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Hypokalemia in women and methadone therapy are the strongest non-cardiologic factors associated with QT prolongation in an emergency department setting

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Abstract

Background—Our primary objective was to determine the adjusted quantitative associations of clinical predictors with QT prolongation, a defining cause of Torsades de Pointes (TdP).

Methods—A retrospective cohort study was performed on consecutive emergency department patients identified by ECG acquisition date, and heart rate corrected QT (QTc) and QRS durations. QTc was modeled as a function of clinical predictors with multiple linear regression.

Results—1,010 patients were included. The strongest predictors of QTc and their coefficients were: antidysrhythmic (26.1ms, 95% CI 15.6–36.6) and methadone (43.6ms, 95% CI 28.1–59.2) therapies, and genetic long QT syndrome diagnosis (32.6ms, 95% CI –4.7–70.0). The association of QTc with serum potassium was approximated by a two piecewise linear function that differed by sex. For potassium below 3.9 mmol/L, QTc increased by 43.0ms (95% CI 26.2–59.7) and 29.5ms (95% CI 19.1–40.0) for every 1 mmol/L decrease in potassium in women and men, respectively. TdP occurred in only 4/686 (0.6%) of patients with QTc>500 and QRS<120, but mortality during the visit including hospitalization was 8.0%.

Conclusions—QTc duration is highly sensitive to hypokalemia, particularly in women. Methadone prolongs QTc remarkably compared to other non-cardiologic medicines. QTc>500 with normal QRS often signifies profound illness and substantial mortality risk, though not necessarily imminent TdP.

Keywords

Long QT Syndrome; Hypokalemia; Methadone; Torsades de Pointes; Cohort Studies

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Introduction

A host of factors may modulate and prolong the electrocardiographic QT interval increasing the risk of Torsades de Pointes (TdP), a life-threatening ventricular tachydysrhythmia.[1–3] These include: genetics,[4] electrolytes,[5,6] pharmacologic and toxicologic agents,[7] myocardial infarction (MI)[8] and cardiomyopathy, intracranial hemorrhage (ICH)[9] or cerebrovascular accident (CVA),[10] and diurnal variation.[11,12]

Though imperfect, Bazett's correction formula is commonly used to adjust for QT interval heart rate dependence.[13,14] The individual unadjusted quantitative contributions of some other factors to QT prolongation including serum potassium,[5,15] calcium,[6] and treatment with sotalol[16] or psychotropics,[17] have been described in specific subpopulations. These estimates may poorly approximate the true associations in a general patient population.

The primary goal of this study was to determine the quantitative relationships between the measured QTc interval and the major known and suspected factors associated with QT duration in all emergency department (ED) patients using a multivariate model. This information can be used to anticipate when dangerous QT prolongation may occur and to suggest the most important factors to treat it and prevent life-threatening TdP. Secondary goals were to determine the prevalence of TdP and mortality during the hospital visit.

Methods

Study Design

A single center retrospective cohort study of ED patients who had an ECG was performed after Partners Healthcare institutional review board approval with waiver of informed consent.

Study Setting and Population

The setting was a 900 bed urban hospital with annual ED census of 100,000. We studied ED patients because the ED visit is a clinical care event where concentrated and contemporaneous evaluation and testing are performed, often before initiation of confounding therapies.

The study was designed with an intention to include two groups of patients: those with QTc greater or less than 500 ms. Upon collecting cases with QTc > 500 ms, it became clear that many had QTc > 500 ms due to QRS > 120 ms. The cases of greatest interest were those with QTc prolongation not due to delayed depolarization. Therefore, a third group was added after initiation of the study to make three (Figure 1): 1) ECG with QTc < 500 ms 2) ECG with QTc ≥ 500 ms, 3) ECG with QTc ≥ 500 ms and QRS < 120 ms. For comparison in Table 1, patients in the second group with QRS < 120 ms were moved to the third group to provide three mutually exclusive groups. A 500 ms threshold was chosen to yield a sample enriched with QTc substantially above normal with increased TdP risk.

Study Protocol

We used a written study protocol, and data collection manual and instrument to guide data abstraction. One investigator who was not blinded to the study objectives inspected all ECG's and collected data from all included cases. One hundred of the first 720 cases were randomly selected for data abstraction reliability analysis. A second investigator blinded to the study goals abstracted data for these cases. Both investigators are practicing board-certified emergency physicians.

We identified ECG's using the hospital MUSE ECG system (GE Healthcare, Milwaukee) based on ED location, date, and QTc and QRS intervals. The first satisfactory ECG obtained for each ED visit was included. If the ECG was noisy obscuring the relevant onset or offsets, incomplete with some leads missing, or rapid with overlap of the terminal T wave and the next cycle P or QRS waves, then the next ECG obtained during the same ED visit was assessed. If there was no satisfactory ECG, then the case was excluded (Figure 1). Only the first visit with a satisfactory ECG was included for patients with multiple ED visits.

ECG's were automatically read with the GE Marquette 12SL algorithm (GE Healthcare, Milwaukee, Wisconsin). One author checked the accuracy of all automated QTc measurements by manual measurement and calculation of the QTc on the electronically viewed magnifiable ECG. The end of the T wave was identified as the return to the TP baseline. If this could not be visualized due to an intervening U or P wave, then we identified the intersection of the tangent to the steepest downslope and the isoelectric line. We preferentially used the automated measurement to remove bias. However, if the automated measurement was grossly incorrect, then we used the manual precordial measurement.

The same author decided to include or exclude a patient based solely on ECG review prior to any other knowledge about the patient or opening any other documents. If the patient was included, then he reviewed the complete medical record.

Measurements

We recorded acute historical data including: the chief complaint reported to the triage nurse, and patient age and sex. Past cardiologic history extracted from the ED or admitting hospital notes included: any dysrhythmias, personal or family history of long QT syndrome, pacemaker or implantable cardioverter defibrillator implantation, coronary artery disease including MI, percutaneous cardiac stent placement or balloon angioplasty, or coronary artery bypass grafting, and measured left ventricular ejection fraction (LVEF).

We recorded the LVEF measured closest temporally within 6 months before the ED visit, the date of the study, and the measurement modality. If no LVEF was measured within 6 months before the ED visit, then the closest before or after the ED visit was recorded. We noted ongoing dialysis for renal failure.

We recorded medicines administered at an outside facility prior to patient transfer or in our ED prior to ECG acquisition. All chronic oral or parenteral medicines were recorded based primarily on the admitting service admission note, or the ED physician notes if the patient

was discharged. We relied primarily on these notes because we believed they most accurately reflected true patient usage before the visit. Inhaled, ophthalmologic, transdermal, and as needed (PRN) medicines were not recorded. Medicines of particular interest including Vaughan Williams class I and III antidysrhythmics, diuretics, and after noting a large association with QTc, methadone, were recorded under separate categories. The Arizona Center for Education and Research on Therapeutics (AzCERT) has published an updated list of medicines with known, possible, or conditional risk of QT prolongation for the past decade.[18] The number of acute and chronic medicines in each of the three QT prolongation risk categories as of November, 2011, but not in the separate categories listed above, was recorded. Since 2011, AzCERT has combined the three categories into a single listing. All medicines newly listed from November 2011 to May 2016 were identified in an additional “newly listed” category.

We recorded heart rate, blood pressure, and temperature, if less than 95 degrees Fahrenheit, obtained closest to the time of ECG acquisition. ECG data recorded included: date and time of acquisition, and automated heart rate, QRS, QT, and QTc interval measurements with manual confirmation. We manually assessed and recorded cardiac rhythm, QRS morphology including bundle branch block or electrical pacing, and left ventricular hypertrophy based on Sokolow or Cornell criteria or right ventricular hypertrophy.

We recorded serum chemistries obtained closest temporally to ECG acquisition within 24 hours including: sodium, potassium, bicarbonate, creatinine, glucose, magnesium, calcium, and serum or urine toxicologic screen. If the specimen was hemolyzed then the next closest available non-hemolyzed specimen results were used for the first five elements listed above. We documented maximal serum troponin and creatine phosphokinase within 3 days after ED evaluation.

We recorded the ED disposition. We reviewed the complete record for any evidence of TdP. Final diagnoses from the ED if discharged or the hospital if admitted were recorded. We particularly noted: ICH or ischemic CVA, MI, and QT prolonging agent overdose. We noted any diagnosis of acute thyroid derangement, eating disorder, or AIDS. We recorded the date and cause of any deaths during the ED visit or hospitalization.

The primary outcome measures were the coefficients in a multiple linear regression model. QTc was the dependent variable and independent variables were drawn from the clinical, pharmacologic, electrocardiographic, cardiologic imaging, and serologic testing QT interval predictor domains. Secondary outcomes included the association of methadone dosing with QTc, and the occurrence of TdP or patient death.

Data Analysis

We developed a parsimonious multiple linear regression model manually with an intention to include all major predictors with the exception of detailed patient genetics, which were unavailable, but avoiding excessive variables that would likely exhibit collinearity and dilute the relevant associations. Sample size calculation assumed 30 independent primary and interaction variables. At least 20 subjects per variable has been recommended for multiple regression,[19] but more may be necessary if some predictors are rare binary events.[20]

Conservatively allowing 30 cases for each independent variable, 900 cases were required. All statistical analyses were performed with SPSS-23 (IBM, Armonk NY) except multiple imputation with chained equations(MICE) was performed with StataSE-14 (Stata, College Station, TX).

Reliability analyses of data abstraction used unweighted kappa statistics and intraclass correlation coefficients(ICC) for nominal and interval data, respectively. Visual assessment of the relationship of interval data predictor variables with QTc was performed by graphing a scattergram of the residuals from the full model absent the predictor of interest against the predictor of interest. A Loess curve was fit to suggest the relationship shape. For serum potassium, the curve approximated a two piecewise linear function(Figure 2A). Thus, a linear spline was used for potassium with knot location identified by scattergram inspection and best fit.

Figure 1 lists missing data. Approximately 2% of cases were missing most or all electrolytes, and these cases were removed listwise because all electrolytes could not be confidently imputed from the clinical data. We assumed the remaining missing data were missing at random (MAR) after considering the association of missingness with the remaining observed data. We imputed these individual predictor variables with missing data: LVEF, magnesium, calcium, or potassium. MICE was performed using all predictor variables and the dependent variable in the final model, and the following auxiliary variables not included in the final model: history of dysrhythmia, device implantation, CAD, current diuretic treatment, and systolic blood pressure.

Multiple linear regression was performed on each of twenty imputed datasets and the results pooled. We computed a pooled R^2 estimate using the untransformed mibeta command. We performed sensitivity analyses by performing MICE with SPSS, and by imputing all missing LVEF values as normal, removing the remaining cases with missing data, and performing multiple linear regression on the single dataset. After reviewing model results, one additional model was constructed removing all nonsignificant predictors and adding interactions of sex with all major predictors.

Results

We assessed 1,565 ECG's. The automated program read the QTc correctly in 1,331 (85%). After exclusions (Figure 1), 1,010 cases were included. Only thirteen (1.3%) of the 1,010 included ECG's required manual over-read of the automated QTc measurement.

Kappa statistics were 0.68 or greater for all nominal variables except for hypothermia where a single case was identified by only one reviewer, and acute MI (kappa=0.39) where both reviewers identified one case with NSTEMI and 96 cases with no MI, but disagreed on 3 cases regarding NSTEMI. ICC was 0.95 or greater for all interval variables except HCO₃. HCO₃ ICC was 0.48 due to a single gross data entry error.

Table 1 tabulates patient characteristics. All ED ECG's acquired during the interval 8/16/11 through 8/19/11 were eligible for inclusion. They provide a sense for the prevalence of long

QT ECG's: 195 (92.9%) with $QTc < 500$ ms, 9 (4.3%) with $QTc \geq 500$ ms and $QRS \geq 120$ ms, and 6 (2.9%) with $QTc \geq 500$ ms and $QRS < 120$ ms.

Serum potassium was modeled with a linear spline with a single knot at 3.9 mmol/L (Figure 2A). Table 2 lists the multiple linear regression model coefficient results. Potassium terms in the model are calculated as $(K - 3.9)$, thus the negative coefficient of -29 for potassium below 3.9 means an average 29 ms *increase* in QTc for every 1 mmol/L decrease in potassium below 3.9. For women, the average increase in QTc for every 1 mmol/L decrease in potassium below 3.9 is the sum of the potassium and (female sex*potassium) interaction terms: $29.53 + 13.44 = 43.0$ ms (95% CI 26.2–59.7) (Figure 2B).

Model R^2 was 0.24 suggesting 24% of the variation in QTc was associated with the included predictors. Sensitivity analyses revealed no substantive difference in coefficients (results not shown).

Methadone total daily dose was available for 27 of 30 patients and averaged 84 mg. Figure 3 demonstrates the relationship between QTc residuals and daily methadone dose. Patients taking methadone were taking an average of 5.3 other medicines including 1.0 known to prolong the QT interval.

Four patients exhibited TdP. Their average QTc and serum potassium were 586 ms and 4.0 mmol/L. One patient was an 89 year old female taking methadone for pain. She expired from recurrent TdP.

Discussion

Our results illuminate the associations of clinical predictors with QTc prolongation. However, although QT prolongation is, by definition, a critical determinant of TdP risk, it is not alone. Other electrophysiologic factors play a role.[21–23]

Sex is a predictor of QTc , and the effect is modulated by interaction with serum potassium. When the sex interaction effects were removed from our model, the coefficient for female sex alone was 6.1. This suggests QTc is an average 6.1 ms longer in women, consistent with prior data.[14,15]

Although the large increase in QTc associated with hypokalemia may partly be due to widening of the T wave and alteration in the rate or homogeneity of repolarization, delayed repolarization appeared to be a primary factor. The strength of association could be exaggerated in this sample if the increase in QTc is a function of the pace of hypokalemia development. Nevertheless, as previously surmised, the large effect observed with anticipated increased incidence of TdP[24] starkly suggests a mechanism for the increased risk of sudden cardiac death (SCD) observed in patients prescribed potassium wasting diuretics.[25,26]

The increase in QTc associated with hypokalemia may seem paradoxical based on strictly potassium concentration gradient considerations. However, potassium channel conductance

also decreases with decreasing extracellular serum potassium leading to QTc prolongation. [27,28]

Our data and others suggest the QTc in women is not only longer on average, but also more sensitive to some perturbations such as hypokalemia[15] or certain medications[29] that increase QTc. This could partly explain the increased risk of TdP associated with QT prolonging medicines observed in women despite a relatively modest average increase in the unmedicated state QTc.[30] The mechanism of increased sensitivity of women to QT prolongation from hypokalemia and the etiology of the U-shaped dependence observed (Figure 2B) are unknown, though estrogen may directly modulate rapid potassium rectifier channel function.[31] After observing this finding, the interactions of sex with other important predictors were checked. No consistent trend or other significant interactions were identified. These terms were not retained.

Previous evidence suggests a positive interaction between antidysrhythmic therapy and lower serum potassium in prolonging QTc.[28,32] We observed no significant effect.

Methadone prescribed at an average daily dose of 84 mg was associated with a 43.6 ms (95%CI 28.1–59.2) increase in QTc. This is on the order of a class III antidysrhythmic and higher than previous estimates.[33,34] Interactions with other medicines, other predictors related to the ED visit, or the underlying genotype[35] possibly enriched the long QT patient sample with patients taking methadone. Measurement bias is also possible if clinicians specifically queried and obtained a history of methadone use from patients after obtaining an ECG with QT prolongation. However, figure 3 may underestimate the association of interest because predictors that are partly collinear with methadone may take on the relevant association with QTc upon construction of the model absent methadone. The mechanism of QTc prolongation due to methadone appears to be block of the rapid potassium rectifier current, I_{Kr} . [36] The implications for SCD risk associated with methadone-induced QT prolongation remain uncertain.[37,38]

Advancing age, low LVEF, circadian variation, QRS duration, and serum creatinine and calcium demonstrated modest adjusted associations with QTc. For every 10 ms increase in QRS, QTc increases by approximately 4 ms. QTc increases progressively with renal insufficiency and this may partly explain the increased incidence of SCD in renal failure patients.[39] The strength of association of hypocalcemia with QT prolongation is a fraction of that observed with hypokalemia. Circadian variation was modeled with a quadratic function with a 10 ms variation range over 24 hours including a maximum at midnight and nadir at 10 AM.

Medicines known to cause QTc prolongation exhibited a coefficient of 14 ms. Agents with possible or conditional risk had smaller point estimates. Assessing medication categories alone clearly oversimplifies the complex pharmacodynamic interactions that can occur leading to QTc prolongation.[2]

Contrary to prior reports,[3,40] serum glucose had little independent association after adjustment. Hypomagnesemia is associated with SCD,[41] and magnesium reportedly suppressed TdP in numerous reports, but our results confirm serum magnesium is not

strongly associated with QTc.[42] Magnesium is thought to treat TdP by other mechanisms such as EAD suppression.[43] Although acute ischemia has been shown to increase QTc,[8] the coefficients for NSTEMI and STEMI were small. Similarly, acute CVA and ICH had minimal effects.

Regarding patients with QTc>500 ms and QRS<120 ms, the prevalence of TdP during the hospital visit was 0.6%. However, mortality was high at 8% reflecting a variety of serious illness. Physicians understood this, admitting 88% of these patients. These data resemble prior results.[44]

Limitations

This study did not include patients without an ECG. The associations observed could differ in them. ECG QT intervals were manually checked by an emergency physician without formal cardiologic training. A retrospective study carries risk for bias, though none was observed on blinded reliability analysis. The single center design limits generalizability particularly based on the specific medicines prescribed in our medical community. Collecting data on all relevant predictors and modelling the complex interactions in determining the QTc is a daunting challenge. We assessed major known clinical factors,[2,3] but there may be other clinical factors not addressed that effect QTc too. Genetic data on the common variants known to affect QTc,[3] were unavailable.

Some included predictors such as STEMI were uncommon and thus power to obtain narrow 95% CI's was limited. Some known predictors including eating disorders and diuretic therapy were specifically excluded from our model due to likely strong collinearity with underlying electrolyte abnormalities. Inclusion of such collinear predictors could bias and increase uncertainty in the fundamental metabolic coefficients. Sporadically tested predictors such as thyroid function were excluded.

Conclusions

We report a multivariate analysis of clinical predictors of QT prolongation. LQTS, class III antidysrhythmic and methadone therapies, and hypokalemia, particularly in women, exhibited the strongest associations in our ED. These may be the most important factors to assess and address when caring for a patient with QT prolongation. QT prolongation with normal QRS is not necessarily associated with imminent TdP, but mortality in these patients is substantial.

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Highlights

- Hypokalemia is the metabolic factor most strongly associated with QTc prolongation, and the association is stronger in women.
- The association of methadone with QTc prolongation stands out among non-cardiologic medicines.
- Serum glucose and magnesium, and acute myocardial infarction or central nervous system event are not strongly associated with QTc after adjustment for other factors.
- QTc > 500 ms with QRS < 120 ms are associated with 8% mortality but low risk of Torsades de Pointes (0.6%) during an emergency department visit and subsequent hospitalization.

Figure 1.

Study Flowchart. Flowchart of recruitment, exclusions, inclusions, and missing data.

Figure 2A

Figure 2B

Figure 2.

QTc Postassium Scattergram

Figure 2A: Residuals from full model absent potassium as a function of serum potassium. Scattergram with Loess curve.

Figure 2B: Adjusted estimates of association of QTc with serum K for women (pink) and men (blue)

Figure 3.

QTc Methadone Dose Scattergram.

Residuals from full model absent methadone predictor as a function of daily dose of prescribed methadone. Scattergram with linear regression line ($y = -11.8 + 0.64 \cdot x$).

Table 1

Patient Characteristics: mean values (standard deviation) or number of cases (% of n)

Patient characteristics:	QTc<500 ms	QTc>=500 ms & QRS>=120 ms	QTc>=500 ms & QRS<120 ms	Total
n (except where noted)	195	129	686	1010
Patient age (years)	59.3 (18.6)	73.7 (13.3)	61.6 (18.0)	62.7 (18.1)
Males	104 (53.3%)	77 (59.7%)	322 (46.9%)	503 (49.8%)
LVEF < 35% *	4 of 124 (3.2%)	30 of 118 (25.4%)	60 of 503 (11.9%)	94 of 745 (12.6%)
Hemodialysis	2 (1.0%)	6 (4.7%)	40 (5.8%)	48 (4.8%)
Hypothermia (<90 deg F)	0 (0.0%)	0 (0.0%)	5 (0.7%)	5 (0.5%)
Antidysrhythmic therapy:				
Amiodarone	1 (0.5%)	20 (15.5%)	31 (4.5%)	52 (5.2%)
Sotalol	1 (0.5%)	1 (0.7%)	13 (1.9%)	15 (1.5%)
Other	0 (0.0%)	1 (0.7%)	5 (0.7%)	6 (0.6%)
Methadone	1 (0.5%)	0 (0.0%)	29 (4.2%)	30 (3.0%)
Known QT prolonging meds (mean #)	0.01 (0.1)	0.02 (0.1)	0.03 (0.2)	0.02 (0.1)
Possible QT prolonging meds (mean #)	0.2 (0.4)	0.1 (0.3)	0.2 (0.5)	0.2 (0.5)
Conditional QT prolonging meds (mean #)	0.2 (0.5)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)
Newly classified QT prolonging meds (post November 2011) (mean #)	0.07 (0.3)	0.08 (0.3)	0.1 (0.4)	0.1 (0.3)
ECG acquisition hour of the day	12.1 (6.2)	12.8 (6.5)	13.1 (6.8)	12.9 (6.6)
Heart rate	79.7 (20.9)	80.7 (18.3)	91.5 (24.3)	87.8 (23.6)
Atrial fibrillation	11 (5.6)	18 (14.0)	81 (11.8)	110 (10.9)
QTc (ms)	434.8 (28.3)	530.5 (27.1)	526.4 (31.7)	509.2 (47.5)
QRS interval duration (ms)	94.6 (20.5)	157.6 (25.9)	93.4 (12.5)	101.8 (27.0)
LVH (Sokolow or Cornell criteria)	28 (14.4%)	19 (14.7%)	151 (22.0%)	198 (19.6%)
Serum sodium (Na) (mmol/L)	137.5 (4.3)	136.9 (4.2)	136.7 (5.1)	136.9 (4.9)
Serum potassium (K) (mmol/L)	4.0 (0.6) (n=193)	4.1 (0.9)	3.6 (0.7)	3.8 (0.7) (n=1008)
Serum bicarbonate (HCO ₃) (mmol/L)	25.9 (3.1)	26.0 (4.5)	24.7 (6.1)	25.1 (5.5)
Serum creatinine (mg/dl)	1.0 (0.6)	1.8 (1.9)	1.6 (2.1)	1.5 (1.9)
Serum glucose (mg/dl)	120.8 (51.2)	138.7 (70.8)	149.8 (99.8)	142.8 (89.6)
Serum magnesium (Mg) (meq/L)	1.7 (0.2) (n=173)	1.8 (0.3) (n=126)	1.7 (0.3) (n=663)	1.7 (0.3) (n=962)
Serum calcium (Ca) (mg/dl)	9.5 (0.6)	9.3 (0.7) (n=128)	9.0 (1.0) (n=683)	9.1 (0.9) (n=1006)
Toxicologic testing	50 (25.6%)	18 (14.0%)	278 (40.5%)	346 (34.3%)
Non-ST elevation MI (NSTEMI)	0 (0.0%)	7 (5.4%)	24 (3.5%)	31 (3.1%)
ST elevation MI (STEMI)	0 (0.0%)	0 (0.0%)	4 (0.6%)	4 (0.4%)
Ischemic cerebrovascular accident (CVA)	2 (1.0%)	0 (0.0%)	18 (2.6%)	20 (2.0%)
Intracranial hemorrhage (ICH)	9 (4.6%)	4 (3.1%)	46 (6.7%)	59 (5.8%)
Overdose of QT prolonging medicine	0 (0.0%)	0 (0.0%)	14 (2.0%)	14 (1.4%)
Known or suspected genetic LQTS	0 (0.0%)	1 (0.8%)	4 (0.6%)	5 (0.5%)
Hospital admission:				
ED Observation Unit	26 (13.3%)	12 (9.3%)	39 (5.7%)	77 (7.6%)
Hospital ward or stepdown unit	83 (42.6%)	84 (65.1%)	393 (57.3%)	560 (55.4%)

Patient characteristics:	QTc<500 ms	QTc>=500 ms & QRS>=120 ms	QTc>=500 ms & QRS<120 ms	Total
ICU	9 (4.6%)	14 (10.9%)	157 (22.9%)	180 (17.8%)
OR or cardiac cath lab	4 (2.1%)	3 (2.3%)	13 (1.9%)	20 (2.0%)
TdP during ED care or admission	0 (0.0%)	0 (0.0%)	4 (0.6%)	4 (0.4%)
Mortality during ED care or admission	0 (0.0%)	2 (1.6%)	55 (8.0%)	57 (5.6%)

* Median absolute difference in days between ECG acquisition and measurement of LVEF was 31 (IQR 1,195).

Abbreviations: ms=milliseconds, LVEF=left ventricular ejection fraction, LVH=left ventricular hypertrophy, LQTS=long QT syndrome, ED=emergency department, ICU=intensive care unit, OR=operating room, TdP=Torsades de Pointes

Table 2

Multiple regression coefficients with QTc as dependent variable

Predictor Name:	Coefficient	Standard Error	Lower 95% CI	Upper 95% CI
Constant	486.60	41.54	405.09	568.12
Age (years)	0.27	0.08	0.11	0.43
Female sex (Y,N)	-0.75	4.06	-8.73	7.22
LVEF < 35% (Y,N)	10.71	4.93	1.03	20.39
Hemodialysis patient (Y,N)	4.63	7.54	-10.17	19.43
Temperature < 90 deg F (Y,N)	-0.71	19.15	-38.28	36.86
Antidysrhythmic medicine (Y,N)	26.10	5.36	15.57	36.62
Antidysrhythmic * K<3.9 (mmol/L)	2.06	7.25	-12.15	16.28
Methadone (Y,N)	43.62	7.94	28.05	59.19
Known Long QT medicine (#)	14.15	9.05	-3.61	31.91
Possible long QT medicine (#)	3.88	2.93	-1.87	9.63
Conditional long QT medicine (#)	4.93	2.31	0.40	9.46
New long QT medicine (#)	-0.34	4.24	-8.65	7.98
Hour of ECG acquisition	-0.97	0.75	-2.44	0.50
(Hour of ECG acquisition) ²	0.05	0.03	-0.01	0.11
QRS duration (ms)	0.37	0.06	0.26	0.48
LVH (Sokolow or Cornell) (Y,N)	0.00	3.47	-6.80	6.80
Serum sodium (Na) (mmol/L)	0.08	0.28	-0.48	0.64
Serum potassium (K) if <3.9 (mmol/L)	-29.53	5.31	-39.95	-19.12
Female sex * K<3.9 (mmol/L)	-13.44	6.70	-26.58	-0.30
Serum potassium (K) if >3.9 (mmol/L)	-8.47	3.98	-16.28	-0.65
Female sex * K>3.9 (mmol/L)	12.20	7.20	-1.93	26.32
Serum bicarbonate (mmol/L)	-0.40	0.28	-0.94	0.15
Serum creatinine (mg/dl)	3.01	0.94	1.17	4.84
Serum glucose (mg/dl)	0.03	0.02	0.00	0.06
Serum magnesium (meq/L)	1.40	4.84	-8.10	10.89
Serum calcium (mg/dl)	-6.63	1.66	-9.90	-3.37
NSTEMI (Y,N)	0.32	7.85	-15.09	15.73
STEMI (Y,N)	1.62	21.23	-40.04	43.28
CVA (Y,N)	0.47	9.66	-18.49	19.44
Intracranial hemorrhage (Y,N)	0.40	5.78	-10.95	11.75
Overdose QT prolonging agent (Y,N)	6.67	11.61	-16.13	29.46
LQTS diagnosis (Y,N)	32.63	19.02	-4.69	69.95

* Notes:

(Y,N) signifies the change in QTc (ms) associated with the presence of the predictor. The presence or absence of the predictor is coded with a dummy variable equal to 1 (predictor present) or 0 (absent).

(#) refers to the change in QTc (ms) associated with ingestion of each medicine in that category. Units such as (mmol/l) refer to the change in QTc (ms) for each 1 mmol/L change in the predictor.

Plasma potassium is coded as the observed value minus 3.9, either above or below. Female gender * $K < 3.9$ is an interaction term multiplying 1 if the patient is female times (plasma K - 3.9) if less than 3.9. Female gender * $K > 3.9$ and Antidysrhythmic * $K < 3.9$ are similar interaction terms.

Abbreviations: LVEF=left ventricular ejection fraction, LVH=left ventricular hypertrophy, NSTEMI=non ST elevation myocardial infarction, STEMI=ST elevation myocardial infarction, CVA=cerebrovascular accident, LQTS=long QT syndrome

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