Association Between QT Interval and Coronary Heart Disease in Middle-aged and Elderly Men

The Zutphen Study

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Background Heart-rate–adjusted QT-interval (QT_c) is prognostic of sudden death in myocardial infarction patients. So far, population studies have yielded conflicting results on the predictive value of QT_c for coronary heart disease morbidity and mortality. Therefore, we investigated this in a longitudinal study of middle-aged and elderly men.

Methods and Results From 1960 to 1985, 877 middle-aged men were followed and repeatedly examined in the Zutphen Study. In 1985 the remaining cohort was extended to 835 elderly men from the same birth cohort and followed until 1990. Men with prolonged QT_c (420 $ms^{1/2}$ or more) had a higher risk of myocardial infarction and coronary heart disease death relative to men with QT_c less than 385 $ms^{1/2}$. Age-adjusted coronary heart disease mortality rate ratios were 4.3 (95% confidence interval, 1.3 to 13.8) in middle-aged men and 3.3 (95% confidence interval, 1.0 to 11.6) in elderly men. These associations could not be attributed to prevalent heart disease and were independent of other cardiovascular risk factors.

Conclusions These results indicate that within the normal range of QT_c in the general population, men with long QT_c are at higher risk for coronary heart disease. Because QT_c is easily determined, it may provide a valuable contribution to risk stratification. (***Circulation*. 1994;90:779-785.**)

Key Words • QT_c • electrocardiography • epidemiology • nervous system, autonomic

Long QT syndrome patients are at high risk of malignant ventricular arrhythmia and sudden death.[1] Also, in myocardial infarction patients and patients who had diagnostic 24-hour electrocardiography,[2,3] an association of heart-rate–adjusted QT-interval (QT_c) with sudden death has been observed, although not in all studies.[4] This elevated risk has been attributed to the predominance of left sympathetic nerve activity[5-7] or myocardial membrane defects[8,9] leading to electrical instability in situations of high sympathetic activity.

Whether QT_c prolongation predicts coronary heart disease mortality in healthy people remains to be clarified. Recently, two studies in the general population came to contradictory conclusions. In the Framingham Heart Study[10] no significant associations with mortality were observed, whereas in the Dutch Civil Servants Study[11] men and women with QT_c prolongation had about a twofold risk of coronary heart disease death. In the present study we investigated the predictive value of QT_c for 25-year coronary heart disease morbidity and mortality in a prospective cohort study of middle-aged men from the general population. Because QT-interval duration gradually increases with age[12] and autonomic function alters as well,[13] the same associations were evaluated in a 5-year follow-up of a cohort of elderly men.

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Methods

Study Population

From 1960 on, the Zutphen Study, a prospective study on coronary heart disease, has been carried out in the frame of the Seven Countries Study.[14] In 1960 a random sample of 1088 men, residents of the town of Zutphen, the Netherlands, and born between 1900 and 1920, were invited for a medical examination and dietary survey. Thirty-two men refused to participate, and 178 took part only in the dietary survey or were examined later than 1960. In 877 of the remaining 878 participants, a 12-lead electrocardiogram was recorded. During follow-up examinations in 1965 and 1970, 717 and 625 men took part, respectively. After exclusion of men who had previous myocardial infarction (see "End Points" below for definition), the resulting study population consisted of 851 middle-aged men in 1960, 685 in 1965, and 582 in 1970. In 1985 the 555 survivors and an additional sample of 711 men, drawn from the same birth cohort (then aged 65 to 85 years) were invited to take part in the elderly study. Of these, 156 did not volunteer and 171 did not participate for various reasons (illness or death, could not be traced, etc). In 54 men no electrocardiogram was made, 49 recordings were lost during follow up, and in 1 man the QT interval could not be determined accurately. Of the remaining 835 men, 115 were excluded because of previously diagnosed myocardial infarction. Thus, the final study population comprised 720 elderly men in 1985. At the follow-up medical examination in 1990, 552 of 656 surviving participants took part. Exclusion of 78 men with previous myocardial infarctions left a study population of 474 men in 1990.

Electrocardiography

Standard resting 12-lead electrocardiographic recording and assessment of cardiovascular risk factors were performed

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according to the protocol of the Seven Countries Study[14] in 1960, 1965, 1970, 1985, and 1990. The electrocardiograms were classified and coded according to the Minnesota Code.[15] In 1992 QT and RR intervals were measured with a digitizing tablet (Calcomp) and personal computer. The resolution of the tablet is 100 lines per millimeter, and the reproducibility is 0.25 mm (corresponding to 10 milliseconds). QT intervals were read from three leads: V_2 and V_6 and of leads I, II, or III, the one with the longest QT. In each lead, QT intervals and the preceding RR intervals were measured in three consecutive normal complexes to reduce measurement error and because QT duration may vary slightly from beat to beat because of concomitant variability of heart rate frequency.[16] The beginning of the QT interval was defined as the first deflection of the QRS complex and the end as the point of maximal change in the slope as the T wave merges with the baseline.[9] All intervals were measured by one observer who was blinded for other baseline information and survival.

Information on Other Variables

At all examinations systolic and diastolic blood pressures were measured twice at the end of the physical examination on the right arm with the subject in the supine position. Between 1960 and 1970, only the last value was recorded. For 1985 and 1990, the mean of duplicate readings was calculated. Serum total cholesterol was determined in a standardized laboratory by the Abell-Kendall[17] method in 1960 and 1965, by the method of Zlatkis et al[18] in 1970, and by the enzymatic method of Siedel et al[19] and Stähler et al[20] in 1985 and 1990, respectively. All methods produced Abell-Kendall equivalents. Body mass index was calculated from height and weight (height was measured in 1960 and 1985 only). Before 1985 smoking was assessed by the Seven Countries Study questionnaire on smoking habits. From 1985 on, a newly developed questionnaire[21] was used.

End Points

Mortality was registered weekly by means of the municipal registry of the town of Zutphen. Causes of death were obtained from death certificates, the hospital, and/or the general practitioner. Follow-up was complete for all participants. Information on cardiovascular disease was collected during the medical examinations. Between 1960 and 1973 medical examinations were performed annually, and after that period in 1977/1978, 1985, and 1990. In addition, questionnaires on health status were filled in by the survivors in 1980 and 1982. The information on morbidity provided was verified by contacting the general practitioner. For the period from 1985 through 1990, hospital discharge data of the members of the cohort who were hospitalized in Zutphen were made available as well. Coding of causes of death was performed according to the International Classification of Diseases[22] (8th revision in the period of 1960 to 1985, 9th from 1985 to 1990). Coronary heart disease mortality was defined as ICD-8 codes 410 and 411.9 through 413.9 and as ICD-9 codes 410 through 414. Myocardial infarction was coded when two of the following three criteria were present: (1) a specific medical history, eg, severe chest pain lasting for more than 20 minutes and not disappearing during rest; (2) electrocardiographic changes corresponding to Minnesota Codes 1.1 (major Q waves), code 1.2 accompanied by 5.1, or 5.2 (lesser Q waves and major T wave findings); or (3) specific enzyme level elevations. Only first occurrence of myocardial infarction (fatal or nonfatal) was recorded. Sudden cardiac death was not coded until recently by one of the authors (J.M.D.). Because of the limitations of the available information, sudden cardiac death in this study was coded in two situations: (1) when it was documented that death occurred within 2 hours after onset of typical symptoms, and no other causes of death were known or (2) in subjects with a history of heart disease when *mors subita* was notified by the physician or death occurred unwitnessed (within 12 hours after men had been observed to be well).

Data Analysis

QT intervals were adjusted for heart rate according to Bazett's formula.[23] Means of three consecutive QT_c were calculated from leads V_2 and V_6 and either lead I, II, or III. The greatest from these was used for the analyses.

Subjects were categorized into three groups: short, intermediate, and long QT_c, with cutoff points of 385 and 420 $ms^{1/2}$, respectively. The first cutoff point separates the lowest tertile in 1960 and the lowest quartile in 1985. To have a sufficient number of middle-aged men in the upper category, the second cutoff point was 420 $ms^{1/2}$ instead of 440 $ms^{1/2}$, which is the usual criterion for definitely prolonged QT_c.

The predictive value of QT_c for the incidence of a first myocardial infarction, coronary heart disease mortality, and sudden death was analyzed using Cox proportional-hazards models. Rate ratios for three partly overlapping, 15-year periods were estimated using 1960, 1965, and 1970 as baseline, respectively. To have full profit of the repeated measurements, in the middle-aged population a time-dependent Cox model was fitted. The resulting coefficients are to be interpreted as short-term (5-year) rate ratios.[24,25]

In all regression analyses, age was included to adjust for confounding. The effect of all other possible confounders (systolic blood pressure, serum total cholesterol, body mass index, and the product of number of cigarettes and years of smoking) was checked by including them simultaneously in multivariate models.

Analyses were repeated after exclusion of subjects with angina pectoris or with electrocardiographic signs of heart disease (Minnesota codes 1.1, 1.2, 3.1, 3.2, 4.1, 4.2, 5.1, 5.2, and 7.1 through 7.4) to study the possibility that observed associations are a consequence of detectable prevalent heart disease (men with prevalent myocardial infarction were excluded from the beginning).

Proportional-hazards assumptions were verified by inspection of log-log survival curves. All data analyses were performed on a VAX computer with SAS software.[26]

Results

The Figure plots the distribution of QT_c at repeated measurements. With time, the mean of the distribution shifted to longer QT_c, and the standard deviation increased. The mean QT_c increased from 395±23 $ms^{1/2}$ (mean±SD) in middle-aged men in 1960 to 410±26 $ms^{1/2}$ in the elderly in 1985. The proportion of men in the long-QT_c category was 12% in 1960 and 35% in 1985. As shown in Table 1, mean age, blood pressure, serum cholesterol, and body mass index showed a positive trend over QT_c categories in 1960 and in 1985. This was similar in the other follow-up examinations. The cumulative incidences of myocardial infarction, coronary heart disease mortality, and sudden death were all higher in the intermediate-QT_c and highest in the long-QT_c category (Table 1). Men who had a first myocardial infarction in the period from 1960 to 1975 had a mean QT_c in 1960 of 399±20 $ms^{1/2}$; men who died of coronary heart disease, 404±20 $ms^{1/2}$; and men who died suddenly, 401±21 $ms^{1/2}$. In the remaining group, mean QT_c was 394±23 $ms^{1/2}$, which was significantly different from the other categories. Table 2 presents risk analysis for middle-aged men. For each of the three periods, the rate of myocardial infarction occurrence in the long-QT_c category was approximately twice that of the short category (not significant for the period 1970 to 1985 only). Risk of both fatal and nonfatal myocardial

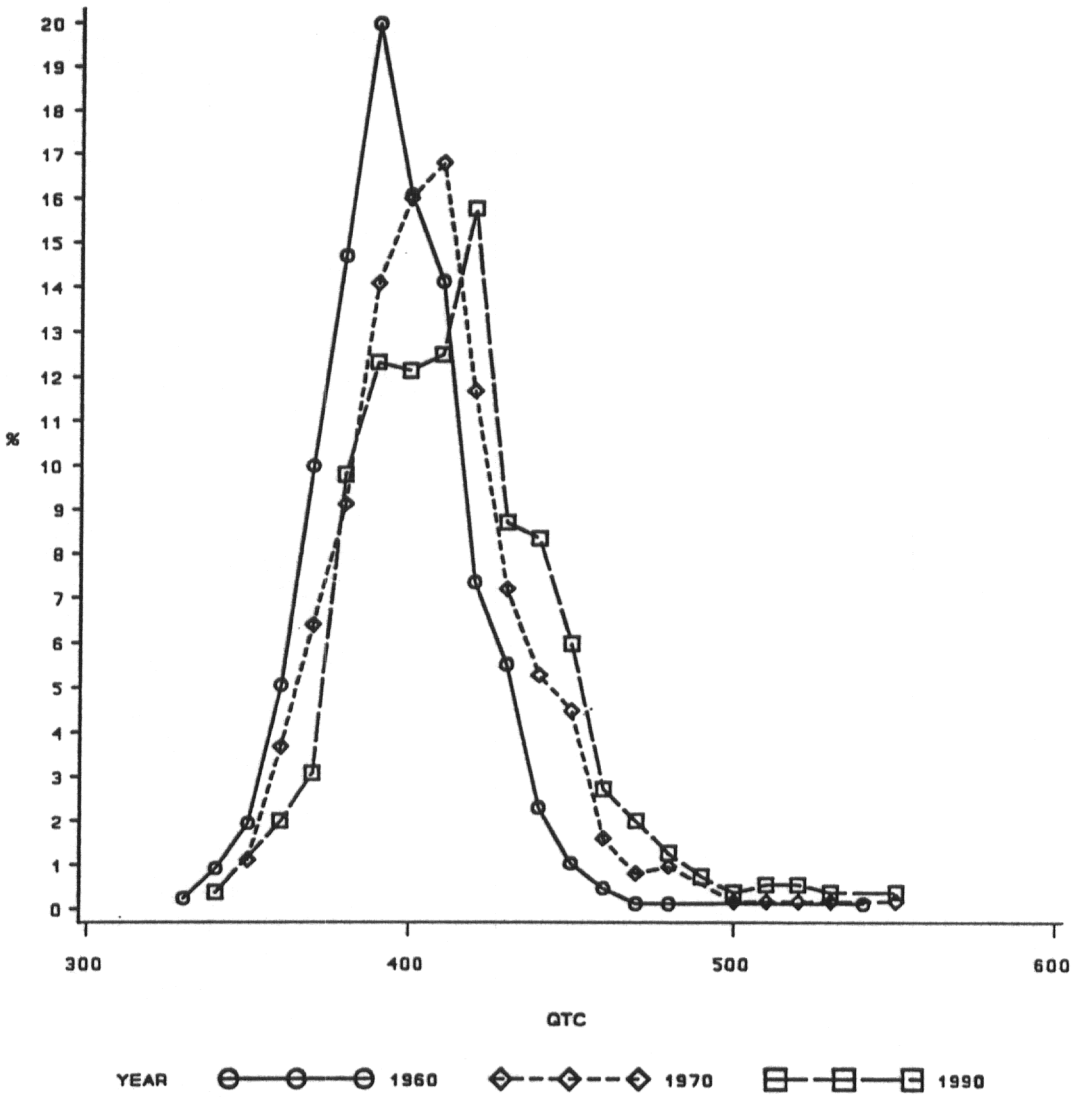

FIG 1. Line graph shows population distributions of heart rate–adjusted QT interval (QTC in figure) in electrocardiograms recorded from 1960 through 1990.

infarctions was associated with QT_c. For coronary heart disease death and sudden death rate ratios were more than 2 in the intermediate-QT_c and more than 3 in the long-QT_c categories. The 5-year rate ratios of coronary heart disease mortality resulting from time-dependent analysis were somewhat higher. The short-term occurrence of myocardial infarction was not clearly associated with QT_c. Adjustment for age, systolic blood pressure, body mass index, total serum cholesterol, and smoking only slightly lowered the observed rate ratios.

Mean QT_c in subjects with angina pectoris or electrocardiographic signs of possible heart disease at baseline (13% in 1960, 22% in 1970) was approximately 10 $ms^{1/2}$ longer than in men without signs of heart disease. However, exclusion of these subjects left the estimates essentially unchanged. Also, exclusion of men who had a QT_c increase of 20 $ms^{1/2}$ or more between repeated measurements did not change the relations.

In the elderly men, similar associations for long QT_c were observed during the available 5 years of follow-up but not for intermediate QT_c (Table 3). A change of the upper cutoff point to 440 $ms^{1/2}$ left 19% of the elderly men in the long-QT_c category. Age-adjusted rate ratios of myocardial infarction incidence and coronary heart disease mortality for this more extreme category were 2.8 (95% confidence interval, 1.0 to 7.5) and 5.0 (1.4 to 18.0), respectively.

In 1985 one third of all subjects had angina pectoris or electrocardiographic signs of heart disease. Their mean QT_c was 425±39 $ms^{1/2}$, which was significantly different from the other men (402±30 $ms^{1/2}$). After these subjects were excluded, the relative rates of myocardial infarction, coronary heart disease death, and sudden death in the long-QT_c category (25% of the remaining men) were even higher.

Discussion

In this prospective cohort study in the general population, men with QT_c of 420 $ms^{1/2}$ or more had an elevated risk for myocardial infarction and even more so for coronary heart disease mortality and sudden death. The association could not be attributed to subjects with signs of prevalent heart disease and was independent of other risk factors for coronary heart disease.

TABLE 1. Population Characteristics and Coronary Heart Disease in Categories of QT_c Interval Length: The Zutphen Study

	QT_c<385	QT_c 385-420	QT_c≥420
1960			
N	278	468	105
Age, y	49.7±5.5	49.9±5.5	50.9±5.5
Systolic blood pressure, mm Hg	139.9±17.4	143.8±20.4*	150.1±22.2*
Serum cholesterol, mmol/L	6.00±1.19	6.09±1.14	6.30±1.33
Body mass index, kg/m²	23.8±2.6	24.1±2.8	24.7±2.7*
Product of cigarettes and years smoking	373±287	367±281	389±279
25-Year (15-year) MI incidence, %	19.1 (7.6)	22.7 (13.3)	26.7 (17.1)
25-Year (15-year) CHD mortality, %	11.1 (2.5)	16.7 (6.8)	21.9 (13.3)
25-Year (15-year) sudden death, %	9.4 (3.6)	13.0 (7.1)	18.1 (10.5)
1985			
N	170	299	251
Age, y	70.7±4.8	72.0±5.1*	72.6±5.5*
Systolic blood pressure, mm Hg	148.5±20.8	150.4±21.1	154.0±21.5*
Serum cholesterol, mmol/L	6.07±1.04	6.03±1.05	6.09±1.05
Body mass index, kg/m²	25.1±2.8	25.4±3.0	26.0±3.5*
Product of cigarettes and years smoking	518±551	485±462	516±508
5-Year MI incidence, %	3.5	4.4	7.6
5-Year CHD mortality, %	1.8	2.0	6.0
5-Year sudden death, %	1.8	2.0	5.2

QT_c indicates heart rate–adjusted QT interval; MI, myocardial infarction; and CHD, coronary heart disease. Values are mean±SD.

*Significant F test ($P<.05$) over the QT_c categories; indicated value significantly different from lowest category (Tukey-Kramer test, $P<.05$).

The study, being an observational epidemiological investigation, is subject to a number of potential errors. Error may have occurred in the measurement of QT interval length. The measurements were performed by only one observer who was blinded for the outcome. Therefore, bias because of differential error in QT measurement and interobserver differences is impossible.

We did not follow the recommendation of Campbell et al[27] to measure QT interval in all available leads. To limit the number of QT intervals to be measured, in the present study leads I, II, or III, lead V_2, and lead V_6 were selected. The axes of these leads are nearly orthogonal, optimizing the ability to detect electrical activity in any direction.

The end of the T wave was defined as the point of maximal change in the slope of the curve as it merges with the baseline. In previous studies the end point has often been defined as the point at which the T wave merges with the electrical baseline. However, especially in the chest leads, U waves often obscure the end of the T. As a consequence, the intervals measured in the present study may be slightly shorter, but precision will be greater.

Misclassification of the study end points is another possible source of bias. Information on morbidity and mortality from specialists and family practitioners was thoroughly checked and evaluated by physicians who were not aware of the present hypothesis. The ascertainment of sudden death was especially prone to misclassification because sudden death was not an item of interest in the Zutphen Study before, and detailed information on time between the first occurrence of symptoms and death was not systematically obtained. Because there is no reason to suspect the presence of differential error in the assessment of exposure or end points, information bias is not a likely explanation for the observed findings.

The use of certain drugs that affect the length of the QT interval could cause bias. Unfortunately, information about drug use was not available before 1985. However, drugs that may influence QT interval length were not frequently prescribed in the 1960s. Therefore, we do not expect a substantial drug effect on the observed QT interval for the periods from 1960 to 1970. In the elderly population, exclusion of men using antiarrhythmics, β-blocking agents, or diuretics did not change the associations.

Because men with angina pectoris or electrocardiographic signs of heart disease had longer QT_c, it may be questioned whether the observed associations resulted from prevalent heart disease. However, exclusion of these men or of men with large increases of QT_c between the consecutive measurements did not weaken the relative rates. Still, the possibility of subclinical heart disease underlying QT_c prolongation cannot be completely ruled out.

The presently reported results confirm previous findings from our group by Schouten et al.[11] In a study of

TABLE 2. Relative Rates of Coronary Heart Disease in QT_c Categories in Middle-aged Men: The Zutphen Study

	N	MI Incidence	CHD Death	Sudden Death
1960-1975		n=101*	n=58	n=54
QT_c<385	278	1.0	1.0	1.0
QT_c 385-420	468	1.8 (1.1-3.0)†	2.7 (1.2-6.2)	2.1 (1.0-4.2)
		1.9 (1.1-3.2)‡	2.6 (1.1-6.2)	1.7 (0.8-3.4)
QT_c≥420	105	2.3 (1.2-4.4)	5.1 (2.1-12.8)	3.2 (1.4-7.6)
		1.9 (1.0-3.7)	4.2 (1.6-11.4)	2.6 (1.1-6.1)
1965-1980		n=98	n=53	n=55
QT_c<385	240	1.0	1.0	1.0
QT_c 385-420	353	1.2 (0.7-1.8)	1.9 (0.9-3.7)	1.5 (0.8-2.8)
		1.0 (0.7-1.6)	1.6 (0.9-3.0)	1.4 (0.8-2.5)
QT_c≥420	92	1.8 (1.0-3.2)	3.0 (1.3-6.9)	1.5 (0.6-3.6)
		1.4 (0.8-2.6)	2.1 (0.9-4.8)	0.9 (0.4-2.3)
1970-1985		n=98	n=68	n=60
QT_c<385	120	1.0	1.0	1.0
QT_c 385-420	315	1.3 (0.7-2.2)	1.6 (0.8-3.4)	2.6 (1.0-6.7)
		1.1 (0.6-2.0)	1.4 (0.7-3.0)	2.2 (0.9-5.8)
QT_c≥420	147	1.5 (0.8-2.8)	2.2 (1.0-4.8)	4.8 (1.8-12.7)
		1.3 (0.7-2.4)	1.8 (0.8-4.0)	3.8 (1.4-10.1)
Pooled data§		n=94	n=39	n=23
QT_c<385		1.0	1.0	1.0
QT_c 385-420		1.4 (0.9-2.4)	3.3 (1.2-9.6)	2.1 (0.7-6.3)
		1.4 (0.8-2.3)	4.0 (1.2-13.4)	1.6 (0.5-5.1)
QT_c≥420		1.5 (0.8-2.8)	4.3 (1.3-13.8)	1.8 (0.5-7.5)
		1.3 (0.7-2.5)	4.4 (1.2-16.4)	1.4 (0.3-5.7)

Definitions are as in Table 1.
*Number of cases.
†Age-adjusted hazards ratio.
‡Hazards ratio adjusted for age, systolic blood pressure, body mass index, total serum cholesterol, and product of number of cigarettes and years smoked.
§Taking measurements in 1960, 1965, and 1970 and subsequent 5 years of follow-up as separate observations, stratified for period.

0 healthy middle-aged men and women, significant year relative risks of death of ischemic heart disease 1.8 and 2.1 in men with intermediate prolongation Γ_c of 420 to 440 $ms^{1/2}$) and definite prolongation (QT_c of 440 $ms^{1/2}$ or more), respectively, were reported. In women, only total mortality was significantly associated with QT_c. Goldberg et al[10] did not observe an association between QT_c and 30-year total and coronary artery

TABLE 3. Relative Rates of Coronary Heart Disease in QT_c Categories in Elderly Men: The Zutphen Study

	N	MI Incidence	CHD Death	Sudden Death
1985-1990		n=38*	n=24	n=22
QT_c<385	170	1.0	1.0	1.0
QT_c 385-420	299	1.2 (0.5-3.3)†	1.3 (0.4-3.3)	1.8 (0.6-5.6)
		1.3 (0.5-3.4)‡	1.3 (0.5-3.3)	1.7 (0.5-5.1)
QT_c≥420	251	2.3 (0.9-5.7)	3.1 (1.3-7.6)	3.7 (1.3-10.9)
		2.4 (0.9-6.1)	3.0 (1.2-7.3)	3.0 (1.0-8.9)

Definitions are as in Table 1.
*Number of cases.
†Age-adjusted hazards ratio.
‡Hazards ratio adjusted for age, systolic blood pressure, body mass index, total serum cholesterol, and product of number of cigarettes and years smoked.

disease mortality or sudden death in the Framingham Heart Study. However, the categorization of QT_c in their study was based on quintiles of QT_c distribution of both sexes combined. Because in general women have longer QT_c and the association with coronary heart disease mortality seems weaker than in men, this may have weakened the power of their study.[28] In addition, a follow-up period of 30 years after a single baseline measurement is very long. In general, even when person-time analysis is used to account for competing mortality, the predictive value of one baseline classification will diminish with time. In the present study, as well as in the study by Schouten and coworkers,[11] the associations were clearly stronger when a shorter follow-up period was considered. The finding of a J-shaped relation in the Framingham Heart Study could not be confirmed in the Zutphen Study. Instead, men with QT_c of 385 $ms^{1/2}$ or less had the lowest risk.

Several studies have reported an increased risk of ventricular arrhythmias and sudden death in subjects with prolonged QT_c in patient populations.[1,7,8] In the present study, subjects with previous myocardial infarction were excluded. Indeed, their mean QT_c was higher, and including them in the analysis produced even higher relative rates.

Only very few middle-aged men had a clearly abnormal QT_c (eg, 440 $ms^{1/2}$ or more). Nevertheless, a considerably elevated risk was observed in the category of QT_c of 420 $ms^{1/2}$ or more. The present findings do not warrant a clear cutoff point. Instead, risk seems to increase gradually within the normal values in the population.

It has been suggested that determination of QT dispersion among the leads may be more informative than QT length per se.[29] Therefore, we also checked the greatest difference between any two leads and the differences between specific leads. Indeed, subjects who had more than a 40-millisecond difference between any lead had a higher risk of coronary heart disease mortality, but these associations were weaker and less consistent than the associations with QT_c length. No association was observed with myocardial infarction incidence.

The predictive value of prolonged QT_c for sudden death and coronary heart disease death can be explained by ventricular electrical instability, particularly in the presence of high sympathetic activity. Such instability is hypothesized to result from left sympathetic predominance, accompanied by dispersion of repolarization[5-7] or from myocardial membrane properties that give rise to early afterdepolarizations.[8,9,30] In both mechanisms, parasympathetic activity exhibits beneficial effects.[31,32] It is conceivable that QT_c is especially prolonged in people with an unfavorable balance between sympathetic and parasympathetic activity. The presently observed increased blood pressure in men with long QT_c is in line with this reasoning. If QT_c reflects autonomic balance, this might explain the association between QT_c and nonfatal myocardial infarction incidence, because people with high sympathetic drive may be more prone to coronary atherosclerosis, or symptoms may occur earlier.[33] Furthermore, norepinephrine levels have been reported to increase with aging,[34] possibly because of reduced physical activity.[13] It could be speculated that such a change of autonomic balance contributes to the age-related prolongation of QT_c.

If our finding is confirmed, it may be of importance with regard to preventive strategies, because the balance between sympathetic and parasympathetic activity can be improved by physical activity[35] and cessation of smoking.[36]

In conclusion, QT_c prolongation predicts coronary heart disease and sudden death in apparently healthy men. Because QT interval length is easily determined, it may contribute to cardiovascular risk stratification. In addition, subjects with prolonged QT_c may especially benefit from preventive measures that affect autonomic balance.

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