ESC European Society of Cardiology

Europace (2018) **20**, f99–f107
doi:10.1093/europace/eux286

Predictors of mortality in high-risk patients with QT prolongation in a community hospital

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Received 31 May 2017; editorial decision 12 August 2017; accepted 15 August 2017; online publish-ahead-of-print 3 October 2017

Aims To determine predictors of mortality in patients with corrected QT interval (QTc) ≥ 500 ms in a community hospital.

Methods and results In this retrospective observational study, we searched the electrocardiogram (ECG) database at Telemark Hospital Trust, Norway, from January 2004 to December 2014. Medication, electrolyte abnormalities, and medical conditions known to prolong the QT interval were recorded. From the medical records, we assessed whether the prolonged QTc was noted by the health care providers. We identified 1531 patients (age = 70 ± 15 years, 59% female) with an ECG with QTc ≥ 500 ms. All-cause mortality during 952 (range 0–4161) days of follow-up was 50% (n = 765/1531). Main predictors of mortality were aborted cardiac arrest [hazard ratio (HR) 2.40, 95% confidence interval (CI) 1.44–4.01; $P = 0.001$], cerebral stroke/head trauma (HR 2.28, 95% CI 1.70–3.05; $P < 0.001$), and heart failure (HR 1.74, 95% CI 1.43–2.12; $P < 0.001$). Females with prolonged QTc had better survival compared with males ($P = 0.006$). We constructed a risk-weighted QTc mortality score. QT prolongation was acknowledged in the medical records in 12% of the cases.

Conclusions QTc ≥ 500 ms was associated with high all-cause mortality with increased mortality in males compared with females. A new QTc mortality score was constructed to predict mortality. Only a minority of cases with prolonged QTc ≥ 500 ms were acknowledged in the medical records.

Keywords QTc mortality score • Gender • QT prolongation

Introduction

Congenital as well as acquired prolonged corrected QT interval (QTc) on electrocardiogram (ECG) is a well-known risk factor for torsades de pointes (TdP) ventricular arrhythmias, all-cause cardiovascular mortality, and sudden cardiac death.[1–3] A number of medical conditions and drugs have been shown to increase the risk for development of QT prolongation and the risk for death.[2–4] In the majority of cases, the QT prolongation is acquired.[5] In drug-induced QT prolongation, the QT interval will return to normal after discontinuation of the causative trigger.[6] On the other hand, if the heart undergoes electrical or structural remodelling due to various triggers, the QT interval may remain prolonged even after the removal of the trigger.

The values for abnormal QTc have been adjusted to avoid overdiagnosing and are now >470 ms for males and 480 ms for females.[7,8] QTc ≥ 500 ms is considered to be highly abnormal and is associated with increased risk for TdP.[4,7] The prevalence of QTc duration ≥ 500 ms varies depending on the investigated population,[9] ranging from 2% to 18%.[2,10] The majority of studies reporting on outcomes in patients with prolonged QTc have been conducted in tertiary care centres[10–12] and data from community hospitals are sparse.

Recently, a pro-QTc score was developed to find the risk factors and the causes of QTc prolongation.[2] The pro-QTc score was also associated with increased mortality. In the present study, we wanted to explore the most important predictors of mortality among the variables in the pro-QTc score and other variables in patients with

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What's new?

- In the majority of patients, the prolonged corrected QT interval (QTc) was not acknowledged in the medical records.
- Females with prolonged QTc had lower mortality compared to males with prolonged QTc.
- On the basis of the results of this study, we presented a new risk-weighted QTc mortality score to predict mortality.

QTc ≥ 500 ms in a community hospital. We aimed to determine the predictors of mortality in patients with QTc ≥ 500 ms and to construct a QTc mortality score. Furthermore, we wanted to explore possible gender differences in risk for mortality and the awareness of QT prolongation among health care providers.

Methods

Patient population

Telemark Hospital Trust is a general community hospital within the Norwegian national health system, serving approximately 170 000, mostly Caucasian, inhabitants. There are no competing clinics treating patients within this area.

Electrocardiogram system and selection of electrocardiograms

From January 2004, Telemark Hospital Trust has used digital 12-lead ECG analysed by the Marquette 12SL ECG analysis program. All digital ECGs, from both inpatients and outpatients, were stored in a central database (GE MUSE database).

The ECG database was searched with the following criteria: QTc (Bazett's formula) ≥ 500 ms, QRS width ≤ 120 ms, age ≥ 15 years, heart rate (b.p.m.) >30 and ≤100 (due to the limitations of Bazett's formula), no acute ST-elevation infarction, no atrial fibrillation, or atrial flutter. An experienced cardiologist manually reviewed all ECGs with QTc ≥ 500 ms. The cardiologist was blinded to clinical data and outcome but not to the automated ECG measurements.

The QT interval was measured manually in the lead showing the longest QT interval as the mean of three consecutive beats. We determined the end of the T wave by the tangent method, and U waves were not included if distinct from T waves.[2,13] The average heart rate over the whole recording was used. For patients who had more than one ECG meeting the specified criteria, the first ECG with QTc ≥ 500 ms was chosen for inclusion. The QTc interval was calculated according to the Bazett's formula. The manually measured QT interval was defined as being in agreement with the automatically measured QT interval if it was within ±10 ms.[2] If the automatically measured QTc value differed by more than 10 ms from the manually measured QTc, the manually measured QTc was used for further analyses.

We manually measured the QTc interval in a random sample of 200 ECGs with automatically measured QTc < 500 ms to estimate the proportion of false-negative ECGs.

Patients with corrected QT interval < 500 ms

We included patients with QTc < 500 ms for comparison. We searched the ECG database with the same criteria as for the patient group with QTc ≥ 500 ms, except for QTc < 500 ms. Patients with QTc < 500 ms were divided into a group with moderately prolonged QTc (males QTc 470–499 ms and females QTc 480–499 ms), and a group without prolonged QTc (males QTc < 470 ms and females QTc < 480 ms). For all participants with more than one ECG in the ECG database, the first ECG that met the search criteria was chosen.

Clinical data of the patients with corrected QT interval ≥ 500 ms

Clinical data were obtained from the patients' medical records at the time of the first ECG with QTc ≥ 500 ms. The medical records were reviewed manually, and a pro-QTc score as proposed by Haugaa *et al.*[2] was calculated for each patient. Each variable was given 1 point. QT-prolonging medications were given one point per medication.[2]

In addition, the main diagnosis for the contact and whether the QT prolongation was acknowledged or not by the clinician were recorded. Any note mentioning the QT prolongation or QT-reducing measures documented in the medical records were recorded as awareness. Date of death and cause of death were obtained from The Norwegian Cause of Death Registry.

Medication

QT-prolonging medication was defined as any medication present on the Arizona CredibleMeds QTdrugs lists, assessed by the end of March 2015.[14] We recorded the number of all QT-prolonging drugs taken by a patient within 7 days prior to the index ECG.

Laboratory data

Any serum electrolyte disturbances detected 48 h before or after the index ECG were recorded. Hypocalcaemia was defined as corrected calcium < 2.17 mmol/L or ionized calcium < 1.18 mmol/L. Hypomagnesaemia was defined as magnesium < 0.71 mmol/L and hypokalaemia as potassium < 3.6 mmol/L.

Statistical analysis

Continuous data were described by mean ± SD or median (range) and compared using the unpaired Student's *t*-test or independent-samples Mann–Whitney *U* test, as appropriate. Categorical data were described as proportions and analysed by the χ^2 test (SPSS version 23.0, IBM, Armonk, NY, USA). Cox regression analysis was performed to identify the predictors of mortality with a backward stepwise multivariate Cox regression analysis. Variables with fewer than 15 events were excluded from the multivariate analysis. We analysed the variance inflation factor to exclude multicollinearity and explored that the predictors satisfied the proportional hazard assumption. The Kaplan–Meier analyses were used to create survival curves with all-cause mortality as outcome. Follow-up was censored after 3 years. The Spearman's correlation coefficient was used for comparison between manually and automatically measured QTc values. A two-sided *P*-value < 0.05 was considered statistically significant.

Ethics

The study complies with the Declaration of Helsinki. The Norwegian Regional Committee for Medical and Health Research Ethics has approved the study, and informed consent has been obtained from the patients.

Results

Cohort and electrocardiogram analyses

The ECG database consisted of 225 117 ECGs from 63 286 unique patients collected during 11 years (from January 2004 to December

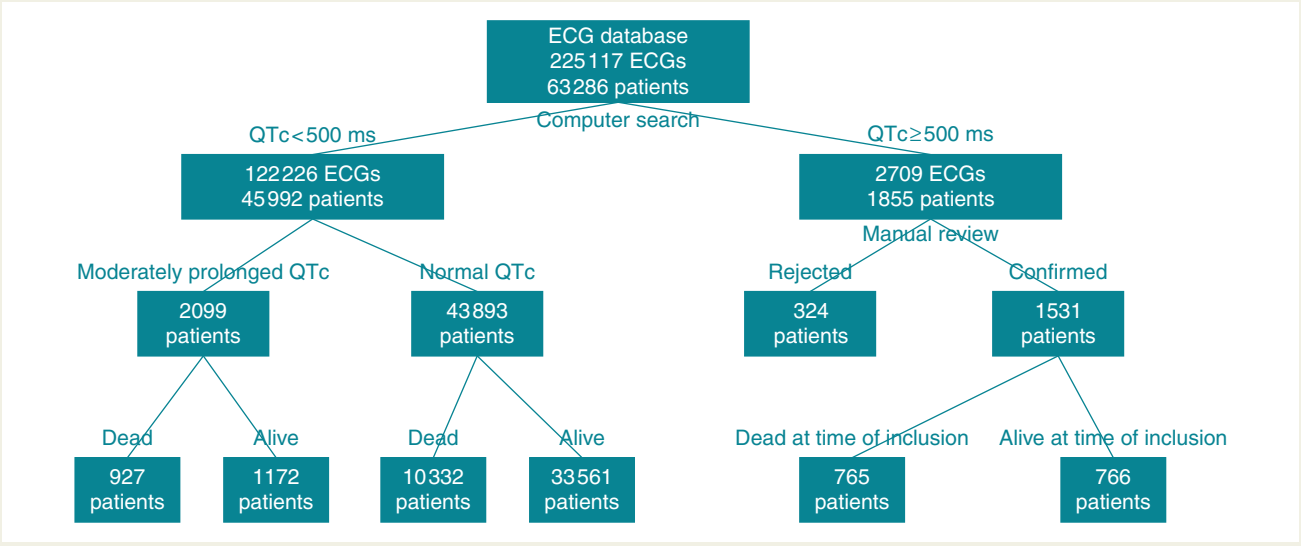

Figure 1 Flow chart illustrating the inclusion process. ECG, electrocardiogram; QTc, corrected QT interval.

2014). The database search for ECGs with QTc ≥ 500 ms generated 1855 unique patients (*Figure 1*). The manual examination of the ECGs with QTc ≥ 500 ms resulted in exclusion of 324 patients (17%). Excluded ECGs had computer-reading errors due to electromechanical noise ($n = 152$), inclusion of P wave or U wave in the calculation of the QT interval ($n = 47$), ventricular bigeminy ($n = 46$), atrial fibrillation ($n = 19$), short supraventricular arrhythmia ($n = 13$), and other reasons ($n = 47$). A total of 1531 patients (2.4% of the unique patients in the ECG database) were consequently included in the study. The correlation between manually and automatically measured QTc values was 0.97 ($P < 0.001$).

In a random sample of 200 ECGs with automatically measured QTc < 500 ms, we found no ECGs with manually measured QTc ≥ 500 ms. The manually measured median QTc was 430 ms (range 339–499) vs. automatically measured median QTc 434 ms (range 346–496). The correlation between the manually and the automatically measured QTc values was 0.91 ($P < 0.001$).

Characteristics in patients with corrected QT interval ≥ 500 ms

In the 1531 patients with QTc ≥ 500 ms, age was 70 ± 15 years, 59% (907/1531) were females, and median QTc was 513 ms (range 500–810 ms). The median number of QT-prolonging medical conditions was 1 (range 0–6), and the median number of QT-prolonging drugs was 1 (range 0–4). The mean pro-QTc score was 2.9 ± 1.6 (*Table 1*).

At least one QT-prolonging medical conditions was present in 862 (56%) patients, 1004 (66%) patients received at least one QT-prolonging drug and 505 (33%) patients had at least one electrolyte disturbance. Only 45 (2.9%) patients had a pro-QTc score of 0 (*Figure 2*). The most frequent QT-prolonging medical condition was heart failure (326/1531, 21%), followed by acute coronary syndrome (295/1531, 19%) and diabetes mellitus types 1 and 2 (261/1531, 17%) (*Table 2*).

A total of 435 (28%) patients received at least one drug from the group 'known risk for torsades de pointes' and 166 (11%) patients received at least one drug from the group 'possible risk for torsades de pointes'. Furthermore, 663 (43%) patients received at least one drug from the group 'conditional risk for torsades de pointes' and 189 (12%) patients received at least one drug from the group 'drugs to be avoided by congenital long QT patients' (*Tables 2, 3*).

The most frequent electrolyte disturbance was hypokalaemia found in 441 patients (29%), followed by hypocalcaemia in 77 (5%) patients and hypomagnesaemia in 39 (3%) patients. Potassium was not analysed in 90 (6%) patients, calcium was not analysed in 1416 (93%) patients, and magnesium was not analysed in 1402 (92%) patients.

Detection of QT prolongation by health care provider

Any note mentioning the QT prolongation or QT-reducing measures documented in the medical records were recorded in 185 (12%) of the cases.

Mortality in patients with corrected QT interval ≥ 500 ms

Median follow-up time was 952 days (range 0–4161) among the patients with QTc ≥ 500 ms. A total of 765 (50%) patients died during follow–up, and 123 (8%) patients died during the same hospitalization period as the index ECG was taken. Estimated 30-day survival was 89%, estimated 6-month survival was 79%, estimated 1-year survival was 75%, and estimated 3-year survival was 60%. Among the 587 (38%) non-survivors in the 3-year follow-up period, median time between index ECG and death was 136 (range 0–1093) days.

The most frequent cause of death was cardiovascular death in 215 (28%) patients, followed by infectious disease in 180 (24%) patients and malignancy in 78 (10%) patients. In 43 (6%) patients, the cause of death was unknown. Two patients died abroad and consequently the causes of death were missing for these patients, while dates of death were obtained from The Norwegian National Registry.

Table 1 Patient characteristics at time of first ECG with QTc ≥ 500 ms

	Total ($n = 1531$)	Survivors ($n = 944$)	Non-survivors ($n = 587$)	*P*-value
Age (years)[a]	70 ± 15	66 ± 15	80 ± 12	<0.001
Females	72 ± 15			
Males	68 ± 15			
Female gender	907 (59%)	582 (62%)	325 (55%)	0.08
Heart rate (b.p.m.)	80 (38–100)	79 (38–100)	82 (40–100)	<0.01
QRS duration (ms)	94 ± 12	94 ± 12	95 ± 13	0.31
QTc (ms)	513 (500–810)	512 (500–810)	513 (500–791)	0.19
S-Creatinine (μmol/L)	81 (11–1382)	77 (17–1382)	89 (11–999)	<0.001
Hypokalaemia	441 (29%)	262 (28%)	179 (30%)	<0.01
Number of QT-prolonging drugs	1 (0–6)	1 (0–5)	1 (0–6)	<0.001
Number of QT-prolonging conditions[b]	1 (0–4)	1 (0–4)	1 (0–4)	<0.001
Pro-QTc score	2.9 ± 1.6	2.8 ± 1.6	3.2 ± 1.7	<0.001

b.p.m., beats per minute; ECG, electrocardiogram; QTc, corrected QT interval.
[a]Females were significantly older than males ($p < 0.001$).
[b]Female gender, electrolyte disturbances, and medication not included.

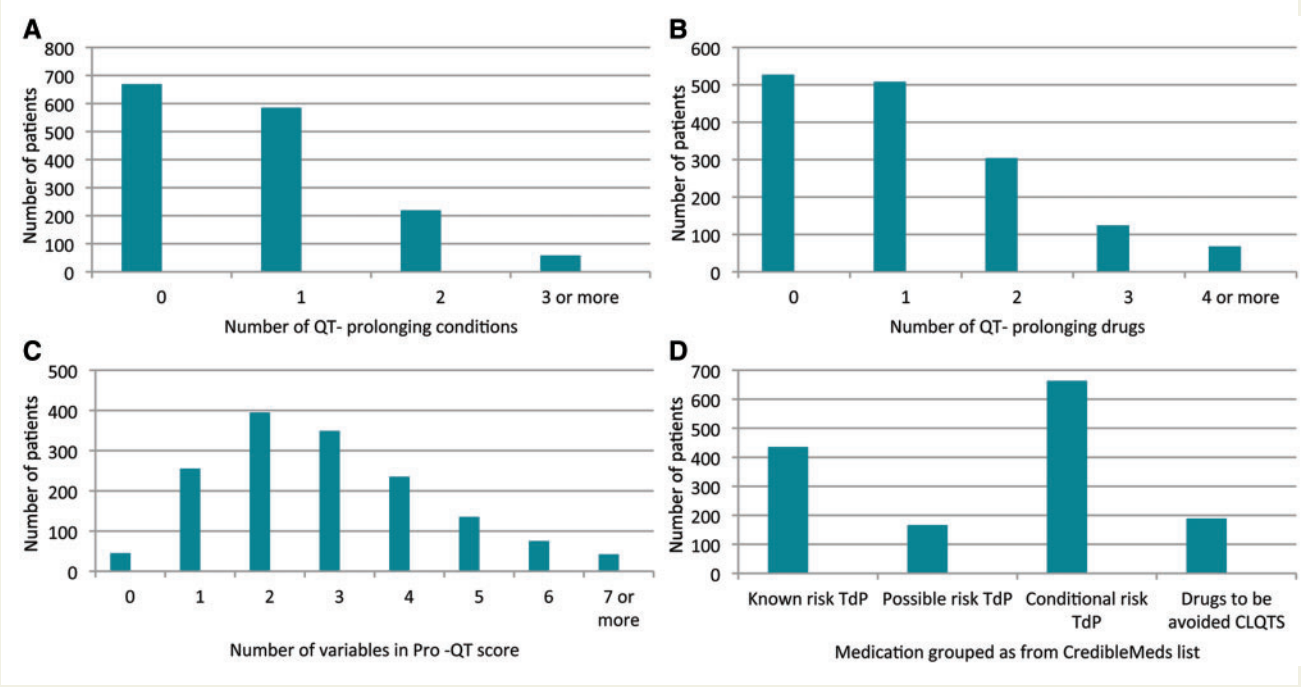

Figure 2 Bar chart showing the number of patients with any QT-prolonging medical conditions excluding female gender, electrolyte disturbances, and medication (*A*), number of patients who were taking any QT-prolonging drugs (*B*), distribution of pro-QTc scores (*C*), and number of patients taking at least one drug from the four subgroups of drugs from the CredibleMeds QTdrugs lists (*D*). CLQTS, congenital long-QT syndrome; QTc, corrected QT interval.

Patients with corrected QT interval < 500 ms

In the 2099 patients with moderately prolonged QTc, age was 67 ± 16 years, 43% (912/2099) were females, and median QTc was 483 ms (range 470–499 ms, by definition). In this group, females were older than males (69 ± 17 years vs. 66 ± 16 years, $P < 0.001$). In the 43 893 patients with normal QTc, age was 59 ± 19 years, 53% (23 129/43 893) were females, and median QTc was 430 ms (range 302–479 ms). Also among these patients, females were older than males (61 ± 19 years vs. 58 ± 18 years, $P < 0.001$) (*Figure 3*).

Table 2 Medical conditions and factors known to prolong QTc at time of first ECG with QTc ≥ 500 ms and corresponding mortality during follow-up

QT-prolonging medical conditions	No. of patients ($n = 1531$)	No. of deaths
Acute coronary syndrome within 7 days	295	108 (37%)
Anorexia or starvation	5	2 (40%)
Heart rate < 45 b.p.m.	8	5 (63%)
Diabetes mellitus types 1 and 2	261	116 (44%)
Ejection fraction < 40%	326	171 (53%)
Female gender	907	325 (36%)
Hypertrophic cardiomyopathy	8	3 (38%)
Hypoglycaemia (in the absence of diabetes)	2	1 (50%)
Intoxication with QT-prolonging drugs	30	6 (20%)
Known genetic long-QT syndrome	1	0
Pheochromocytoma	1	0
Renal dialysis	25	11 (44%)
Status < 7 days after AF conversion	76	16 (21%)
Status < 24 h after cardiac arrest	25	16 (64%)
Status < 24 h after syncope or seizure	60	18 (30%)
Status < 7 days after stroke, subarachnoid haemorrhage, or head trauma	78	51 (65%)
Serum electrolyte disturbances	505	213 (42%)
Drugs with known risk TdP	435	184 (42%)
Drugs with possible risk TdP	166	75 (45%)
Drugs with conditional risk TdP	663	279 (42%)
Drugs to be avoided by congenital long QT patients	189	78 (41%)

AF, atrial fibrillation; b.p.m., beats per minute; TdP, torsades de pointes.

Comparison on mortality between patients with corrected QT interval (QTc) ≥ 500 ms, patients with moderately prolonged QTc, and patients with normal QTc

The Kaplan–Meier survival analyses of the patients with QTc ≥ 500 ms, patients with moderately prolonged QTc and normal QTc showed higher mortality in patients with QTc ≥ 500 ms than in the patients with moderately prolonged QTc (log-rank $P < 0.001$). Furthermore, patients with moderately prolonged QTc had higher mortality than the patients with normal QTc (log-rank $P < 0.001$) (*Figure 3A*).

The Kaplan–Meier survival analyses of the three groups by their QTc and stratified by gender showed that there was a lower mortality in females compared with males when the QTc was ≥ 500 ms (log-rank $P = 0.006$) and when the QTc was moderately prolonged (log-rank $P = 0.024$). There was no significant survival difference between the genders when the QTc interval was <470 ms for males and <480 ms for females (log-rank $P = 0.45$) (*Figure 3*).

Predictors of mortality

Aborted cardiac arrest, stroke/subarachnoid haemorrhage/head trauma, heart failure, any electrolyte disturbances, and age were all predictors of mortality (*Table 4*). In contrast, acute coronary syndrome, female gender, and atrial fibrillation conversion were associated with lower mortality. Diabetes mellitus and syncope/seizure were not significant predictors of mortality. Anorexia/starvation, bradycardia, hypertrophic cardiomyopathy, hypoglycaemia, known genetic long QT syndrome, pheochromocytoma, and renal dialysis were excluded from the multivariate Cox regression analysis because of few cases or deaths.

The subgroups 'medication with known risk for torsades de pointes' and 'medication with possible risk for torsades de pointes' were significant predictors of mortality, while 'drugs to be avoided by congenital long QT patients' were not. 'Drugs with conditional risk for torsades de pointes' showed borderline significance ($P = 0.07$).

Numbers of QT-prolonging drugs were predictors of mortality with the hazards of one QT-prolonging drug [hazard ratio (HR) 1.32, 95% confidence interval (CI) 1.07–1.63; $P = 0.009$], two QT-prolonging drugs (HR 1.39, 95% CI 1.10–1.76; $P = 0.007$), three QT-prolonging drugs (HR 1.49, 95% CI 1.08–2.05; $P = 0.014$), and four or more QT-prolonging drugs (HR 2.14, 95% CI 1.48–3.09; $P < 0.001$).

Pro-corrected QT interval (QTc) score and QTc mortality score for patients with QTc ≥ 500 ms

The Kaplan–Meier survival analyses of patients grouped according to pro-QTc score showed a trend towards increased mortality with higher pro-QTc scores, but the pro-QTc score was not linearly correlated with mortality (*Figure 4A*).

We constructed a QTc mortality score to improve the prediction of mortality in our population. Variables with HRs < 1 and variables that were not statistically significant predictors of mortality in our multivariate Cox regression analyses were excluded from the QTc mortality score. Consequently, acute coronary syndrome, female gender, diabetes mellitus, atrial fibrillation, syncope/seizure, and 'drugs to be avoided by congenital long QT patients' were excluded. Variables with HRs > 2 in the previous mentioned multivariable cox model (aborted cardiac arrest and stroke/subarachnoid haemorrhage/head trauma) were scored 2 points. The remaining variables scored 1 point.

The Kaplan–Meier survival analyses were performed comparing patients with different QTc mortality scores. There was a statistically significant difference in mortality between all the groups with increased mortality with increasing QTc mortality score (*Figure 4B*). The QTc mortality score predicted mortality adjusted for age and gender with an HR of 1.40 (95% CI 1.30–1.52; $P < 0.001$).

Discussion

We found a prevalence of QTc prolongation ≥ 500 ms in 2.4% of patients who had taken an ECG in a community hospital. All-cause mortality in these individuals was high with a mortality of 50% during 952 (range 0–4161) days of follow-up. Females with prolonged QTc had lower mortality risk compared with males, whereas mortality

Table 3 Number of drugs from the CredibleMeds QTdrugs lists at time of first ECG with QTc ≥ 500 ms

Known risk TdP ($n = 488$)	Possible risk TdP ($n = 194$)	Conditional risk TdP ($n = 839$)	Drugs to be avoided CLQTS ($n = 256$)
Amiodarone ($n = 131$)	Venlafaxine ($n = 44$)	Furosemide ($n = 218$)	Salbutamol ($n = 94$)
Citalopram ($n = 80$)	Mirtazapine ($n = 42$)	Pantoprazole ($n = 203$)	Salmeterol ($n = 76$)
Escitalopram ($n = 50$)	Olanzapine ($n = 24$)	Hydrochlorothiazide ($n = 146$)	Formoterol ($n = 37$)
Sotalol ($n = 43$)	Lithium ($n = 17$)	Metoclopramide ($n = 74$)	Noradrenaline ($n = 12$)
Haloperidol ($n = 30$)	Tolterodine ($n = 17$)	Metronidazole ($n = 36$)	Trimethoprim-sulfamethoxazole ($n = 7$)
Donepezil ($n = 26$)	Trimipramine ($n = 8$)	Sertraline ($n = 34$)	Trimethoprim-sulfamethoxazole
Methadone ($n = 22$)	Clomipramine ($n = 7$)	Amitriptyline ($n = 34$)	Terbutaline ($n = 7$)
Ciprofloxacin ($n = 22$)	Risperidone ($n = 7$)	Hydroxyzine ($n = 32$)	Amphetamine ($n = 5$)
Flecainide ($n = 18$)	Famotidine ($n = 6$)	Paroxetine ($n = 21$)	Dopamine ($n = 5$)
Erythromycin ($n = 16$)	Promethazine ($n = 6$)	Solifenacin ($n = 18$)	Dobutamine ($n = 2$)
Propofol ($n = 16$)	Tamoxifen ($n = 4$)	Quetiapine ($n = 10$)	
Fluconazole ($n = 10$)	Tacrolimus ($n = 4$)	Doxepin ($n = 4$)	
Ondansetron ($n = 7$)	Aripiprazole ($n = 2$)	Fluoxetine ($n = 4$)	
Chloroquine ($n = 5$)	Nortriptyline ($n = 1$)	Amisulpride ($n = 1$)	
Levomepromazine ($n = 3$)	Foscarnet ($n = 1$)	Ziprasidone ($n = 1$)	
Ibutilide ($n = 2$)	Sertindole ($n = 1$)	Ritonavir ($n = 1$)	
Disopyramide ($n = 2$)	Pazopanib ($n = 1$)	Voriconazole ($n = 1$)	
Clarithromycin ($n = 2$)	Mirabegron ($n = 1$)	Galantamine ($n = 1$)	
Chlorpromazine ($n = 1$)	Sorafenib ($n = 1$)		
Azithromycin ($n = 1$)			
Dronedarone ($n = 1$)			

CLQTS, congenital long-QT syndrome; TdP, torsades de pointes.

was similar in those with normal QTc. Awareness of these high-risk individuals was low with only a minority of acknowledged cases.

The prevalence of QT prolongation varies between populations.[2,9,10,12] Our findings suggest that pronounced QT prolongation was a relatively frequent condition that most clinicians across all medical disciplines at a community hospital need to be aware of.

Heart failure, aborted cardiac arrest, stroke/subarachnoid haemorrhage/head trauma, electrolyte disturbances, age, medication with known risk for TdP, and medication with possible risk for TdP were predictors of mortality. On the other hand, female patients, patients with acute coronary syndrome, and patients who had undergone an atrial fibrillation conversion had lower mortality. Especially the 'protective' effect of acute coronary syndrome may seem to be a paradox. Possible explanations are that these patients are usually forwarded to a coronary intervention centre for revascularization with standardized and close follow-up and with a good prognosis.

An important finding was the lower mortality in females compared to males with prolonged QTc. Females had better survival than men both in the group with QTc ≥ 500 ms and in the group with moderately prolonged QTc despite older age. There was no difference in mortality between the genders in the group with normal QTc. It is well known that females have longer QTc than men, which is also reflected in the different cut-off values for prolonged QTc between genders.[8] Our findings additionally indicated that females tolerate higher QTc values than men. It may be speculated that the cut-off values for prolonged QTc may be further adjusted in females to indicate risk for mortality and future studies may explore this question.

In line with previous studies, medication was the greatest contributor to QT-prolongation.[2,5] Several studies have shown that QT-prolonging medication is associated with increased risk for cardiovascular death and TdP.[9,15–17] In our study, patients using QT-prolonging medication with known risk for TdP had the highest risk of mortality, whereas patients using drugs with conditional risk for TdP showed only borderline significant increased mortality. Therefore, our study supports the ranking of the four medication groups according to the CredibleMeds QTdrugs lists.

The numbers of QT-prolonging drugs were predictors of mortality. It is not unexpected that people taking medication have an increased mortality due to underlying disease. In our study, there may be confounders that affect the association between QT-prolonging drugs and mortality. In a previous study of patients with severely prolonged QTc interval, in which the most important culprits were QT-prolonging medications, the in-hospital mortality was high, but only 4% of the patients experienced arrhythmic deaths.[5]

There was a trend towards increased mortality by increasing pro-QTc score as previously proposed,[2] but the pro-QTc score was not linearly correlated with mortality. However, the different variables in the pro-QTc score were determined for their risk of QT-prolongation and not for risk of mortality. Furthermore, the variables in the pro-QTc score were not weighted according to the risk, but were considered equipotent. In this study, we proposed a risk-weighted QTc mortality score based on the mortality in our population to give added value in risk assessment of patients with prolonged QTc (to directly compare the population in the current study with

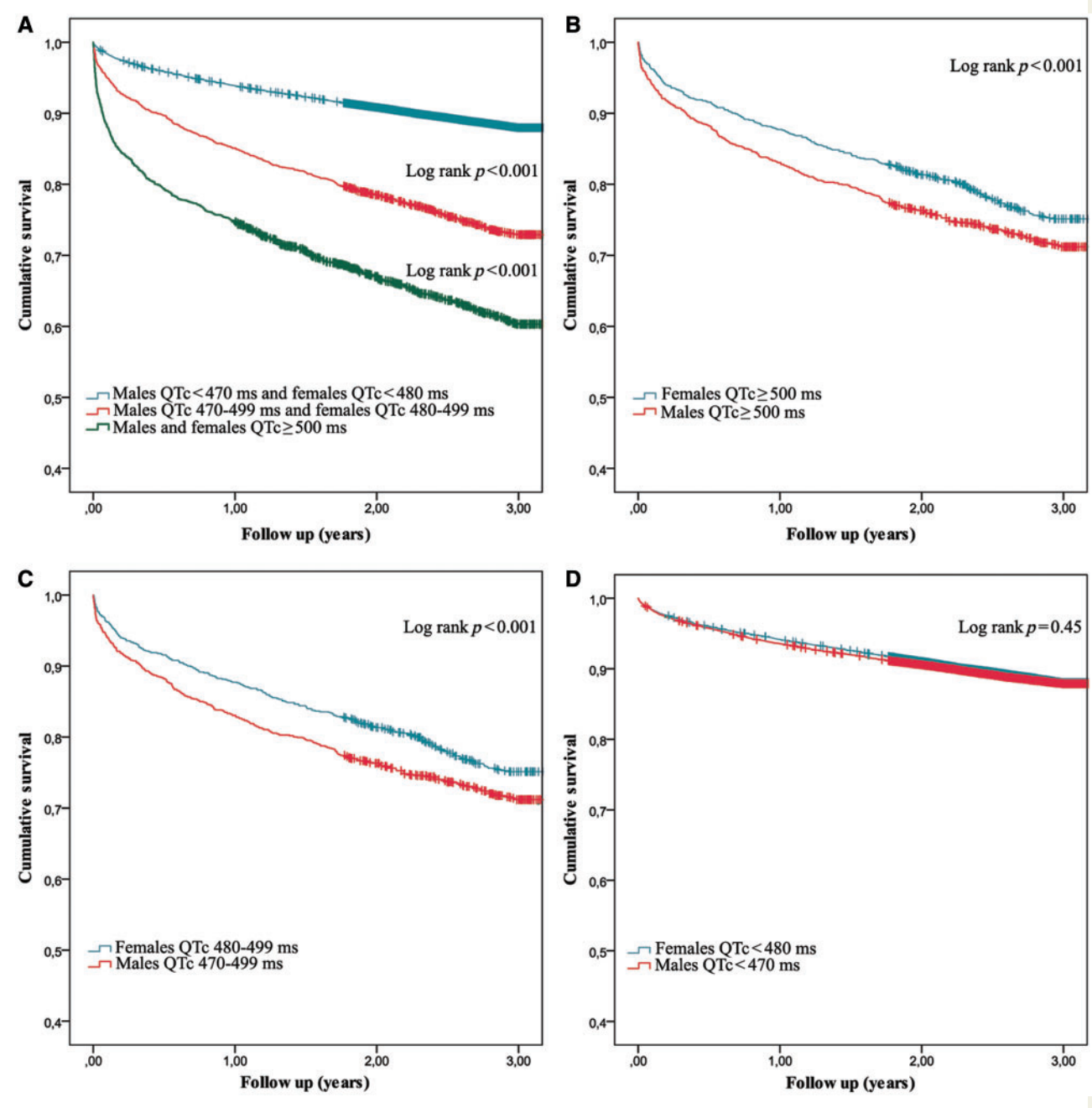

Figure 3 The Kaplan–Meier survival plots of 1531 patients with QTc ≥ 500 ms compared with 2099 patients with moderately prolonged QTc (QTc 470–499 ms for males and QTc 480–499 ms for females) and 43 893 patients with normal QTc (QTc < 470 ms for males and QTc < 480 ms for females) (*A*). The Kaplan–Meier survival plots comparing 907 females with QTc ≥ 500 ms with 624 males with QTc ≥ 500 ms (*B*). The Kaplan–Meier survival plots comparing 1187 males with QTc 470–499 ms with 912 females with QTc 480–499 ms (*C*). The Kaplan–Meier survival plots comparing 23 129 females with QTc < 480 ms with 20 764 males with QTc < 470 ms (*D*). QTc, corrected QT interval.

the population in the previous study of Haugaa *et al.*[2], see Supplementary material online, *Figures S1* and *S2*). The findings in our population may be generalizable to other similar heterogeneous hospital populations. It is possible that the risk factors should be weighted differently in different populations.

A prolonged QT interval should be easy to discover, but clinical trials have shown difficulties in accurately measuring the QT interval and to calculate the QTc.[18] An even greater problem is that a prolonged QTc is often missed. Furthermore, even if QT prolongation is recognized, it is often ignored. In our study, QT prolongation was only acknowledged in the medical records in 12% of the cases. The unawareness of the QT-prolonging potential of many conditions and drugs may expose patients to unnecessary risk.

Table 4 Cox regression analyses of mortality for 1531 patients with QTc ≥ 500 ms

	Univariate analyses			Multivariate analyses			Predictors of mortality after stepwise removal of insignificant predictors		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Status < 24 h after cardiac arrest	2.75	1.67–4.52	<0.001	2.31	1.36–3.91	<0.01	2.40	1.44–4.01	<0.01
Status < 7 days after cerebral stroke, SAH or head trauma	2.52	1.89–3.37	<0.001	2.37	1.76–3.18	<0.001	2.28	1.70–3.05	<0.001
Ejection fraction < 40%	1.76	1.47–2.10	<0.001	1.71	1.41–2.09	<0.001	1.74	1.43–2.12	<0.001
Electrolyte disturbances	1.29	1.09–1.53	<0.01	1.34	1.12–1.59	<0.01	1.37	1.15–1.62	<0.001
Drugs with known risk TdP	1.22	1.03–1.46	0.02	1.36	1.11–1.61	<0.01	1.37	1.14–1.65	<0.01
Drugs with possible risk TdP	1.22	0.96–1.55	0.11	1.29	1.01–1.65	0.04	1.31	1.03–1.67	0.03
Drugs with conditional risk TdP	1.26	1.07–1.49	<0.01	1.16	0.99–1.38	0.07			
Drugs to be avoided by CLQTS	1.13	0.89–1.44	0.31	1.09	0.85–1.40	0.50			
Diabetes mellitus	1.23	1.00–1.51	0.05	1.14	0.93–1.40	0.22			
Acute coronary syndrome within 7 days	0.93	0.76–1.15	0.51	0.76	0.60–0.95	0.02	0.76	0.61–0.96	0.02
Status < 24 h after syncope/seizure	0.67	0.42–1.08	0.10	0.84	0.53–1.36	0.48			
Status < 7 days after AF conversion	0.47	0.28–0.76	<0.01	0.40	0.24–0.66	<0.001	0.40	0.24–0.67	<0.001
Age (years)	1.05	1.04–1.06	<0.001	1.05	1.04–1.06	<0.001	1.05	1.04–1.06	<0.001
Female gender	0.80	0.68–0.94	<0.01	0.66	0.56–0.78	<0.001	0.65	0.55–0.77	<0.001
Heart rate (b.p.m.)	1.01	1.00–1.02	<0.01	1.02	1.01–1.02	<0.001	1.02	1.01–1.02	<0.001
QTc (ms)	1.00	0.99–1.00	0.23	1.00	1.00–1.01	0.19			

Medication divided into four subgroups according to CredibleMeds QTdrugs lists.
AF, atrial fibrillation; 95% CI, 95% confidence interval; CLQTS, congenital long-QT syndrome; HR, hazard ratio; SAH, subarachnoid haemorrhage; TdP, torsades de pointes.

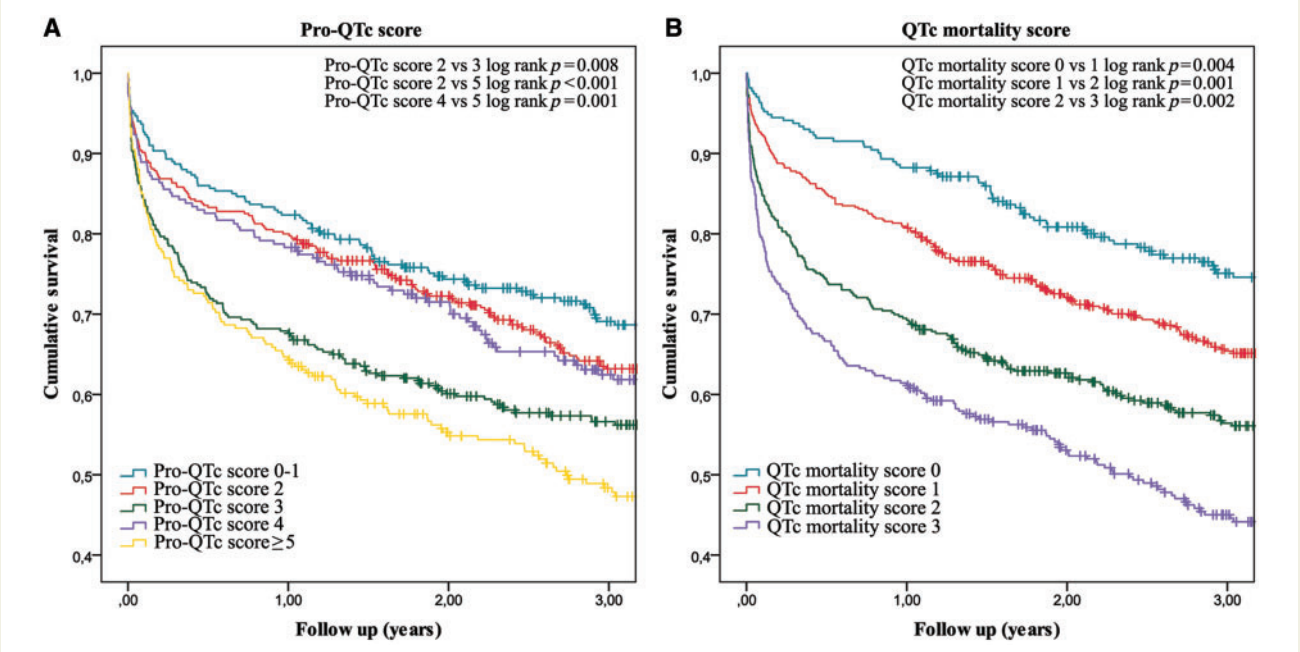

Figure 4 The Kaplan–Meier survival plots comparing 1531 patients with QTc ≥ 500 ms grouped according to pro-QTc score (*A*) or QTc mortality score (*B*). QTc, corrected QT interval.

Limitations

The study was performed at a single centre, which may reduce its generalizability. The retrospective design is in itself a limitation due to confounding and missing data. We evaluated only the first ECG with QTc > 500 ms in each patient. Future studies should explore QTc in multiple ECG recordings to assess transient QT prolongation. U waves on ECG and the impact on QTc and outcome were not explored. The fact that serum magnesium and serum calcium were analysed only in a minority of the patients may underestimate the effect of electrolyte disturbances. Most patients died outside the hospital, and medication at the time of death may have changed from our in-hospital registration. The frequent out-of-hospital death also limited the possibility to explore arrhythmia-related death. The cardiologist was not blinded to the automated ECG measurements. This may have overestimated the correlation between manually and automatically measured QTc values. Amiodarone has a long half-life, and patients on long-term medication may exhibit QT-prolongation longer than 7 days after discontinuation of the drug, which may have underestimated the effect of amiodarone in causing QT prolongation. The QTc mortality score must be validated in future studies to assess the clinical value.

Conclusions

QTc ≥ 500 ms was associated with an estimated 3-year survival of 60%. Mortality was highest in patients with aborted cardiac arrest, cerebral stroke or trauma, heart failure, electrolyte disturbances, and in patients using QT-prolonging medication. We constructed a risk-weighted QTc mortality score to help risk stratification in patients with QTc ≥ 500 ms. Female gender was associated with better survival in those with moderately and severely prolonged QTc. QT prolongation was only acknowledged in the medical records in 12% of the cases, indicating the need for increased awareness of this condition among clinicians.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: none declared.

Funding

This work was supported by a grant from Telemark Hospital Trust, Ulefossvegen 55, 3710 Skien, Norway.

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