PHARMACOTHERAPY

Predictive Analytics for Identification of Patients at Risk for QT Interval Prolongation: A Systematic Review

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Prolongation of the heart rate–corrected QT (QTc) interval increases the risk for torsade de pointes (TdP), a potentially fatal arrhythmia. The likelihood of TdP is higher in patients with risk factors that include female sex, older age, heart failure with reduced ejection fraction, hypokalemia, hypomagnesemia, concomitant administration of two or more QTc interval-prolonging medications, among others. Assessment and quantification of risk factors may facilitate prediction of patients at highest risk for developing QTc interval prolongation and TdP. Investigators have utilized the field of predictive analytics, which generates predictions using techniques including data mining, modeling, machine learning, and others, to develop methods of risk quantification and prediction of QTc interval prolongation. Predictive analytics have also been incorporated into clinical decision support (CDS) tools to alert clinicians regarding patients at increased risk of developing QTc interval prolongation. The objectives of this article are to assess the effectiveness of predictive analytics for identification of patients at risk of drug-induced QTc interval prolongation and to discuss the efficacy of incorporation of predictive analytics into CDS tools in clinical practice. A systematic review of English-language articles (human subjects only) was performed, yielding 57 articles, with an additional 4 articles identified from other sources; a total of 10 articles were included in this review. Risk scores for QTc interval prolongation have been developed in various patient populations including those in cardiac intensive care units (ICUs) and in broader populations of hospitalized or health system patients. One group developed a risk score that includes information regarding genetic polymorphisms; this score significantly predicted TdP. Development of QTc interval prolongation risk prediction models and incorporation of these models into CDS tools reduce the risk of QTc interval prolongation in cardiac ICUs and identify health system patients at increased risk for mortality. The impact of these QTc interval prolongation predictive analytics on overall patient safety outcomes, such as TdP and sudden cardiac death relative to the cost of development and implementation, requires further study.

Key Words QT interval, torsade de pointes, risk factors, predictive analytics, clinical decision support.
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Prolongation of the heart rate–corrected QT (QTc) interval on the electrocardiogram (ECG) increases the risk of the ventricular arrhythmia known as torsade de pointes (TdP), which can result in sudden cardiac death.[1, 2] The 99th percentile for the QTc interval is 480 milliseconds (ms) and 470 ms in adult women and men, respectively.[3] The risk of TdP increases

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markedly when the QTc interval is greater than 500 ms.[4–6] Each 10 ms increase in the QTc interval confers ~6% increase in the risk of a cardiac event.[7] The risk of TdP also increases when the QTc interval lengthens more than 60 ms compared with the baseline value.[8]

QTc interval prolongation may be inherited (congenital long QT syndrome [LQTS])[9] or acquired, which is caused most commonly by medications. More than 150 drugs available in the United States prolong the QTc interval and have the potential to cause TdP.[10] Drugs from a wide variety of therapeutic classes can prolong the QTc interval and cause TdP including antimicrobials (macrolides, fluoroquinolones, azole antifungals), cardiovascular agents (antiarrhythmic drugs), antidepressants, antipsychotics, anticancer agents, methadone, and many others.[10] QTc interval-prolonging drugs are prescribed frequently; nearly 23% of ~5 million outpatients filled at least one prescription for a QTc interval-prolonging medication during a 1-year period.[11]

QTc interval prolongation occurs commonly. About 18% of patients admitted to cardiac intensive care units (ICUs) have a QTc interval greater than 500 ms on admission, and ~42% of those patients subsequently receive QTc interval-prolonging drugs while hospitalized.[12] A QTc interval prolongation develops in 24–52% of adult patients hospitalized in ICUs[13, 14] and is present in as many as 35% of patients in emergency departments (EDs) where the prevalence of markedly prolonged QTc interval (greater than 500 ms) is 1–8%.[15, 16, 17] QTc interval prolongation has been shown to be associated with increased risk for total and cardiovascular mortality.[17]

Numerous risk factors have been identified for QTc interval prolongation and TdP and include older age, female sex, heart failure due to reduced ejection fraction, acute myocardial infarction, electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia), bradycardia, and concurrent use of more than one QTc interval-prolonging drug. Other risk factors include sepsis, increases in plasma concentrations of QTc interval-prolonging drugs due to rapid intravenous infusion, pharmacokinetic interactions, and inadequate dose adjustment of renally eliminated or hepatically metabolized QTc interval-prolonging drugs in patients with kidney or liver disease, respectively.[3, 18, 19] Risk factors are important with respect to the development of QTc interval prolongation and the occurrence of TdP. In comparison with patients with no risk factors, the odds ratio (OR) for QTc interval prolongation in patients with one risk factor is 3.2 (95% confidence interval [CI] 2.1–5.5). The OR for QTc interval prolongation increases substantially in patients with two risk factors (7.3, 95% CI 4.6–11.7) and three or more risk factors (9.2, 95% CI 4.9–17.4).[20] In an analysis of 144 published journal articles describing 249 patients who experienced TdP induced by noncardiovascular drugs, nearly 100% had at least one risk factor; 71% of the patients had at least two risk factors.[21] TdP in the absence of risk factors is exceedingly rare.

The field of predictive analytics endeavors to generate predictions about the future using a variety of techniques including data mining, modeling, machine learning, and others.[22] In view of the importance of risk factors for the development of QTc interval prolongation and TdP, methods of risk stratification and awareness of magnitude of risk may be valuable for reducing the likelihood of a potentially catastrophic arrhythmia. A number of investigators have developed methods for risk quantification and prediction of the development of QTc interval prolongation and/or TdP. In addition, some investigators have incorporated predictive analytics into clinical decision support (CDS) tools to alert clinicians regarding patients at increased risk of developing QTc interval prolongation. This article reviews the effectiveness of predictive analytics for identification of patients at risk for drug-induced QTc interval prolongation and discusses the efficacy of incorporating predictive analytics into CDS tools in clinical practice.

Methods

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[23] Medline (1879–December 2017), the Cochrane database (1966–December 2017), Embase (1991–December 2017), and Ovid (1946–2017) were reviewed for English-language articles using the search terms "QTc interval prolongation OR QT interval prolongation OR Torsade de pointes AND risk score AND QT risk score OR genetic variant risk score AND decision support AND QT alert system OR QT alert." Figure 1 presents our PRISMA flow diagram. A total of 10 studies were included in the final qualitative synthesis.

Predictive Analytics for Assessing Risk of QTc Interval Prolongation

Investigators at the Mayo Clinic developed a QTc interval risk score, which they named the pro-QTc score.[24] Over a period of 7 months, 86,107 ECGs were performed in 52,579 patients. The investigators collected data retrospectively from medical records on clinical diagnoses, abnormal laboratory values, and drugs known to prolong the QTc interval, and they summarized these data in the pro-QTc score. Rather than assigning weights to individual components of the score, each factor was considered equipotent and assigned a score of 1. Table 1 presents components of the pro-QTc score. The investigators reported that 99% of 470 patients with a QTc interval of 500 ms or more had at least one risk factor (excluding female sex). The mean (± SD) pro-QTc score in patients with QTc interval of 500 ms or more was 3.1 ± 1.6. After exclusion of 45 patients with congenital LQTS, the mean pro-QTc score in patients with a QTc interval of 500 ms or more was 3.2 ± 1.7. Medications were the greatest contributors to the pro-QTc score (score proportion 37%), followed by a QT interval-prolonging diagnosis (23%) and electrolyte abnormalities (22%). A pro-QTc score of 4 or higher predicted mortality (hazard ratio [HR] 1.72, 95% CI 1.11–2.66, p<0.001). The number of QTc interval-prolonging medications and electrolyte abnormalities were the only components of the score significantly associated with death; female sex and number of QTc interval-prolonging diagnoses were not. Mortality was better predicted using the pro-QTc score including electrolyte abnormalities and QTc interval-prolonging medications only in a multivariate analysis together with age, serum creatinine, QRS duration, and cardiovascular admission diagnosis, compared with using a pro-QTc score that included female sex and diagnoses/conditions known to be associated with QTc interval prolongation (HR 1.26, 95% CI 1.10–1.44). Limitations of this analysis include the retrospective design and the absence of weighting of

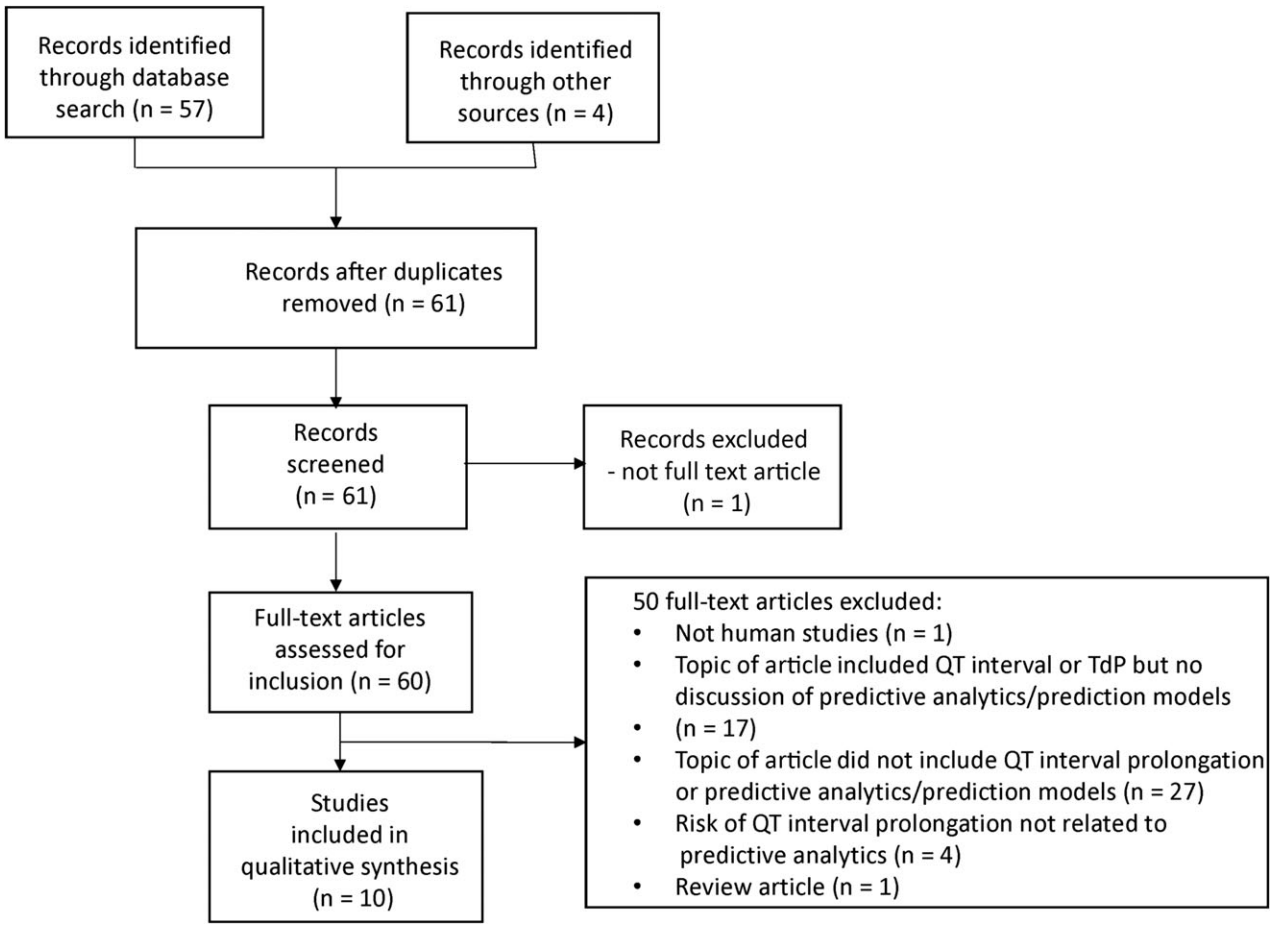

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. TdP = torsade de pointes.

components of the risk score. In addition, sensitivity, specificity, and positive and negative predictive values of the pro-QTc score for prediction of mortality were not reported.

Our research group sought to quantify the risk of drug-induced QTc interval prolongation through development and validation of a QTc interval prolongation risk score.[19] In a prospective observational study, we collected data from 1200 patients admitted to two 28-bed cardiac ICUs in a tertiary care academic medical center. Initially, we developed a QTc interval prolongation risk score model in 900 consecutive patients admitted to these units. Using logistic regression analysis, we identified independent risk factors for QTc interval prolongation, defined as a QTc interval more than 500 ms or an increase of 60 ms or more from the admitting value occurring at any time during the hospitalization. We determined ORs with 95% CI for the independent risk factors and assigned to each independent variable a weighted point score (1, 2, or 3) based on the log OR (Table 2). Risk scores were categorized as low, moderate, or high based on predictive accuracy using the C-statistic from receiver operating characteristics curves. Risk scores lower than 7, 7–10, and 11 or above were categorized as "low," moderate," and "high" risk, respectively. The resulting risk score was then validated in an additional population of 300 patients admitted to these units. The predictive performance of the QTc interval risk score was good with respect to sensitivity, specificity, and positive and negative predictive value (Table 3). Limitations of this study include the fact that the investigation was conducted at a single institution in two nearly identical cardiac ICUs; the results may not apply to patients in general medical units or other areas where QTc interval-prolonging drugs may be used (such as cancer centers, ambulatory care clinics, and methadone clinics). In addition, our analysis was based on a relatively small sample of patients.

Another risk score for QTc interval prolongation, called RISQ-PATH, was developed in hospitalized patients receiving haloperidol or a QTc interval-prolonging antibiotic/antimycotic in an academic tertiary care medical center in Belgium.[25] In this prospective observational study, patients underwent a baseline ECG before the administration of the QTc interval-prolonging medication and a follow-up ECG at the time of expected steady-state plasma concentration (between 3 and 11 days after initiation of therapy). The investigators collected demographic, disease-related, and laboratory data from the medical record. Points were allocated to risk factors for QTc interval prolongation previously identified in the literature, based on the investigators' assessment of the strength of the evidence: 6 points for strong evidence, 3 points for moderate evidence, and 1 point for low evidence. QTc interval-prolonging drugs were scored based on the QT drugs list on the CredibleMeds.org[10] website: known risk = 3 points, possible risk = 0.5 points, conditional risk = 0.25 points. The maximum value in the RISQ-PATH score was 40.5 plus the sum of the scores for QTc interval-prolonging drugs.

The investigators reported that 26 of 178 (14.6%) patients developed QTc interval prolongation, of which 25 had a RISQ-PATH score of 10 or higher. A RISQ-PATH score lower than 10 demonstrated good sensitivity and negative predictive value for predicting QTc interval prolongation (Table 3). However, the specificity and positive predictive value of the score were low, likely as a result of the strategy of allocation of points based on assessment of strength of literature evidence. The QT drugs list at CredibleMeds.org is based on assessment of whether QTc interval-prolonging drugs are known to be

Table 1. Diagnoses/Conditions Included in the Pro-QTc Risk Score[24]

Acute coronary syndrome (≤ 7 days)
Anorexia nervosa or starvation
Bradycardia (heart rate < 45 beats/min)
Heart failure (left ventricular ejection fraction < 40%)
Diabetes mellitus (types 1 and 2)
Female sex
Hypertrophic cardiomyopathy
Hypoglycemia (documented and in the absence of diabetes)
Intoxication with QT interval-prolonging drug (≤ 24 hrs)
Long QT syndrome
Pheochromocytoma
Kidney dialysis
Status after conversion of atrial fibrillation to sinus rhythm (7 days after cardioversion, radiofrequency ablation, or the Maze procedure)
Status after cardiac arrest (24 hrs)
Status after syncope or seizure (24 hrs)
Stroke, subarachnoid hemorrhage, head trauma (≤ 7 days)
Electrolyte disturbances
Hypocalcemia (calcium < 4.65 mg/dl)
Hypokalemia (potassium < 3.6 mmol/L)
Hypomagnesemia (magnesium < 1.7 mg/dl)
One or more QTc interval-prolonging medication from CredibleMeds[10] within previous 7 days

Table 2. Components of Risk Score for QTc Interval Prolongation

Risk factors	Points
Age ≥ 68 yrs	1
Female	1
Loop diuretic	1
Serum $K^+ \leq 3.5$ mEq/L	2
Admitting QTc interval ≥ 450 ms	2
Acute myocardial infarction	2
Sepsis	3
Heart failure with reduced ejection fraction	3
One QTc interval-prolonging drug	3[a]
Two or more QTc interval-prolonging drugs	3[a]
Maximum score	21

[a]If a patient is receiving two or more QTc interval-prolonging drugs, he or she is assigned a total score of 6: 3 points for receiving one QTc interval-prolonging drug and 3 points for receiving two or more QTc interval-prolonging drugs.
Source: Adapted with permission from reference 19.

associated with TdP or whether there is a possible or conditional risk of TdP.[10] However, drugs within any given category may lengthen QTc interval by substantially different degrees, which may have influenced the specificity and predictive accuracy of this score. Another limitation is that the investigators included risk variables in the score for which there is minimal evidence of an independent association with QTc interval prolongation or TdP, such as cigarette smoking, body mass index 30 kg/m^2 or higher, C-reactive protein greater than 5 mg/ml, and hypertension.

One group developed the first genetic risk score for drug-induced QTc interval prolongation and TdP.[26] The investigators hypothesized that response to one or multiple QTc interval-prolonging drugs can be predicted by a weighted combination of common genetic variants identified by genome-wide association studies. Twenty-two healthy subjects were enrolled in a double-blind placebo-controlled crossover trial and randomized to each of four QTc interval-prolonging drugs (dofetilide, quinidine, ranolazine, and verapamil hydrochloride) or placebo. Verapamil data were not included in the final analysis because the dose administered did not prolong the QTc interval in the study subjects. A washout period of 7 days between each drug administration was observed, and triplicate 10-second ECG measurements were collected at 15 specific time points over the course of 24 hours.

The genetic risk score was calculated based on a pool of 61 common variants that were shown to influence the QTc interval in subjects of European or African descent.[27] Although some of these were variants known to be associated with congenital LQTS genes, others were

Table 3. Comparison of Published Predictive Analytics Tools to Predict Risk of or Identify Patients with QTc Interval Prolongation

	Mayo Clinic pro-QTc score[24]	Tisdale et al risk score[19]	RISQ-PATH score[25]
Study design	Retrospective	Prospective observational	Prospective observational
Study setting	Mayo Clinic	Cardiac ICU	Tertiary care center
Study patients, n	52,570	900 development, 300 validation	178
QTc interval prolongation definition	> 500 ms	> 500 ms or increase ≥ 60 ms from baseline	≥ 450 (males) ≥ 470 (females)
QTc interval prolongation prevalence (%)	1145/52,570 (2)	274/900 (30.4)	26/178 (14.6)
Mortality in patients with QTc interval prolongation, %	20	NA	NA
Risk score factors weighted	No: 1 point per risk factor	Yes: 1–3 points per risk factor	Yes: 0.5–6 points per risk factor
Validation	No	Yes	No
Sensitivity, %	NA	74,[a] 67[b]	96.2 (95% CI 78.4–99.8)
Specificity, %	NA	77,[a] 88[b]	32.9 (25.6–41.0%)
Positive predictive value, %	NA	79,[a] 55[b]	19.7 (13.4–27.9%)
Negative predictive value, %	NA	76,[a] 88[b]	98 (88.2–99.9%)
Identifies patients at high risk of QTc interval prolongation before developing it	No	Yes	Yes
Predicts patients at highest risk of mortality	Yes	No	No

CI = confidence interval; ICU = intensive care unit; NA = not applicable.
[a]High risk.
[b]Moderate risk.

variants in genes encoding proteins that were not previously known to influence ventricular repolarization. Investigators assigned a weight to each allele based on the observed Fridericia-corrected QTc interval effect and multiplied that by its frequency in the population. The sum of the weighted QTc effect of each allele resulted in an individual genetic QTc score ranging from 0–122. This genetic score described 27% of the variability (p=0.03) in pretreatment QTc intervals among subjects of European descent. The risk score significantly described 30% of the variability in QTc interval response to dofetilide (r = 0.55, 95% CI 0.09–0.81, p=0.02) and 27% of the QTc interval response variability to ranolazine (r = 0.52, 95% CI 0.05–0.80, p=0.03). The risk score was not able to describe the QTc interval response variability (23%) to quinidine (r = 0.48, 95% CI 0.03–0.79, p=0.06).

Among the four subjects of African descent, it was difficult to determine precisely the degree of QTc interval variability explained by the genetic risk score due to the small sample size. Despite this, the genetic risk score was significantly associated with baseline QTc intervals (p=0.03) in this population. A significant correlation was also established between the baseline QTc interval and response to dofetilide, but not quinidine or ranolazine, among the subjects of African descent. Some of the limitations of this analysis were a small study sample, particularly among subjects of African descent, and the lack of inclusion of subjects of other races. In addition, the study only enrolled healthy volunteers; the predictive accuracy of the genetic risk score in patients with cardiovascular comorbidities or other risk factors exposed to chronic treatment with QTc interval-prolonging drugs remains to be determined.

The investigators subsequently tested their genetic risk score in an independent population of 216 patients who had experienced TdP to predict the risk of drug-induced TdP compared with 771 controls.[26] The genetic risk score significantly predicted risk of drug-induced TdP ($r^2 = 0.12$, $p=1.3 \times 10^{-7}$). This study represents the first example of a genetic risk score used as an analytical predictive tool to determine degree of response to drug-induced QTc interval prolongation and to predict the occurrence of TdP.

Incorporation of Predictive Analytics into Clinical Decision Support Tools

A number of investigators have incorporated predictive analytics into CDS tools that have been tested for their ability to alert clinicians regarding patients who are at risk for QTc interval prolongation or who already have QTc interval prolongation. We incorporated our validated QTc interval prolongation risk score into a CDS computer alert and tested this alert to assess its effectiveness for reducing the risk of QTc interval prolongation in the cardiac ICUs at Indiana University Health Methodist Hospital in Indianapolis.[28] With the assistance of information technology specialists, we developed and implemented a CDS computer alert using information extracted from patients' electronic medical records. When a drug known to be associated with TdP was prescribed to a patient with moderate or high risk of QTc interval prolongation as designated by application of our QTc interval risk score, a computer alert appeared on the screen of the pharmacist entering the order. A computer alert did not appear for patients prescribed a torsadogenic drug for which the risk of QTc interval prolongation was designated low risk by our risk score. Therefore, when the CDS alert appeared, the pharmacist (and prescribers contacted by the pharmacist) knew that the alert was appearing only to patients at a certain level of risk. The CDS computer alert also described the risk factors present that contributed to the risk score in each patient. When an alert appeared for a patient at moderate or high risk of QTc interval prolongation, the pharmacist contacted the prescriber to discuss, as appropriate for each specific patient, the need for electrolyte replacement, more intensive QTc interval monitoring, and whether alternative non-QTc interval-prolonging drug therapy could be substituted to minimize the risk. We then determined the risk of QTc interval prolongation (defined as a QTc interval more than 500 ms or an increase of more than 60 ms from the admitting value occurring at any time during the hospitalization) over 1 year before (1200 patients) and 8 months following (1200 patients) implementation of the CDS computer alert in our cardiac ICUs.

Implementation of the CDS computer alert significantly reduced the adjusted OR for QTc interval prolongation (OR 0.65, 95% CI 0.56–0.89, p<0.0001). Implementation of the CDS computer alert did not significantly influence the prescribing of QTc interval-prolonging drugs overall (OR 0.87, 95% CI 0.77–1.23, p=0.13). However, implementation of the CDS computer alert significantly reduced the prescribing of noncardiovascular QTc interval-prolonging drugs

(OR 0.79, 95% CI 0.63–0.91, p<0.03). After implementation of the CDS computer alert, of the 470 alert triggers, 82% were overridden for a variety of reasons. Therefore implementation of a risk-quantified CDS computer alert did not completely eliminate "alert fatigue," although an 82% override rate is lower than the 93–96% alert override rate reported in hospitalized patients.[29] Despite the override rate, implementation of this CDS computer alert significantly reduced the odds of QTc interval prolongation in these cardiac ICUs and significantly reduced prescribing of noncadiovascular QTc interval-prolonging drugs. Limitations of this analysis include the fact that we employed a "pre-post" design, which can introduce temporal bias. A randomized parallel-group study of implementation of this CDS computer alert versus usual care would be valuable. Since the completion of this research, Indiana University Health has implemented this CDS computer alert at most of its institutions across the state of Indiana.

At the Mayo Clinic, an institution-wide computer-based QTc interval alert system was developed and implemented.[24] This alert system screens all ECGs performed and applies an automated algorithm to determine whether an ECG displays marked QTc interval prolongation. The algorithm initially excludes ECGs exhibiting atrial fibrillation or flutter. An automated QTc interval alert is sent to providers for adult patients with QRS duration less than 120 ms, a QTc interval 500 ms or longer, and a heart rate of 100 beats or less per minute (bpm) and for those with QRS duration of 120 ms or longer, a QTc interval of 550 ms or more, and a heart rate of 100 bpm or less. An automated QTc interval alert is sent to providers for pediatric patients with QRS duration less than 120 ms, a QTc interval of 470 ms or longer, and a heart rate of 150 bpm or less and for those with a QRS duration of 120 ms or more, a QTc interval of 550 ms or longer, and a heart rate of 150 bpm or less. The Mayo Clinic QTc interval alert was sent for 2% of patients, of whom 41% had no other identifiable reason for QTc interval prolongation (such as a functioning ventricular pacemaker). In contrast to the CDS alert developed by our group, designed to alert clinicians when patients are at moderate to high risk of developing QTc interval prolongation so steps can be taken to prevent QTc interval prolongation, the Mayo Clinic CDS alert is designed to notify providers when patients have developed QTc interval prolongation. However, implementation of the Mayo Clinic CDS alert resulted in a significant reduction in the proportion of completed orders for QTc interval-prolonging drugs per ordering attempt (94% vs 77%, p<0.001), which resulted in a 13.9% decrease in administration of QTc interval-prolonging medications.[30] In addition, implementation of the Mayo Clinic CDS alert for QTc interval prolongation resulted in significant increases in the frequency of ECG monitoring and acknowledgment of the issue of QTc interval prolongation in the electronic health record.[31]

In a follow-up study, the Mayo Clinic investigators utilized their institution-wide QTc interval alert system to assess the prevalence of QTc interval prolongation in pediatric patients and determine the causes.[32] Over a period of 8 months, 1303 pediatric ECGs were performed, and 68 children (5%) had QTc interval prolongation. The average pro-QTc score in children with QTc prolongation was 1.4 ± 0.8. More than 50% of the pediatric population with QTc interval prolongation had congenital LQTS, which was not unexpected because the Mayo Clinic is a major referral center for such patients. In patients without congenital LQTS, the most common cause of QTc interval prolongation was administration of QTc interval-prolonging drugs, followed by comorbidities and electrolyte abnormalities. The QT alert system used in this study in a pediatric population was clinically useful for two reasons. First, it identified a child with previously undiagnosed congenital LQTS. Second, it singled out potentially modifiable factors that were causing QTc prolongation in a pediatric population. Utilization of the QTc interval alert system resulted in relevant changes in the prescribing practices of QTc interval-prolonging medications; prescribers changed ~80% of the QTc interval-prolonging medications after they received the QTc interval alert.[32]

In another follow-up investigation, the Mayo Clinic investigators used their QTc interval prolongation alert system to determine the prevalence of QTc interval prolongation among 7522 adult patients who were admitted to the ED and who had at least one 12-lead ECG associated with their ED visit.[16] The QTc alert was activated (indicating QTc interval prolongation) in 93 (1.2%) patients. The mean pro-QT score of subjects with QTc interval prolongation was 3.0 ± 1.6. Most of the ED patients (64%) had more than one condition associated with QTc interval prolongation, the most common of which was receiving at least one QTc interval-

prolonging drug (77%). Mortality at 30 days was significantly higher in ED patients identified by the QTc interval alert than in those who did not have QTc interval prolongation (13% vs 3.7%, $p<0.001$). In addition, as in the study in the pediatric population, the Mayo Clinic alert enabled the diagnosis of a patient with previously undiagnosed congenital LQTS.

Summary and Conclusions

Heart rate–corrected QT (QTc) interval prolongation occurs commonly, particularly in hospitalized patients, who tend to have a larger number of risk factors. Risk factors are important for the development of QTc interval prolongation and TdP, which are much more likely to occur when patients have one or more risk factors. Risk scores for QTc interval prolongation have been developed in patients from various patient populations including those in cardiac ICUs and in broader populations of hospitalized or health system patients. One group developed a risk score that includes information regarding genetic polymorphisms; this risk score significantly predicted the occurrence of TdP. Future research is required to determine the value of developing a risk score that combines genetic information with other known risk factors for QTc interval prolongation. CDS tools have been developed to alert clinicians when patients are at moderate or high risk for developing QTc interval prolongation or to alert clinicians when patients have already developed QTc interval prolongation. Implementation of these CDS approaches have been shown to reduce the risk of QTc interval prolongation in cardiac ICUs and identify patients at increased risk for mortality so interventions can be taken to modify the risk. Development and implementation of CDS alerts for QTc interval prolongation require time and resources. Although these CDS alerts for QTc interval prolongation have been shown to modify the risk of this ECG abnormality, the impact of these CDS systems on overall patient safety outcomes, such as TdP and sudden cardiac death, relative to the cost of development and implementation, requires further study.

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