortality and cardiovascular events. Subjects comprised 3455 men and women aged 30 to 60 years. Subgroup analyses were conducted for individuals with (821) and without (2269) cardiovascular disease at baseline. The mean baseline QTc interval was of 405 milliseconds for the entire cohort, 400 milliseconds for the group

Table 1. Association of QTc Interval Prolongation and Risk of Mortality in Prospective Cohort Studies (cont)

Study	Population Size	Follow-up, y	QTc, Range, ms	Relative Risk Compared With the Reference QTc*				
				CV Morbidity	Total Mortality	CV Mortality	Coronary Mortality	Sudden Death
Finnish[9]	10 717	23						
Men	5598		<353		1.06 (0.78-1.46)	1.04 (0.67-1.63)	0.93 (0.54-1.62)	0.73 (0.18-2.96)
			353-371		0.99 (0.86-1.15)	1.03 (0.85-1.26)	1.07 (0.85-1.35)	0.86 (0.49-1.51)
			372-410†		1.0	1.0	1.0	1.0
			411-430		0.99 (0.86-1.13)	1.07 (0.09-1.27)	1.04 (0.84-1.27)	1.21 (0.79-1.87)
			>430		1.33 (1.08-1.63)	1.42 (1.09-1.84)	1.44 (1.06-1.96)	1.50 (0.78-2.89)
No CV disease			>430		1.21 (0.96-1.53)	1.25 (0.92-1.70)	1.29 (0.90-1.85)	1.48 (0.67-3.26)
CV disease			>430		1.92 (1.23-3.0)	2.12 (1.25-3.59)	2.11 (1.14-3.88)	2.17 (0.63-7.45)
Women	5119		<358		1.19 (0.77-1.85)	0.92 (0.45-1.86)	0.86 (0.34-2.31)	
			358-377		0.99 (0.80-1.24)	1.04 (0.76-1.41)	0.87 (0.56-1.37)	
			378-417†		1.0	1.0	1.0	
			418-437		1.04 (0.85-1.26)	1.10 (0.83-1.44)	1.21 (0.85-1.73)	
			>437		0.98 (0.70-1.37)	1.32 (0.89-1.97)	1.38 (0.81-2.36)	
No CV disease			>437		0.91 (0.62-1.34)	1.28 (0.80-2.02)	1.32 (0.71-2.46)	
CV disease			>437		1.22 (0.62-2.41)	1.50 (0.66-3.41)	1.62 (0.54-4.87)	
Danish[10]	3455	13 for total mortality	310-380†		1.0	1.0		
			380-440		1.60 (0.97-2.65)	1.79 (0.64-5.03)		
			≥440		1.89 (1.04-3.37)	3.31 (1.04-9.91)		
No CV disease at baseline	2269	11 for CV mortality	310-380†		1.0			
			380-440		1.3 (0.70-2.42)			
			≥440		1.17 (0.43-2.87)			
CV disease at baseline	821		310-380†		1.0	1.0		
			380-440		2.84 (0.98-9.01)	4.08 (0.55-30.17)		
			≥440		3.83 (1.14-12.87)	8.09 (1.04-62.82)		
Rotterdam[11]	5269	3-6						
Men	2093		<406†		1.0	1.0		
			406-421		0.9 (0.6-1.4)	0.7 (0.3-1.5)		
			421-437		1.2 (0.8-1.9)	0.7 (0.3-1.5)		
			>437		1.5 (1.0-2.3)	1.3 (0.7-2.4)		
Women	3176		<418†		1.0	1.0		
			418-432		1.3 (0.8-2.0)	1.0 (0.4-2.6)		
			432-446		1.5 (1.0-2.3)	1.8 (0.8-4.1)		
			>446		1.9 (1.3-2.9)	2.4 (1.1-5.3)		

Abbreviations: CV, cardiovascular; LVD, left ventricular dysfunction; M, men; MI, myocardial infarction; W, women.
*Values are given as relative risk (95% confidence interval) unless otherwise indicated. Blank spaces indicate that no data were available.
†Reference QTc interval.

without cardiovascular disease, and 413 milliseconds for individuals with cardiac disease at baseline. There were a total of 313 individuals with a QTc interval greater than 440 milliseconds.

There were significant associations between QTc interval duration and total as well as cardiovascular mortality only for individuals in the most extreme category of QTc interval prolongation (>440 milliseconds). Subgroup analyses demonstrated that in patients with cardiovascular disease at baseline, the magnitude of association for total and cardiovascular mortality was greater than in the overall population. In contrast, in analyses restricted to healthy individuals without cardiovascular disease at baseline, there were no significant associations between QTc interval duration and either total mortality or cardiovascular morbidity. Cardiovascular mortality could not be analyzed in this subgroup owing to the small number of cardiovascular deaths in this subgroup (Table 1).

The Rotterdam Study

In this study,[11] the association of QTc interval with total and cardiovascular mortality was examined in 5269 elderly subjects (mean age, 68 years) followed up for 3 to 6 years. Individuals with arrhythmias or bundle branch block at baseline were excluded. The data for men and women were analyzed separately. Median baseline QTc interval values were 421 milliseconds for men and 432 milliseconds for women.

In analyses based on quartiles of QTc interval duration, there were significant associations for total mortality in both men and women. In subgroup analyses, women whose QTc interval duration was in the most extreme quartile (>446 milliseconds) had a significant, approximately 2-fold increase in risks of total and cardiovascular mortality. In the subgroup of men, the risks of total and cardiovascular mortality were only modest and not statistically significant. Results reached with different methods (the Bazzett, Fridericia, linear regression, nomogram, and QT index methods) to correct for heart rate did not affect the results (Table 1).

QUALITATIVE OVERVIEW

Among the 36031 individuals included in these prospective cohort studies there were 2677 individu-

als with prolonged QTc interval (≥440 milliseconds) representing 8.7% of the general population. While 1 study[5] reported no association between prolonged QTc interval and mortality (relative risk, 1.02; 95% confidence interval, 0.70-1.49) the other 6 studies[6-11] reported inconsistent associations between QTc interval prolongation and mortality. In most studies, the magnitude and significance of associations were inconsistent across various subgroups. The only consistent findings were for patients with cardiovascular disease at baseline. In patients with prior cardiovascular disease and prolonged QTc interval the relative risks from 1.1 to 3.8 for total mortality ranged, from 1.2 to 8.0 for cardiovascular mortality, from 1.0 to 2.1 for coronary mortality, and from 1.0 to 2.1 for sudden death. Further, in individuals without cardiovascular disease at baseline, associations were either absent or weak. Specifically, in individuals with a prolonged QTc interval and no prior cardiovascular disease, the relative risks ranged from 0.9 to 1.6 for total mortality, from 1.2 to 1.7 for cardiovascular mortality, from 0.8 to 1.3 for coronary mortality, and from 1.3 to 2.4 for sudden death.

Table 2. Cox Regression Models of Risk Factors for Subsequent Adverse Cardiac Events in the Prospective Longitudinal Study of Families With Congenital Long QT Syndrome*

Risk Factor	Hazard Ratio (95% Confidence Interval)	*P* Value
Model 1: Total population (n = 1496)		
QTc	1.052 (1.017-1.088)	<.01
History of cardiac event	3.1 (1.3-1.7)	<.01
Heart rate	1.017 (1.004-1.031)	.01
Model 2: Probands (n = 235)		
QTc	1.055 (1.017-1.094)	<.01
Heart rate	1.018 (1.003-1.033)	.02
Model 3: Family members (n = 1264)		
History of cardiac event	6.2 (2.1-18)	<.01
Female sex	3.9 (1.1-15)	.04

*Reproduced with permission from Moss.[1]

COMMENT

In this qualitative overview, there is no consistent association between prolonged QTc interval and total and cardiovascular mortality or morbidity, except perhaps in patients with prior cardiovascular disease. Even in this subgroup, however, the data are not entirely consistent. For example, in the Rotterdam QT Project the association between prolonged QTc interval and sudden death was not significant in the subgroup of patients with left ventricular dysfunction. In addition, in the Zutphen Study the authors concluded that the observed association was not attributable to prior cardiovascular disease. The lack of consistency of findings across various subgroups increases the likelihood that chance, bias, and/or uncontrolled confounding are plausible alternative explanations.[12] Chance could play a role since some studies had insufficient statistical power to detect differences between various subgroups, especially for sudden death. Bias may be present because of imprecise measurements of the QTc interval and/or differences in duration and completeness of follow-up. With respect to imprecise measurements, categorization of individuals by QTc interval was based, in general, on a single ECG and was related to clinical outcomes usually occurring many years later. Given the marked intraindividual variability in QTc interval over a 24-hour period, repeated measures of QTc interval taken under strictly uniform conditions may be needed to reliably detect associations. Bias may also result from differences in the prevalence of cardiovascular disease at baseline. The observation that patients with a QTc interval of 440 milliseconds or greater have a greater risk of total and cardiovascular mortality than patients with a QTc interval of 440 milliseconds or less may reflect the role of QTc interval as a marker of underlying cardiovascular disease. In support of this hypothesis, most of the general population studies that performed subgroup analyses in individuals without previous cardiovascular disease found no association between the QTc interval and total as well as cardiovascular mortality. Finally, none of the studies was designed to test the hypothesis that QTc interval is associated with cardiovascular morbidity and with mortality, total and cardiovascular; therefore, uncontrolled confounding due to variables not collected or not known may have influenced the results in either direction.

It is important to note that these data cannot directly address clinically relevant issues of QTc interval prolongation related to congenital or other causes such as medication use and electrolyte abnormalities, as the available data do not address these particular subgroups of patients. In this regard, a prospective longitudinal study of 328 families with congenital long QT syndrome[13] reported separate survival analyses for the probands (n=328), affected (n=88) and unaffected family members (n=1004), and the entire population to identify risk factors for the first occurrence of syncope or probable long QT syndrome–related death, defined as arrhythmic death before the age of 40 years. For the probands as well as for the entire population—which included the probands—QTc duration was a significant risk factor; however, when the analysis was restricted to the family members, QTc duration was no longer a statistically significant predictor (**Table 2**). These findings are compatible with a recent reanalysis of this same population.[14]

In summary, if QTc interval duration predicts total mortality, cardiovascular mortality, or sudden death in the general population, that risk is likely to be small and difficult to detect reliably. Further research is needed,[15] which should include serial measurements of the QTc interval by trained expert readers organized in an ECG core laboratory. These studies should be designed specifically to test the

hypothesis that QTc interval prolongation is associated with total and cardiovascular mortality.

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