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

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Abstract

Background—Identifying hospitalized patients at risk for QT interval prolongation could lead to interventions to reduce the risk of torsades de pointes (TdP). 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 (DG). The score was then applied to 300 additional patients in a validation group (VG). Corrected QT (QT_c) interval prolongation (defined as QT_c > 500 ms and/or an increase of > 60 ms from baseline) occurred in 274 (30.4%) and 90 (30.0%) patients in the DG and VG, respectively. Independent predictors of QT_c prolongation included: female (odds ratio [OR], 1.5; 95% confidence interval [CI], 1.1–2.0), diagnosis of myocardial infarction [2.5 (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 (1.0–1.8)], serum K^+ < 3.5 mEq/L [2.1 (1.5–2.9)], and admitting QT_c > 450 ms [2.3; CI (1.6–3.2)]. Risk scores were developed by assigning points based on Log ORs. Low, moderate and high risk ranges of 0–6, 7–10 and 11–21 points, respectively, best predicted QT_c 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 VG, the incidences of QT_c prolongation were 15% (low risk); 37% (moderate risk); 73% (high risk).

Conclusions—A risk score using easily obtainable clinical variables predicts patients at highest risk for QT_c prolongation and may be useful in guiding monitoring and treatment decisions.

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Keywords

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 electrocardiogram (ECG).[1,2] Many medications, including drugs prescribed for non-cardiac indications, can cause QT interval prolongation and trigger TdP,[3] which may degenerate into ventricular fibrillation and result in sudden cardiac arrest. Therefore, TdP can be a catastrophic event in hospitalized patients.[4]

QT interval prolongation is recognized as an ECG sign that portends an increased risk for TdP.[4] The risk for developing TdP increases as the QT_c interval increases.[5,6] In patients with the congenital long QT syndrome (LQTS), each 10 ms increase in Bazett's-corrected QT (QT_c) interval prolongation leads to an approximately 5–7% increase in the risk of TdP.[6] QT_c interval > 500 ms increases the risk of TdP 2–3 fold in patients with LQTS. The risk of drug-induced TdP has also been shown to increase when the QT_c interval exceeds 500 ms.[3,7–9] Therefore, prolongation of the QT_c 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 QT_c interval prolongation (defined as ≥ 470 ms in males and ≥ 480 ms in females), and nearly 1 in 5 have admitting QT_c intervals > 500 ms.[10] Further, 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.[4,10] A substantial proportion of hospitalized patients with QT_c interval prolongation on admission subsequently receive QT interval-prolonging drugs,[10] thus enhancing their risk of proarrhythmia. Prolongation of the QT_c 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 drug-induced QT interval prolongation and TdP in hospitalized patients.[4] This statement emphasized the importance of awareness of risk factors in order to minimize the likelihood of occurrence of drug-induced TdP.[4] However, some of the fully automated QT_c interval monitoring strategies suggested for use by the AHA/ACCF are labor-intensive, and are dependent on expensive technology. Identification of patients at highest risk of drug-induced QT_c 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 QT_c 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 factors,[3,13] and is an extremely rare occurrence in patients without concomitant risk factors.[13] Identification of patients at highest risk of drug-induced QT_c 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 in order to reduce the likelihood of TdP. However, while risk factors for QT_c interval prolongation and TdP have been well-described, few data exist regarding means of quantification of the risk in individual patients.

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

In order to achieve the long-term goal of reducing the risk of drug-induced QT_c 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. In order 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 conducted in the Cardiac Critical Care Units (CCCU) Indiana University (IU) Health Methodist Hospital, a 747-bed university-affiliated tertiary care teaching hospital located in Indianapolis, Indiana. The CCCU consists of two 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 Indiana University/ Purdue University 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, were discharged from the unit in less than 24 hours, or if they were not receiving daily ECGs or continuous bedside cardiac rhythm monitoring. Patients with completely paced ventricular rhythms were also excluded due to 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 the patient during hospitalization were recorded. Drugs were considered to be QT interval-prolonging if substantial evidence for causing QT interval prolongation and/or TdP was available from published trials or case reports.[3,14] Table 1 lists the drugs on the IU Health Methodist Hospital formulary which 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, as they are not routinely ordered for every patient. Creatinine clearances were calculated from serum creatinine concentrations using the Cockcroft and Gault

equation.[15] For purposes of assessing QT_c interval prolongation risk associated with serum potassium, magnesium, calcium and creatinine concentrations, we used the values recorded at the time that QT_c 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 (HJ, ~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 approximately 5% of the ECGs (Kappa = 0.90). QT intervals were measured from 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 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 three 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 (QT_c), per standard clinical practice.[16] QT_c interval prolongation was defined as a QT_c interval ≥ 500 ms or an increase in QT_c interval of ≥ 60 ms compared with the admitting value at any time during hospitalization.

Determination of Independent Risk Factors for QT_c Interval Prolongation

In order to determine risk factors for QT_c interval prolongation, the incidence of known risk factors for QT_c interval prolongation and TdP and other cardiovascular morbidities and treatments were compared in patients who developed QT_c 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 regarding factors known to increase the risk of QT_c interval prolongation. In patients who developed QT_c interval prolongation, laboratory values at the time of first occurrence of QT_c interval prolongation, active diagnoses, and past medical history were used in the analysis. In patients who did not develop QT_c 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’s t-test was used to compare continuous variables, assuming equal or unequal variances between the groups, and Chi-Square or Fisher’s Exact test, as appropriate, was used for categorical variables. Comparisons for non-normally distributed continuous parameters were performed using the non-parametric Wilcoxon Rank Sum test. In order to determine independent predictors of QT_c 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 Chi square or Fisher’s Exact test as appropriate. Odds ratios (OR) with 95% confidence intervals (CI) were determined for each variable. Statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA).

After determination of odds ratios, a QT_c interval prolongation risk score was then created based on the OR for the independent predictors of QT_c 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 $\beta \leq 0.44$ = 1 point; $\beta = 0.45 – 0.94$ = 2 points; $\beta \geq$

0.95 = 3 points. In order to arrive at a risk score for QT_c interval prolongation, the sum of all points was calculated for each patient. In order to determine cut-off points for low, moderate and high risk of QT_c interval prolongation, patients were stratified by total point scores and the proportion of patients with QT_c 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 "Risk Score Model Development.": All patients underwent continuous cardiac telemetry monitoring and/or a baseline 12-lead ECG was obtained within 4 hours of admission. QT_c interval were measured and corrected as described in the "Risk Score Model Development" section above. The number of patients in the validation group that received specific QT interval-prolonging drugs is presented in Table 1.

In order to determine how well the developed risk score predicted QT_c interval prolongation, test characteristics (area under the receiver operating characteristic (ROC) curve, sensitivity, specificity, positive and negative predictive values) were calculated.

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.

QT_c Interval Risk Score Risk Score Development

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

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

Based on odds ratios for each independent risk factor for QT_c 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 best highest area under the ROC curve (c-statistic = 0.832) is presented in Table 6.

QT_c Interval Risk Score Validation

Of the 300 patients included in the risk score validation group, n=23 (7.7%) were patients who had been included in the risk score derivation group during the derivation period (September 2008-March 2009) and were readmitted to the CCCU during the validation

study period (April 2009 – 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 QT_c interval risk score stratification are presented in Table 7. The performance of the QT_c interval risk score during the validation phase is presented in Figure 1. Using the risk score stratification of low (score < 7), moderate (score 7–10) and high (score ≥ 11), the incidence of QT_c interval prolongation in the low, moderate and high groups was 15%, 37% and 73%, respectively. Figure 2 shows a plot of the observed versus predicted frequencies of QT_c interval prolongation.

Discussion

In this study, a risk score predicting the development of QT_c interval prolongation was developed using easily obtainable clinical variables that are independent risk factors for prolonged QT_c interval in hospitalized patients in cardiac care units. The QT_c 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 QT_c interval prolongation from those at low risk.

QT_c interval prolongation occurs commonly in patients in cardiac care units, and patients with QT_c interval are routinely prescribed QT_c interval prolonging drugs, despite the enhanced risk.[10] While independent risk factors for QT_c interval prolongation and associated TdP are well-documented,[1,3,4] 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 at least one risk factor and 71% have two or more risk factor.[13] 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 QT_c interval contributes approximately a 5% to 7% exponential increase in risk for TdP in these patients.[6] In addition, QT-interval prolongation has been reported as an independent risk factor for sudden cardiac death.[17] Identification of patients at highest risk of QT_c 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 QT_c 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 hospitalized patients.[4] The AHA/ACCF emphasize awareness of risk factors and monitoring of patients at risk in order to minimize the likelihood of occurrence of drug-induced TdP.[4] While the QT_c interval monitoring strategies proposed for use by the AHA/ACCF are likely to be effective for identifying QT_c interval prolongation after it has occurred, the QT_c interval risk score that we have developed and validated has the advantage of the ability to identify patients who are at greatest risk of developing QT_c interval prolongation before it occurs, so that measures may be taken to reduce the risk and potentially prevent the actual occurrence of QT_c interval prolongation and TdP.

We developed this risk score with the broader long-term goal of reducing the risk of drug-induced QT_c interval prolongation and TdP in hospitalized patients through the development and implementation of a computer-alert CDSS for QT_c interval prolongation. This CDSS has been designed to incorporate this validated QT_c interval risk score in the following manner: when a patient is admitted to the hospital, the hospital's computer system uses this

QT_c interval risk score to determine whether the patient's risk of QT_c interval prolongation is low, moderate or high. If an order for a drug that is known to prolong the QT_c interval is entered into the hospital's computer system, and if the patient's risk of QT_c 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 QT_c interval prolongation could be substituted. Alternatively, the clinician may decide to implement risk mitigation strategies. For example, patients identified by this risk score tool in the CDSS with a score in the moderate or high range could be targeted for more frequent and intensive ECG monitoring, with either telemetry or serial 12-lead ECGs, and correctable risk factors for QT_c interval prolongation, such as hypokalemia and hypomagnesemia, could be ameliorated. In addition, for patients with a risk score that places them in the high-risk category, discontinuation of QT_c interval-prolonging medications and substitution with non-QT_c interval-prolonging drugs could be considered. While not always possible or clinically appropriate, in many cases QT_c interval-prolonging antimicrobial agents can be replaced with a non-QT_c 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 QT_c interval prolongation in patients hospitalized in cardiac care units.

In this study, we identified sepsis an independent risk factor for QT_c interval prolongation, which is a disease state that has not previously been reported as a risk factor for QT_c interval prolongation or TdP. Underlying mechanisms explaining a relationship between sepsis and QT_c interval prolongation are not clear. Varriale et al[18] reported a single case of a patient who developed sepsis-associated cardiomyopathy resulting in QT_c interval prolongation. In a retrospective study of a series of 22 patients with acute noncardiac illness,[19] three patients had sepsis, which was associated with regional wall motion abnormalities on echocardiogram, depressed left ventricular ejection fraction, and progressive QT_c interval lengthening. These patients had no evidence of underlying coronary artery disease and were not undergoing treatment with QT_c interval prolonging drugs. Therefore, it seems possible that sepsis may be associated with transient underlying left ventricular dysfunction that may prolong the QT_c interval. The association between sepsis and QT_c interval prolongation and mechanisms underlying this phenomenon require further study.

In this analysis, receiving one QT_c interval-prolonging drug was associated with similar odds of QT_c interval prolongation as receiving ≥ two QT_c interval-prolonging drugs. One might have expected that receiving ≥ two QT_c interval-prolonging drugs would confer a greater risk than receiving only one QT_c interval-prolonging drug. Additive effects of QT_c interval prolonging drugs, such as antipsychotic agents combined with antidepressants,[20] on QT_c interval prolongation have been reported. In addition, there are numerous reports of TdP associated with combinations of drugs known to prolong the QT_c interval.[3] However, some data have not supported the hypothesis of a higher risk associated with therapy with combinations of QT_c interval-prolonging drugs. In some studies, combinations of QT_c interval-prolonging drugs did not provoke a greater degree of QT_c interval prolongation than receiving a single QT_c interval-prolonging drug.[21] In addition, in an isolated perfused heart study, concomitant perfusion of guine pig hearts with two I_{Kr} inhibitors did not produce additive effects on monophasic action potential duration.[22] Further, 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.[23] The influence of concomitant therapy with ≥ 2 QT_c interval prolonging drugs on ventricular action potential duration, QT_c interval, and risk of TdP requires further study.

Although hypomagnesemia is known to be a risk factor for TdP,[3] it was not an independent risk predictor of QTc interval prolongation in this study. This is likely due to the fact that, during the course of routine clinical practice, serum magnesium concentration are not routinely determined in all patients admitted to the CCCU, and were 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 QT_c interval prolongation serum magnesium concentrations were obtained in a larger proportion of our 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 four cases of TdP per 1,000,000 persons annually.[24] 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 proarrhythmia, the AHA/ACCF 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] Identification of hospitalized patients at greatest risk for QT_c interval prolongation, and subsequently taking measures to modify the risk, may provide great opportunity for reducing the risk of drug-induced TdP by identifying and mitigating risk, rather than treating proarrhythmia once it occurs.

Limitations of this study include the fact that the study was conducted in two cardiac critical care units 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 QT_c interval prolongation. The positive predictive value of the QT_c interval risk stratification was not as high as desired, but the sensitivity, specificity and negative predictive performance were strong. There are inherent limitations associated with measurement of QT intervals from 12-lead ECGs and ECG rhythm strips, and measurement and rate-correction of QT intervals is often performed incorrectly.[25] However, we have extensive experience in QT interval measurement and correction, and we believe that the QT measurements reported herein are accurate. In addition, while not perfect, the methods described in this manuscript 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 QT_c interval prolongation during hospitalization and may be useful in guiding monitoring and treatment decisions. Additional studies are under way to determine the utility of incorporating quantification of risk of QT_c interval prolongation into clinical decision-making, including in a computer-based CDSS for reducing the incidence of QT_c interval prolongation and, ultimately, the risk of TdP and sudden cardiac death..

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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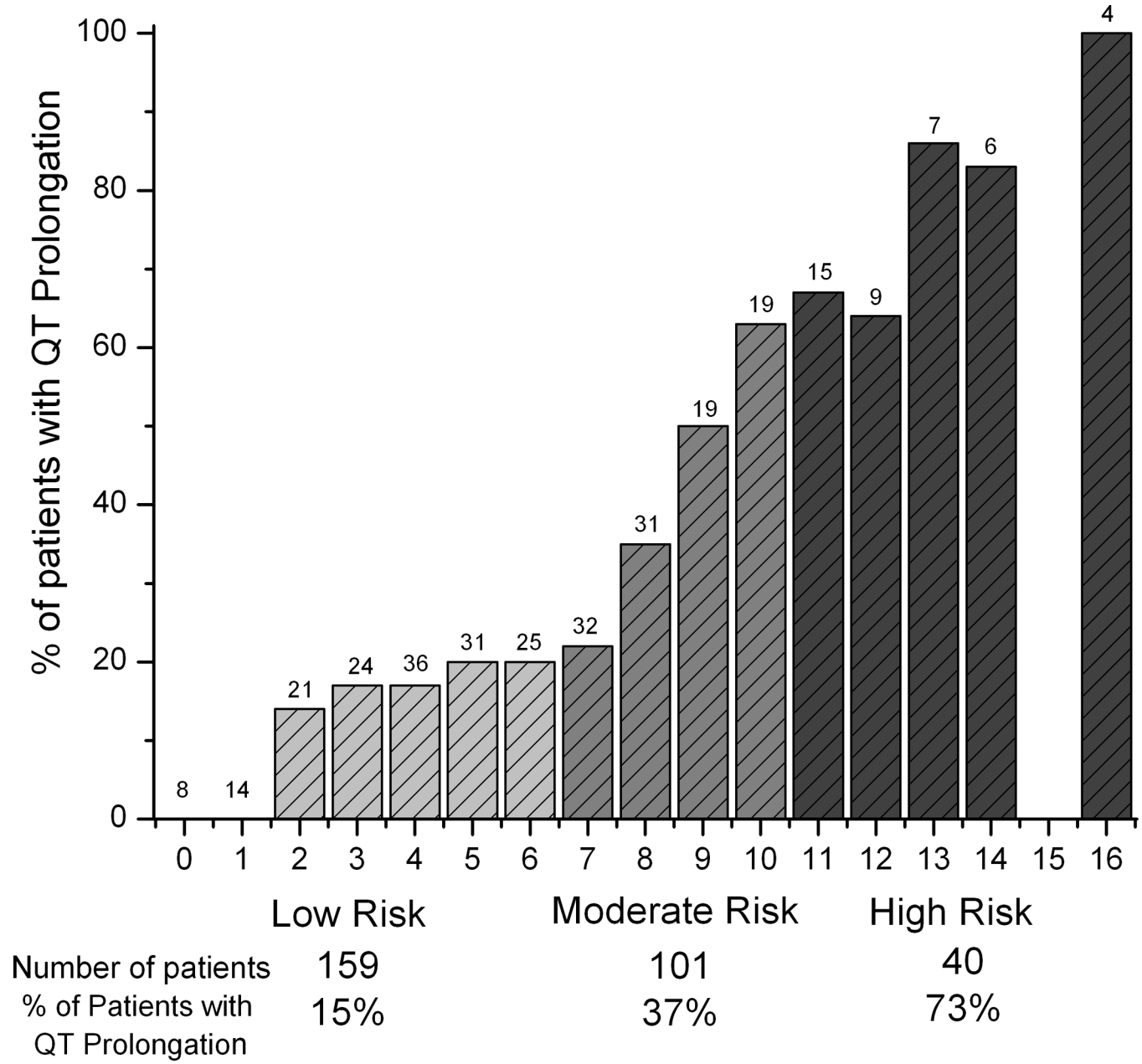

Figure 1.
Predictive performance of the QT_C interval risk score stratification
Hosmer-Lemeshow test for goodness of fit p=0.603

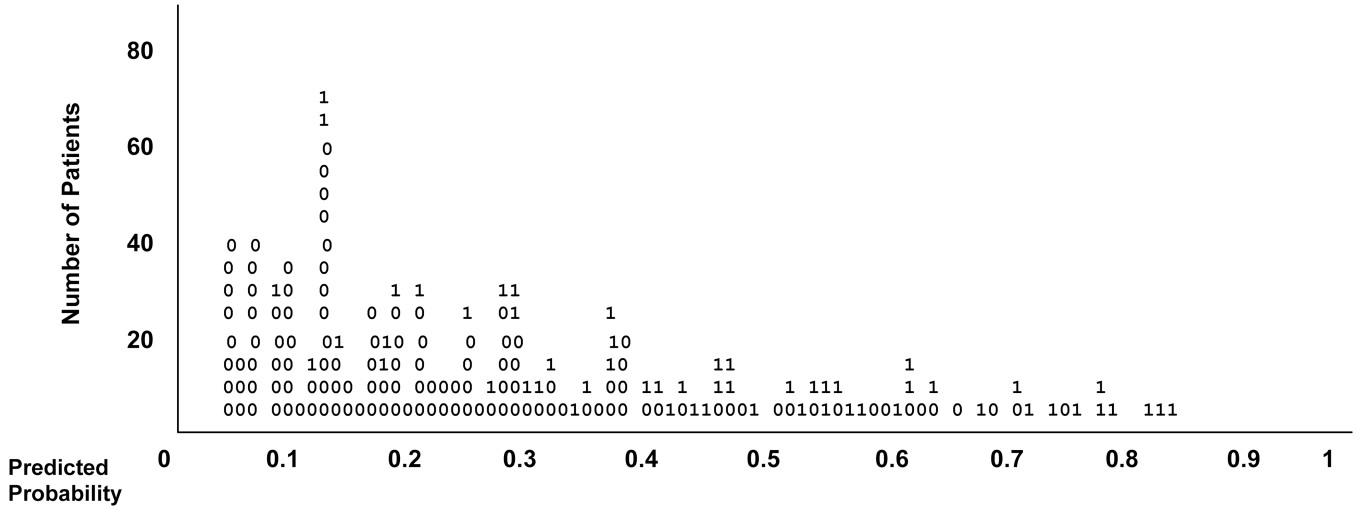

Figure 2.

Observed versus predicted probability of developing QT_c interval prolongation

0= No QT_c interval prolongation

1= QT_c interval prolongation

Each symbol (0 or 1) represents n=5 cases

Table 1

Number of patients in the derivation and validation groups who received QT_c interval-prolonging drugs on the hospital formulary

Drug Class	Drug	# of Patients (DG)*	# of Patients (VG)*
Antiarrhythmic	Amiodarone	94 (10.4%)	28 (9.3%)
	Disopyramide	2 (0.22%)	0
	Dofetilide	18 (2.0%)	4 (1.3%)
	Dronedarone	0	8 (2.7%)
	Ibutilide	2 (0.22%)	0
	Procainamide	1 (0.11%)	1 (0.33%)
	Quinidine	1 (0.11%)	0
	Sotalol	27 (3.0%)	9 (3.0%)
Anti-infective	Azithromycin	60 (6.7%)	14 (4.7%)
	Clarithromycin	2 (0.22%)	1 (0.33%)
	Ciprofloxacin	26 (2.9%)	6 (2.0%)
	Erythromycin	2 (0.22%)	1 (0.33%)
	Fluconazole	10 (1.1%)	2 (0.67%)
	Levofloxacin	22 (2.4%)	4 (1.3%)
	Moxifloxacin	7 (0.78%)	11 (3.7%)
	Pentamidine	0	0
	Voriconazole	0	1 (0.33%)
Psychotropic	Chlorpromazine	1 (0.11%)	1 (0.33%)
	Droperidol	0	0
	Haloperidol	35 (3.9%)	11 (3.7%)
	Pimozide	0	0
	Risperidone	4 (0.44%)	1 (0.33%)
	Thioridazine	0	0
	Ziprasidone	2 (0.22%)	2 6.7%)
Other	Methadone	5 (0.55%)	1 (0.33%)
	Ranolazine	2 (0.22%)	0

* # of patients in each group that received specific QT interval-prolonging drugs. Sum adds up to greater than n=900 or n=300, respectively, because some patients received >1 QT interval prolonging drug

DG = Derivation group (n=900)

VG = Validation group (n=300)

Table 2

Summary of baseline patient characteristics*

Characteristic†	Risk Score Derivation Group (n=900)	Risk Score Validation Group (n=300)
Age (years)	65 715	65 714
Female	452 (50%)	154 (51%)
Race (Caucasian)	635 (71%)	205 (68%)
Admission diagnosis		
Acute AF	187 (21%)	58 (19%)
Acute cardiac arrest	23 (3%)	5 (2%)‡
Acute MI	121 (13 %)	46 (15%)
Acute HF	290 (32%)	94 (31%)
Unstable angina	220 (24%)	84 (28%)
COPD exacerbation	85 (9%)	26 (9%)
Acute infection (UTI, pneumonia)	92 (10%)	28 (9%)
Sepsis	60 (7%)	25 (8%)
Acute kidney failure	160 (18%)	45 (15%)
Comorbidities		
CAD	457 (51%)	152 (51%)
HF	243 (24%)	82 (27%)
Hypertension	638 (71%)	211 (70%)
Diabetes mellitus	264 (29%)	95 (32%)
COPD	147 (16%)	54 (18)%
CKD	264 (29%)	74 (25%)
Medications		
β-blocker	537 (60%)	172 (57%)
ACE inhibitor	384 (43%)	128 (43%)
ARB	130 (14%)	48 (16%)
Digoxin	134 (15%)	30 (10%)¶
Loop diuretic	430 (48%)	135 (45%)
1 QT interval-prolonging drug	287 (32%)	85 (28%)
≥ 2 QT interval- prolonging drugs	36 (4%)	9 (3%)
Laboratory values		
Serum K^+ (mEq/L),	3.8 1.2	3.7 0.7
Serum K^+ < 3.5 mEq/L	353 (40%)	120 (40%)
Serum Mg^{++} < 1.6 mg/dL	56 (16%,n=355)	18 (18%,n=102)
Serum Ca^{++} (mg/dL)	9.1 1.2	9.3 1.0
Estimated creatinine clearance ≤ 50 mL/min	337 (37%)	110 (37%)
ECG‡		
QT_c (ms)	452 41	449 40
JT_c (ms)	360 41	357 40
Heart rate (bpm)	86 33	88 47

Characteristic†	Risk Score Derivation Group (n=900)	Risk Score Validation Group (n=300)
Heart rate < 60 bpm	101 (11%)	25 (8%)

ACE = Angiotensin converting-enzyme; AF = Atrial fibrillation; ARB = Angiotensin receptor-blocker; CAD = Coronary artery disease; CKD = Chronic kidney disease; COPD = Chronic obstructive pulmonary disease; ECG = Electrocardiogram; HF = Heart failure; K^{+} = Potassium; Mg^{++} = Magnesium; MI = Myocardial infarction

*Except as indicated, all comparisons p> 0.05

†Continuous variables are expressed as mean standard deviation; dichotomous variables are expressed as number (%)

‡p<0.0001

¶p=0.04

♯On admission

Table 3

Univariate analysis of variables associated with QT_c interval prolongation

Variable*	QT_c Prolongation (n=276)	No QT_c Prolongation (n=624)	p	Mean difference/ OR† (95% CI)
Age (years)	68 15	64 16	<0.001	4.0 (1.8–6.2)
Female	158 (57%)	295 (47%)	0.007	0.4 (0.1–0.7)
Caucasian	188 (68%)	447 (72%)	0.22	−0.2 (−0.5–0.1)
Hypertension	196 (71)%	442 (71%)	0.62	0.01 (−0.3 – 0.3)
CAD	145 (5)	313 (50%)	0.51	0.1 (−0.2 – 0.4)
Acute AF	60 (22%)	124 (20%)	0.64	0.1 (−0.2 – 0.5)
Acute cardiac arrest	8 (3%)	23 (4%)	0.87	−0.2 (−1.0–0.6)
Acute MI	47 (17%)	74 (12%)	0.001	0.4 (0.03–0.8)
Acute HF	127 (46%)	163 (26%)	<0.001	0.9 (0.6–1.2)
Sepsis	30 (11%)	30 (5%)	0.001	0.9 (0.4–1.4)
COPD	66 (2%)	147 (24%)	0.12	0.02 (−0.3–0.4)
CKD	91 (33%)	173 (28%)	0.83	0.2 (−0.1–0.6)
Diabetes mellitus	94 (34%)	170 (27%)	0.17	0.3 (0.02–0.6)
Severe liver disease	8 (3%)	12 (2%)	0.33	0.4 (−0.5–1.3)
β-blockers	163 (59%)	374 (60%)	0.54	−0.04 (−0.3–0.3)
ACE inhibitors	119 (43%)	265 (43%)	0.94	0.03 (−0.3–0.3)
ARBs	44 (16%)	86 (14%)	0.57	0.2 (−0.2–0.6)
Loop diuretics	171 (62%)	259 (42%)	<0.001	0.8 (0.5–1.1)
Digoxin	33 (12%)	101 (16%)	0.46	−0.4 (−0.8–0.1)
Statin	130 (47%)	281 (45%)	0.61	0.1 (−0.2–0.4)
Administration of 1 QT prolonging drug	138 (50%)	149 (24)%	<0.001	1.2 (0.9–1.5)
Administration of ≥ 2 QT-prolonging drugs	25 (9%)	11 (2%)	<0.001	1.7 (1.0–2.4)
Serum Mg^{2+} ≤ 1.6 mg/dL	15 (15%, n=102)	67 (19%, n=355)	0.11	−0.3 (−0.9–0.3)
Serum K^+ ≤ 3.5 mEq/L	188 (68%)	165 (26%)	<0.001	1.8 (1.5–2.1)
Serum Ca^{2+} (mg/dL)	9.0 1.4	9.1 1.6 0.91	0.1 (0.1–0.3)	
CrCl <50 mL/min,	108 (39%)	229 (37%)	0.33	0.1 (−0.3–0.5)
Admission QT_c (ms)	467752	445 33 <0.001	22 (16–28)	
Admission JT_c (ms)	375 46)	353 38 <0.001	23 (16–27)	
Admission QRS (ms)	102 25	101 24 0.79	1 (−2–4)	
Maximum QT_c (ms)	493 44	459 25 <0.001	34 (29–39)	
Maximum change in QT_c from baseline (ms)	51 29	25 13	<0.001	26 (23–29)
Admission heart rate (bpm)	83 26	87 36	0.12	−4 (−9–1)
Bradycardia (HR ≤ 60 bpm)	33 (12%)	68 (11%)	0.26	−0.1 (−0.4–0.3)

ACEI – Angiotensin converting-enzyme; AF = Atrial fibrillation; ARB = Angiotensin receptor-blocker; bpm = beats per minute; Ca^{2+} = 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; Mg^{2+} = Magnesium; OR = Odds ratio

*Continuous variables are expressed as mean standard deviation; 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 QT_c interval prolongation

Variable	Regression Coefficient	Odd Ratio (95% CI)	p
Age ≥ 68 years	0.3	1.3 (1.0–1.9)	0.04
Female sex	0.4	1.5 (1.1–2.0)	0.03
Loop diuretic	0.5	1.4 (1.0–2.0	0.007
Serum K^+ ≤ 3.5 mEq/L	0.7	2.1 (1.5–2.9)	<0.001
Admission QT_c ≥ 450 ms	0.8	2.3 (1.6–3.2)	<0.001
Acute MI	0.9	2.4 (1.6–3.9)	<0.001
≥ 2 QT_c-prolonging drugs	0.9	2.6 (1.9–5.6)	0.02
Sepsis	0.9	2.7 (1.5–4.8)	0.002
Heart failure	1.0	2.7 (1.6–5.0)	<0.001
One QT_c-prolonging drug	1.1	2.8 (2.0–4.0)	<0.001

K^+ = Potassium; MI = Myocardial infarction

Table 5

Calculation of risk score for QT_c interval prolongation

Risk Factor	Points
Age ≥ 68 years	1
Female sex	1
Loop diuretic	1
Serum K^+ ≤ 3.5 mEq/L	2
Admission QT_c ≥ 450 ms	2
Acute MI	2
≥ 2 QT_c-prolonging drugs	3
Sepsis	3
Heart failure	3
One QT_c-prolonging drug	3
Maximum Risk Score	**21**

K^+ = potassium; MI = Myocardial infarction

Table 6

QT_c interval risk score stratification*

Risk Score Category	Risk Score	# QT_c Interval Prolongation Derivation Group (%)	# QT_c Interval Prolongation Validation Group (%)
Low	< 7	456 (51%)	159 (53%)
Moderate	7–10	319 (35%)	101 (34%)
High	>11	125 (14%)	40 (13%)

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

Table 7

Predictive performance of the QT_c interval risk score

Risk Category	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Moderate Risk	0.67	0.88	0.55	0.88
High Risk	0.74	0.77	0.79	0.76