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Effectiveness of a Clinical Decision Support System for Reducing the Risk of QT Interval Prolongation in Hospitalized Patients

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Abstract

Background—We evaluated the effectiveness of a computer clinical decision support system (CDSS) for reducing the risk of QT interval prolongation in hospitalized patients.

Methods and Results—We evaluated 2400 patients admitted to cardiac care units at an urban academic medical center. A CDSS incorporating a validated risk score for QT_c prolongation was developed and implemented using information extracted from patients' electronic medical records. When a drug associated with torsades de pointes was prescribed to a patient at moderate or high risk for QT_c interval prolongation, a computer alert appeared on the screen to the pharmacist entering the order, who could then consult the prescriber on alternative therapies and implement more intensive monitoring. QT_c interval prolongation was defined as QT_c interval >500 ms or increase in QT_c of ≥60 ms from baseline; for patients who presented with QT_c >500 ms, QT_c prolongation was defined solely as increase in QT_c ≥ 60 ms from baseline. End points were assessed before (n=1200) and after (n=1200) implementation of the CDSS. CDSS implementation was independently associated with a reduced risk of QT_c prolongation (adjusted odds ratio, 0.65; 95% confidence interval, 0.56–0.89; P<0.0001). Furthermore, CDSS implementation reduced the prescribing of noncardiac medications known to cause torsades de pointes, including fluoroquinolones and intravenous haloperidol (adjusted odds ratio, 0.79; 95% confidence interval, 0.63–0.91; P=0.03).

Conclusions—A computer CDSS incorporating a validated risk score for QT_c prolongation influences the prescribing of QT-prolonging drugs and reduces the risk of QT_c interval prolongation in hospitalized patients with torsades de pointes risk factors.

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Disclosures

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Keywords

electrocardiography; medical decision making; computer-assisted; risk score; torsades de pointes

Torsades de pointes (TdP) is a potentially life-threatening polymorphic ventricular tachycardia associated with QT interval prolongation.[1] More than 50 medications available in the United States may induce QT interval prolongation.[2] TdP can be catastrophic in hospitalized patients, as it may degenerate into ventricular fibrillation and cause sudden cardiac arrest.[3] The risk for TdP increases as the heart rate-corrected QT (QT_c) interval increases,[4,5] particularly when it exceeds 500 ms.[6–8] Consequently, QT_c interval prolongation is used widely as a marker of increased risk of TdP.

Hospitalized patients may be at greater risk of drug-induced QT_c interval prolongation and TdP than outpatients because of a greater preponderance of risk factors, including structural heart disease, advanced age, electrolyte abnormalities, bradycardia, or kidney or liver disease.[3] As many as 28% of patients admitted to cardiac care units present with QT_c interval prolongation, and ≈1 of 5 have admitting QT_c intervals >500 ms.[9] Furthermore, more than one third of hospitalized patients with QT_c interval prolongation on admission subsequently receive QT interval–prolonging drugs.[9] QT_c interval prolongation in critically ill patients is associated with increased duration of hospital stay, greater odds of in-hospital mortality,[10] and increased risk of TdP.[3]

The American Heart Association and the American College of Cardiology Foundation published a scientific statement to raise awareness on the risk, ECG monitoring, and management of drug-induced QT interval prolongation and TdP in hospitalized patients.[3] The document emphasized risk factor knowledge and assessment and adequate monitoring of higher risk patients to minimize the likelihood of drug-induced TdP.[3] However, reliable, effective strategies to mitigate the risk of drug-induced QT interval prolongation and TdP in high-risk hospitalized patients have not been developed.

Computerized clinical decision support systems (CDSSs) are information systems designed to improve clinical decision making.[11] CDSS may improve prescribing of drugs, including warfarin, heparin, aminoglycosides, and others.[11] Limited data suggest that implementation of specific CDSS may improve some patient outcomes.[11] A primary limitation of many CDSS is alert desensitization, or alert fatigue, where clinicians frequently override alerts because of alert nonspecificity and the perception that the alert appears for all patients receiving specific drugs, rather than for patients truly at risk for the adverse drug reaction or drug interaction of interest.[12,13] Incorporation of risk quantification into a CDSS, such that the appearance of the alert indicates that a patient is at increased risk of experiencing a specific adverse effect, may potentially minimize routine alert overrides and maximize CDSS use and effectiveness.

We tested the hypothesis that implementation of a computer CDSS incorporating a validated risk assessment for QT_c interval prolongation reduces the prescribing of medications known to cause drug-induced TdP and decreases the associated risk of QT_c interval prolongation in hospitalized patients with known TdP risk factors.

Methods

Study Setting

This study was conducted in the cardiac care units (CCU) at Indiana University Health Methodist Hospital, a 747-bed university-affiliated tertiary care teaching institution located in Indianapolis. The CCU consists of one 28-bed cardiac critical care unit and one 28-bed cardiac progressive care unit, which primarily admit patients with cardiac diseases alone or with other medical problems. Typical diagnoses include acute myocardial infarction, heart failure, cardiac arrest, kidney disease, respiratory failure, and sepsis. A variety of physician staff attend these units, including cardiologists, heart failure specialists, critical care physicians and hospitalists. The study was approved by the Institutional Review Board at Indiana University Purdue University Indianapolis. The requirement for informed consent was waived.

Study Design

The design of this prospective, observational study is presented in Figure 1. The study consisted of 3 phases: (1) preintervention, during which the incidence of the primary and secondary end points were assessed before activation of the CDSS, (2) development of the CDSS, implementation into the institution's computer system, functionality testing, modification and optimization of functionality, and healthcare provider education on CDSS function, and (3) activation of the computerized CDSS and subsequent assessment of primary and secondary study end points.

Phase 1: Preintervention Phase—Before implementation and activation of the computerized CDSS, data were collected from 1200 patients admitted to the CCU from October 2008 to October 2009. Exclusion criteria included <18 years of age, discharge from the unit in <24 hours, and those who were not undergoing daily ECGs or continuous cardiac rhythm monitoring. Patients with completely paced ventricular rhythms were excluded because of the difficulty in accurately measuring duration of ventricular repolarization with a paced QRS complex, and the lack of normative data on JT intervals as an alternative to the QT interval in paced rhythms. Patients were enrolled at the time of admission, and data were collected at admission and daily during hospitalization.

Data collected from computer and paper medical records included demographics, admitting diagnosis, current medical problems, past medical history, past and current medications, daily progress notes, and laboratory tests. All medications during hospitalization were recorded. Drugs were considered to be QT interval prolonging if evidence for causing QT interval prolongation and TdP was available from published trials or case reports.[2] Table 1 lists the drugs on the Indiana University Health Methodist Hospital formulary that were considered to be QT interval–prolonging drugs. Laboratory data were collected on admission and daily. Serum magnesium concentrations were available for some, but not all patients. Creatinine clearances were calculated from using the Cockcroft–Gault equation.[14] Serum potassium, magnesium, calcium, and creatinine concentration values are those at the time that QT_c interval prolongation was initially documented. For patients who did not

develop QT_c interval prolongation, these values are the lowest (potassium, magnesium, and calcium) or highest (creatinine clearance) reported during the patient's hospitalization.

A baseline 12-lead ECG was obtained within 4 hours of admission in 867 (72.3%) patients. All patients underwent continuous cardiac telemetry monitoring. Daily QT intervals were measured by an investigator (H.J.; ≈90% of ECGs) or technician (≈10% of ECGs) from lead II of 12-lead ECGs or from continuous lead II telemetry strips using computer-enhanced magnification and electronic calipers when possible (MUSE Cardiology Information System, GE Healthcare, Waukesha, WI). Inter-rater reliability was determined by comparing measurements on ≈5% of the ECGs (κ=0.90). QT intervals were measured from beginning of the earliest onset of the QRS complex to the end of the T wave, determined by extending a tangent from steepest portion of the downslope of the T wave until it crossed the T-P segment.[15] During normal sinus rhythm, QT and R-R intervals were averaged from 3 consecutive complexes. During other rhythms, QT and R-R 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).

QT_c interval prolongation was defined as 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; for patients who presented with QT_c >500 ms, QT_c interval prolongation was defined solely as increase in QT_c of ≥60 ms from admitting value. As secondary analyses, the following alternate definitions of QT_c prolongation were used[16]: (1) QT_c interval ≥500 ms or an increase in QT_c interval of ≥30 ms compared with the admitting value (for patients who presented with QT_c >500 ms, the definition was increase in QT_c interval of ≥30 ms from admitting value); (2) increase in QT_c of ≥60 ms from admitting value; and (3) increase in QT_c of ≥30 ms from admitting value.

Phase 2: Development of the CDSS, Functionality Testing, CDSS Modification, and Healthcare Provider Education—A computerized CDSS was developed that extracted information from electronic medical records of patients admitted to the CCU. The CDSS incorporated a validated risk score for QT_c interval prolongation,[17] and patient information extracted by the CDSS was based on known risk factors for QT_c interval prolongation that are included in this risk score. Development and validation of the QT_c prolongation risk score have been described previously.[17] The QT_c interval prolongation risk score is presented in Table 2. Serum magnesium concentrations are not included in the score because they were only obtained in 38% of patients admitted to the CCU. Patients were classified as being at low, moderate, or high risk of developing QT_c interval prolongation during their hospitalization, based on risk scores of <7, 7 to 10, or ≥11, respectively.[17]

The computerized CDSS was incorporated into the institution's computer platform (Cerner Corporation, North Kansas City, MO). Queries were designed and refined to extract information necessary to calculate the QT_c interval prolongation risk score. When a patient was admitted to the CCU, the computerized CDSS immediately extracted patient information from the medical record to calculate the score. Age and sex were extracted from

demographics data. Serum potassium concentration closest to the time of order entry was used; point of care testing results were excluded. Other information extracted to calculate the risk score included diagnoses of acute myocardial infarction, determined by troponin >0.2 ng/mL (≈3× the upper limit of normal) or physician diagnosis; heart failure with reduced ejection fraction; sepsis; therapy with loop or thiazide diuretics; and QT_c interval–prolonging drugs. Medications were documented from the active medication list within 48 hours of order entry. The QT_c interval closest to the time of order entry from a 12-lead ECG loaded into the computer system was used to calculate the risk score. The computerized CDSS then calculated a QT_c interval prolongation risk score for each patient admitted to the CCU. However, the CDSS was not displayed on the computer screen unless the following conditions were met: (1) an order was written for a QT_c interval–prolonging drug; (2) the patient's QT_c interval prolongation risk score classified the patient as moderate risk (risk score, 7–10; corresponding to a 34%–50% risk) or high risk (risk score, ≥ 11; corresponding to a >50% risk) of developing QT_c prolongation during the hospitalization; or (3) the patient's admitting QT_c interval was >500 ms. The list of QT_c interval–prolonging drugs on the hospital's formulary that was programmed into the computer to trigger the CDSS is presented in Table 1. The computerized CDSS was programmed into the institution's computer system and was tested for functionality from October 2009 to March 2011, during which the computer alerts did not appear to clinicians, but ran in the background for CDSS testing and optimization.

Before activation of the computerized CDSS, pharmacy and physician staff were educated about the alert system. Pharmacy staff received 2 educational modules. The first was a web-based program reviewing the clinical problem of QT_c interval prolongation and TdP. The second was an in-person training session provided by pharmacists who acted as resources for the staff who reviewed functionality of the computerized CDSS and allowed the pharmacists time to practice with the CDSS. Physician staff underwent education during monthly meetings and received a brief email message describing the CDSS alert and the pharmacist's role in the alert process. In addition, a cardiologist (R.K.) acted as resource and was available to physician staff to answer questions. Education was repeated as part of the orientation process for both pharmacists and physicians new to the hospital. The education process emphasized the fact that the appearance of the computer alert was based on validated risk assessment. Unlike many other computerized CDSS programs, particularly for drug interactions, these alerts did not appear for every patient for whom a QT_c interval–prolonging drug was prescribed, but only for those patients for whom there was a moderate (34%–50% risk) to high (>50%) risk of developing QT_c interval prolongation based on the calculated QT_c interval prolongation risk score.[17] The computerized CDSS did not appear for patients for whom the calculated risk of developing QT_c interval prolongation was low.

The computerized CDSS was activated in March 2011. The alert revealed the patient's QT_c prolongation risk score, categorized the patient's risk as moderate or high, and indicated the specific risk factors that were contributing to the score. As computer physician order entry was not available at Indiana University Health Methodist Hospital at the time this study was conducted, the alert was directed to the pharmacists entering medication orders into the computer system. When an order for a QT_c interval–prolonging medication was received by the hospital pharmacy, it was entered into the computer by a pharmacist. If the patient had a

calculated QT_c interval prolongation risk score in the moderate or high range, the computer alert appeared on the screen to the pharmacist entering the order. When the alert appeared, the pharmacist had the following options: overriding the alert and taking no further action; contacting the prescribing physician, alerting him/her to the fact that the patient was at moderate or high risk, discussing risk mitigation strategies such as correction of serum electrolytes, where necessary, and performing more frequent measurement of QT_c intervals; and where appropriate, discussing with the prescriber whether the QT_c interval–prolonging drug could be discontinued and replaced with therapy with an alternate agent with less or no potential to cause QT_c interval prolongation. The prescriber could also recommend that the alert be overridden, with no further action taken.

Intervention Testing: Effect of CDSS Implementation and Activation on Study End Points—Effectiveness of the CDSS was tested from March 2011 to October 2011. Data were collected prospectively from 1200 patients consecutively admitted to the CCU. The same exclusion criteria applied to the implementation group as to the preimplementation group. Data collected from computer and paper medical records were the same as those listed under preintervention phase. All patients underwent continuous cardiac telemetry monitoring and a baseline 12-lead ECG was obtained within 4 hours of admission. QT_c intervals were measured and corrected as described in the pre-intervention phase.

Study End Points

Primary and secondary end points after implementation of the computerized CDSS were compared with those in the preintervention phase. Primary end points were (1) odds ratio (OR) for developing QT_c interval prolongation, defined as a QT_c interval >500 ms or an increase from admitting value of >60 ms at any time during the CCU hospitalization; for patients who presented with QT_c >500 ms, the definition was increase in QT_c interval from admitting value of ≥60 ms at any time during the CCU hospitalization; (2) OR for receiving therapy with a QT_c interval–prolonging medication from any drug class; and (3) OR for receiving therapy with a noncardiac QT_c interval–prolonging medication.

Secondary end points included (1) OR for developing QT_c interval prolongation using alternate definitions of QT_c interval prolongation: (a) QT_c interval ≥ 500 ms or an increase in QT_c interval of ≥30 ms compared with admitting value at any time during hospitalization (for patients who presented with QT_c >500 ms, the definition was increase in QT_c of ≥30 ms from admitting value), (b) increase in QT_c interval of ≥60 ms from admitting value,[16] and (c) increase in QT_c interval of ≥30 ms from admitting value[16]; (2) proportion of patients who presented with pre-existing QT_c interval prolongation (defined as admitting QT_c interval ≥500 ms) who subsequently received therapy with a QT_c interval–prolonging drug during the CCU hospitalization; (3) proportion of patients who had QT_c interval prolongation directly associated with a QT_c interval–prolonging medication; (4) proportion of patients with their highest documented QT_c interval prolongation risk score of moderate versus high; (5) proportion of patients who experienced ≥1 episode of nonsustained monomorphic ventricular tachycardia (defined as ≥3 beats, but <30 seconds); and (6) proportion of computer CDSS alerts that were overridden.

Statistical Analysis

Unpaired Student *t* tests were used to compare continuous variables, assuming equal or unequal variances between the groups, and χ^2 or Fisher exact test, as appropriate, was used for categorical variables. Non-normally distributed continuous parameters were compared using the Wilcoxon rank-sum test. To calculate adjusted odds of QT_c interval prolongation, independent predictors of QT_c prolongation were determined. Univariate variables with *P* value ≤0.10 were incorporated into a bivariate logistic regression model in a forward stepwise fashion in descending order of those most strongly associated with QT_c 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 χ^2 or Fisher exact test as appropriate. ORs with 95% confidence intervals (CIs) were determined for each variable. Analyses were performed using SPSS 17.0 (SPSS, Inc, Chicago, IL).

Results

Patient Characteristics

Characteristics of patients in both study phases are presented in Table 3. The CDSS implementation group had a significantly lower proportion of women, white, and patients >67 years and a significantly higher proportion of patients with heart failure with reduced ejection fraction.

Primary End Points

Implementation of the CDSS resulted in a significant reduction in the adjusted OR of QT_c interval prolongation in patients in the CCU (OR, 0.65; 95% CI, 0.56–0.89; Figure 2). Implementation of the CDSS did not result in a significant reduction in the adjusted OR of prescribing any QT_c interval–prolonging drug (OR, 0.87; 95% CI, 0.77–1.12; Figure 2). However, implementation of the CDSS led to a significant reduction in the adjusted OR of prescribing noncardiac QT_c interval–prolonging drugs (OR, 0.79; 95% CI, 0.63–0.91; Figure 2), primarily fluoroquinolone antibiotics and intravenous haloperidol.

Independent risk factors for developing QT_c interval prolongation are presented in Figure 3. The odds of developing QT_c prolongation were increased by known risk factors for QT_c interval lengthening, including female sex, respiratory distress, diabetes mellitus, acute myocardial infarction, any arrhythmia, and receiving a loop diuretic or ≥1 QT_c interval–prolonging medication. Implementation of the CDSS was independently associated with a significant reduction in the odds of developing QT_c interval prolongation.

Secondary End Points

Using the definition QT_c interval ≥500 ms or increase in QT_c interval of ≥30 ms compared with the admitting value during hospitalization (for patients who presented with QT_c >500 ms, defined as increase in QT_c of ≥30 ms from admitting value), implementation of the CDSS significantly reduced the adjusted OR of QT_c interval prolongation (OR, 0.78; 95% CI, 0.63–0.97). Using the definition increase in QT_c interval of ≥60 ms from admitting value, implementation of the CDSS did not reduce the odds of QT_c interval prolongation

(OR, 0.98; 95% CI, 0.87–1.39). Using the definition increase in QT_c interval of ≥30 ms from admitting value, implementation of the CDSS did not reduce the odds of QT_c interval prolongation (OR, 0.93; 95% CI, 0.79–1.33).

The proportion of patients who presented with pre-existing QT_c interval prolongation who subsequently received a QT_c interval–prolonging drug during the CCU hospitalization was reduced after implementation of the CDSS compared with the preintervention phase (57/163 [35%] versus 64/97 [66%]; $P<0.0001$).

The proportion of patients who developed QT_c interval prolongation directly associated with a medication was lower after implementation of the computerized CDSS than in the preintervention phase (116/1200 [9.7%] versus 203/1200 [16.9%]; $P<0.001$). The incidence of nonsustained monomorphic ventricular tachycardia was not significantly different in the preintervention phase than after implementation of the CDSS (3.8% versus 3.3%; $P=0.29$). No patients developed TdP in either study phase.

The proportion of patients with a high QT_c interval prolongation risk score was lower after implementation of the CDSS compared with preintervention (4.4% versus 10.3%; $P<0.0001$). In contrast, the proportion of patients with a moderate QT_c interval risk score was higher after implementation of the CDSS (41.1% versus 35.5%; $P=0.003$). There was no difference in the proportion of patients with a low QT_c interval risk score after CDSS implementation compared with preintervention (54.5% versus 54.2%; $P=0.87$).

After CDSS implementation, there were 470 alert triggers. Of these, 382 (82%) were overridden: 59% of these were overridden by physician request, and 41% were overridden by pharmacists (Table 4). Of the 470 alert triggers, 51 (13%) resulted in additional monitoring including ECGs or more frequent laboratory monitoring or treatment of modifiable risk factors such as discontinuing other QT-prolonging medications and replacing electrolytes. The most common medication for which alerts were overridden was amiodarone (n=136).

The 470 alert triggers resulted in discontinuation of 84 (17.9%) medication orders. The most common drugs that were discontinued were intravenous haloperidol (n=23) and ciprofloxacin (n=18).

Discussion

A computer CDSS incorporating a validated QT_c prolongation risk score reduced the odds of QT_c interval prolongation and the prescribing of noncardiac QT_c interval–prolonging drugs in patients in a CCU. Implementation of the computer CDSS also reduced the prescribing of QT_c interval–prolonging drugs to patients admitted to the CCU with pre-existing QT_c interval prolongation.

QT_c interval prolongation occurs commonly in patients in cardiac units.[9] Furthermore, patients in cardiac units with pre-existing QT_c interval prolongation are routinely prescribed QT_c interval–prolonging drugs.[9] Although risk factors for QT_c prolongation and TdP are well documented,[1,3] methods of identifying hospitalized patients at greatest susceptibility

for developing QT_c interval prolongation have not been described previously. The odds for QT interval prolongation increase as the number of risk factors increases. Each 10-ms increase in QT_c interval contributes to a ≈5% to 7% increase in risk for TdP.[4] QT interval prolongation increases the odds of in-hospital mortality[10] and is an independent risk factor for sudden cardiac death.[18] The American Heart Association and the American College of Cardiology Foundation have sought to raise awareness among healthcare professionals about the risk of drug-induced QT interval prolongation and TdP in hospitalized patients,[3] particularly on risk factors and monitoring, to minimize the likelihood of drug-induced TdP. The American Heart Association/American College of Cardiology Foundation encourages QT_c interval–monitoring strategies to identify patients who develop QT_c interval prolongation.[3] However, few strategies have been described to identify patients at greatest risk so that proactive steps may be taken to reduce the risk of progressing to QT_c interval prolongation.

At the Mayo Clinic, Haugaa et al[19] developed and implemented an institution-wide computer-based QT interval alert system, which screens all ECGs performed and alerts clinicians when the QT_c interval is ≥500 ms. These investigators also developed a pro-QT_c score, which assigned 1 point to diagnoses and conditions associated with QT_c interval prolongation. The study found that all-cause mortality was higher in patients with QT_c interval ≥500 ms compared with those with QT_c interval <500 ms (19% versus 5%; P <0.001). The pro-QT_c score predicted all-cause mortality. The authors reported that this QT interval alert system may increase clinicians' awareness of prolonged QT_c interval as a high-risk indicator, and that reducing modifiable factors contributing to the pro-QT_c score may facilitate life-saving interventions. Our work complements this work at the Mayo Clinic in several ways. First, we have developed and validated a QT_c interval risk score that accurately predicts patients that are at moderate to high risk for developing QT_c interval prolongation.[17] Second, incorporation of that risk score into a computerized CDSS reduced the risk of QT_c interval prolongation in patients in cardiac care units, in part, by encouraging amelioration of modifiable risk factors, as well as through influencing and reducing the prescribing of noncardiac QT_c interval–prolonging medications. Therefore, although the Mayo Clinic alert notifies clinicians that a patient's QT_c interval exceeds 500 ms, our alert notifies clinicians when a patient is at moderate or high risk of developing QT_c interval prolongation, so that steps can be taken to reduce the likelihood that QT_c interval prolongation actually develops.

In the present study, we used as our primary end point a definition of QT_c interval prolongation of >500 ms or an increase in QT_c interval of ≥60 ms compared with the admitting value at any time during hospitalization (or for patients who presented with QT_c >500 ms, an increase in QT_c of ≥60 ms from admitting value). This end point was chosen based on data in patients with the long QT syndrome indicating that QT_c interval >500 ms is associated with a 2- to 3-fold higher risk of TdP than QT_c interval <500 ms[20,21] and also based on data in patients with drug-induced TdP, which show a similar increased risk when the QT_c interval is >500 ms.[6–8] However, as there is no universally accepted consensus on the definitions of QT_c interval prolongation, we also analyzed our data using other definitions.[16] Using the definition QT_c interval >500 ms or an increase of ≥30 ms compared

with admitting value (or for patients who presented with QT_c >500 ms, an increase in QT_c of ≥30 ms from admitting value), implementation of the CDSS significantly reduced the OR for QT_c interval prolongation. A potential disadvantage of the above 2 definitions is that a patient could be admitted with a QT_c interval between 490 and 500 ms, for example, and then during drug therapy experience a relatively small percentage increase from baseline to >500 ms and be counted in the QT_c interval prolongation group. However, only 6% of patients in our study population presented with QT_c interval 490 to 499 ms. We also analyzed the data using 2 definitions that did not include prolongation to >500 ms: an increase in QT_c interval by ≥60 ms from admitting value and an increase in QT_c interval by ≥30 ms from admitting value. Using these definitions, CDSS implementation did not result in reduction in the odds of QT_c interval prolongation. However, it should be pointed out that the QT_c interval prolongation risk score that was incorporated into the CDSS and which identified patients as being at low, moderate, or high risk was developed and validated using the QT_c interval prolongation definition used for our primary end point. Therefore, the validity of our QT_c interval risk score using an alternate definition of QT_c interval prolongation is unknown. Further, as described above, data indicate that QT_c interval >500 ms seems to be a critical threshold for an increased risk of TdP, rather than any specific increase in the interval from baseline. Using 2 definitions of QT_c interval prolongation that included QT_c interval >500 ms, our CDSS was effective for reducing the risk of QT_c interval prolongation.

One of the primary limitations of many CDSS is alert fatigue, where clinicians frequently override alerts because of lack of specificity.[12,13] Incorporation of risk assessment into a CDSS could minimize routine alert overrides and maximize CDSS use and effectiveness. In this study, our computer CDSS alert for QT_c interval prolongation was specific and selective. Rather than appearing for every patient prescribed a QT_c interval–prolonging drug, this alert was only displayed for patients prescribed a QT_c interval–prolonging drug for whom there was a moderate to high risk of QT_c interval prolongation based on assessment of QT_c prolongation risk factors.[17] Therefore, pharmacists who viewed an alert and physicians who were contacted about an alert knew that it was based on a validated quantification of risk. The CDSS alert override rate in this study was 82%, which is lower than override rates routinely reported in CDSS studies (often ≥90%).[12,22,23] The lower alert override rate in this study may be a result of the more specific, selective nature of the CDSS alerts. Furthermore, overriding of an alert did not necessarily mean that no action was taken; in many cases, overriding of an alert meant that the QT_c interval–prolonging medication that was ordered was not discontinued, but electrolyte supplementation was administered, another medication was discontinued, or more intensive QT_c interval monitoring was performed.

In this study, implementation of the CDSS did not reduce the odds of prescribing of QT_c interval–prolonging cardiovascular drugs, primarily amiodarone, but also including sotalol and other antiarrhythmic agents. Prolongation of ventricular repolarization is a major component of the efficacy of antiarrhythmic drugs. Furthermore, it is often difficult to replace a QT_c interval–prolonging agent with a non–QT_c interval-prolonging drug for arrhythmia management. Conversely, implementation of the CDSS significantly reduced the prescribing of noncardiac QT_c-prolonging drugs, particularly fluoroquinolone antibiotics

and intravenous haloperidol. This suggests that implementation of the CDSS enhanced prescriber awareness of the problem of QT_c interval prolongation, such that prescribers, where possible and appropriate, selected non–QT_c interval-prolonging medications for the management of noncardiac conditions.

There were no occurrences of TdP in the CCU in this study. Even in the highest risk populations, TdP occurs rarely; Swedish investigators estimated an incidence of 4 cases of TdP per 1 000 000 persons annually.[24] In our patients with cardiac disease and TdP risk factors, the incidence of TdP may be somewhat higher. Larger numbers of patients monitored for longer periods of time would be needed to demonstrate a survival benefit for a risk mitigation strategy. Although TdP occurs relatively rarely, it is a potentially avoidable catastrophic event in hospitalized patients, and consequently the American Heart Association/American College of Cardiology Foundation strongly recommends increased awareness of QT interval prolongation, TdP risk, QT interval monitoring, and avoidance of QT interval–prolonging medications where possible in hospitalized patients.[3] Reducing the risk of drug-induced QT_c interval prolongation with CDSS or other measures may reduce the risk of drug-induced TdP and possibly all-cause in-hospital mortality; this hypothesis requires testing in further studies.

Limitations of this work include the fact that the study was conducted in 2 cardiac 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. However, although the patient population was limited to cardiovascular/critical care, there were a variety of noncardiologist physician specialties represented among the physicians attending patients in these units. Although patients completely paced ventricular rhythms were excluded, patients with QRS duration >120 ms were included because clinicians working with this CDSS must make decisions about patients who may develop QT_c interval prolongation, including those presenting with QRS >120 ms. Therefore, we included those patients to maximize external clinical applicability of the findings. The study used a pre- and postinterventional design, which can introduce temporal bias. The CDSS development phase included an educational component that was not included in the preintervention phase; the influence of the educational component on the intervention is unclear and requires assessment in future studies. These findings should be confirmed in a prospective, randomized, parallel group study, in which the educational component is accounted for; the current study provides support for such a trial.

In conclusion, a computer CDSS incorporating a validated risk score for QT_c interval prolongation influences the prescribing of noncardiac QT_c interval–prolonging drugs and reduces the risk of QT_c interval prolongation in hospitalized patients with TdP risk factors. The results of this study provide support for a prospective, parallel group randomized study to evaluate the effectiveness of this or similar computer CDSS for reducing the risk of QT_c interval prolongation and associated outcomes, including incidence of TdP and sudden cardiac death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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WHAT IS KNOWN

- QT interval prolongation is a risk factor for torsades de points, a life-threatening arrhythmia.
- Reliable, effective strategies to mitigate the risk of drug-induced QT interval prolongation and torsades de pointes have not been developed.

WHAT THE STUDY ADDS

- A computer clinical decision support system was developed, incorporating a validated risk score for QT interval prolongation.
- This clinical decision support system alerted pharmacists entering orders for drugs that could provoke QT interval prolongation among specific patients at moderate or high risk of developing QT interval prolongation; the pharmacists then contacted prescribers to discuss risk mitigation strategies.
- Implementation of the computer clinical decision support system resulted in a significant reduction in the prescribing of noncardiac QT interval–prolonging medications and the risk of QT interval prolongation in patients hospitalized in cardiac care units.

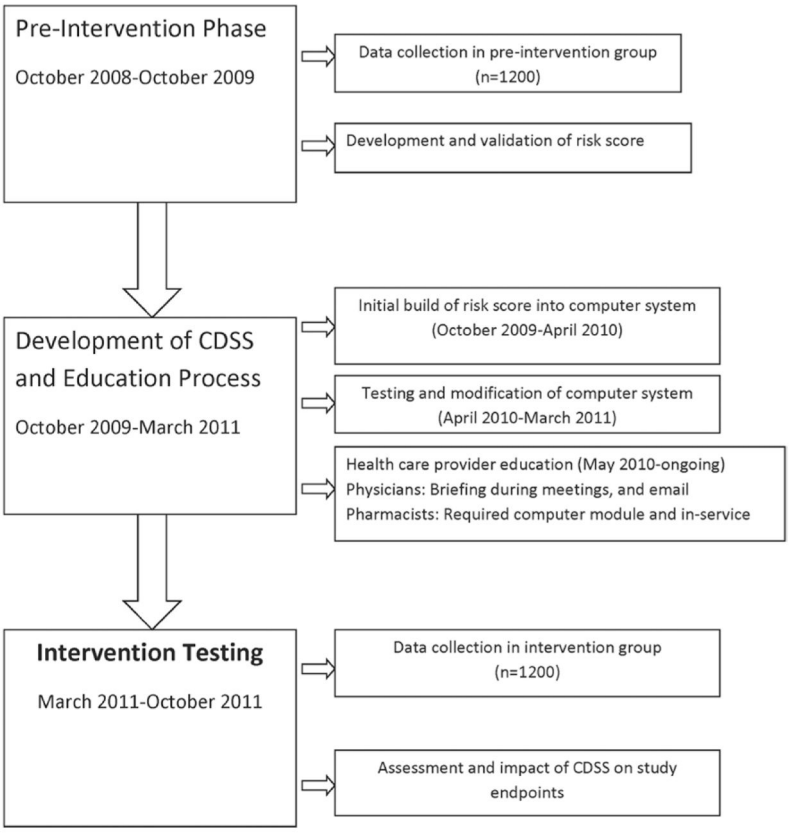

Figure 1.
Study design. CDSS indicates clinical decision support system.

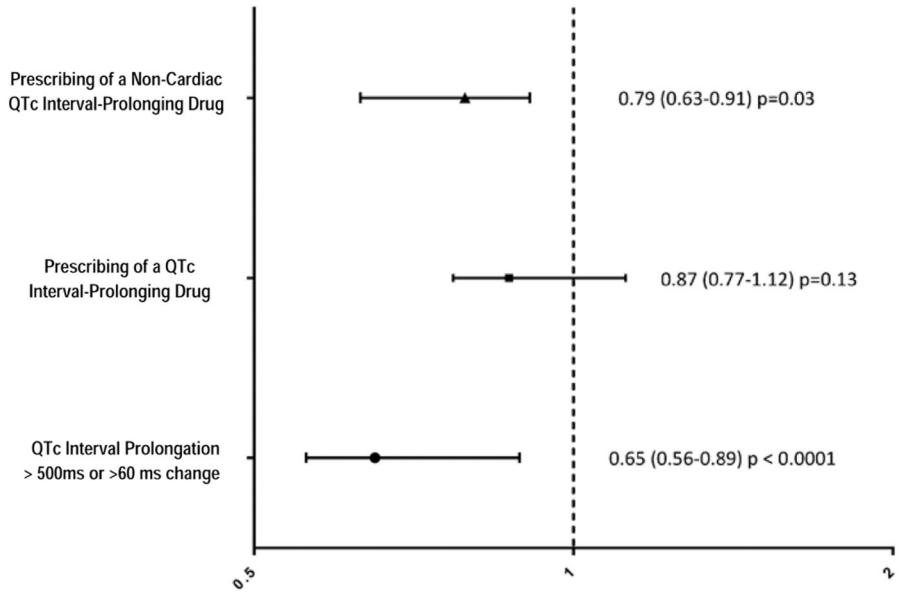

Figure 2.

Influence of a computerized clinical decision support system on the adjusted odds of developing QT_c prolongation, the adjusted odds of prescribing of QT_c interval–prolonging drugs from any drug class, and the adjusted odds of prescribing noncardiac QT_c interval–prolonging drugs.

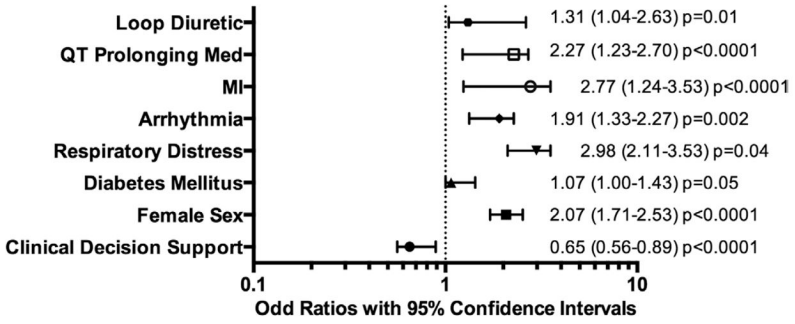

Figure 3.

Independent risk factors for developing QT_c prolongation during hospitalization in cardiac critical care units. MI indicates myocardial infarction.

Table 1

QT_c Interval–Prolonging Drugs on the Hospital Formulary That Were Programmed to Trigger the Appearance of the QT_c Interval Prolongation Risk Alert if the Risk Score Classified the Patient as Moderate or High Risk

Drug Class	Drug	No. of Patients (Pre-CDSS)	No. of Patients (After CDSS Activation)	*P* Value
Antiarrhythmic	Amiodarone	122 (10%)	142 (12%)	0.19
	Disopyramide	2 (0.2%)	0 (0%)	0.50
	Dofetilide	22 (2%)	4 (0.3%)	<0.0001
	Dronedarone	8 (1%)	11 (1%)	0.81
	Ibutilide	2 (0.2%)	0 (0%)	0.50
	Procainamide	2 (0.2%)	0 (0%)	0.50
	Quinidine	1 (0.1%)	0 (0%)	>0.99
	Sotalol	36 (3%)	29 (2%)	0.45
Anti-infective	Azithromycin	74 (6%)	65 (5%)	0.48
	Clarithromycin	3 (0.3%)	0 (0%)	0.25
	Ciprofloxacin	32 (3%)	24 (2%)	0.34
	Erythromycin	3 (0.3%)	1 (0.1%)	0.62
	Fluconazole	12 (1%)	8 (1%)	0.50
	Levofloxacin	26 (3%)	16 (1%)	0.16
	Moxifloxacin	18 (2%)	25 (2%)	0.36
	Pentamidine	0 (0%)	0 (0%)	>0.99
	Voriconazole	1 (0.1%)	2 (0.2%)	>0.99
Psychotropic	Chlorpromazine	2 (0.2%)	0 (0%)	0.50
	Droperidol	0 (0%)	0 (0%)	>0.99
	Haloperidol	46 (4%)	29 (2%)	0.06
	Pimozide	0 (0%)	0 (0%)	>0.99
	Risperidone	5 (0.4%)	2 (0.2%)	0.45
	Thioridazine	0 (0%)	0 (0%)	>0.99
	Ziprasidone	4 (0.3%)	3 (0.3%)	>0.99
Other	Methadone	6 (0.5%)	2 (0.2%)	0.29
	Ranolazine	2 (0.2%)	3 (0.3%)	>0.99

CDSS indicates clinical decision support system.

Table 2

Calculation of Risk Score for QT_c Interval Prolongation[17]

Risk Factor	Points
Age ≥68 y	1
Female sex	1
Loop diuretic	1
Serum $K^+ \leq$ 3.5 mEq/L	2
Admission $QT_c \geq$ 450 ms	2
Acute MI	2
1 QT_c interval–prolonging drug	3
≥2 QT_c interval–prolonging drugs	3
Sepsis	3
Heart failure	3
Maximum risk score	21

K^+ indicates potassium; and MI, myocardial infarction.

Table 3

Summary of Patient Characteristics

Characteristics*	Preintervention Group (n=1200)	CDSS Implementation Group (n=1200)	*P* Value
Age >67 y	576 (48%)	468 (39%)	<0.0001
Women	606 (51%)	516 (43%)	0.0003
Race (white)	840 (70%)	792 (66%)	0.04
Admission diagnosis			
Acute AF	245 (20%)	264 (22%)	0.34
Acute cardiac arrest	28 (2%)	38 (3%)	0.26
Acute MI	139 (12%)	228 (19%)	<0.0001
Acute HF	435 (36%)	465 (39%)	0.21
Unstable angina/PCI	304 (25%)	276 (23%)	0.18
COPD exacerbation	111 (9%)	103 (9%)	0.61
Acute infection (UTI, pneumonia)	120 (10%)	128 (11%)	0.58
Sepsis	85 (7%)	82 (7%)	0.81
Acute kidney injury	338 (28%)	302 (25%)	0.10
Comorbidities			
CAD	609 (51%)	601 (50%)	0.74
HFrEF	325 (27%)	398 (33%)	0.0001
Hypertension	849 (71%)	869 (72%)	0.37
Diabetes mellitus	480 (40%)	528 (44%)	0.05
COPD	201 (17%)	210 (18%)	0.63
CKD	338 (28%)	305 (25%)	0.13
Medications			
β-blocker	709 (59%)	741 (62%)	0.18
ACE inhibitor	512 (43%)	522 (44%)	0.68
ARB	178 (15%)	189 (16%)	0.53
Digoxin	164 (14%)	143 (12%)	0.20
Loop diuretic	603 (50%)	625 (52%)	0.37
1 QT interval–prolonging drug	372 (31%)	351 (29%)	0.35
≥2 QT interval–prolonging drugs	45 (4%)	52 (4%)	0.47
Laboratory values			
Serum K^+ (mEq/L)	3.8±1.0	3.8±1.1	>0.99
Serum K^+ <3.5 mEq/L	492 (41%)	452 (38%)	0.09
Serum Mg^{2+} <1.6 mg/dL	27 (6%; n=457)	60 (9%; n=677)	0.09
Serum Ca^{2+}, mg/dL	9.1±1.0	9.1±1.2	0.94
Estimated creatinine clearance ≤50 mL/min	447 (37%)	430 (36%)	0.47
ECG			
Admission QT_c, ms	451±41	450±55	0.87
Maximum QT_c, ms	471±37	474±43	0.14
QT interval prolonged on admission	168 (14%)	179 (15%)	0.52

Characteristics*	Preintervention Group (n=1200)	CDSS Implementation Group (n=1200)	*P* Value
QT interval prolongation during hospitalization	340 (28%)	311 (26%)	0.18
Heart rate, bpm	86±36	81±44	0.12
Heart rate <60 bpm	126 (11%)	111 (9%)	0.30

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; bpm, beats per minute; CAD, coronary artery disease; CDSS, clinical decision support system; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; K^+, potassium; Mg^{2+}, magnesium; MI, myocardial infarction; PCI, percutaneous coronary intervention; and UTI, urinary tract infection.

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

Table 4

Reasons for Computer Alert Overrides (n=382)

Reason for Override	n (%)
Physician-notified; ordered to continue medication	225 (59)
Patient's condition warrants drug administration	58 (15)
Therapy appropriate as ordered	48 (9)
Laboratory test to be repeated, continue treatment	20 (5)
Not applicable to formulation	6 (2)
Patient on dialysis, continue treatment as ordered	2 (1)
Reference consulted, treatment appropriate	3 (1)
Treatment plan requirement	9 (2)
Other/unknown	11 (3)