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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

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Aims. To evaluate the prognostic value of the QT interval and QT interval dispersion in total and in cardiovascular mortality, as well as in cardiac morbidity, in a general population.

Methods and results. The QT interval was measured in all leads from a standard 12-lead ECG in a random sample of 1658 women and 1797 men aged 30–60 years. QT interval dispersion was calculated from the maximal difference between QT intervals in any two leads. All cause mortality over 13 years, and cardiovascular mortality as well as cardiac morbidity over 11 years, were the main outcome parameters. Subjects with a prolonged QT interval (430 ms or more) or prolonged QT interval dispersion (80 ms or more) were at higher risk of cardiovascular death and cardiac morbidity than subjects whose QT interval was less than 360 ms, or whose QT interval dispersion was less than 30 ms. Cardiovascular death relative risk ratios, adjusted for age, gender, myocardial infarct, angina pectoris, diabetes mellitus, arterial hypertension, smoking habits, serum cholesterol level, and heart rate were 2·9 for the QT interval (95% confidence interval 1·1–7·8) and 4·4 for QT interval dispersion (95% confidence interval 1·0–19·1). Fatal and non-fatal cardiac morbidity relative risk ratios were similar, at 2·7 (95% confidence interval 1·4–5·5) for the QT interval and 2·2 (95% confidence interval 1·1–4·0) for QT interval dispersion.

Conclusion. Prolongation of the QT interval and QT interval dispersion independently affected the prognosis of cardiovascular mortality and cardiac fatal and non-fatal morbidity in a general population over 11 years.
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Key Words: QT interval dispersion, QT interval, epidemiology, morbidity, mortality.

See page 1279 for the Editorial comment on this article

Introduction

A number of studies have indicated that there is a relationship between mortality, a prolonged QT (or heart rate corrected QT (QTc)) interval, and increased QT interval (or QTc) dispersion, in coronary heart disease. Two epidemiological studies[1–3] have investigated the link between prolonged QTc and mortality in a general population with conflicting results, and only one study has evaluated the prognostic value of QTc in cardiac morbidity[3]. The association between increased QT interval dispersion, or QTc dispersion, and cardiovascular mortality or morbidity in a general population has not been evaluated. As prolongation of the QT interval or QTc may reflect ischaemic heart diseases[4], increased QT interval dispersion — which may mirror discrepant repolarization characteristics of different areas of the heart[5,6] — could indicate ischaemic disorders of the heart. Measurement of QT interval dispersion in this manner might enhance a non-invasive prognostic index. The aim of this study was to examine the relationship between mortality and morbidity, and the QT interval, QTc, QT interval dispersion, and QTc dispersion in a general population.

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Methods

Study population

In 1982–1984 a random sample of 4807 individuals from the catchment area of Glostrup hospital (Copenhagen, Denmark) (individuals aged 30, 40, 50 or 60 years with equal gender distribution) were invited to participate in a population health survey study. Three thousand seven hundred and eighty one subjects (about 80%) agreed to participate[7]. The cohort consisted of approximately 450 subjects in each age and gender stratum. A detailed medical history was obtained by a structured interview, medical staff performed a physical examination, and a standard 12-lead electrocardiogram (ECG) was recorded. From our retrospective analysis, 28 subjects were excluded because of bundle branch block and 10 because of atrial fibrillation (only subjects in sinus rhythm were included). Seventy-eight subjects were not studied because of missing ECGs or their ECGs were not technically measurable. To avoid any confounding effect due to a reduction in the number of leads in which the QT interval was measurable, ECGs with less than nine measurable leads (n = 210, 5% of all) were not included in the analysis. This resulted in a cohort of 1658 women and 1797 men.

Electrocardiographic measurements

The ECGs were obtained at a paper speed of $25\ mm\ .\ s^{-1}$, a gain of 10 mV and a paper format of 3×4. The interval measurements were obtained by two observers using a digitizing tablet (Cherry, Mk III Graphic tablet, resolution 0·1 mm) connected to a personal computer. The observers were blinded in respect of baseline information and survival data. The RR interval, the QJ interval, the QT interval and, in the presence of a U-wave, the QU interval were obtained from one complex in all measurable leads. The end of the T wave was defined as the point of return to the iso-electric line. In the presence of a U-wave, the end of the T-wave was defined as the point of the TU nadir. In case of a flat T wave or a TU merge without nadir, the end of the T wave could not be determined and the lead was excluded from measurements. The QT was adjusted for heart rate according to Bazett's formula[8]. The mean RR interval (the RR interval), mean QT interval (the QT interval), and the mean QTc (QTc) were calculated from all measurable leads in each ECG. QT interval dispersion and QTc dispersion were defined as the maximum difference between the QT interval and QTc, respectively, in any two leads. For the current study, the ECGs were retrospectively evaluated. QTc and QTc dispersion are given in $ms^{1/2}$ and QT interval and QT interval dispersion are given in ms.

Reproducibility

Because of the known difficulties concerning definition of the end of the T wave, reproducibility was assessed twice by the same observer (inter observer reproducibility), as well as by the two observers (intra observer reproducibility). In addition, ECGs found to have high (above 100 ms) and low (beneath 30 ms) QT interval dispersion were measured twice by the same observer.

End points

Information on all-cause mortality until December 1995 (follow up 13 years) was obtained from the Danish Central Personal Register where all deaths in the country are registered within 2 weeks. Morbidity data and information of causes of death until December 1993 (11 years of follow-up) were obtained from the Danish Board of Health and the Danish Institute for Clinical Epidemiology (DIKE). Coding of causes of death or hospitalization was performed according to the 8th International Classification of Disease.

Cardiovascular mortality was defined as ICD-5 codes 390.00–449.00 and cancer mortality as ICD codes 140.00–240.00. Non-fatal or fatal cardiac morbidity was defined as first hospitalization or death from one of the following (later called a cardiac event):

Atherosclerotic cardiac disease (ICD codes 410.00–414.99); symptomatic heart disease (ICD codes 427.00–429.99); cardiomyopathy (defined as ICD codes 425.99).

Data analysis

In addition to the total population, the following two subgroups were considered: A 'normal' subgroup consisting of 2269 participants without any known circulatory or other disease, not on any medical therapy, with blood pressure below 160/95 and with a normal ECG according to the Minnesota code[9]. A 'Cardiovascular' subgroup consisting of 821 subjects who, at the time of investigation, had had a myocardial infarction and/or angina pectoris, and/or claudicatio intermitens, and/or arterial hypertension, and/or diabetes mellitus and/or stroke and/or were in current medical therapy with nitrates and/or digoxin.

Differences between the two groups in discrete and continuous data were tested by the chi-square test and the Wilcoxon signed rank sum test, or by multiple regression methods. The data are presented as mean ± SD unless otherwise stated. The relative risk of an, 'all-causes' death or cardiovascular death was determined as a hazard ratio using a Cox proportional hazard regression model. The exposure variables in this study were the QT interval, QTc, QT interval dispersion and QTc dispersion. These variables were included in the separate models, together with possible confounder variables, known to be associated with mortality, and to prolonged QT interval/QT interval dispersion. These confounders were: age, gender, heart rate, arterial hypertension, previous myocardial infarction, angina

Table 1 Demographic data and ECG measurements for the total population and in the two subgroups.

	Total population (3455)	Normal (2269)	Cardiovascular (821)	*P*
Deaths (n)	331	140	150	
Age (years)	44 ± 11	43 ± 11	48 ± 11	*
Male gender (%)	52	56	53	ns
Angina pectoris (n(%))	53 (2)	—	53 (7)	
Previous MI (n(%))	47 (1)	—	47 (6)	
Hypertension (n(%))	634 (18)	—	634 (74)	
Diabetes mellitus (n(%))	70 (2)	—	70 (8)	
Current smokers (%)	59	61	55	*
Se-cholesterol (mmol . l^{-1})	6·0 ± 1·2	5·9 ± 1·2	6·36 ± 1·4	*
QTc	405 ± 25	400 ± 23	413 ± 26	*[1]
QT interval	392 ± 29	392 ± 27	393 ± 32	ns[1]
QTc dispersion	60 ± 25	58 ± 23	61 ± 28	ns[1]
QT interval dispersion	50 ± 22	49 ± 20	53 ± 26	ns[1]
Heart rate	65 ± 11	63 ± 10	67 ± 12	*[1]

Hypertension = arterial hypertension; MI = myocardial infarction; *Indicates *P*-value below 5% comparing the cardiovascular subgroup with the normal subgroup. ns = not significant. [1]The *P*-values are calculated from multiple regression analyses to correct for different age and gender distribution in the different subgroups.

pectoris and diabetes mellitus. Other explanatory variables known to be risk factors for cardiac mortality and morbidity were also included: smoking, and serum cholesterol. The exposure variable was included into the regression models as a discrete variable, where the lowest level of the value was used as the reference value. The cut-off points separated the lowest and the highest 10% of the values approximately. Proportional hazard assumptions were verified by inspection of log-log survival curves. All data analyses were performed on a personal computer with SAS software version 6.12.

Results

Demographic data

Demographic data and the measured ECG parameters in the total population and in the two selected subgroups are shown in Table 1. Of the measured ECG parameters, QTc and heart rate were significantly higher in the 'cardiovascular' subgroup compared to the normal subgroup ($P<0·05$). Figure 1 shows the distribution of causes of death in the three groups. Figure 2 shows the distribution of reasons for hospitalization for those subjects who survived to be hospitalized for a cardiac reason (n = 218, 20 out of the 238 with a cardiac event died before hospitalization). From the figure it is seen that the main reason for hospitalization was acute myocardial infarction.

All-cause mortality, univariate analysis

Figure 3 shows all-causes mortality per 1000 person years in relation to increasing values of QTc and QT interval dispersion, in the total population, in the normal subgroup and in the cardiovascular subgroup. The figure shows that mortality increases alongside

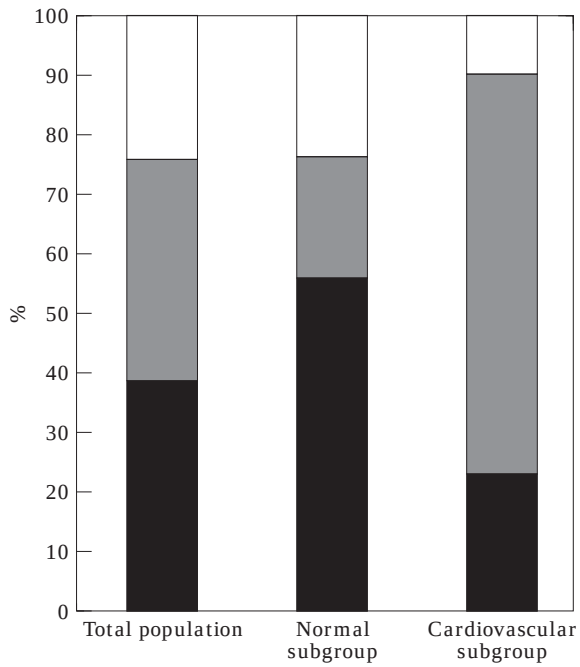

Figure 1 **The distribution of causes of death in the three subgroups. Comparison of the normal and cardiovascular subgroups, shows there were significantly more cardiovascular deaths in the cardiovascular subgroup ($P<0·01$) and significantly more cancer deaths in the normal subgroup ($P<0·01$). ■ = death caused by cancer, see definition in text; ▨ = death caused by cardiovascular disease, see definition in text; □ = all other causes of death.**

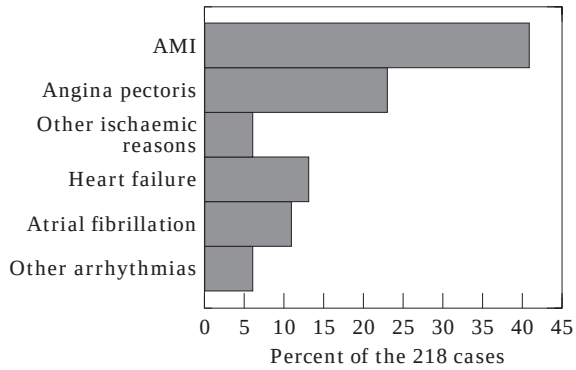

Figure 2 **The distribution of reasons for hospitalizing the 218 subjects who survived to be hospitalized for a cardiac reason. AMI = acute myocardial infarction.**

increasing values of QTc and QT interval dispersion in the total population and in the cardiovascular subgroup. In normal subjects mortality from increasing values of QTc and QT interval dispersion is weak or absent. The figure reveals no clear cut-off point after which mortality increases dramatically.

All-cause mortality and cardiovascular mortality, multivariate analysis

Proportional hazard regression models (Cox) were studied to evaluate whether the QT interval, QTc, QT interval dispersion, or QTc dispersion were independently indicative of mortality. Table 2 shows the result for the total population. The table shows the risk ratio, 95% confidence intervals and *P* values for the different categories of the explanatory variables, which were studied in separate models. The table shows that having a QT interval above 430 ms compared with a QT interval in the range 300–360 ms revealed a relative risk of all-cause death of nearly 1·9, independent of age, gender, previous myocardial infarction, angina pectoris,

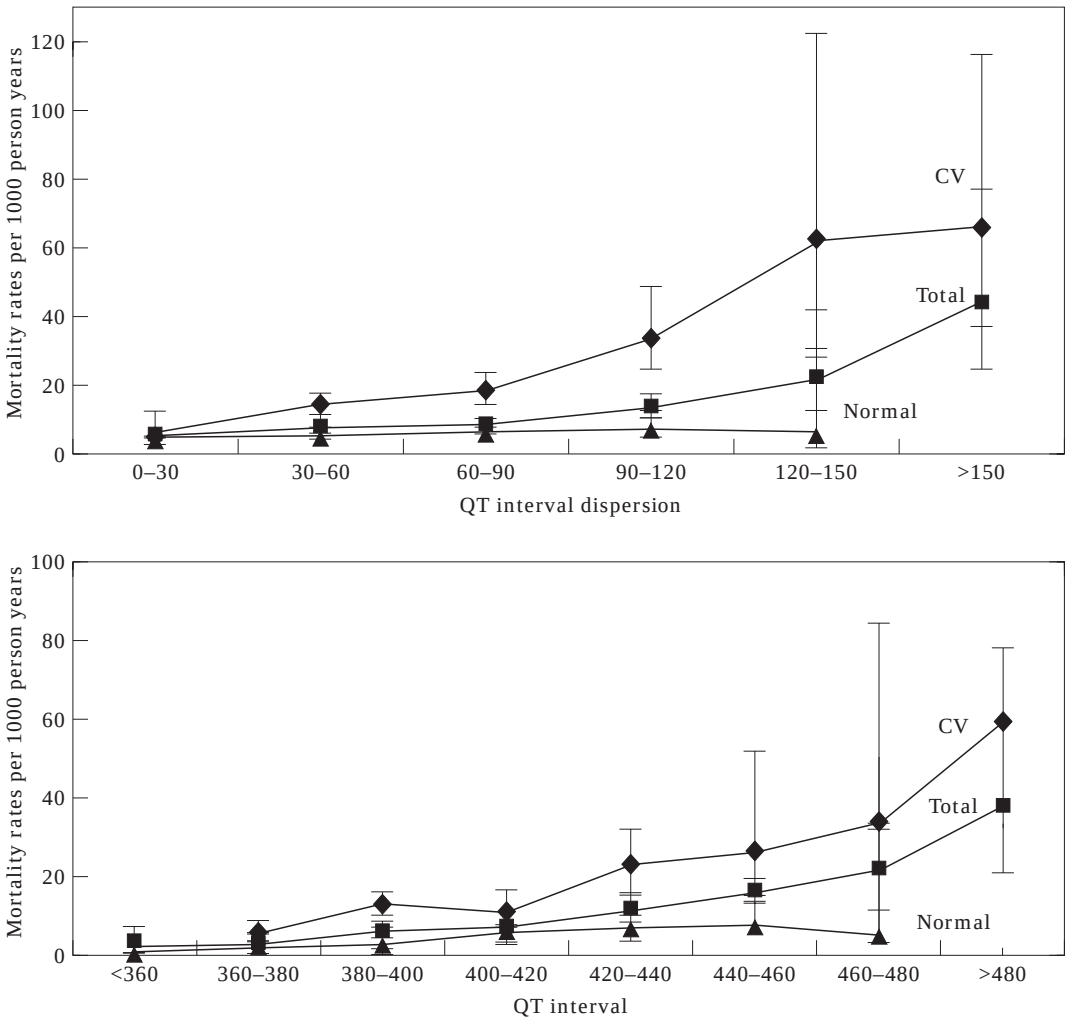

Figure 3 **The mortality rates per 1000 person years for increasing values of The error bars indicates the 90% confidence interval.CV = cardiovascular subgroup.**

Table 2 QT interval, QTc, QT interval dispersion and QTc dispersion in total and cardiovascular mortality in the total population

	Total mortality (n = 3455, events = 331)			Cardiovascular mortality (n = 3455, events = 100)	
	n	RR[1]	95% CI	RR[1]	95% CI
QT interval: 300–360	383	1·0		1·0	
QT interval: 360–430	2716	1·41	0·95–2·10	1·45	0·69–3·02
QT interval: ≥430	356	1·87	1·06–3·27	2·93	1·09–7·84
QT dispersion: 0–30	325	1·0		1·0	
QT dispersion: 30–80	2731	1·65	0·96–2·51	3·47	0·88–14·22
QT dispersion: ≥80	399	1·80	1·05–3·07	4·43	1·03–19·06
QTc: 310–380	427	1·0		1·0	
QTc: 380–440	2715	1·60	0·97–2·65	1·79	0·64–5·03
QTc: ≥440	313	1·89	1·04–3·37	3·31	1·04–9·91
QTc dispersion: 0–40	273	1·0		1·0	
QTc dispersion: 40–90	2856	1·36	0·91–2·01	3·09	0·97–9·88
QTc dispersion: ≥90	326	1·45	0·91–2·27	3·87	1·15–13·03

RR = risk ratio; 95%CI = 95% confidence interval; QT dispersion = QT interval dispersion. [1]All risk ratios are adjusted for age, gender, myocardial infarction, angina pectoris, arterial hypertension, diabetes mellitus, serum cholesterol, smoking habits and heart rate by including these variables in the models.

arterial hypertension, diabetes mellitus, current smoking, serum cholesterol and heart rate. Similarly, QTc as an indicator for total mortality has a relative risk of nearly 1·9, when comparing levels of QTc above 440 $ms^{1/2}$ are compared with levels in the range 310–380 $ms^{1/2}$. QT interval dispersion indicated independent prognostic importance as regards total mortality (risk ratio 1·8, $P<0·05$) but this was not the case for QTc dispersion (risk ratio 1·5, $P=0·1$). Table 2 shows a similar analysis for cardiovascular mortality in the total population. All the exposure variables had independent prognostic value, but the 95% confidence intervals shows high uncertainty in the estimates of the risk ratios.

Table 3 carries the same analysis for the subgroup of apparently healthy individuals. Here none of the exposure variables had independent prognostic value for total mortality. Because only 26 of the 140 deaths in this subgroup were of cardiovascular origin the data were not analysed for cardiovascular mortality. Table 4 shows the same multivariate analysis in the cardiovascular subgroup. QTc and the QT interval, as well as QTc dispersion and QT interval dispersion, all independently indicated total mortality, QT interval and QTc were independently indicative of cardiovascular mortality. QTc, the QT interval, QTc dispersion and QT interval dispersion carried no independent prognostic value for cancer mortality in either the total population or in the two selected subgroups.

Fatal and non-fatal cardiac morbidity, multivariate analysis

Table 5 shows the risk ratios and 95% confidence intervals of the QT interval, QTc, QT interval dispersion and QTc dispersion for the development of a fatal and a non-fatal cardiac event. The prognostic value of the QT interval, QTc, QT interval dispersion and QTc dispersion were all independently of value in demonstrating an 11-year cardiac fatality and non-fatal morbidity.

In order to examine whether the QT interval and QT interval dispersion were still prognostically of value if only non-fatal cardiac morbidity was analysed for the total population, we performed the same analysis while excluding the 75 subjects who developed a fatal cardiac

Table 3 The values of the QT interval, QTc, QT interval dispersion and QTc dispersion for total mortality in the normal subgroup

	Total mortality (n = 2269, events = 140)		
	n	RR[1]	95% CI
QT interval: 300–360	227	1·0	
QT interval: 360–430	1828	1·82	0·96–3·46
QT interval: ≥430	214	1·51	0·54–4·28
QT dispersion: 0–30	214	1·0	
QT dispersion: 30–80	1808	1·15	0·60–2·20
QT dispersion: ≥80	247	0·96	0·43–2·15
QTc: 310–380	350	1·0	
QTc: 380–440	1803	1·3	0·70–2·42
QTc: ≥440	116	1·17	0·43–2·87
QTc dispersion:0–40	303	1·0	
QTc dispersion: 40–90	1696	1·34	0·75–2·40
QTc dispersion: ≥90	270	0·90	0·42–1·92

Abbreviations as in Table 2; [1]All risk ratios are adjusted for age, gender, serum cholesterol, smoking habits and heart rate by including these variables in the models.

Table 4 The values of QT interval, QTc, QT interval dispersion and QTc dispersion for total and cardiovascular mortality in the cardiovascular subgroup

	Total mortality (n=821, events=155)			Cardiovascular mortality (n=821, events=73)	
	n	RR[1]	95% CI	RR[1]	95% CI
QT interval: 300–360	102	1·0		1·0	
QT interval: 360–430	634	1·44	0·80–2·60	1·52	0·63–3·67
QT interval: ≥430	85	2·18	1·00–4·79	3·15	1·10–9·83
QT dispersion: 0–30	74	1·0		1·0	
QT dispersion: 30–80	666	2·40	0·97–5·92	2·53	0·61–10·50
QT dispersion: ≥80	81	3·42	1·31–8·85	3·51	0·80–15·52
QTc: 310–380	74	1·0		1·0	
QTc: 380–440	633	2·84	0·98–9·01	4·08	0·55–30·17
QTc: ≥440	139	3·83	1·14–12·87	8·09	1·04–62·82
QTc dispersion: 0–40	102	1·0		1·0	
QTc dispersion: 40–90	615	1·47	0·76–2·82	2·19	0·69–7·06
QTc dispersion: ≥90	104	2·05	1·01–4·19	2·89	0·84–10·00

Abbreviations as in Table 2; [1]All risk ratios are adjusted for age, gender, myocardial infarction, angina pectoris, arterial hypertension, diabetes mellitus, serum cholesterol, smoking habits and heart rate by including these variables in the models.

Table 5 The value of the QT interval, QT interval dispersion, QTc and QTc dispersion for development of cardiac fatal- and non-fatal morbidity in the total population

	Fatal and non-fatal cardiac events (n=3455, events=238)			Non-fatal cardiac events (n=3455, events=172)	
	n	Risk ratio[1]	95% CI	Risk ratio[1]	95% CI
QT interval: 300–360	383	1·0		1·0	
QT interval: 360–430	2716	1·95	1·16–3·30	2·05	1·01–3·89
QT interval: ≥430	356	2·74	1·36–5·53	2·88	1·24–6·67
QT dispersion: 0–30	317	1·0		1·0	
QT dispersion: 30–80	2739	1·58	0·86–2·93	1·30	0·68–2·49
QT dispersion: ≥80	399	2·18	1·12–4·03	1·75	0·85–3·59
QTc: 310–380	427	1·0		1·0	
QTc:380–440	2715	1·24	0·73–2·10	1·25	0·68–2·30
QTc: ≥440	313	1·87	1·00–3·50	1·91	0·92–3·96
QTc dispersion: 0–40	463	1·0		1·0	
QTc dispersion: 40–90	2580	1·76	1·02–3·04	1·72	0·92–3·19
QTc dispersion: ≥90	412	2·28	1·25–4·18	2·11	1·05–4·23

Abbreviations as in Table 2; [1]All risk ratios are adjusted for age, gender, arterial hypertension, myocardial infarction, angina pectoris, diabetes mellitus, serum cholesterol, smoking habits and heart rate.

event. In Table 5 it is shown that the tendency in the results was the same. Table 6 shows that there was no independent prognostic information on either 'fatal or non-fatal cardiac events' or 'non-fatal cardiac events' in the normal subgroup.

Influence of heart rate

Due to the known weakness of Bazett's formula, we have analysed the relationship between heart rate and the QT interval both before (QT interval) and after (QTc) correction for heart rate, and we have done the same for QTc dispersion and QT interval dispersion. Figure 4 shows the relationship between the QT interval, QTc, QT interval dispersion, QTc dispersion, and heart rate in the normal population. There was a significant negative correlation between the QT interval and heart rate (slope of regression line $-0{\cdot}25$ ms . beats . $\min^{-1}$, $P<0{\cdot}0001$), and a significant positive correlation between QTc and heart rate (slope of regression line $0{\cdot}21$ $ms^{1/2}$. beats . $\min^{-1}$, $P<0{\cdot}0001$). There were no

Table 6 The value of QT interval, QT interval dispersion, QTc and QTc dispersion for development of cardiac fatal- and non-fatal morbidity in the normal population

	Fatal and non-fatal cardiac events			Non-fatal cardiac events (n=2269, events=56)	
	n	Risk ratio[1]	95% CI	Risk ratio[1]	95% CI
QT interval: 300–360	227	1·0		1·0	
QT interval: 360–430	1828	2·02	0·73–5·58	2·19	0·64–7·50
QT interval: ≥430	214	3·55	0·84–13·33	4·06	0·81–20·39
QT dispersion: 0–30	214	1·0		1·0	
QT dispersion: 30–80	1808	2·41	0·58–3·57	1·88	0·45–7·82
QT dispersion: ≥80	247	2·97	0·66–4·67	2·79	0·61–12·72
QTc: 310–380	350	1·0		1·0	
QTc: 380–440	1803	1·60	0·71–9·91	2·30	0·81–6·55
QTc: ≥440	116	1·10	0·26–13·26	2·09	0·42–10·33
QTc dispersion: 0–40	303	1·0		1·0	
QTc dispersion: 40–90	1696	2·48	0·77–7·96	1·94	0·6–6·32
QTc dispersion: ≥90	270	3·56	1·02–12·39	3·14	0·88–11·20

Abbreviations as in Table 2; [1]All risk ratios are adjusted for age, gender, serum cholesterol, smoking habits and heart rate.

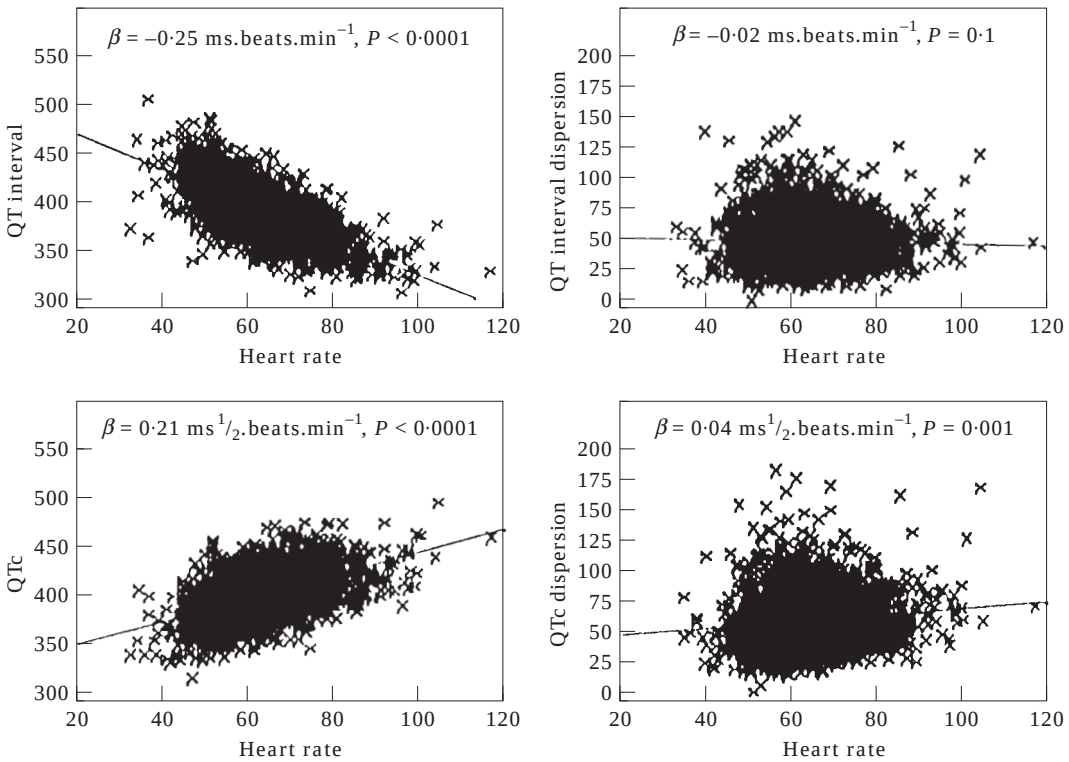

Figure 4 **The relationship between the QT interval, QTc, QT interval dispersion, QTc dispersion and heart rate in the normal subgroup. *β* is the slope of the linear regression line. The *P*-value indicates whether the slope of the regression line differs significantly from zero and is calculated from an univariate linear regression model.**

correlation between QT interval dispersion and heart rate (slope of regression line $-0{\cdot}02$ ms . beats . min^{-1}, $P=0{\cdot}1$) but there was a significant correlation between QTc dispersion and heart rate (slope of regression line 0·04 ms$^{1/2}$/beats . min^{-1}2 $P<0{\cdot}0001$).

Reproducibility

The inter-observer and the intra-observer reproducibility, expressed as relative errors, are shown in Table 7. There were no systematic differences in the repeated

Table 7 Inter observer and Intra observer reproducibility

Inter-observer n = 100	Observer 1	Observer 2	RD
QT interval	404 ± 31	405 ± 32	2%
QT interval dispersion	59 ± 26	64 ± 31	27%
Heart rate	66 ± 12	65 ± 11	2%

Inter observer reproducibility: The two observers measured QT interval, QT interval dispersion and heart rate in the same 100 ECGs and the table shows the mean value ± SD for each observer and the calculated relative difference (RD).

Intra-observer n = 80	Observer 1 (First measurement)	Observer 1 (Second measurement)	RD
QT interval	405 ± 30	395 ± 30	2%
QT interval dispersion	51 ± 19	49 ± 19	25%
Heart rate	64 ± 11	65 ± 12	2%

Intra-observer reproducibility: the same observer measured the same 80 ECGs twice and the table shows the mean value ± SD for the two different measurements and the calculated relative difference (RD).

measurements by the two observers. The results of re-analysing the 60 ECGs with high (above 100 ms) and low (under 30 ms) QT interval dispersion are shown in Fig. 5. The figure shows that (a) the inter-measurement error was the same for high and low QT interval dispersion values, and (b) that QT interval dispersion measured as above 100 ms can be measured as low as 40 ms by the next measurement and that QT interval dispersion measured as under 30 ms at the first measurement can be as high as 80 ms at the next measurement.

Discussion

There were two main findings in this study. (1) The QT interval, QTc, QT interval dispersion and QTc dispersion carried independent prognostic information as regards cardiovascular mortality in the general population. This information could also be found in subjects with known cardiovascular disease at the time of ECG recording, whereas it was absent in a subgroup of apparently healthy subjects. (2) Information about fatal cardiac and non-fatal morbidity in the general population was also evident from the QT interval and QT interval dispersion, but again only in subjects with pre-existing diseases; these findings were not in evidence in the subgroup of apparently healthy subjects.

Many studies have shown that subjects with ischaemic heart disease have increased levels of QT interval and QT interval dispersion compared to healthy controls[10,11]. Sporton *et al.*[12] in a recent study showed that myocardial ischaemia induced by incremental atrial

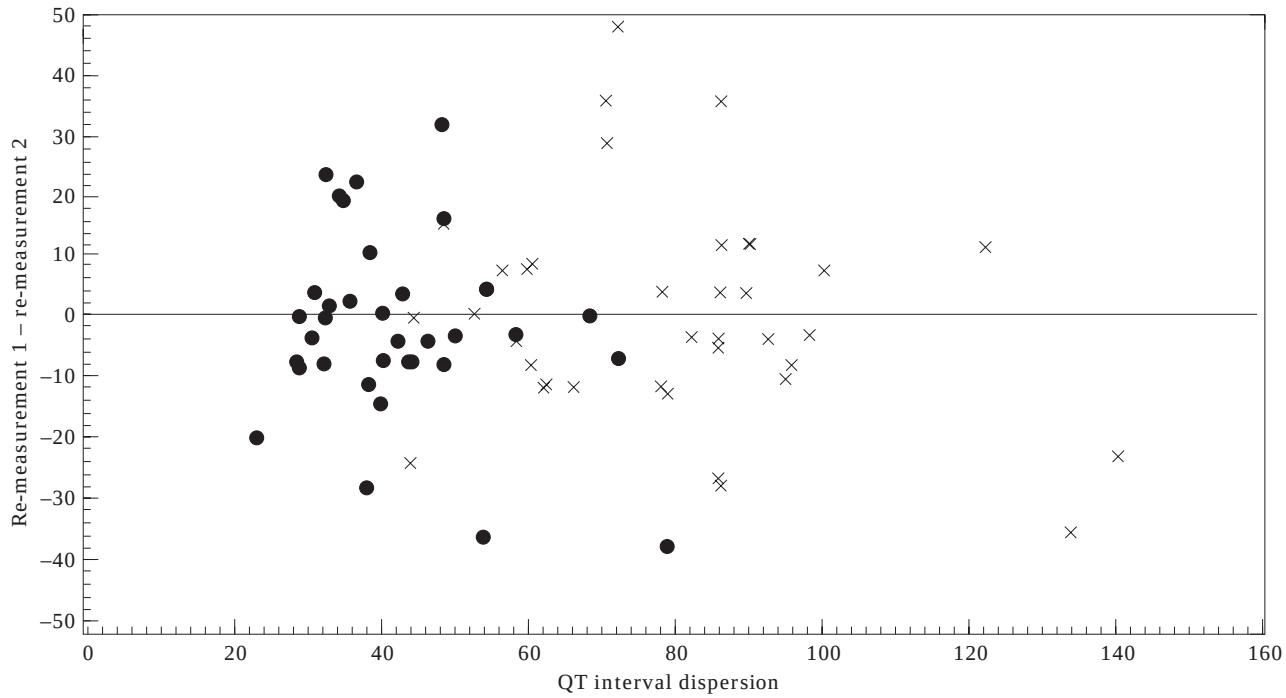

Figure 5 **The reproducibility of high and low levels of QT interval dispersion. ECGs with an initial measurement of high (QT interval dispersion above 100 ms) and low (QT interval dispersion below 40 ms), respectively, were re-measured twice by the same observer. The differences between these two re-measurements (y-axis) are shown by the means of the two re-measurements (x-axis). ● = Indicates ECGs with an initial QT interval value of 40 ms or below; ✖ = Indicates ECGs with an initial QT interval value of 100 ms or above.**

pacing provided a marked increase in QT interval dispersion in subjects with coronary artery disease, but normal values of QT interval dispersion at rest. Imbalances in the autonomic nervous system are associated with increased QT interval and QT interval dispersion[13,14]. Increases in sympathetic drive are believed to be associated with increases in the risk of developing of atherosclerosis[15]. So it is very likely that the QT interval and QT interval dispersion could act as markers for clinical or sub-clinical ischaemic heart disease and thereby posses prognostic information on future fatal as well as non-fatal cardiac morbidity.

Total and cardiovascular mortality

The prognostic importance of QTc in total and cardiovascular mortality confirms previous findings from two studies from The Netherlands[2,3]. During a 15-year follow up, Schouten *et al*.[2] found QTc to be an independent risk factor for total as well as cardiovascular mortality. However, data from the Framingham Heart Study failed to demonstrate the prognostic value of QTc in a 30-year follow-up[1]. The variations in the lengths of follow-up periods may explain the different outcomes. It is possible that QTc prolongation is an acquired indicator for heart disease, which is exhausted as a prognostic marker after some time. Unlike our results, Schouten *et al*.[2] found QTc to be predictive of death in a subgroup of individuals with no signs of coronary heart disease. The main difference between the results may be because we included heart rate in the multivariate survival models. If we omitted heart rate from the models QTc was found to be an independent predictor of all cause mortality in our normal subgroup.

This study is the first to report the prognostic value for total and cardiovascular mortality of QT interval dispersion in a general population. We found that prognostic information from QT interval dispersion was present among subjects with already known cardiovascular disease. The prognostic information was related to cardiovascular mortality as no ECG variables had prognostic value for cancer mortality, which is the other major cause of death.

Fatal and non-fatal cardiac morbidity

This is the first study to present the prognostic value of QT interval dispersion in cardiac morbidity. One previous study has dealt with the prognostic value of the QT interval and QTc in cardiac morbidity: In the Zupten study, Dekker *et al*.[3] had results very similar to ours. They examined QTc in 40–60 year old males and found a relative risk for a fatal or non-fatal myocardial infarction of 1·9 over 15 years of follow up for males, with a QTc above 420 $ms^{1/2}$, compared to males with a QTc below 385 $ms^{1/2}$.

Influence of heart rate

From previous studies it is known that heart rate is an independent predictor of death[16]. Heart rate is strongly related to the QT interval. The QT interval decreases as heart rate increases, and therefore heart rate is an important confounder to be included in the models which analyse the indeoendent prognostic value of the QT interval. If Bazett's formula for calculating the heart rate corrected QT interval (QTc) was ideal, we would not expect to find a relationship between QTc and heart rate. However, as shown in Fig. 4, QTc varied significantly with heart rate, which indicates that Bazett's formula was not ideal to apply on our data. The inappropriateness of Bazett's formula has also been demonstrated in other epidemiological studies[17]. Therefore, heart rate must be included in the multivariate models, no matter whether it is the importance of the QT interval, or the importance of QTc, which is going to be studied.

It is not known whether QT interval dispersion should be corrected for heart rate. Animal studies, as well as studies in humans, have shown that QT interval dispersion decreases as heart rate increases[12,18–20]. In this study we found no relationship between QT interval dispersion and resting heart rate. Nevertheless we think it is important to include the heart rate in multivariate models where QT interval dispersion or QTc dispersion are analysed, because of the importance by heart rate itself. Perhaps it is preferable to express 'dispersion' as QT interval dispersion rather than as heart rate corrected QT interval dispersion (QTc dispersion) to avoid the influence of Bazett's formula[21].

Limitations of the study

The study was retrospective, but since necessary data were available on nearly every subject and the overall study was, in general, designed to analyse cardiovascular risk we consider the risk of bias caused by the retrospective design small. End-points in the study were derived from the moderate amounts of information available on death certificates and hospital discharge diagnoses. By such classification cardiac causes of death are often over-estimated[22] and cardiovascular diagnoses may not always be accurate[23]. Furthermore, only admission to hospital was included in the analysis of cardiac morbidity, and subjects who met the end-point morbidity criteria were probably those with the most severe morbidity.

Inaccurate determination of the end of the T wave is a well-known problem[24,25], which is well known to cause low levels of reproducibility in QT interval dispersion. In Fig. 5, which shows the distribution of re-measured values of QT interval dispersion, there was a noticeable tendency of 'regression towards the mean', that is 'extreme' values of QT interval dispersion tended towards less extreme values when re-measured. Therefore it is likely that the importance of QT interval

dispersion was underestimated in this study rather than indicating importance with no relation to reality.

The implication of this study is that the QT interval, QTc or the QT interval dispersion do not contribute important prognostic information about mortality and morbidity in healthy subjects. Such measurements should be restricted to subgroups with pre-existing disorders related to ischaemic heart disease. Among these subjects, QT interval as well as QT interval dispersion might add important prognostic information on future cardiovascular mortality and cardiac morbidity. Because of the many unsolved problems as regards standardization of QT interval measurement and a definition of QT interval dispersion, these values are still not of clinical use. Further studies are needed to address the link between ischaemic heart disease, mortality and QT interval/QT interval dispersion and to solve the methodological problems.

References

[1] Goldberg RJ, Bengtson J, Chen Z, Anderson KM, Locati E, Levy D. Duration of the QT interval and total and cardiovascular mortality in healthy persons. (The Framingham Study Experience). Am J Cardiol 1991; 67: 55–8.

[2] Schouten EG, Dekker JM, Kok FJ, Vandenbroucke JP, Pool J. QT Interval prolongation predicts cardiovascular mortality in an apparently healthy population. Circulation 1991; 84: 1516–23.

[3] Dekker JM, Schouten EG, Klootwijk P, Pool J, Kromhout D. Association between QT interval and coronary heart disease in middle-aged and elderly men. Circulation 1994; 90: 779–85.

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

[5] Zabel M, Portnoy S, Franz M. Electrocardiographic indexes of dispersion of ventricular repolarization. An isolated heart validation study. Am J Cardiol 1995; 25: 746–52.

[6] Higham PD, Hilton CJ, Aitcheson JD, Furniss SS, Bourke JP, Campbell R. Does QT dispersion reflect dispersion of ventricular recovery? Circulation 1992; 86 (Suppl. I): 392.

[7] Kirchhoff M, Torp-Pedersen C, Hougaard K *et al*. Casual blood pressure in a general Danish Population. Relation to age, sex, weight, height, diabetes, serum lipids and consumption of coffee, tobacco and alcohol. J Clin Epidemiol 1994; 5: 469–74.

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

[9] Prineas RJ, Crow RA, Blackburn H. The Minnesota Code — manual of electrocardiographic findings. Bristol: John Wright, 1982.

[10] Perkiomaki JS, Koistinen JM, Yli-mäyry S, Huikuri HV. Dispersion of the QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. J Am Coll Cardiol 1995; 26: 174–9.

[11] Doi Y, Takada K, Mihara H *et al*. QT dispersion in acute myocardial infarction with special reference to left ventriculographic findings. Jpn Heart J 1995; 36: 573–81.

[12] Sporton SC, Taggart P, Sutton PM, Walker JM, Hardman SM. Acute ischaemia: a dynamic influence on QT dispersion. Lancet 1997; 349: 306–9.

[13] Abildskov JA. Neural mechanisms involved in the regulation of ventricular repolarization. Eur Heart J 1985; 6 (Suppl D): 31–9.

[14] Surawicz B, Surawicz B. Electrophysiologic basis of ECG and cardiac arrhythmias. Malvern: William and Wilkins, 1995.

[15] Yeung A, Vekshtein V, Krantz D *et al*. The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. N Engl J Med 1991; 325: 1551–6.

[16] Kannel WB, Kannel C, Paffenbarger RS, Cupples A. Heart rate and cardiovascular mortality: The Framingham Study. Am Heart J 1987; 113: 1489–94.

[17] Sagie A, Larson M, Goldberg RJ, Bengtson JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). Am J Cardiol 1992; 70: 797–801.

[18] Endresen K. Rate-dependent change in dispersion of repolarisation during ventricular pacing in man. Int J Cardiol 1989; 23: 199.

[19] Rosenbaum DS. Repolarization inhomogeneities in ventricular myocardium change dynamically with abrupt cycle length shortening. Circulation 1991; 84: 1333–45.

[20] Han J. Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate. Am Heart J 1966; 71: 481.

[21] Malik M, Camm AJ. Mystery of QTc interval dispersion. Am J Cardiol 1997; 79: 785–7.

[22] Asnæs S, Östergaard K. Dödsatestens pålidelighed. Ugeskrift for Læger 1980; 4: 265–6.

[23] Mosbech J, Jrgensen J, Madsen M, Rostgaard K, Thornberg K, Poulsen TD. Landspatientregisteret. Evaluering af datakvaliteten. Ugeskrift for Læger 1995; 157: 3741–5.

[24] Kautzner J, Yi G, Camm J, Malik M. Short- and long-term reproducibility of QT, QTc and QT dispersion measurement in healthy subjects. Pace 1994; 17 (Part I): 928–37.

[25] Elming H, Jun L, Torp-Pedersen C, Köber L, Malik M. Measurement of QT Interval Dispersion. Cardiac Electrophysiol Rev in press.