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# Prevalence of QT Interval Prolongation in Patients Admitted to Cardiac Care Units and Frequency of Subsequent Administration of QT Interval-Prolonging Drugs

## A Prospective, Observational Study in a Large Urban Academic Medical Center in the US

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## Abstract

**Background:** Cardiac arrest due to torsades de pointes (TdP) is a rare but catastrophic event in hospitals. Patients admitted to cardiac units are at higher risk of drug-induced QT interval prolongation and TdP, due to a preponderance of risk factors. Few data exist regarding the prevalence of QT interval prolongation in patients admitted to cardiac units or the frequency of administering QT interval-prolonging drugs to patients presenting with QT interval prolongation.

**Objective:** The aim of this study was to determine the prevalence of Bazett's-corrected QT ($QT_c$) interval prolongation upon admission to cardiac units and the proportion of patients presenting with $QT_c$ interval prolongation who are subsequently administered QT interval-prolonging drugs during hospitalization.

**Methods:** This was a prospective, observational study conducted over a 1-year period (October 2008–October 2009) in 1159 consecutive patients admitted to two cardiac units in a large urban academic medical centre located in Indianapolis, IN, USA. Patients were enrolled into the study at the time of admission to the hospital and were followed daily during hospitalization. Exclusion criteria were age <18 years, ECG rhythm of complete ventricular pacing, and patient designation as 'outpatient' in a bed and/or duration of stay <24 hours. Data collected included demographic information, past

medical history, daily progress notes, medication administration records, laboratory data, ECGs, telemetry monitoring strips and diagnostic reports. All patients underwent continuous cardiac telemetry monitoring and/or had a baseline 12-lead ECG obtained within 4 hours of admission. QT intervals were determined manually from lead II of 12-lead ECGs or from continuous lead II telemetry monitoring strips. $QT_c$ interval prolongation was defined as ≥470 ms for males and ≥480 ms for females. In both males and females, $QT_c$ interval >500 ms was considered abnormally high. A medication was classified as QT interval-prolonging if there were published data indicating that the drug causes QT interval prolongation and/or TdP. Study endpoints were (i) prevalence of $QT_c$ interval prolongation upon admission to the Cardiac Medical Critical Care Unit (CMCCU) or an Advanced Heart Care Unit (AHCU); (ii) proportion of patients admitted to the CMCCU/AHCU with $QT_c$ interval prolongation who subsequently were administered QT interval-prolonging drugs during hospitalization; (iii) the proportion of these higher-risk patients in whom TdP risk factor monitoring was performed; (iv) proportion of patients with $QT_c$ interval prolongation who subsequently received QT-prolonging drugs and who experienced further $QT_c$ interval prolongation.

**Results:** Of 1159 patients enrolled, 259 patients met exclusion criteria, resulting in a final sample size of 900 patients. Patient characteristics: mean (± SD) age, 65 ± 15 years; female, 47%; Caucasian, 70%. Admitting diagnoses: heart failure (22%), myocardial infarction (16%), atrial fibrillation (9%), sudden cardiac arrest (3%). $QT_c$ interval prolongation was present in 27.9% of patients on admission; 18.2% had $QT_c$ interval >500 ms. Of 251 patients admitted with $QT_c$ interval prolongation, 87 (34.7%) were subsequently administered QT interval-prolonging drugs. Of 166 patients admitted with $QT_c$ interval >500 ms, 70 (42.2%) were subsequently administered QT interval-prolonging drugs; additional $QT_c$ interval prolongation ≥60 ms occurred in 57.1% of these patients.

**Conclusions:** $QT_c$ interval prolongation is common among patients admitted to cardiac units. QT interval-prolonging drugs are commonly prescribed to patients presenting with $QT_c$ interval prolongation.

Torsades de pointes (TdP) is a potentially life-threatening polymorphic ventricular tachycardia associated with prolongation of the QT interval.[1,2] More than 50 drugs on the US market, from a variety of drug classes, have the potential to cause TdP.[3] Cardiac arrest due to TdP is an uncommon but catastrophic event in hospitalized patients.[4] The risk of drug-induced TdP may be greater in hospitalized patients than in outpatient populations, because hospitalized patients are more likely to have risk factors, such as underlying heart disease, advanced age, electrolyte abnormalities, bradycardia, or kidney or liver disease.[3,4] Recently, the American Heart Association (AHA) and the American College of Cardiology (ACC) Foundation released a scientific statement with the purpose of raising awareness among those who care for hospitalized patients about the risk of TdP in hospitalized patients, and recommended ECG monitoring and management of drug-induced

 

long QT interval syndrome.[4] However, the proposed monitoring protocols are both technology-dependent and labour intensive. Identification of patients at highest risk and avoidance of drugs or drug combinations in vulnerable patients may be a simpler and more cost-effective mechanism of reducing in-hospital risk.

In particular, patients admitted to cardiac care units may be at especially high risk of drug-induced QT interval prolongation and TdP as a result of the presence of underlying heart disease, the likelihood of electrolyte abnormalities and the potential for concomitant liver or kidney disease. Despite the potential for a higher risk of drug-induced TdP, few published data exist regarding the proportion of patients admitted to cardiac care units with QT interval prolongation, or the frequency with which QT interval-prolonging drugs are prescribed to patients presenting to cardiac care units with QT interval prolongation. The objectives of this study were to (i) determine the prevalence of QT interval prolongation upon admission to a Cardiac Medical Critical Care Unit (CMCCU) or an Advanced Heart Care Unit (AHCU); and (ii) estimate the proportion of patients admitted to a CMCCU/AHCU with QT interval prolongation who are subsequently administered QT interval-prolonging drugs during hospitalization.

## Methods

This prospective, observational study was conducted from October 2008 to October 2009 in 1159 consecutive patient admissions to the CMCCU or AHCU, which comprise a total of 56 beds, at Indiana University Health Methodist Hospital, a 747-bed tertiary-care institution in Indianapolis, IN, USA. The study was approved by the Institutional Review Board at Indiana University-Purdue University Indianapolis; informed consent was waived.

Patients were enrolled at the time of admission to the hospital, and were followed daily during hospitalization. One of the investigators (HW) acted as an independent observer who did not intervene in patients' care. Criteria for exclusion of patients from the study were age <18 years, ECG rhythm of complete ventricular pacing, and patient designation as 'outpatient' in a bed and/or duration of stay <24 hours. Data collected included demographic information, past medical history, daily progress notes, medication administration records, laboratory data, ECGs, telemetry monitoring strips, and diagnostic reports.

All patients underwent continuous cardiac telemetry monitoring and/or a baseline 12-lead ECG obtained within 4 hours of admission. QT intervals were determined manually by an investigator (HW, approximately 90% of ECGs) or a technician (approximately 10% of ECGs) from lead II of 12-lead ECGs or from continuous lead II telemetry monitoring strips. Inter-rater reliability was determined by comparing QT interval measurements on approximately 5% of the ECGs (Kappa = 0.90). QT intervals were measured from the earliest QRS deflection to the end of the T wave, determined by return to isoelectric baseline. During normal sinus rhythm, QT and RR intervals were averaged over three consecutive complexes. During other rhythms, QT and RR intervals were averaged over all complexes on the 6-second rhythm strips or lead II on the 12-lead ECGs. QT intervals were measured only from ECGs on which the end of the T wave was clearly discernable. QT intervals were corrected for heart rate using Bazett's correction ($QT_c$), per standard clinical practice.[5]

$QT_c$ interval prolongation was defined as ≥470 ms for males and ≥480 ms for females.[3] In both males and females, $QT_c$ interval >500 ms was considered abnormally high.[4,6-8] The following were considered risk factors for TdP:[3,4] age >65 years, female sex, heart failure due to left ventricular systolic dysfunction, myocardial infarction, hypokalaemia (defined as serum potassium <3.5 mEq/L), hypomagnesaemia (defined as serum magnesium <1.8 mEq/L), hypocalcaemia (defined as serum calcium <7.0 mg/dL), treatment with diuretics, bradycardia; concurrent use of >1 QT-prolonging drug. A medication was classified as QT interval-prolonging if there are published data indicating that the drug causes QT interval prolongation and/or TdP. This information was obtained using the Agency for Healthcare Research and Quality-funded website (www.qtdrugs.org)

 

and verifying that published literature exists by using the electronic link to PubMed feature on that website.

Study endpoints were (i) prevalence of $QT_c$ interval prolongation upon admission to the CMCCU/AHCU; (ii) proportion of patients admitted to the CMCCU/AHCU with $QT_c$ interval prolongation who were subsequently administered QT interval-prolonging drugs during hospitalization; (iii) the proportion of these higher-risk patients in whom TdP risk factor monitoring was performed; (iv) proportion of patients with $QT_c$ interval prolongation who subsequently received QT-prolonging drugs and who experienced further $QT_c$ interval prolongation.

Since many patients with cardiovascular diseases have intraventricular conduction delays (IVCD) that influence QT interval measurement and interpretation, we also determined study endpoints separately in patients who had IVCD (defined as QRS ≥0.11 s)[9] on admission and in those patients without IVCD.

Statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) utilizing the unpaired Student's t-test for continuous variables, assuming equal or unequal variances between the groups, or Chi-Square or Fisher's Exact test, as appropriate, for categorical variables. Comparisons for non-normally distributed continuous parameters were performed using the non-parametric Wilcoxon Rank Sum test. For all comparisons, $\alpha$ was set at 0.05.

## Results

### Overall Population

A total of 1159 consecutive patients admitted to the CMCCU/AHCU were evaluated for inclusion. After application of exclusion criteria, a total of 900 patients were included. Reasons for exclusion were age <18 years (n = 3), ECG rhythm of complete ventricular pacing (n = 47), patient designation as 'outpatient' in a bed and/or <24-hour duration of stay (n = 209). Of the 900 patients included, 790 presented in normal sinus rhythm, 76 presented in atrial fibrillation and 34 presented with frequent ventricular premature depolarizations or premature atrial contractions. In 41 patients (4.5%), a baseline 12-lead ECG was unavailable, and a telemetry strip was used for QT interval determination.

The mean $QT_c$ interval on admission was 462 ± 47 ms. There was no significant difference between men and women in mean $QT_c$ interval on admission (452 ± 54 vs 465 ± 48; p = 0.10). Demographics of the overall population are presented in table I.

Of the 900 patients included in this study, n = 289 were receiving QT interval-prolonging drugs on admission. Characteristics of these patients are presented in table II. $QT_c$ interval prolongation was present on admission in 91 (31.5%) of these patients. Compared with patients admitted while taking QT interval-prolonging drugs who did not have QT interval prolongation, patients admitted while taking QT interval-prolonging drugs who had $QT_c$ interval prolongation on admission had a significantly larger number of TdP risk factors and a higher prevalence of acute heart failure, acute myocardial infarction, resuscitation from sudden cardiac arrest, and left ventricular systolic dysfunction.

QT interval-prolonging drugs being taken by patients on admission (per patient/family self-report or available medical record) are listed in table III. Common QT interval-prolonging drugs included intravenous or oral amiodarone, fluoroquinolone or macrolide antibacterials, methadone, ranolazine and ziprasidone. Many patients received intravenous amiodarone prior to admission; in these cases, amiodarone was administered intravenously in the field, in the ambulance or in the Emergency Department for the management of ventricular tachycardia, ventricular fibrillation, or new-onset or uncontrolled atrial fibrillation. In many cases, these QT interval-prolonging medications were continued following admission.

#### *Prevalence of $QT_c$ Interval Prolongation on Admission*

$QT_c$ interval prolongation was present in 251 (27.9% [95% CI 25.1, 30.9]) patients on admission, including 164 (18.2% [95% CI 15.8, 20.9]) patients with $QT_c$ >500 ms (table IV). There was no difference in the proportion of men versus

**Table I.** Comparison of patients who were admitted to a Cardiac Medical Critical Care Unit or an Advanced Heart Care Unit with $QT_c$ interval prolongation with those who were admitted with normal $QT_c$ intervals[a]

| Patient characteristics | $QT_c$ interval prolongation (n = 251/900) | No $QT_c$ interval prolongation (n = 649/900) | p-Value |
|---|---|---|---|
| Age (years) | 66 ± 17 | 65 ± 15 | 0.39 |
| Female sex (%) | 46 | 48 | 0.18 |
| Caucasian race (%) | 71 | 70 | 0.84 |
| $QT_c$ interval prolonging drug(s) prior to admission (%) | 36 | 31 | 0.18 |
| Admission serum $K^+$ (mEq/L) | 3.5 ± 0.7 | 3.8 ± 0.6 | 0.001 |
| Admission serum $Mg^{++}$ (mg/dL) | 1.7 ± 0.5[b] | 1.9 ± 0.8[c] | 0.02 |
| Number of TdP risk factors | 3.9 ± 1.3 | 2.2 ± 1.4 | 0.001 |
| **Admitting diagnoses (%)** | | | |
| Acute heart failure | 32 | 18 | 0.001 |
| Acute MI | 24 | 13 | 0.001 |
| PCI | 22 | 16 | 0.05 |
| Acute atrial fibrillation | 8 | 9 | 0.69 |
| Sudden cardiac arrest | 4 | 2 | 0.10 |
| Diabetes mellitus | 36 | 31 | 0.18 |
| Coronary artery disease | 33 | 32 | 0.62 |
| LV systolic dysfunction | 43 | 25 | 0.001 |
| Acute infection (any) | 34 | 17 | 0.001 |
| Acute respiratory distress (not cardiac related) | 17 | 7 | 0.001 |
| Chronic COPD/asthma | 25 | 13 | 0.001 |
| Kidney disease (acute and/or chronic) | 40 | 36 | 0.41 |
| Hepatic dysfunction (acute and/or chronic) | 3 | 3 | 0.99 |

a Data are mean ± standard deviation unless otherwise indicated.

b n = 108.

c n = 214.

**COPD** = chronic obstructive pulmonary disease; **$K^+$** = potassium; **LV** = left ventricular; **$Mg^{++}$** = magnesium; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **$QT_c$** = Bazett's-corrected QT interval; **TdP** = Torsades de pointes.

women who presented with $QT_c$ interval prolongation (30.1% [95% CI 24.9, 36.2] vs 25.7% [95% CI 20.9, 31.6]; p = 0.16). There was also no difference in the proportion of men versus women with admitting $QT_c$ interval >500 ms (18.7% (95% CI 15.4, 22.4] vs 17.8% [95% CI 14.3, 21.3%]; p = 0.63). The mean (±SD) $QT_c$ interval in patients with admitting $QT_c$ interval prolongation compared with those without admitting QTc interval prolongation was 500 ± 27 (range 470–660 ms) versus 433 ± 28 (range 304–479 ms), p = 0.001. Patients with $QT_c$ interval prolongation on admission had lower serum potassium concentrations and nearly twice the number of TdP risk factors (table I). Serum magnesium concentrations were only measured in 322 (35.8%) patients, but were significantly lower in patients with admitting $QT_c$ interval prolongation. More patients presenting with $QT_c$ interval prolongation had an admitting diagnosis of acute heart failure or myocardial infarction, as well as underlying left ventricular dysfunction (table I).

### *Proportion of Patients Presenting with $QT_c$ Interval Prolongation who were Subsequently Administered QT Interval-Prolonging Drugs during Hospitalization*

Of the 251 patients admitted with $QT_c$ interval prolongation, 87 (34.7%) subsequently received ≥1 QT interval-prolonging drugs. There was no difference in the proportion of men versus women who presented with $QT_c$ interval prolongation who subsequently received a QT interval-prolonging drug (35.1% [95% CI 27.5, 43.4] vs 34.5% [26.4–43.5%]; p = 0.92).

Of the 166 patients who were admitted with $QT_c$ interval >500 ms, 70 (42.2%) subsequently received QT interval-prolonging drugs. A significantly higher proportion of males who presented with $QT_c$ interval >500 ms were subsequently administered QT interval-prolonging drugs compared with females (45.4% [95% CI 34.8, 56.0%] vs 38.5% [95% CI 28.0, 49.0%]; p = 0.04).

The QT interval-prolonging medications that were administered to patients who presented with $QT_c$ interval prolongation are presented in figure 1. Amiodarone, initially administered intravenously, followed by oral administration in most cases, accounted for approximately one-third of these drugs. Anti-infective drugs, most commonly fluoroquinolone antibacterials, also accounted for approximately one-third of these medications. Intravenous haloperidol for delusional agitation accounted for nearly 20% of the administered QT interval-prolonging drugs. Approximately 20% of patients received ≥2 QT interval-prolonging medications.

Additional $QT_c$ interval prolongation (defined as $QT_c$ interval lengthening to >500 ms or an increase in the $QT_c$ interval of ≥60 ms) occurred in 30 (34.5%) of the 87 patients who presented with $QT_c$ interval prolongation and who subsequently received QT interval-prolonging medications. Of these 30 patients, 16 (53%) were female and 14 (47%) were male. Of the 70 patients who presented with $QT_c$ interval >500 ms who subsequently received QT interval-prolonging medications, 40 (57.1%) developed additional $QT_c$ interval prolongation (≥60 ms beyond presenting value). The distribution of females versus males among these 40 patients was 58% versus 42%. No patients in this study experienced TdP.

### *Torsades de pointes Risk Factor Monitoring*

There was no significant difference between patients who presented with $QT_c$ interval prolongation and those who did not in the proportion of patients who had at least one $QT_c$ interval measured within 24 hours of receiving a QT interval-prolonging drug (figure 2). The proportion of patients who underwent monitoring of serum potassium or magnesium concentrations following the administration of QT interval-prolonging drugs is presented in figure 2. Overall, more than

**Table II.** Characteristics of patients receiving QT interval-prolonging medications on admission to a Cardiac Medical Critical Care Unit or an Advanced Heart Care Unit[a]

| Patient characteristics | $QT_c$ interval prolongation (n = 91/289) | No $QT_c$ interval prolongation (n = 198/289) | p-Value |
|---|---|---|---|
| Age (years) | 66 ± 16 | 64 ± 18 | 0.36 |
| Female sex (%) | 46 | 43 | 0.18 |
| Caucasian race (%) | 68 | 68 | 0.84 |
| Admission serum $K^+$ (mEq/L) | 3.7 ± 0.6 | 3.8 ± 0.6 | 0.19 |
| Admission serum $Mg^{++}$ (mg/dL) | 1.7 ± 0.5 (n = 84) | 1.9 ± 0.9 (n = 127) | 0.07 |
| Number of TdP risk factors (excluding receiving QT interval-prolonging drugs) | 3.1 ± 1.4 | 1.5 ± 0.8 | 0.001 |
| **Admitting diagnoses (%)** | | | |
| Acute heart failure | 47 | 25 | 0.001 |
| Acute MI | 55 | 22 | 0.001 |
| PCI | 27 | 18 | 0.10 |
| Acute atrial fibrillation | 31 | 22 | 0.70 |
| Sudden cardiac arrest | 21 | 2 | 0.001 |
| Diabetes mellitus | 44 | 36 | 0.24 |
| Coronary artery disease | 46 | 39 | 0.39 |
| LV systolic dysfunction | 49 | 41 | 0.001 |

a Data are mean ± standard deviation unless otherwise indicated.

**$K^+$** = potassium; **LV** = left ventricular; **$Mg^{++}$** = magnesium; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **$QT_c$** = Bazett's-corrected QT interval; **TdP** = Torsades de pointes.

**Table III.** QT interval-prolonging medications administered to patients within 48 hours prior to admission to a Cardiac Medical Critical Care Unit or an Advanced Heart Care Unit

| Medications | Number of patients | Number of patients continued on medication during hospitalization[a] |
|---|---|---|
| Amiodarone (oral) | 98 | 73 |
| Amiodarone (intravenous)[b,c] | 88 | 51 |
| Azithromycin | 28 | 21 |
| Ciprofloxacin | 7 | 5 |
| Cocaine positive[d] | 3 | 0 |
| Erythromycin | 2 | 2 |
| Fluconazole | 5 | 2 |
| Levofloxacin | 12 | 3 |
| Methadone[e] | 11 | 7 |
| Moxifloxacin | 15 | 0 |
| Procainamide | 1 | 1 |
| Ranolazine | 12 | 8 |
| Risperidone | 7 | 6 |
| Sotalol | 9 | 6 |
| Ziprasidone | 10 | 8 |
| Two or more QT-interval prolonging medications | 19 | 15 |

a Restarted at any time during hospitalization; medications not continued were at times changed to intravenous form or medication within the same class.

b Given outside of hospital or in emergency room prior to admission to unit.

c Patients who were on oral amiodarone prior to admission and then received intravenous amiodarone within 48 hours were only included in the intravenous amiodarone count.

d Patient tested positive for cocaine in urine drug screen within 48 hours of admission.

e Two patients with overdose involving methadone.

90% of patients had a serum potassium concentration measured within 24 hours of receiving a QT interval-prolonging drug. There was no significant difference in the incidence of serum potassium concentration monitoring between patients who presented with $QT_c$ interval prolongation and those patients who did not. However, only approximately 30% of patients underwent monitoring of serum magnesium concentration within 24 hours of receiving a QT interval-prolonging drug. There was no significant difference in the incidence of serum magnesium concentration monitoring between patients who presented with $QT_c$ interval prolongation and those patients who did not present with $QT_c$ interval prolongation who subsequently received a QT interval-prolonging drug.

### Patients with Intraventricular Conduction Delays Compared with those with Normal QRS Duration

Compared with patients who presented with normal QRS duration, patients who presented with IVCD were significantly older, with a preponderance of males, and had a significantly greater number of TdP risk factors (table V). Admitting diagnoses of acute heart failure, myocardial infarction, atrial fibrillation, sudden cardiac arrest, diabetes mellitus and history of left ventricular dysfunction were more prevalent in patients with IVCD.

The proportion of patients with IVCD who presented with $QT_c$ interval prolongation was larger than in patients with normal QRS duration (table IV). In contrast, the proportion of patients with IVCD who presented with $QT_c$ interval >500 ms was lower than in patients with normal QRS duration (table IV). The mean (±SD) $QT_c$

**Table IV.** Comparison of QT interval-prolongation data among overall study population and in patients with and without intraventricular conduction delays on admission

| Patient characteristics | All patients [%] (n = 900) | IVCD [%] (n = 243) | No IVCD [%] (n = 657) |
|---|---|---|---|
| $QT_c$ interval prolongation on admission | 27.9 (251/900) | 34.6 (84/243) | 25.4 (167/657) |
| $QT_c$ interval >500 ms on admission | 18.4 (166/900) | 14.8 (36/243) | 19.8 (130/657) |
| Patients with $QT_c$ interval prolongation on admission who subsequently received $QT_c$ interval-prolonging drugs | 34.7 (87/251) | 67.9 (57/84) | 18.0 (30/167) |
| Patients with $QT_c$ interval >500 ms on admission who subsequently received QTc interval-prolonging drugs | 42.2 (70/166) | 77.8(28/36) | 32.3 (42/130) |

**IVCD** = intraventricular conduction delay; **$QT_c$** = Bazett's-corrected QT interval.

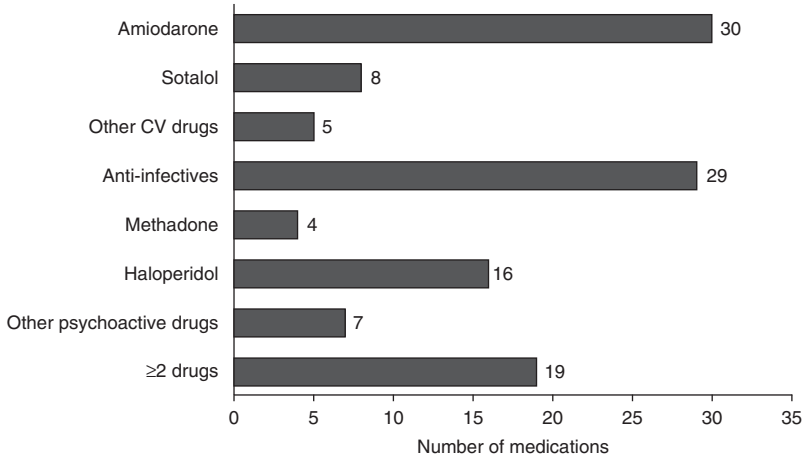


**Fig. 1.** QT interval-prolonging drugs administered to patients presenting with $QT_c$ interval prolongation. Other CV drugs: dofetilide (n = 4), ranolazine (n = 1). Anti-infectives: azithromycin (n = 15), ciprofloxacin (n = 5), fluconazole (n = 3), erythromycin (n = 2), levofloxacin (n = 2), moxifloxacin (n = 2). Other psychoactive drugs: ziprasidone (n = 5), risperidone (n = 2). ≥2 drugs: azithromycin/amiodarone (n = 3); azithromycin/haloperidol (n = 2); all others (n = 1): azithromycin/fluconazole; azithromycin/sotalol; azithromycin/ciprofloxacin; azithromycin/amiodarone/haloperidol; amiodarone/sotalol; amiodarone/ciprofloxacin; amiodarone/dofetilide; amiodarone/moxifloxacin; amiodarone/erythromycin; amiodarone/haloperidol; ciprofloxacin/haloperidol; ciprofloxacin/ziprasidone; methadone/fluconazole/azithromycin; sotalol/haloperidol. **CV** = cardiovascular; **$QT_c$** = Bazett's-corrected QT interval.

interval in patients with IVCD and admitting $QT_c$ interval prolongation compared with those with IVCD but without admitting QTc interval prolongation was 503 ± 22 (range 470–660 ms) versus 435 ± 25 (range 364–479 ms), p = 0.001.

Of the 84 patients with IVCD admitted with $QT_c$ interval prolongation, 67.9% subsequently received ≥1 QT interval-prolonging drug, compared with 18.0% of the 167 patients with normal QRS duration who were admitted with $QT_c$ interval prolongation (table IV). Of the 36 patients with IVCD who were admitted with $QT_c$ interval >500 ms, 77.8% were subsequently administered QT interval-prolonging drugs, compared with 32.3% of the 130 patients with normal QRS duration who were admitted with $QT_c$ interval >500 ms (table IV).

Additional $QT_c$ interval prolongation (defined as $QT_c$ interval >500 ms or an increase in the QTc interval of 60 ms or more) occurred in 33.3% of the 57 patients with IVCD who presented with $QT_c$ interval prolongation and who subsequently received QT interval-prolonging medications, compared with 26.7% of the 30 patients with normal QRS duration. Of the 28 patients with IVCD who presented with $QT_c$ interval >500 ms who subsequently received QT interval-prolonging medications, 32.1% developed additional $QT_c$ interval prolongation (≥60 ms beyond baseline value), compared with 14.3% of the 42 patients with normal QRS duration who presented with $QT_c$ interval >500 ms and who subsequently received QT interval-prolonging medications.

## Discussion

This study found that more than 25% of patients admitted to a CMCCU/AHCU had $QT_c$ interval prolongation on admission, with nearly 20% of patients having admitting $QT_c$ interval >500 ms. In addition, more than one-third of the patients who presented with $QT_c$ interval prolongation received a QT interval-prolonging drug during hospitalization, and over 40% of patients presenting with $QT_c$ interval >500 ms subsequently received a QT interval-prolonging drug. Additional $QT_c$ interval prolongation occurred in approximately one-third of patients who presented with $QT_c$ interval prolongation and who subsequently received QT interval-prolonging medications, and in >50% of patients who presented with $QT_c$ interval >500 ms who subsequently received

QT interval-prolonging medications. Furthermore, many patients who presented with $QT_c$ interval prolongation did not undergo QT interval monitoring within 24 hours of receiving a QT interval-prolonging drug, and only about one-third of all patients underwent measurement of a serum magnesium concentration during hospitalization.

Few published data exist regarding the prevalence of QT interval prolongation in patients admitted to hospitals, and no previously published data exist in patients admitted to cardiac care units. Lubart et al.[10] reported that $QT_c$ interval prolongation was present in 32% of elderly patients admitted to an acute geriatric ward, and that the presence of heart failure, ischaemic heart disease, and use of hypnotic drugs was associated with $QT_c$ interval prolongation upon admission. In a population of 76 newly admitted geriatric psychiatric patients, the incidence of $QT_c$ interval prolongation was 25%.[11] Seftchick et al.[12] reported that 35% of 1558 patients presenting to the Emergency Department of a tertiary care academic medical centre had pre-existing $QT_c$ interval prolongation; 8% of these patients had admitting QTc interval >500 ms. In a study of 258 patients admitted to a general medical service, 25.2% had prolonged $QT_c$ interval on admission, with 3.5% having $QT_c$ intervals >500 ms.[13] Pasquier et al.[14] reported that 22% of medical inpatients had a prolonged QTc interval, and that 51% of those patients were subsequently prescribed QT interval-prolonging drugs. Liver disease, hypokalaemia, and taking QT interval-prolonging drugs on admission were independent predictors of $QT_c$ interval prolongation.[14] These previous studies defined $QT_c$ interval prolongation as >450–470 ms for women and >450 ms for men,[10-13] which are less stringent definitions of $QT_c$ interval prolongation than currently recommended.[4] Based on the recent scientific statement from the AHA/ACC Foundation, the upper limit of normal (99th percentile) for $QT_c$ interval is 470 ms in males and 480 ms in females.[4] In the present study, despite using the more stringent $QT_c$ interval

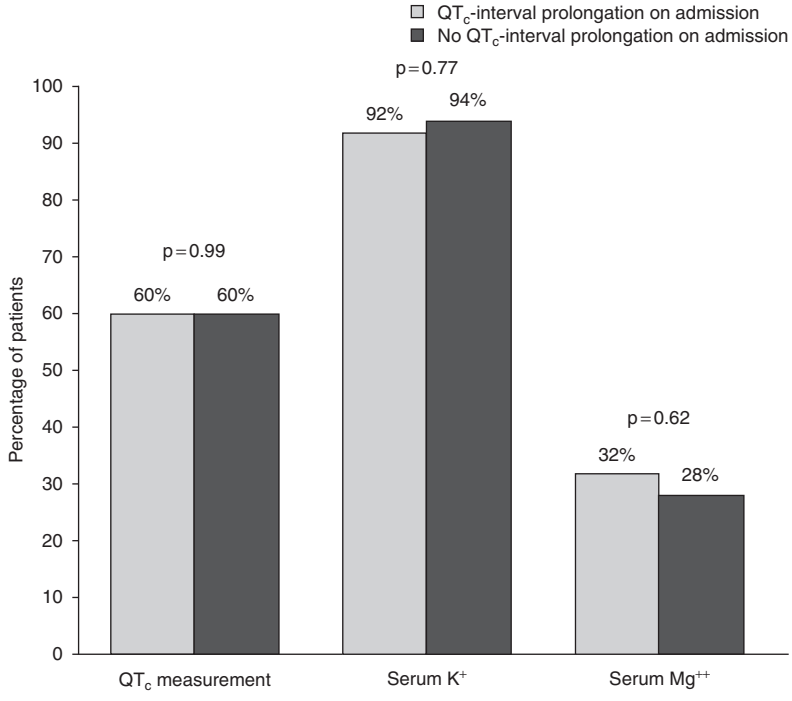


**Fig. 2.** Proportion of patients admitted to a Cardiac Medical Critical Care Unit or an Advanced Heart Care Unit who received QT interval-prolonging drugs and who underwent $QT_c$ interval risk factor monitoring. **$K^+$** = potassium; **$Mg^{++}$** = magnesium; **$QT_c$** = Bazett's-corrected QT interval.

**Table V.** Comparison of patients who were admitted to a Cardiac Medical Critical Care Unit or an Advanced Heart Care Unit with intraventricular conduction delays versus those with normal QRS intervals[a]

| Patient characteristics | IVCD (n = 243/900) | No IVCD (n = 657/900) | p-Value |
|---|---|---|---|
| Age (years) | 72 ± 14 | 62 ± 18 | 0.001 |
| Female sex (%) | 38 | 56 | 0.001 |
| Caucasian race (%) | 70 | 71 | 0.86 |
| $QT_c$ interval-prolonging drug(s) prior to admission (%) | 34 | 30 | 0.26 |
| Admission $QT_c$ interval (ms) | 453 ± 41 | 450 ± 41 | 0.89 |
| Admission serum $K^+$ (mEq/L) | 3.8 ± 1.1 | 3.6 ± 0.6 | 0.05 |
| Admission serum $Mg^{++}$ (mg/dL) | 1.8 ± 0.4[b] | 1.8 ± 0.8[c] | 0.99 |
| Number of TdP risk factors | 3.1 ± 1.6 | 2.5 ± 1.3 | 0.001 |
| **Admitting diagnoses (%)** | | | |
| Acute heart failure | 40 | 16 | 0.001 |
| Acute MI | 20 | 12 | 0.001 |
| PCI | 22 | 16 | 0.05 |
| Acute atrial fibrillation | 16 | 7 | 0.001 |
| Sudden cardiac arrest | 6 | 1 | 0.001 |
| Diabetes mellitus | 54 | 18 | 0.001 |
| Coronary artery disease | 33 | 32 | 0.99 |
| LV systolic dysfunction | 59 | 20 | 0.001 |

a Data are mean ± standard deviation unless otherwise indicated.

b n = 92.

c n = 230.

**IVCD** = intraventricular conduction delay; **$K^+$** = potassium; **LV** = left ventricular; **$Mg^{++}$** = magnesium; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **$QT_c$** = Bazett's-corrected QT interval; **TdP** = Torsades de pointes.

values as recommended by the AHA/ACC Foundation scientific statement,[4] the prevalence of $QT_c$ interval prolongation was similar to those previously reported, and the prevalence of patients with admitting $QT_c$ intervals >500 ms was markedly higher than in previous reports. These data indicate that a substantial proportion of patients admitted to cardiac care units are at risk for drug-induced TdP.

In the current study, there were no occurrences of TdP in the CMCCU/AHCU. Even in high-risk populations, TdP is a rare event. The precise incidence of TdP is not known. Swedish investigators estimated an incidence of four cases of TdP per 1 000 000 persons annually.[15] In our population of patients in the CMCCU/AHCU, who have cardiac disease and risk factors for TdP, the incidence of TdP could be expected to be higher, but is likely still relatively small. Therefore, larger numbers of patients monitored for longer periods of time would be needed to confirm a survival benefit for a risk mitigation strategy. However, although TdP occurs relatively rarely, it is a catastrophic event in hospitalized patients, and, because of the severity of this proarrhythmia, the AHA/ACC Foundation strongly recommends increased awareness of QT interval prolongation and TdP risk and QT interval monitoring and avoidance of QT interval-prolonging medications where possible in hospitalized patients.[4]

Hospitalized patients may be at higher risk of drug-induced TdP than outpatients, due to a greater number of risk factors.[4] Patients admitted to cardiac units may be at particularly high risk, due to cardiovascular disease and a greater number of TdP risk factors.[4] In the present study, admitted patients had an average of nearly three TdP risk factors, and those with $QT_c$ interval prolongation had an average of four risk factors. Common risk factors on admission in patients in this study included hypokalaemia, hypomagnesaemia, acute

myocardial infarction and heart failure due to left ventricular systolic dysfunction. The coronary and intensive care units of hospitals may provide great opportunity for reducing the risk of drug-induced TdP by identifying and mitigating risk, rather than treating proarrhythmia once it occurs.

In this study, a higher proportion of patients with IVCD received QT interval-prolonging drugs than those with normal QRS durations. Reasons for this likely include the fact that patients with IVCD are more likely to have diseases associated with arrhythmias, particularly heart failure, and therefore are more likely to present with arrhythmias requiring therapy with antiarrhythmic drugs.

Limitations of this study include the fact that this was an uncontrolled observational study conducted at a single site. In addition, Bazett's method[5] was used for heart-rate correction of QT intervals. Limitations of Bazett's correction method include the fact that this method overcorrects QT intervals at higher heart rates.[16] To avoid this issue, other correction factors, such as Fridericia, Hodges or Framingham, have been recommended.[17] However, in this study, we wished to reflect clinical practice with respect to QT interval assessment and subsequent administration of QT interval-prolonging drugs. Since Bazett's formula is uniformly used in clinical practice, and is the correction formula that most clinicians use and recognize, we chose to use it. In addition, the main purpose of the study was to determine the proportion of patients who can be classified as having QT interval prolongation. Literature and clinical practice definitions of QT prolongation are uniformly provided using Bazett's correction – there are no literature- or practice-based definitions of QT interval prolongation using the Fridericia, Hodges or any other method. Use of another rate-correction method would have precluded us from assigning patients to the classification of QT interval prolongation. Therefore, we elected to use Bazett's correction method. QT interval measurements in this study were made from lead II from 12-lead ECGs or from lead II from continuous telemetry rhythm strips, rather than solely from 12-lead ECGs. QT intervals were determined manually by an investigator or a technician, and while inter-rater reliability was good, intra-observer variability was not determined.

The AHA recommends QT interval monitoring in patients who are initiated on a QT interval-prolonging drug.[18] However, in the present study, only 60% of patients had ≥1 QT interval measured within 24 hours of receiving a QT interval-prolonging drug. In addition, less than one-third of patients underwent serum magnesium concentration monitoring within 24 hours of receiving a QT interval-prolonging drug. This underscores the need for monitoring of TdP risk factors and QT intervals in patients receiving proarrhythmic drugs. In addition, a substantial proportion of patients in this study with $QT_c$ interval prolongation on admission subsequently received therapy with a QT interval-prolonging drug. Moreover, >40% of patients with pre-existing $QT_c$ interval >500 ms subsequently received a QT interval-prolonging drug; $QT_c$ interval >500 ms is considered 'dangerous' and a 'critical threshold'.[4] In patients with $QT_c$ interval >500 ms, the AHA/ACC Foundation recommends 'alternate pharmacotherapy' that does not prolong the QT interval.[4] These findings underscore the importance of awareness of QT intervals in hospitalized patients, and awareness of methods of monitoring and risk reduction.

## Conclusions

$QT_c$ interval prolongation is common among patients admitted to cardiac care units. In addition, administration of QT interval-prolonging drugs to cardiac care unit patients with pre-existing $QT_c$ interval prolongation, including $QT_c$ interval >500 ms, occurs commonly, often resulting in additional $QT_c$ interval prolongation. $QT_c$ interval and serum electrolyte monitoring are not performed with greater frequency in patients with admitting $QT_c$ interval prolongation who subsequently receive QT interval-prolonging drugs. Increased awareness of $QT_c$ interval prolongation in patients admitted to cardiac care units is needed. Strategies should be developed to reduce the risk of QT interval prolongation, and potentially TdP, in hospitalized patients.

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