Development and Validation of a Risk Score to Predict QT Interval Prolongation in Hospitalized Patients

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Background—Identifying hospitalized patients at risk for QT interval prolongation could lead to interventions to reduce the risk of torsades de pointes. Our objective was to develop and validate a risk score for QT prolongation in hospitalized patients.

Methods and Results—In this study, in a single tertiary care institution, consecutive patients (n=900) admitted to cardiac care units comprised the risk score development group. The score was then applied to 300 additional patients in a validation group. Corrected QT (QTc) interval prolongation (defined as QTc>500 ms or an increase of >60 ms from baseline) occurred in 274 (30.4%) and 90 (30.0%) patients in the development group and validation group, respectively. Independent predictors of QTc prolongation included the following: female (odds ratio, 1.5; 95% confidence interval, 1.1–2.0), diagnosis of myocardial infarction (2.4 [1.6–3.9]), sepsis (2.7 [1.5–4.8]), left ventricular dysfunction (2.7 [1.6–5.0]), administration of a QT-prolonging drug (2.8 [2.0–4.0]), ≥2 QT-prolonging drugs (2.6 [1.9–5.6]), or loop diuretic (1.4 [1.0–2.0]), age ≥68 years (1.3 [1.0–1.9]), serum K+ <3.5 mEq/L (2.1 [1.5–2.9]), and admitting QTc >500 ms (2.3; confidence interval [1.6–3.2]). Risk scores were developed by assigning points based on log odds ratios. Low-, moderate-, and high-risk ranges of 0 to 6, 7 to 10, and 11 to 21 points, respectively, best predicted QTc prolongation (C statistic=0.823). A high-risk score ≥11 was associated with sensitivity=0.74, specificity=0.77, positive predictive value=0.79, and negative predictive value=0.76. In the variable group, the incidences of QTc prolongation were 15% (low risk); 37% (moderate risk); and 73% (high risk).

Conclusions—A risk score using easily obtainable clinical variables predicts patients at highest risk for QTc prolongation and may be useful in guiding monitoring and treatment decisions. (Circ Cardiovasc Qual Outcomes. 2013;6:479-487.)

Key Words: electrocardiography • predictors • QT interval • risk factors • torsades de pointes

Torsades de pointes (TdP) is a potentially life-threatening polymorphic ventricular tachycardia associated with prolongation of the QT interval on the ECG. Many medications, including drugs prescribed for noncardiac indications, can cause QT interval prolongation and trigger TdP, which may degenerate into ventricular fibrillation and result in sudden cardiac arrest. Therefore, TdP can be a catastrophic event in hospitalized patients.

QT interval prolongation is recognized as an ECG sign that portends an increased risk for TdP.1 The risk for developing TdP increases as the QTc interval increases.5 In patients with the congenital long QT syndrome, each 10-ms increase in Bazett-corrected QT (QTc) interval prolongation leads to an ≈5% to 7% increase in the risk of TdP.6 QTc interval >500 ms increases the risk of TdP 2- to 3-fold in patients with long QT syndrome. The risk of drug-induced TdP has also been shown to increase when the QTc interval >500 ms.7 Therefore, prolongation of the QTc interval is used as an ECG marker of increased risk of TdP.

As many as 28% of patients admitted to cardiac care units may present with QTc interval prolongation (defined as ≥2470 ms in males and ≥2480 ms in females), and nearly 1 in 5 have admitting QTc intervals ≥500 ms.10 Furthermore, the risk of drug-induced TdP may be greater in hospitalized patients than in outpatient populations because the former are more likely to have risk factors, such as underlying heart disease, advanced age, electrolyte abnormalities, bradycardia, or kidney or liver disease.4,10 A substantial proportion of hospitalized patients with QTc interval prolongation on admission subsequently receive QT interval–prolonging drugs,10 thus, enhancing their risk of proarrhythmia. Prolongation of the QTc interval in critically ill hospitalized patients is associated with increased duration of hospital stay and greater odds of in-hospital mortality.11

The American Heart Association (AHA) and the American College of Cardiology Foundation (ACCF) released a scientific statement to raise awareness among healthcare professionals about the risk, ECG monitoring, and management of...
WHAT IS KNOWN

- QT interval prolongation is a risk factor for the life-threatening arrhythmia torsades de pointes.
- Risk factors for QT interval prolongation and torsades de pointes have been identified, but a validated, reproducible method of quantifying the risk for hospitalized patients has not been developed.

WHAT THE STUDY ADDS

- A risk score for QT interval prolongation, based on log odds ratios for bivariate independent risk factors for QT prolongation, was developed and validated.
- This risk score incorporates easily obtainable clinical variables and predicts hospitalized patients at highest risk of developing drug-induced QT interval prolongation.
- This QT interval prolongation risk score may be useful for guiding monitoring and treatment decisions in patients at risk for drug-induced QT interval prolongation.

Drug-induced QT interval prolongation and TdP in hospitalized patients.4 This statement emphasized the importance of awareness of risk factors to minimize the likelihood of occurrence of drug-induced TdP.4 However, some of the fully automated QTc interval monitoring strategies suggested for use by the AHA/ACCF are labor-intensive and dependent on expensive technology. Identification of patients at highest risk of drug-induced QTc interval prolongation and development of strategies to mitigate the risk may be a simpler and more cost-effective means of reducing the likelihood of drug-induced QTc interval prolongation and TdP in hospitalized patients.

Numerous risk factors for TdP have been identified.5-12 The occurrence of TdP is largely dependent on the presence of underlying risk factors5,11 and is an extremely rare occurrence in patients without concomitant risk factors.5-12 Identification of patients at highest risk of drug-induced QTc interval prolongation and TdP could facilitate measures to modify the risk, such as discontinuation of QT interval–prolonging drugs (when possible) and managing modifiable risk factors to reduce the likelihood of TdP. However, although risk factors for QTc interval prolongation and TdP have been described well, there is a paucity of information about methods of quantification of the risk in individual patients.

A valid method of quantification of risk of drug-induced QTc interval prolongation could be integrated into clinical practice in numerous ways. For example, a QTc interval prolongation risk score could be incorporated into clinical decision support systems (CDSSs) in hospital or health-system computer systems to alert clinicians that specific patients for whom QTc interval–prolonging drugs have been prescribed (or are being considered for therapy) are at substantial risk of drug-induced QTc interval prolongation. This could lead clinicians to select lower risk drug therapy, apply more intense QTc interval monitoring in susceptible patients, or implement other interventions (such as closer monitoring of serum electrolyte concentrations) to mitigate the risk.

To achieve the long-term goal of reducing the risk of drug-induced QTc interval prolongation and TdP in hospitalized patients, we sought to develop a CDSS that could alert clinicians to patients at greatest risk, such that steps could be taken to mitigate the risk. To accomplish this, a valid method of risk quantification was required. Therefore, the purpose of this study was to develop and validate a clinical risk score to quantify the risk of QT interval prolongation in hospitalized patients.

Methods

Study Setting

This study was performed in the Cardiac Critical Care Units (CCCU) at the Indiana University (IU) Health Methodist Hospital, a 747-bed university-affiliated tertiary care teaching hospital located in Indianapolis, IN. The CCCU consists of 2 cardiac intensive care units, each comprising 28 beds, which focus primarily on patients with cardiac problems alone or in conjunction with other medical problems. Typical diagnoses include acute myocardial infarction, heart failure, cardiac arrest, kidney disease, respiratory failure, and sepsis. The study was approved by the Institutional Review Board at IU/Purdue University/Indianapolis (IUPUI), and the requirement for informed consent was waived.

Risk Score Model Development

In this prospective, observational study, data were collected from a total of 1200 patients admitted to the CCCU. The risk score model was developed using data from the first 900 consecutive patients admitted to these units. The study population comprised all patients consecutively admitted to the CCCU between September 2008 and March 2009. Patients were excluded if they were <18 years of age, discharged from the unit in <24 hours, or not receiving daily ECGs or continuous bedside cardiac rhythm monitoring. Patients with completely paced ventricular rhythms were also excluded because of the difficulty in accurately measuring QT intervals. Data were collected for each patient at admission and daily during hospitalization. Patients were included at the time of admission to the hospital and were followed daily during hospitalization.

The following data were collected from computerized and paper medical records: demographics information, admitting diagnosis, current medical problems, past medical history, past and current medications, daily progress notes, and laboratory tests. All oral and intravenous medications administered to patients during hospitalization were recorded. Drugs were considered to be QT interval prolonging if substantial evidence for causing QT interval prolongation or TdP was available from published trials or case reports.5-14 Table 1 lists the drugs on the IU Health Methodist Hospital formulary that were considered to be QT interval–prolonging drugs. Laboratory data were collected on admission as well as daily thereafter. Serum magnesium concentrations were available for some, but not all, patients because they are not routinely ordered for every patient. Creatinine clearances were calculated from serum creatinine concentrations using the Cockcroft and Gault equation.13 For purposes of assessing QTc interval prolongation risk associated with serum potassium, magnesium, calcium, and creatinine concentrations, we used the values recorded at the time that QTc interval prolongation was initially documented.

A baseline 12-lead ECG was obtained within 4 hours of admission in 867 (96.3%) patients. All patients underwent continuous cardiac telemetry monitoring. Daily QT intervals were measured manually by an investigator (H.J.; ≈90% of ECGs) or a technician (≈10% of ECGs) from lead II of 12-lead ECGs or from continuous lead II telemetry strips using computer-enhanced magnification (MUSE Cardiology Information System, GE Healthcare, Waukesha, WI). Inter-rater
reliability was determined by comparing QT interval measurements on ≈5% of the ECGs (κ = 0.90). QT intervals were measured from the beginning of the earliest onset of the QRS complex to the end of the T-wave. The end of the T-wave was determined by extending a tangent from the steepest portion of the downslope of the T-wave until it crossed the T-P segment. During normal sinus rhythm, QT and RR intervals were averaged over 3 consecutive complexes. During other rhythms, QT and RR intervals were averaged over all complexes on the 6-second rhythm strips or 10-second lead II rhythm strip on the 12-lead ECGs. QT intervals were corrected for heart rate using Bazett’s formula (QTc) per standard clinical practice. QTc interval prolongation was defined as a QTc interval ≥500 ms or an increase in QTc interval of ≥60 ms compared with the admitting value at any time during hospitalization.

### Determination of Independent Risk Factors for QTc Interval Prolongation

To determine risk factors for QTc interval prolongation, the incidence of known risk factors for QTc interval prolongation, TdP, and other cardiovascular morbidities and treatments were compared in patients who developed QTc interval prolongation during hospitalization versus those who did not using univariate analysis. Variables were included in the univariate analysis based on review of the published literature and expert opinion about factors known to increase the risk of QTc interval prolongation. In patients who developed QTc interval prolongation, laboratory values at the time of first occurrence of QTc

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>No. of Patients (DG,)*</th>
<th>No. of Patients (VG,)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic</td>
<td>Amiodarone</td>
<td>94 (10.4)</td>
<td>28 (9.3)</td>
</tr>
<tr>
<td></td>
<td>Disopyramide</td>
<td>2 (0.22)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dofetilide</td>
<td>18 (2.0)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Dronedarone</td>
<td>0</td>
<td>8 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Ibutilide</td>
<td>2 (0.22)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Procainamide</td>
<td>1 (0.11)</td>
<td>1 (0.33)</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>1 (0.11)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
<td>27 (3.0)</td>
<td>9 (3.0)</td>
</tr>
<tr>
<td>Anti-infective</td>
<td>Azithromycin</td>
<td>60 (6.7)</td>
<td>14 (4.7)</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>2 (0.22)</td>
<td>1 (0.33)</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>26 (2.9)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>2 (0.22)</td>
<td>1 (0.33)</td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td>10 (1.1)</td>
<td>2 (0.67)</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>22 (2.4)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>7 (0.78)</td>
<td>11 (3.7)</td>
</tr>
<tr>
<td></td>
<td>Pentamidine</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td>0</td>
<td>1 (0.33)</td>
</tr>
<tr>
<td>Psychotropic</td>
<td>Chlorpromazine</td>
<td>1 (0.11)</td>
<td>1 (0.33)</td>
</tr>
<tr>
<td></td>
<td>Droperidol</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>35 (3.9)</td>
<td>11 (3.7)</td>
</tr>
<tr>
<td></td>
<td>Pimozide</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>4 (0.44)</td>
<td>1 (0.33)</td>
</tr>
<tr>
<td></td>
<td>Thoridazine</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone</td>
<td>2 (0.22)</td>
<td>2 (0.67)</td>
</tr>
<tr>
<td>Other</td>
<td>Methadone</td>
<td>5 (0.55)</td>
<td>1 (0.33)</td>
</tr>
<tr>
<td></td>
<td>Ranolazine</td>
<td>2 (0.22%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**DG** indicates derivation group (n=900); and **VG**, validation group (n=300).

* No. of patients in each group who received specific QT interval–prolonging drugs.
intervals prolongation, active diagnoses, and past medical history were used in the analysis. In patients who did not develop QTc interval prolongation, the lowest documented serum potassium, calcium, or magnesium concentration and the highest recorded serum creatinine concentration were used in the analysis, as well as all diagnoses and medications administered during the hospitalization.

Unpaired Student t test was used to compare continuous variables, assuming equal or unequal variances between the groups, and χ2 or Fisher Exact test, as appropriate, was used for categorical variables. Comparisons for non-normally distributed continuous parameters were performed using the nonparametric Wilcoxon Rank Sum test. To determine independent predictors of QTc interval prolongation, univariate variables with a P value ≤0.10 were then incorporated into a bivariate logistic regression model in a forward stepwise fashion in descending order of those most strongly associated with QTc interval prolongation based on univariate P value. Significant continuous variables were dichotomized based on the results of the univariate analysis. Dichotomized variables were compared using the χ2 or Fisher Exact test as appropriate. Odds ratios (ORs) with 95% confidence intervals were determined for

### Table 3. Univariate Analysis of Variables Associated With QTc Interval Prolongation

<table>
<thead>
<tr>
<th>Variable*</th>
<th>QTc Prolongation</th>
<th>No QTc Prolongation</th>
<th>P Value</th>
<th>Mean difference/ (n=276) (n=624) OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68±15</td>
<td>64±16</td>
<td>&lt;0.001</td>
<td>4.0 (1.8 to 6.2)</td>
</tr>
<tr>
<td>Female</td>
<td>158 (57%)</td>
<td>295 (47%)</td>
<td>0.007</td>
<td>0.4 (0.1 to 0.7)</td>
</tr>
<tr>
<td>White</td>
<td>188 (68%)</td>
<td>447 (72%)</td>
<td>0.22</td>
<td>−0.2 (−0.5 to 0.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>196 (71%)</td>
<td>442 (71%)</td>
<td>0.62</td>
<td>0.01 (−0.3 to 0.3)</td>
</tr>
<tr>
<td>CAD</td>
<td>145 (53%)</td>
<td>313 (50%)</td>
<td>0.51</td>
<td>0.1 (−0.2 to 0.4)</td>
</tr>
<tr>
<td>Acute AF</td>
<td>60 (22%)</td>
<td>124 (20%)</td>
<td>0.64</td>
<td>0.1 (−0.2 to 0.5)</td>
</tr>
<tr>
<td>Acute cardiac arrest</td>
<td>8 (3%)</td>
<td>23 (4%)</td>
<td>0.87</td>
<td>−0.2 (−1.0 to 0.6)</td>
</tr>
<tr>
<td>Acute MI</td>
<td>47 (17%)</td>
<td>74 (12%)</td>
<td>0.001</td>
<td>0.4 (0.03 to 0.8)</td>
</tr>
<tr>
<td>Acute HF</td>
<td>127 (46%)</td>
<td>163 (26%)</td>
<td>&lt;0.001</td>
<td>0.9 (0.6 to 1.2)</td>
</tr>
<tr>
<td>sepsis</td>
<td>30 (11%)</td>
<td>30 (5%)</td>
<td>0.001</td>
<td>0.9 (0.4 to 1.4)</td>
</tr>
<tr>
<td>COPD</td>
<td>66 (24%)</td>
<td>147 (24%)</td>
<td>0.12</td>
<td>0.02 (−0.3 to 0.4)</td>
</tr>
<tr>
<td>CKD</td>
<td>91 (33%)</td>
<td>173 (28%)</td>
<td>0.83</td>
<td>0.2 (−0.1 to 0.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>94 (34%)</td>
<td>170 (27%)</td>
<td>0.17</td>
<td>0.3 (0.02 to 0.6)</td>
</tr>
<tr>
<td>Severe liver disease</td>
<td>8 (3%)</td>
<td>12 (2%)</td>
<td>0.33</td>
<td>0.4 (−0.5 to 1.3)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>163 (59%)</td>
<td>374 (60%)</td>
<td>0.54</td>
<td>−0.04 (−0.3 to 0.3)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>119 (43%)</td>
<td>265 (43%)</td>
<td>0.94</td>
<td>0.03 (−0.3 to 0.3)</td>
</tr>
<tr>
<td>ARBs</td>
<td>44 (16%)</td>
<td>86 (14%)</td>
<td>0.57</td>
<td>0.2 (−0.2 to 0.6)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>171 (62%)</td>
<td>259 (42%)</td>
<td>&lt;0.001</td>
<td>0.8 (0.5 to 1.1)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>33 (12%)</td>
<td>101 (16%)</td>
<td>0.46</td>
<td>−0.4 (−0.8 to 0.1)</td>
</tr>
<tr>
<td>Statin</td>
<td>130 (47%)</td>
<td>281 (45%)</td>
<td>0.61</td>
<td>0.1 (−0.2 to 0.4)</td>
</tr>
<tr>
<td>Administration of 1 QT-prolonging drug</td>
<td>138 (50%)</td>
<td>149 (24%)</td>
<td>&lt;0.001</td>
<td>1.2 (0.9 to 1.5)</td>
</tr>
<tr>
<td>Administration of ≥2 QT-prolonging drugs</td>
<td>25 (9%)</td>
<td>11 (2%)</td>
<td>&lt;0.001</td>
<td>1.7 (1.0 to 2.4)</td>
</tr>
<tr>
<td>Serum Mg2+ ≤1.6 mg/dL</td>
<td>15 (15%; n=102)</td>
<td>67 (19%; n=355)</td>
<td>0.11</td>
<td>−0.3 (−0.9 to 0.3)</td>
</tr>
<tr>
<td>Serum K+ ≤3.5 mEq/L</td>
<td>188 (68%)</td>
<td>165 (26%)</td>
<td>&lt;0.001</td>
<td>1.8 (1.5 to 2.1)</td>
</tr>
<tr>
<td>Serum Ca2+, mg/dL</td>
<td>9.0±1.4</td>
<td>9.1±1.6</td>
<td>0.91</td>
<td>0.1 (0.1 to 0.3)</td>
</tr>
<tr>
<td>CrCl &lt;50 mL/min</td>
<td>108 (39%)</td>
<td>229 (37%)</td>
<td>0.33</td>
<td>0.1 (−0.3 to 0.5)</td>
</tr>
<tr>
<td>Admission QTc ms</td>
<td>467±52</td>
<td>445±33</td>
<td>&lt;0.001</td>
<td>22 (16 to 28)</td>
</tr>
<tr>
<td>Admission JTc ms</td>
<td>375±46</td>
<td>353±38</td>
<td>&lt;0.001</td>
<td>23 (16 to 27)</td>
</tr>
<tr>
<td>Admission QRS, ms</td>
<td>102±25</td>
<td>101±24</td>
<td>0.79</td>
<td>1 (−2 to 4)</td>
</tr>
<tr>
<td>Maximum QTc, ms</td>
<td>493±44</td>
<td>459±25</td>
<td>&lt;0.001</td>
<td>34 (29 to 39)</td>
</tr>
<tr>
<td>Maximum change in QTc from baseline, ms</td>
<td>51±29</td>
<td>25±13</td>
<td>&lt;0.001</td>
<td>26 (23 to 29)</td>
</tr>
<tr>
<td>Admission heart rate, bpm</td>
<td>83±26</td>
<td>87±36</td>
<td>0.12</td>
<td>−4 (−9 to 1)</td>
</tr>
<tr>
<td>Bradycardia (HR≤60 bpm)</td>
<td>33 (12%)</td>
<td>68 (11%)</td>
<td>0.26</td>
<td>−0.1 (−0.4 to 0.3)</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; bpm, beats per minute; Ca2+, calcium; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; HF, heart failure; HR, heart rate; K+, potassium; MI, myocardial infarction; Mg2+, magnesium; and OR, odds ratio.

*Continuous variables are expressed as mean±SD; dichotomous variables are expressed as number (%).

†For continuous variables, the mean difference between the groups is presented with the 95% CI; for dichotomous variables, the log-transformed odds ratio is presented with the 95% CI.
Table 4. Independent Risk Factors for QTc Interval Prolongation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression Coefficient</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥68 y</td>
<td>0.3</td>
<td>1.3 (1.0–1.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.4</td>
<td>1.5 (1.1–2.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>0.5</td>
<td>1.4 (1.0–2.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum K⁺ ≤3.5 mEq/L</td>
<td>0.7</td>
<td>2.1 (1.5–2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission QTc ≥450 ms</td>
<td>0.8</td>
<td>2.3 (1.6–3.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute MI</td>
<td>0.9</td>
<td>2.4 (1.6–3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥2 QTc-prolonging drugs</td>
<td>0.9</td>
<td>2.6 (1.9–5.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>sepsis</td>
<td>0.9</td>
<td>2.7 (1.5–4.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.0</td>
<td>2.7 (1.6–5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>One QTc-prolonging drug</td>
<td>1.1</td>
<td>2.8 (2.0–4.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; K⁺, potassium; and MI, myocardial infarction.

Each variable. Statistical analyses were performed using SPSS 17.0 (SPSS, Inc, Chicago, IL).

After determination of ORs, a QTc interval prolongation risk score was then created based on the OR for the independent predictors of QTc interval prolongation. For each independent variable, a weighted point score (1, 2, or 3 points) was assigned based on the log OR for each significant independent risk factor. Using the log OR, we determined the risk score as follows: independent variable β≤0.44=1 point; β=0.45 to 0.94=2 points; β≥0.95=3 points. To arrive at a risk score for QTc interval prolongation, the sum of all points was calculated for each patient. To determine cutoff points for low, moderate, and high risk of QTc interval prolongation, patients were stratified by total point scores, and the proportion of patients with QTc interval prolongation was examined for each point score.

Risk Score Validation

An independent data set was used to validate the model. Data were collected prospectively from an additional 300 patients admitted to the CCCU between April 2009 and June 2009. The same exclusion criteria applied to the validation group as to the risk score development group. Data collected from computerized and paper medical records were the same as those listed above under the section Risk Score Model Development. All patients underwent continuous cardiac telemetry monitoring, and a baseline 12-lead ECG was obtained within 4 hours of admission. QTc interval was measured and corrected as described in the Risk Score Model Development section above. The number of patients in the validation group who received specific QT interval–prolonging drugs is presented in Table 1.

To determine how well the developed risk score predicted QTc interval prolongation, test characteristics (such as area under the receiver-operating characteristic curve, sensitivity, specificity, and positive and negative predictive values) were calculated.

Table 5. Calculation of Risk Score for QTc Interval Prolongation

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥68 y</td>
<td>1</td>
</tr>
<tr>
<td>Female sex</td>
<td>1</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>1</td>
</tr>
<tr>
<td>Serum K⁺ ≤3.5 mEq/L</td>
<td>2</td>
</tr>
<tr>
<td>Admission QTc ≥450 ms</td>
<td>2</td>
</tr>
<tr>
<td>Acute MI</td>
<td>2</td>
</tr>
<tr>
<td>≥2 QTc-prolonging drugs</td>
<td>3</td>
</tr>
<tr>
<td>sepsis</td>
<td>3</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3</td>
</tr>
<tr>
<td>One QTc-prolonging drug</td>
<td>3</td>
</tr>
<tr>
<td>Maximum Risk Score</td>
<td>21</td>
</tr>
</tbody>
</table>

K⁺ indicates potassium; and MI, myocardial infarction.

Results

Patient Characteristics

A summary of baseline patient characteristics is presented in Table 2. There were no significant differences between the risk score development group and the risk score validation group, with the exception of a higher proportion of patients admitted with acute cardiac arrest or receiving digoxin in the risk score derivation group.

QTc Interval Risk Score Development

Of the 900 patients, 276 (30.7%) developed QTc interval prolongation. Results of the univariate analysis are shown in Table 3. Patients in the QTc interval prolongation group were older, with a higher proportion of females. More patients in the QTc interval prolongation group had an admitting diagnosis of acute myocardial infarction, sepsis and acute heart failure. A higher proportion of patients in the QTc interval prolongation group were receiving loop diuretics and ≥1 QTc interval–prolonging medication and had lower serum potassium concentrations and higher QTc intervals on admission.

Independent risk factors for QTc interval prolongation are presented in Table 4 and included female sex, diagnosis of myocardial infarction, sepsis left ventricular systolic dysfunction, administration of 1 QTc interval–prolonging drug, administration of ≥2 QTc interval–prolonging drugs, admission of a loop diuretic, ≥68 years of age, serum K⁺ ≤3.5 mEq/L, and admission QTc ≥450 ms.

Based on log ORs for each independent risk factor for QTc interval prolongation, a point total was assigned to each risk factor (Table 5). Based on total points, the risk score was further stratified into low, moderate, and high risk. Numerous risk score iterations were tested; the risk score stratification with the highest area under the receiver-operating characteristic curve (c-statistic=0.832) is presented in Table 6.

QTc Interval Risk Score Validation

Of the 300 patients included in the risk score validation group, 23 (7.7%) had been included in the risk score derivation group during the derivation period (September 2008 to March 2009) and were readmitted to the CCCU during the validation study period (April 2009 to June 2009). The remaining 92.3% of patients in the validation group were not in the derivation group.

The sensitivity, specificity, positive predictive value, and negative predictive value of the QTc interval risk score stratification are presented in Table 7. The performance of the QTc interval risk score during the validation phase is presented in...
Using the risk score stratification of low (score < 7), moderate (score = 7–10), and high (score ≥ 11), the incidence of QTc interval prolongation in the low-, moderate-, and high-risk groups was 15%, 37%, and 73%, respectively. Figure 2 shows a plot of the observed versus predicted frequencies of QTc interval prolongation.

**Discussion**

In this study, a risk score predicting the development of QTc interval prolongation was developed using easily obtainable clinical variables that are independent risk factors for prolonged QTc interval in hospitalized patients in cardiac care units. The QTc interval risk score was subsequently validated in a separate population of patients from the same cardiac units. The risk score effectively distinguished hospitalized patients at moderate or high risk for QTc interval prolongation from those at low risk.

QTc interval prolongation occurs commonly in patients in cardiac care units, and patients with QTc interval are routinely prescribed QTc interval–prolonging drugs despite the enhanced risk. Although independent risk factors for QTc interval prolongation and associated TdP are well documented, validated methods of quantifying the risk for the purpose of identifying hospitalized patients at greatest susceptibility have not been previously described. TdP is an adverse drug reaction that is highly dependent on the presence of risk factors, and drug-induced TdP is an extremely rare event in patients without any risk factors. Over 90% of patients who develop TdP have ≥1 risk factor, and 71% of patients have ≥2 risk factor. The odds for QT interval prolongation have been shown to increase exponentially as the number of risk factors present increases; each 10-ms increase in QTc interval contributes ≈5% to 7% exponential increase in risk for TdP in these patients. In addition, QT interval prolongation has been reported as an independent risk factor for sudden cardiac death. Identification of patients at highest risk of QTc interval prolongation using methods of risk quantification, such as a validated risk score, has the potential to facilitate methods of risk reduction in patients with the greatest degree of susceptibility to drug-induced QTc interval prolongation.

The AHA and the ACCF have taken measures to raise awareness among healthcare professionals about the risk of drug-induced QT interval prolongation and TdP in

Table 6. QTc Interval Risk Score Stratification*

<table>
<thead>
<tr>
<th>Risk Score Category</th>
<th>QTc Interval Prolongation Derivation Group, n (%)</th>
<th>QTc Interval Prolongation Validation Group, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low &lt;7</td>
<td>456 (51)</td>
<td>159 (53)</td>
</tr>
<tr>
<td>Moderate 7–10</td>
<td>319 (35)</td>
<td>101 (34)</td>
</tr>
<tr>
<td>High ≥11</td>
<td>125 (14)</td>
<td>40 (13)</td>
</tr>
</tbody>
</table>

*Area under the receiver-operating characteristic curve (c-statistic)=0.832.

Table 7. Predictive Performance of the QTc Interval Risk Score

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate risk</td>
<td>0.67</td>
<td>0.88</td>
<td>0.55</td>
<td>0.88</td>
</tr>
<tr>
<td>High risk</td>
<td>0.74</td>
<td>0.77</td>
<td>0.79</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Figure 1. Predictive performance of the QTc interval risk score stratification. Hosmer–Lemeshow test for goodness of fit (P=0.603).
hospitalized patients. The AHA and the ACCF emphasize the awareness of risk factors and monitoring of patients at risk to minimize the likelihood of occurrence of drug-induced TdP. Although the QTc interval monitoring strategies proposed for use by the AHA and the ACCF are likely to be effective for identifying QTc interval prolongation after it has occurred, the QTc interval risk score that we have developed and validated has the ability to identify patients who are at greatest risk of developing QTc interval prolongation before it occurs, so that measures may be taken to reduce the risk and potentially prevent the actual occurrence of QTc interval prolongation and TdP.

We developed this risk score with the broader long-term goal of reducing the risk of drug-induced QTc interval prolongation and TdP in hospitalized patients through the development and implementation of a computer-alert CDSS for QTc interval prolongation. This CDSS has been designed to incorporate this validated QTc interval risk score in the following manner: when a patient is admitted to the hospital, the hospital computer system uses this QTc interval risk score to determine whether the patient’s risk of QTc interval prolongation is low, moderate, or high. If an order for a drug that is known to prolong the QTc interval is entered into the computer system, and if the patient’s risk of QTc interval prolongation is moderate or high (but not low), the CDSS appears on the computer screen to the pharmacist entering the order, who then can notify the prescriber of the degree of risk. The prescriber may then consider whether the specific high-risk medication is needed or whether an alternative drug with a lower (or no) risk of QTc interval prolongation could be substituted. Although not always possible or clinically appropriate, in many cases, QTc interval–prolonging antimicrobial agents can be replaced with non-QTc interval–prolonging anti-infectives, intravenous haloperidol can be replaced with lorazepam, etc. Implementation of this computer-alert CDSS is currently under investigation to determine whether it is effective at ameliorating the risk of QTc interval prolongation in patients hospitalized in cardiac care units.

In this study, we identified sepsis as an independent risk factor for QTc interval prolongation, which is a disease state not previously reported as a risk factor for QTc interval prolongation or TdP. Underlying mechanisms explaining a relationship between sepsis and QTc interval prolongation are not clear. Varriale et al reported a single case of a patient who developed sepsis-associated cardiomyopathy, resulting in QTc interval prolongation. In a retrospective study of a series of 22 patients with acute noncardiac illness, 3 patients had sepsis, which was associated with regional wall motion abnormalities on echocardiogram, depressed left ventricular ejection fraction, and progressive QTc interval lengthening. These patients had no evidence of underlying coronary artery disease and were not undergoing treatment with QTc interval–prolonging drugs. Therefore, it seems possible that sepsis may be associated with transient underlying left ventricular dysfunction that may prolong the QTc interval. The association between sepsis and QTc interval prolongation and mechanisms underlying this phenomenon require further study.

In this analysis, receiving 1 QTc interval–prolonging drug was associated with similar odds of QTc interval prolongation as receiving ≥2 QTc interval–prolonging drugs. One might have expected that receiving ≥2 QTc interval–prolonging drugs would confer a greater risk than receiving only 1 QTc interval–prolonging drug. Additive effects of QTc interval–prolonging drugs, such as antipsychotic agents combined with antidepressants, on QTc interval prolongation have been reported. In addition, there are numerous reports of TdP associated with combinations of drugs known to prolong the QTc interval. However, some data have not supported...
the hypothesis of a higher risk associated with therapy with combinations of QTc interval–prolonging drugs. In some studies, combinations of QTc interval–prolonging drugs did not provoke a greater degree of QTc interval prolongation than receiving a single QTc interval–prolonging drug. In addition, in an isolated perfused heart study, concomitant perfusion of guinea pig hearts with 2 Iₐ₅₄ inhibitors did not produce additive effects on monophasic action potential duration. Furthermore, in a study in a canine model of TdP, the combinations of sotalol and quinidine did not confer a higher risk of TdP than administration of sotalol alone. The influence of concomitant therapy with ≥2 QTc interval–prolonging drugs on ventricular action potential duration, QTc interval, and risk of TdP requires further study.

Although hypomagnesemia is known to be a risk factor for TdP, it was not an independent risk predictor of QTc interval prolongation in this study. This finding is likely because, during the course of routine clinical practice, serum magnesium concentration is not routinely determined in all patients admitted to the CCCU and was only determined in 38% of patients admitted to the CCCU during the study period. It is possible that hypomagnesemia may have emerged as an independent predictor of QTc interval prolongation if serum magnesium concentrations had been obtained in a higher proportion of patients.

In the current study, there were no occurrences of TdP in the CCCU. Even in the highest-risk populations, TdP is a rare event, although the precise incidence is not known. Swedish investigators estimated an incidence of 4 cases of TdP per 1 million people annually. In our population of patients with cardiac disease and risk factors for TdP, the incidence of TdP could be expected to be higher but is likely still relatively low. Therefore, larger numbers of patients monitored for longer periods of time would be needed to demonstrate 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 proarhythmia, the AHA and the ACCF strongly recommend 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. Identification of hospitalized patients at greatest risk for QTc interval prolongation and, subsequently, taking measures to modify the risk may provide a great opportunity for reducing the risk of drug-induced TdP by identifying and mitigating risk, rather than treating proarhythmia once it occurs.

Limitations of this study include the fact that the study was performed in 2 CCCU in a single tertiary care institution, which may limit the generalizability of the results; the findings may not apply to patients in general medical wards. Prospective validation in other clinical care settings would add strength to the concept of clinical prediction of QTc interval prolongation. The positive predictive value of the QTc interval risk stratification was not as high as desired, but the sensitivity, specificity, and negative predictive performance were strong. Inherent limitations are associated with measurement of QT intervals from 12-lead ECGs and ECG rhythm strips, and measurement and rate-correction of QT intervals are often performed incorrectly. However, we have extensive experience in QT interval measurement and correction, and we believe that the QT measurements reported herein are accurate. In addition, although not perfect, the methods described in this article can easily be performed in clinical practice in the hospital setting.

In conclusion, a risk score using easily obtainable clinical risk factors predicts patients at highest risk for QTc interval prolongation during hospitalization and may be useful in guiding monitoring and treatment decisions. Additional studies are under way to determine the usability of incorporating quantification of risk of QTc interval prolongation into clinical decision making, including in a computer-based CDSS for reducing the incidence of QTc interval prolongation and, ultimately, the risk of TdP and sudden cardiac death.

Disclosures
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References


Development and Validation of a Risk Score to Predict QT Interval Prolongation in Hospitalized Patients


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In the article by Tisdale et al, “Development and Validation of a Risk Score to Predict QT Interval Prolongation in Hospitalized Patients,” which appeared in the July 2013 issue of the journal (Circ Cardiovasc Qual Outcomes, 2013;6:479–487), there is an error in terminology. Throughout the paper, the term “septic shock” should have been reported as “sepsis.” This error occurs in the Abstract, in Tables 2, 3, 4 and 5, and on pages 483 and 485.

These corrections have been made online. The authors regret the error.