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

Running Title: Prediction of QT Interval Prolongation

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Conflict of Interest Statement

Dr. Tomaselli Muensterman completed an internship at Takeda Pharmaceuticals U.S.A., Inc. during the summer of 2017. Dr. Tisdale is a volunteer member of the Advisory Board for the QT drugs list at CredibleMeds.org, which is discussed in this manuscript. The authors have no other conflicts of interest or industry relationships.

ABSTRACT

Prolongation of the heart rate-corrected QT (QTc) interval increases the risk for torsades de pointes (TdP), a potentially fatal arrhythmia. The likelihood of TdP is higher in patients with risk factors, which include female sex, older age, heart failure with reduced ejection fraction, hypokalemia, hypomagnesemia, concomitant administration of ≥ 2 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 paper 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 reduces the risk of QTc interval prolongation in cardiac ICUs and identifies 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.

Prolongation of the heart rate-corrected QT (QTc) interval on the electrocardiogram (ECG) increases the risk of the ventricular arrhythmia known as torsades 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] Risk of TdP increases markedly when the QTc interval is < 500 ms.[4-6] Each 10 ms increase in the QTc interval confers roughly a 6% increase in the risk of a cardiac event.[7] The risk of TdP also increases when the QTc interval lengthens > 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, antineoplastic agents, methadone, and many others.[10] QTc interval-prolonging drugs are prescribed frequently; nearly 23% of approximately 5 million outpatients filled at least one prescription for a QTc interval-prolonging medication during a one-year period.[11]

QTc interval prolongation occurs commonly. About 18% of patients admitted to cardiac intensive care units (ICUs) have a QTc interval > 500 ms on admission, and approximately 42% of those patients subsequently receive QTc interval-prolonging drugs while hospitalized.[12] QTc interval prolongation develops in 24-52% of adult patient hospitalized in ICUs,[13,14] and is present in as many as 35% of patients in emergency departments where the prevalence of markedly prolonged QTc interval (> 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 and increases in plasma concentrations of QTc interval-prolonging drugs due to rapid intravenous infusion, pharmacokinetic interactions, and inadequate dose adjustment of renally cleared 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 1 risk factor is 3.2 (95% confidence interval [CI] 2.1-5.5). The OR for QTc interval prolongation increases substantially in patients with 2 risk factors (7.3, 95% CI 4.6-11.7) and 3 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, while 71% of the patients had at least 2 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 for the purpose of alerting clinicians regarding patients at increased risk of developing QTc interval prolongation. The objectives of this paper are to review the effectiveness of predictive analytics for identification of patients at risk of drug-induced QTc interval prolongation and discuss the efficacy of incorporation of 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 Torsades de pointes AND risk score AND QT risk score OR genetic variant risk score AND decision support AND QT alert system OR QT alert." Our PRISMA flow diagram is presented in Figure 1. A total of 10 studies were included in the final qualitative synthesis.

Predictive Analytics for Assessing Risk of QTc Interval Prolongation

A QTc interval risk score, named the pro-QTc score, was developed by investigators at the Mayo Clinic.[24] Over a period of seven 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 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. Components of the pro-QTc score are presented in Table 1. The investigators reported that 99% of 470 patients with QTc interval ≥ 500 ms had at least one risk factor (excluding female sex). The mean (± standard deviation [SD]) pro-QTc score in patients with QTc interval ≥ 500 ms was 3.1 ± 1.6; after exclusion of 45 patients with congenital LQTS, the mean pro-QTc score in patients with QTc interval ≥ 500 ms was 3.2 ± 1.7. Medications were the greatest contributors to the pro-QTc score (score-proportion 37%), followed by QT interval-prolonging diagnosis (23%) and electrolyte abnormalities (22%).

A pro-QTc score of ≥ 4 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 that were 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 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 > 500 ms or an increase of ≥ 60 ms from 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-score from receiver operating characteristics curves. Risk scores of < 7, 7-10, and ≥ 11 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 prior to 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 $\geq$ 10. A RISQ-PATH score < 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 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 $\underline{of}$ 30 kg/m^2 or more, C-reactive protein greater than 5 mg/mL, and hypertension.

Strauss and colleagues 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. Healthy subjects (n=22) were enrolled in a double-blind, placebo-controlled, crossover trial and randomized to one of four QTc interval-prolonging drugs (dofetilide, quinidine, ranolazine, and verapamil hydrochloride) or placebo. Verapamil data were not included in the final analysis as 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] While some of these were variants known to be associated with congenital LQTS genes, others were variants in genes encoding proteins that were not previously known to influence cardiac 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 to 122. This genetic score described 27% of the variability (p=0.03) in pre-treatment 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% 0.05-0.80, p=0.03). The risk score was not able to significantly describe the QTc interval response variability (23%) to quinidine (r=0.48, 95% CI -0.03-0.79, p=0.06).

Among subjects of African descent (n=4), it was difficult to precisely determine the degree of QTc interval variability that was 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 African subjects. 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=12%, p=1x10^{-7}). This study represents the first example of a genetic risk score being 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, which 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, Indiana.[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 to 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 > 500 ms or an increase of > 60 ms from the admitting value occurring at any time during the hospitalization) over a one-year prior to (n=1200) and eight months following (n=1200) implementation of the CDS computer alert in our cardiac ICUs.

Implementation of the CDS computer alert significantly reduced the adjusted odds ratio 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 (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, there were 470 alert triggers, of which 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 noncardiovascular QTc interval-prolonging drugs. Limitations of this analysis include the fact that the analysis was "pre-post," 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 has been 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 < 120 ms, a QTc interval ≥ 500 ms, and a heart rate ≤ 100 beats per minutes (bpm) and for those with QRS duration ≥ 120 ms, a QTc interval ≥ 550 ms, and a heart rate ≤ 100 bpm. An automated QTc interval alert is sent to providers for pediatric patients with QRS duration < 120 ms, a QTc interval ≥ 470 ms, and a heart rate ≤ 150 bpm and for those with a QRS duration ≥ 120 ms, a QTc interval ≥ 550 ms, and a heart rate ≤ 150 bpm. 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, which is designed to alert clinicians when patients are at moderate to high risk of developing QTc interval prolongation so that 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 to patients.[30] In addition, implementation of the Mayo Clinic CDS alert for QTc interval prolongation resulted in significant increases in frequency of ECG monitoring and acknowledgement 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. Over 50% of the pediatric population with QTc interval prolongation had congenital LQTS, which was not unexpected as 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 utilized in this study in a pediatric population was proven to be 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 approximately 80% of the QTc interval-prolonging medications after they received the QTc interval alert.[32]

In another follow-up investigation, the Mayo Clinic investigators utilized their QTc interval prolongation alert system to determine the prevalence of QTc interval prolongation among 7522 adult patients who were admitted to the emergency department (ED) and who had at least one 12-lead ECG associated with their ED visit.[33] 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. The majority 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

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 has been shown to reduce the risk of QTc interval prolongation in cardiac ICUs and identify patients at increased risk for mortality so that interventions can be taken to modify the risk. Development and implementation of CDS alerts for QTc interval prolongation require time and resources. While 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.

References

1. Schwartz PJ, Woosley RL. Predicting the unpredictable: drug-induced QT prolongation and torsades de pointes. J Am Coll Cardiol 2016;67:1639-50.

2. Trinkley KE, Page II RL, Lien H, Yamanouye K, Tisdale JE. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. Curr Med Res Opin 2013;29:1719-26.

3. Drew BJ, Ackerman MJ, Funk M, et al, on behalf of the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, the Council on Cardiovascular Nursing, and the American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2010;55:934-47.

4. Sharma ND, Rosman HS, Padhi ID, Tisdale JE. Torsades de Pointes associated with intravenous haloperidol in critically ill patients. Am J Cardiol 1998;81:238-40.

5. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome. Prospective longitudinal study of 328 families. Circulation 1991;84:1136-44.

6. Pratt CM, Al-Khalidi HR, Brum JM, et al. Cumulative experience of azimilide-associated torsades de pointes ventricular tachycardia in the 19 clinical studies comprising the azimilide database. J Am Coll Cardiol 2006;48:471-7.

7. Zareba W, Moss AJ, Schwartz PJ, et al. Influence of genotype on the clinical course of the long-QT syndrome. International Long-QT Syndrome Registry Research Group. N Engl J Med 1998;339:960-5.

8. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for industry. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. October 2005. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf. Accessed April 16, 2018.

9. Priori SG, Wilde AA, Horie M, et al. HRA/EHRA/APHRS Expert Consensus Statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Heart Rhythm 2013;10:1932-63.

10. *Woosley, RL, Heise, CW and Romero, KA, www.CredibleMeds.org, QTdrugs List, [March 29, 2018], AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755.*

11. Curtis LH, Ostbye T, Sendersky V, et al. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. Am J Med 2003;114:135-41.

12. Tisdale JE, Wroblewski HA, Overholser BR, Kingery JR, Trujillo TN, Kovacs RJ. Prevalence of QT interval prolongation in patients admitted to cardiac care units and frequency of subsequent administration of QT interval-prolonging drugs. A prospective, observational study in a large urban medical center in the US. Drug Safety 2012;35:459-70.

13. Pickham D, Helfenbein E, Shinn JA, et al. High prevalence of corrected QT interval prolongation in acutely ill patients is associated with mortality: results of the QT in Practice (QTIP) study. Crit Care Med 2012;40:394-9.

14. Hoogstraaten E, Rijkenberg S, van der Voort PH. Corrected QT-interval prolongation and variability in intensive care patients. J Crit Care 2014;29:835-9.

15. Seftchick MW, Adler PH, Hsieh M, et al. The prevalence and factors associated with QTc prolongation among emergency department patients. Ann Emerg Med 2009;54:763-8.

16. Anderson HN, Bos JM, Haugaa KH, et al. Prevalence and outcome of high-risk QT prolongation recorded in the emergency department from an institution-wide QT alert system. J Emerg Med 2018;54:8-15.

17. Montanez A, Ruskin JN, Hebert PR, Lamas GA, Hennekens CH. Prolonged QTc interval and risks of total and cardiovascular mortality and sudden death in the general population: a review and qualitative overview of the prospective cohort studies. Arch Intern Med 2004;164:943-8.

18. Tisdale JE. Drug-induced QT interval prolongation and torsades de pointes: role of the pharmacist in risk assessment, prevention and management. Can Pharm J 2016;149:139-52.

19. Tisdale JE, Jaynes HA, Kingery JR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. Circ Cardiovasc Qual Outcomes 2013;6:479-87.

20. Pickham D, Helfenbein E, Shinn JA, Chan G, Funk M, Drew BJ. How many patients need QT interval monitoring in critical care units? Preliminary report of the QT in Practice study. J Electrocardiol 2010;43:572-6.

21. Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S. Torsade de pointes due to noncardiac drugs; most patients have easily identifiable risk factors. Medicine 2003;82:282-90.

22. Suresh S. Big data and predictive analytics. Pediatr Clin North Am 2016;63:357-66.

23. Moher, D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1-9.

24. Haugaa KH, Bos JM, Tarrell RF, Morlan BW, Caraballo PJ, Ackerman MJ. Institution-wide QT alert system identifies patients with a high risk or mortality. Mayo Clin Proc 2013;88:315-25.

25. Vandael E, Vandenberk B, Vandenberghe J, Spriet I, Willems R, Foulon V. Development of a risk score for QTc-prolongation: the RISQ-PATH study. Int J Clin Pharm 2017;39:424-32.

26. Strauss DG, Vicente J, Johannesen L, et al. Common genetic variant risk score is associated with drug-induced prolongation and torsade de pointes risk. A pilot study. Circulation 2017;135:1300-10.

27. Arking DE, Pulit SL, Crotti L, et al. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. Nat Genet 2014;46:826-36.

28. Tisdale JE, Jaynes HA, Kingery JR, et al. Effectiveness of a clinical decision support system for reducing the risk of QT interval prolongation in hospitalized patients. Circ Cardiovasc Qual Outcomes 2014;7:381-90.

29. Straichman Z, Kurnik D, Matok I, et al. Prescriber response to computerized drug alerts for electronic prescriptions in hospitalized patients. Int J Med Inform 2017;107:70-5.

30. Sorita A, Bos JM, Morlan BW, Tarrell RF, Ackerman MJ, Caraballo PJ. Impact of clinical decision support preventing the use of QT-prolonging medications for patients at risk of torsades de pointes. J Am Med Inform Assoc 2015;22:e21-7.

31. Sharma S, Bos JM, Tarrell RF, et al. Providers' response to clinical decision support for

QT prolonging drugs. J Med Syst 2017;41:161.

32. Anderson HN, Bos JM, Haugaa KH et al. Phenotype of children with QT prolongation identified using an institution-wide QT alert system. Pediatr Cardiol 2015;36:1350-6.

33. Anderson HN, Bos JM, Haugaa KH, et al, Prevalence and outcome of high-risk QT prolongation recorded in the Emergency Department from an institution-wide QT alert system. J Emerg Med 2017; S0736-4679(17)30782-5.

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/minute)

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 drugs (≥ 24 hours)

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 hours)

Status after syncope or seizure (24 hours)

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)

≥1 QTc interval-prolonging medication from CredibleMeds®[10] within previous 7 days

Table 2. Components of Risk Score for QTc Interval Prolongation (adapted with permission from reference 19)

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

[a]If a patient is receiving $\geq$ 2 QTc interval-prolonging drugs he/she is assigned a total score of 6; 3 points for receiving 1 QTc interval prolonging drugs and 3 points for receiving $\geq$ 2 QTc interval-prolonging drugs.

Table 3. Comparison of Published Predictive Analytics Tools to Predict Risk of or Identify

Patients with QTc Interval Prolongation

	Mayo 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%	N/A	N/A
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	Yes	No	No

mortality			

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

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.