Effect of Replacing Vendor QTc Alerts with a Custom QTc Risk Alert in Inpatients

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Abstract

Objective The aim of the study is to implement a customized QTc interval clinical decision support (CDS) alert strategy in our electronic health record for hospitalized patients and aimed at providers with the following objectives: minimize QTc prolongation, minimize exposure to QTc prolonging medications, and decrease overall QTc-related alerts. A strategy that was based on the validated QTc risk scoring tool and replacing medication knowledge vendor alerts with custom QTc prolongation alerts was implemented.

Methods This is a retrospective quasi-experimental study with a pre-intervention period (August 2019 to October 2019) and post-intervention period (December 2019 to February 2020). The custom alert was implemented in November 2019.

Results In the pre-implementation group, 361 (19.3%) patients developed QTc prolongation, and in the post-implementation group, 357 (19.6%) patients developed QTc prolongation (OR: 1.02, 95% CI: 0.87–1.20, $p = 0.81$). The odds ratio of an action taken post-implementation compared with pre-implementation was 18.90 (95% CI: 14.03–25.47, $p < 0.001$). There was also a decrease in total orders for QTc prolonging medications from 7,921 (5.5%) to 7,566 (5.3%) with an odds ratio of 0.96 (95% CI: 0.93–0.99, $p = 0.01$).

Conclusion We were able to decrease patient exposure to QTc prolonging medications while not increasing the rate of QTc prolongation as well as improving alert action rate. Additionally, there was a decrease in QTc prolonging medication orders which illustrates the benefit of using a validated risk score with a customized CDS approach compared with a traditional vendor-based strategy. Further research is needed to confirm if an approach implemented at our organization can reduce QTc prolongation rates.

Keywords
- clinical decision support
- drug–drug interaction
- electronic health records
- alert fatigue
- inpatient

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Background and Significance

A prolongation in the heart rate-corrected QT interval (QTc) above 500 milliseconds (ms) or an increase of ≥60 milliseconds from baseline is a risk factor for ventricular arrhythmias, particularly Torsade de Pointes (TdP), and sudden cardiac death.[1] Numerous medications and patient-specific factors have been associated with QTc prolongation (QTc ≥450 in males or ≥460 in females) including female gender, age ≥65 years, cardiovascular history, liver or kidney failure, and electrolyte imbalances.[1–3] Therefore, in the hospital setting, it is not surprising to see patients with multiple factors associated with QTc prolongation, especially in intensive care units (ICUs). It has been shown that QTc prolongation was present at ICU admission in nearly 28% of cardiac care unit patients, and that nearly 30% of those patients experience additional QTc prolongation throughout their stay.[2] In particular, 57% of the patients who were admitted with QTc intervals ≥500 milliseconds had an additional increase in QTc interval of at least 60 milliseconds.[2] Critically-ill patients with QTc prolongation have longer lengths of hospitalization and a threefold increase in odds for mortality than those without prolongation.[4]

While severe complications from QTc prolongation are rare, monitoring of patients with a prolonged QTc and minimization of risk factors are recommended in order to decrease the risk of adverse outcomes.[1,5] The American Heart Association (AHA) and the American College of Cardiology Foundation (ACCF) published a statement regarding the prevention of TdP in the hospital setting in regards to the risk of QTc interval prolongation, appropriate and consistent electrocardiogram (ECG) monitoring, and management of QTc interval prolongation including minimization of offending drugs and replacement of electrolytes.[1] In addition to ECG monitoring, computerized alerts in the electronic health record (EHR) for QTc interval prolonging drug–drug interactions (DDIs) provide additional level of support for providers to mitigate risk factors for prolongation.

However, given the set-up with clinical decision support (CDS) DDI alerts in the EHR provided by medication knowledge vendors, this type of CDS is prone to alert fatigue and potentially causes providers to ignore more important QTc-related DDIs.[6–8] A 90% override rate for DDI alerts has been reported, and this has been the experience at our institution despite ongoing work at optimizing and removing less severe DDI pairs.[9,10] Recommendations to improve the usability of DDI CDS alerts include integration of contextual information or modifying factors.[7,11] This includes patient-specific factors such as age, predisposing diseases, laboratory results, medication dose, timing of co-administration with QT prolonging medications, etc.[11] DDI alerts provided by medication knowledge vendors in EHRs typically are based on an active interval between one medication co-ordered with another interacting medication and therefore lack this key component of applying to a particular specific patient context. EHRs provide the ability for an organization to develop custom alerts using patient contextual information, and given the high frequency of QTc-related DDI alerts and override rates at our organization, we focused our attention instead upon examining opportunities to convert our medication knowledge vendor QTc DDI CDS to a more custom-based approach.

Utilization of customized QTc DDI CDS has been previously described. A large university-associated, tertiary care teaching institution implemented a CDS alerting tool for reducing the risk of QTc prolongation in hospitalized cardiac care unit patients and showed that implementing a validated risk score for QTc prolongation significantly decreased ordering of non-cardiac QTc prolonging drugs and significantly reduced the risk of QTc prolongation.[12,13] The risk score was calculated based on factors including age, female gender, serum potassium ≤3.5 mmol/L, admission QTc ≥450 milliseconds, diagnosis of acute myocardial infarction, sepsis, or heart failure, and presence of a loop diuretic or one or two medications known to prolong the QTc interval. An alert is generated to pharmacists entering medications into the computer system if the risk score is ≥7, and pharmacists had the option to contact the provider and intervene by recommending an alternative agent with a lower risk of QTc prolongation.[12,13]

Several other studies since then have compared pre- and post-implementation of a QTc CDS alert based on QTc >500 milliseconds and placement of medication orders with a risk of prolonging the QTc interval.[14–16] Two studies found a significant reduction in ordering QTc prolonging medications following implementation of the alert. One study found no difference in QTc prolonging medications avoided, though there was a significant improvement in the action rate, primarily in ECG monitoring. In all three studies, the medication knowledge vendor traditional DDI alert was continued, and all three QTc CDS strategies primarily based the alert on an elevated QTc interval without using additional patient risk factors such as those examined by Tisdale and colleagues.

At our health care organization, our goal was to implement a customized QTc CDS alert strategy in our EHR for hospitalized patients aimed at providers with the following objectives: minimize QTc prolongation, minimize exposure to QTc prolonging medications, and decrease overall QTc-related alerts. To best accomplish this goal and related outcomes, we examined a strategy that was based on a validated QTc risk scoring tool and replaced our medication knowledge vendor alerts with custom QTc alerts. This study will evaluate and describe the results and outcomes of our customized QTc CDS approach. To our knowledge no other published research has examined an approach such as ours.

Methods

Design and Setting

This is a retrospective quasi-experimental unblinded study performed at a 1,000+ bed tertiary academic medical center (Michigan Medicine) with three inpatient towers (adult, cardiovascular and women's/pediatrics) and uses an Epic-based EHR (Epic Systems, Verona, Wisconsin, United States; currently version May 2021). First Databank (FDB) (San

Bruno, California, United States), is the medication knowledge vendor integrated into our EHR and provides content for medication warning data (e.g., drug dose checking, drug allergy, DDI and drug–disease interactions, aged-based precautions and duplicate therapy). Medication warnings/alerts (e.g., DDI alerts) trigger during signing of a new medication order (e.g., typically by a provider) when there is either an interaction with an active medication or with another new medication in the order entry activity. These alerts additionally trigger during medication verification by the pharmacist. The new or existing interacting medication may be removed or discontinued from the alert. An acknowledgment/override reason if not taking action on the alert is optional. The intervention described below received approval by our organization's Clinical Decision Support Subcommittee and was deemed as exempt and not regulated status by the University of Michigan Institutional Review Board.

Intervention

Prior to November 2019, all QTc-related DDI alerts were based on FDB content—contraindicated and severe severity levels (traditional DDI alerting) (►Fig. 1). In November 2019, a custom QTc CDS alert based on the QTc-interval prolonging risk scoring tool by Tisdale et al was implemented for adult inpatients including the emergency department (►Fig. 2).[12,13] The alert was configured using Epic's best practice advisory (BPA) functionality. Given that the Tisdale et al risk score tool has only been validated in adult inpatients, traditional QTc DDI alerts continued for ambulatory/outpatient context orders, inpatients <18 years old (Pediatrics). Note that traditional DDI alerts that involved a pharmacokinetic-type interaction that could influence QTc interval (e.g., elevated levels of a drug augmenting effects on the QTc through metabolic inhibition by another drug) continued in all patients. The custom BPA triggers during signing of a medication order with known or possible risk of TdP as defined by CredibleMeds (https://crediblemeds.org) and including the presence of other patient-specific risk factors as defined in the risk scoring tool that would result in a high risk level (score ≥11) in inpatients (≥18 years old—adults).[13,17] A risk score of 11 was selected by our Clinical Decision Support Committee and multidisciplinary group of cardiology providers and pharmacists as it was felt that this threshold was a good balance between too many alerts and clinical utility/patient safety based on pilot BPA data. The alert allows the ordering clinician to remove the triggering medication from order entry and/or place an order for an ECG. The user must select an acknowledgment reason if continuing with the medication order and not placing an ECG order. See ►Fig. 3 for an example of alert contents. A similar interruptive BPA (without the option to place an ECG order) was also implemented in the pharmacist's verification screen and will trigger upon medication order verification. Due to the inherent proarrhythmic potential of Class IA, IC, and III anti-arrhythmic drugs, an additional custom BPA was created to mimic the traditional DDI alert and in all patients ≥18 years old with new or active antiarrhythmic medication orders and a QTc risk score <11. This antiarrhythmic DDI BPA similarly triggers during signing or verifying the medication order (►Fig. 4).

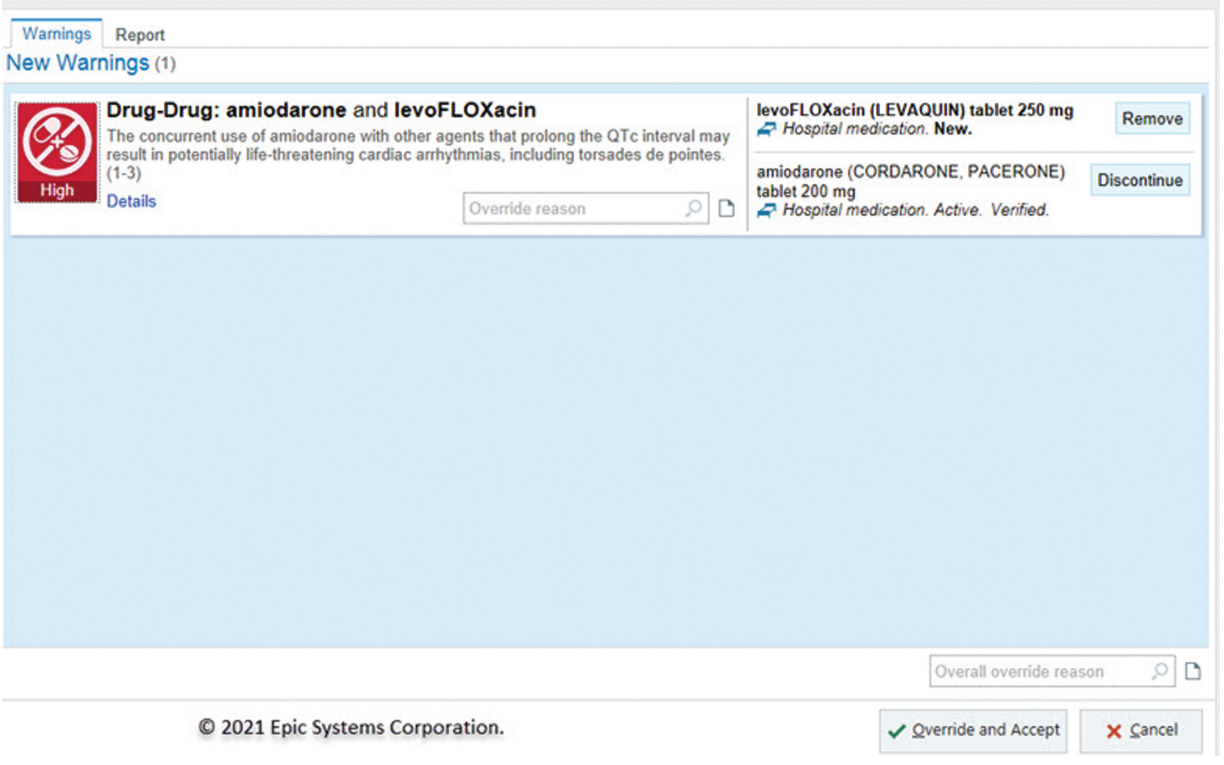

Fig. 1 Traditional DDI QTc alert. DDI, drug–drug interaction.

Risk Factor	Points
• Age ≥ 68	1
• Female	1
• Loop diuretic[a]	1
• Serum potassium ≤ 3.5 m.olmol/L	2
• Most recent QTc >= 450 ms	2
• Acute MI on problem list	2
• One other active QTc prolonging medication	3
• Sepsis[b]	3
• Heart failure on problem list or last recorded ejection fraction < 40	3
• QTc prolonging medication currently being ordered	3

Risk Score Stratification	
Risk score category	Risk score total
Low	< 7
Medium	7-10
High	>=11

Fig. 2 Calculation of QTc prolongation risk score.[a] Active loop diuretic order (based on FDB pharmaceutical class) or any loop diuretic received in last 12 hours.[b] Based on Epic's sepsis predictive scoring algorithm (risk score ≥6). FDB, First Databank.

Outcomes

Using QTc prolongation criteria adapted by Tisdale et al, the primary outcome for this study was to compare the occurrence of QTc prolongation following the implementation of a custom QTc CDS alert. QTc prolongation was defined as the following: (1) patients with initial QTc interval <500 milliseconds following admission—either an increase in the QTc ≥500 milliseconds or an increase in the QTc ≥60 milliseconds at any point during hospitalization; (2) patients with an initial QTc interval ≥500 milliseconds—an increase in the QTc ≥60 milliseconds from baseline during any point in the hospitalization.[10]

Secondary outcomes included the evaluation of the following measures between pre- and post-implementation of the custom QTc CDS alert: (1) the number of QTc prolonging medication orders broken down by total, pharmaceutical class, and number of patients with one or two administrations of a QTc prolonging medications administered between phases. (2) Number of QTc alerts and percentage overridden by ordering clinician. The incidence of TdP between groups was also evaluated based on manual chart review.

Patients and Study Sample

Patients with the following characteristics were included: (1) ≥18 years of age, (2) at least 2 QTc results following admission, and (3) greater than a 24-hour hospital encounter. Patients with the following characteristics were excluded: (1) <18 years old; (2) only one QTc result available following admission; (3) discharged within 24 hours of admission; or (4) receiving cardiac pacing. Data was collected over two periods for the study: pre-intervention (prior to implementation of the QTc BPA) from August to October, 2019, and post-intervention (following implementation of the custom QTc BPA) from December to February, 2020. Since implementation of the BPA was in early November 2019, that month was designated as a washout period. Given potential confounding effects of the COVID-19 pandemic affecting our organization in March 2020, data collection ceased at the end of February.

Data Collection and Statistical Methods

An SQL-based report (Oracle, Austin, Texas, United States) was used to extract necessary information to evaluate study primary and secondary objectives for both pre- and post-intervention periods from the EHR's relational database. Data reported here utilizes descriptive statistics. For categorical variables, a p-value was calculated using a Chi-square test and a 2×2 contingency table. All p-values are two sided, and $p \leq 0.05$ was interpreted to indicate statistical significance. Odds ratios were used to examine the effect of the new alert.

Results

There were 1,871 patients in the pre-implementation group and 1,820 patients in the post-implementation group after exclusions were applied (►Fig. 5). The primary study end point was the occurrence of QTc prolongation pre- and post-implementation of QTc-interval prolongation alert. In the pre-implementation group, 361 (19.3%) patients developed QTc prolongation, and in the post-implementation group, 357 (19.6%) patients developed QTc prolongation (OR: 1.02, 95% CI: 0.87–1.20, $p = 0.81$).

When evaluating QTc-related medication outcomes, all verified medication orders were examined, and CredibleMeds (https://crediblemeds.org) was used to determine what medications were considered QTc prolonging (►Appendix A). QTc prolonging medications were examined as a proportion of total medication orders and as a proportion of the medication class. This was done to identify any trends in ordering habits due to the new alert. There was a total of 144,300 medication orders in the pre-implementation group, and 143,353 in the post-implementation group. When examining QTc medication ordering out of total medication orders, there was a statistically significant difference for total QTc prolonging medication orders and for QTc prolonging antipsychotics, antiemetics, and methadone. When examining QTc prolonging medication ordering out of the medication categories, there was a statistically significant difference for QTc prolonging macrolides, antifungals, and antiemetics. ►Tables 1 and 2 contain further details on QTc prolonging medication order outcomes.

In the pre-implementation group, there were 1,112 (59.4%) patients that were administered at least one QTc prolonging agent and 468 (25%) patients that were administered at least two QTc prolonging agents. In the post-implementation group, there were 1,076 (59.1%) patients that were administered at least one QTc prolonging agent and 435 (23.9%) patients who were administered at least two QTc prolonging agents. The odds of a patient receiving at least one QTc prolonging agent post-implementation of the alert was 0.99 (95% CI: 0.87–1.13, $p = 0.85$) and the odds of a patient

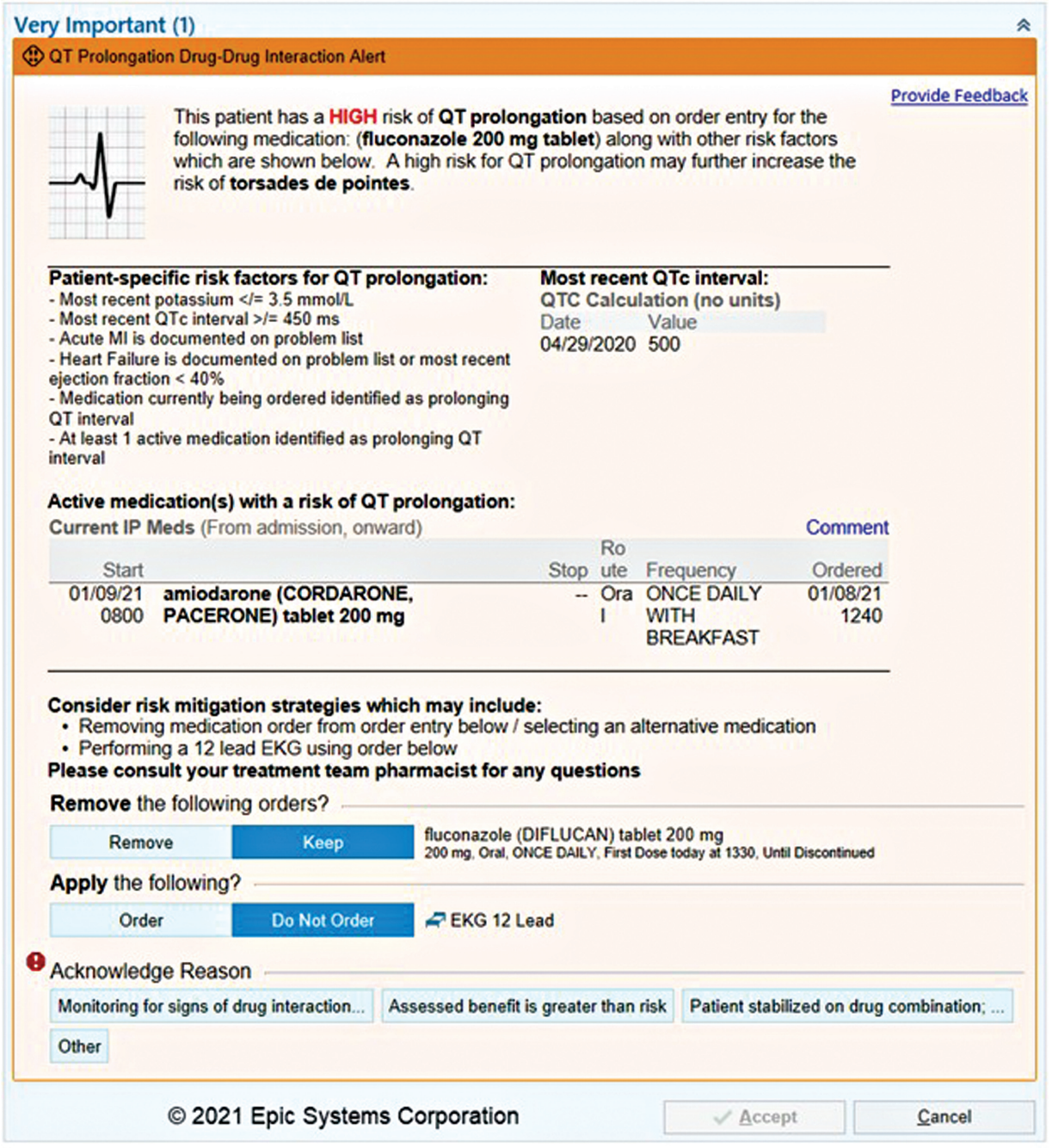

Fig. 3 Custom QTc CDS alert. CDS, clinical decision support.

receiving at least two QTc prolonging agents post-implementation of the alert was 0.94 (95% CI: 0.81–1.09, $p = 0.43$).

When examining alert-related outcomes, the odds ratio of an action taken post-implementation compared with pre-implementation was 18.90 (95% CI: 14.03–25.47, $p < 0.001$). When excluding the additional antiarrhythmic DDI alert, the odds ratio of an action taken was 20.34 (95% CI: 15.09–27.43, $p < 0.001$). ►Table 3 contains QTc alert-related outcomes on order entry, and ►Table 4 contains the rationale if no action was taken.

For alerts on pharmacist order verification, there were 1,912 total alerts in the pre-implementation group and 3,333 alerts in the post-implementation group. The median was used to investigate the large increase in alert counts during verification. In the pre-implementation phase, each unique alert was triggered for a median of 1.5 times, and in the post-implementation phase, each unique alert was triggered for a median of three times.

The ratio of QTc prolongation alerts to QTc prolonging medication orders was 0.30 in the pre-implementation phase and 0.35 in the post-implementation phase. When excluding the antiarrhythmic DDI alert, the ratio of QTc prolonging alerts to QTc prolongation medication orders in the post-implementation phase is 0.32.

Lastly, a chart review was done to see if any patient experienced TdP during the study period. No patients in

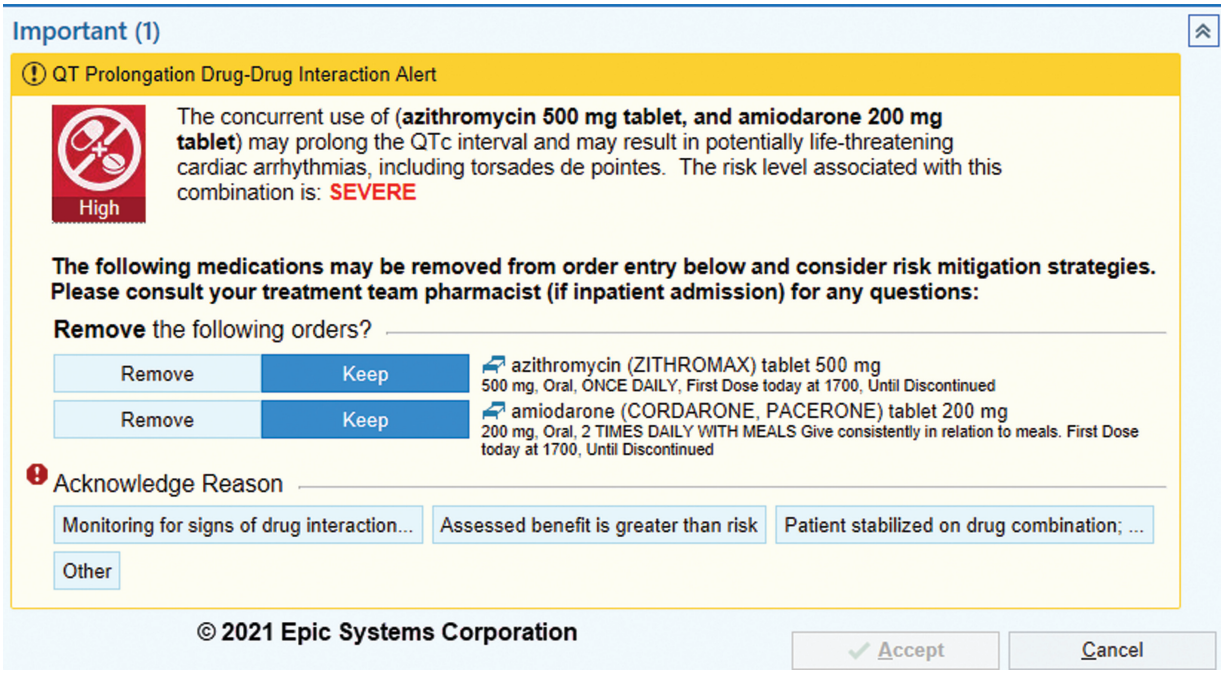

Fig. 4 Custom antiarrhythmic DDI alert in post-intervention adult patients (risk score< 11). DDI, drug–drug interaction.

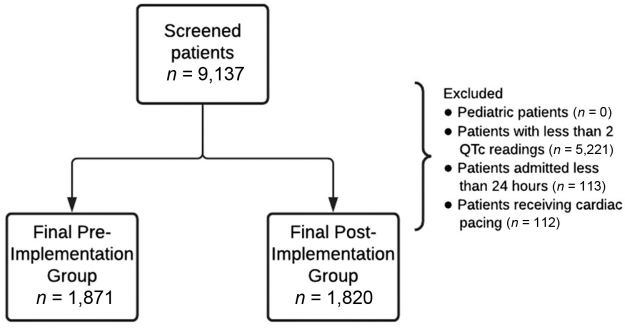

Fig. 5 Study patient population.

the pre-implementation and one patient in the post-implementation phase experience TdP during hospitalization. Prior to the episode of TdP, ECG readings showed no evidence of QTc prolongation, and Torsade was precipitated by R on T phenomenon. The cardiology consult notes state Torsade was possibly precipitated by ischemia.

Discussion

This study reports that the implementation of a customized alert based on a validated scoring tool did not result in a difference in QTc prolongation rates. There were significant differences in QTc prolonging medication orders as well as actions taken on alerts. Previous traditional vendor-based QTc alerts utilized at our health system were limited in scope and only examined DDIs that could potentially prolong the QTc interval. Use of a customized alert that is based on a validated risk score such as demonstrated by Tisdale et al provides a more precise method of examining patient-specific QTc prolongation risk factors that potentially provides outcome benefits.[13]

Tisdale et al demonstrated a statistically significant difference in QTc prolongation.[13] However, our study did not demonstrate a significant difference in rates of QTc prolongation. This could be attributed to institutional differences, such as differences in electrolyte replacement or sepsis protocols, and there may be further value in customizing our alert by taking into account these conditions. A study by Chernoby et al also implemented Tisdale et al's risk score in a customized alert but did not report the incidence of QTc prolongation.[14] When compared with Tisdale et al's study, we did not limit our intervention exclusively to the cardiac care unit and expanded our intervention across the entire adult hospital population. Tisdale's risk score for QTc prolongation was developed and validated in cardiac care units within the same institution.[12] While their study showed a statistically significant difference in rates of QTc prolongation post-implementation, the applicability of the risk score may be limited when implementing it in other institutions and patient populations. Other variables or risk factors may contribute to the development of QTc prolongation, and certain risk factors may have a different weight for a non-cardiac care unit patient population.

When examining the ordering rates of medications, our study was able to show significant reductions in overall QTc prolonging medication orders as well as certain non-cardiac medication categories which includes antiemetics, antipsychotics, and certain antibiotic classes. This is similar to other studies that have CDS for QTc prolonging medications. Sorita et al implemented a custom QTc prolonging medication alert that resulted in statistically significant reductions of antiemetic, antiarrhythmic, antipsychotic, immunosuppressant, and antibiotic medication classes.[15] Tisdale et al additionally demonstrated statistically significant reductions in the ordering rate for non-cardiac QTc prolonging agents.[13] In our

Table 1 QTc Prolonging medication orders verified for study patients out of total orders for all medications[a]

	Pre-implementation (%) $n = 144{,}300$ total orders	Post-implementation (%) $n = 143{,}354$ total orders	Odds ratio [95% CI]	*p*-Value (Chi-square)
Total orders for QTc prolonging meds	7,921 (5.5)	7,566 (5.3)	0.96 [0.93–0.99]	0.01
QTc Antiarrhythmic	1,193 (0.8)	1,266 (0.9)	1.07 [0.99–1.16]	0.10
QTc Fluoroquinolone	252 (0.2)	231 (0.2)	0.92 [0.77–1.10]	0.38
QTc Macrolide	171 (0.1)	144 (0.1)	0.85 [0.68–1.06]	0.14
QTc Azole antifungal	282 (0.2)	259 (0.2)	0.92 [0.78–1.09]	0.36
QTc Antipsychotic	579 (0.4)	793 (0.6)	1.38 [1.24–1.54]	<0.001
QTc Antiemetic	3,675 (2.6)	3,247 (2.3)	0.89 [0.85–0.93]	<0.001
Methadone	101 (0.1)	42 (< 0.1)	0.42 [0.29–0.60]	<0.001

[a]CredibleMeds was used to determine QTc prolonging medications.

Table 2 QTc Prolonging medication orders verified for study patients out of total orders within each medication category[a]

	Pre-Implementation (%)	Post-Implementation (%)	Odds ratio [95% CI]	*p*-Value (Chi-square)
Total antiarrhythmic	1,350	1,424		
QTc Antiarrhythmic	1,193 (88.4)	1,266 (88.9)	1.06 [0.83–1.33]	0.66
Total fluoroquinolone	252	231		
QTc Fluoroquinolone[b]	252 (100)	231 (100)	–	–
Total macrolide	174	154		
QTc Macrolide	171 (98.3)	144 (93.5)	0.25 [0.07–0.94]	0.03
Total antifungal	337	363		
QTc Azole antifungal	282 (83.7)	259 (71.4)	0.49 [0.34–0.70]	<0.001
Total antipsychotic	914	1,263		
QTc Antipsychotic	579 (63.4)	793 (62.8)	0.98 [0.82–1.17]	0.79
Total antiemetic	6,456	6,064		
QTc Antiemetic	3,675 (56.9)	3,247 (53.6)	0.87 [0.81–0.94]	<0.001

[a]CredibleMeds was used to determine QTc prolonging medications.
[b]There were no non-QTc prolonging fluoroquinolones ordered during the study period.

study, there were decreased odds of ordering a QTc prolonging antiemetic when compared with total antiemetic orders which was mostly attributed to the decreased use of ondansetron and the increased use of other antiemetic agents and trimethobenzamide. This aligns with institutional guidelines and order sets which often have trimethobenzamide as a second line antiemetic agent to ondansetron. There was also a statistically significant increase in the odds of ordering a QTc prolonging antipsychotics when compared with total medication orders. However, there was a large increase in total antipsychotic orders as well as QTc prolonging antipsychotic orders in the post-implementation phase, so the increased odds ratio may not be directly attributed to the QTc prolongation alert. There was also a statistically

Table 3 QTc-Prolongation alert-related outcomes

	Pre-implementation (%)	Post-implementation (%)	Odds ratio [95% CI]	*p*-Value (Chi-square)
Order entry alert[a]	2,404	2,430		
Action taken[c]	48 (2)	712 (29.3)	20.34 [15.09–27.43]	<0.001
No action taken[d]	2,356 (98)	1,718 (70.7)	0.05 [0.04–0.07]	<0.001
Additional antiarrhythmic DDI alert[b]	–	199		
Action taken	–	19 (9.6)		
No action taken	–	180 (90.5)		
Total QTc alerts	2,404	2,629		
Action taken	48 (2)	731 (27.8)	18.90 [14.03–25.47]	<0.001
No action taken	2,356 (98)	1,898 (72.2)	0.05 [0.04–0.07]	<0.001

Abbreviation: DDI, drug–drug interaction.
[a]Traditional knowledge vendor DDI alert vs. custom QTc-prolongation alert.
[b]Traditional knowledge vendor DDI alert for antiarrhythmic medications in patients low or medium risk.
[c]Action taken by ordering clinician: (1) cancelled alert and exited order entry; (2) removed interacting medication from the alert (or discontinued active interacting medication—in traditional/pre-intervention alert); (3) ordered ECG from the custom QTc alert.
[d]No action taken by ordering clinician: overrode the alert and did not take any of the above actions 1 to 3.

Table 4 Documented reasons why no action was taken

	Total	Percentage
Pre-implementation alert[a]	220	
Aware of dose; monitoring for signs of toxicity	77	35
Assessed benefit is greater than risk	70	31.8
Monitoring for signs of drug interaction/ordered combination	43	19.6
Patient has previously tolerated this drug/dose	28	12.7
Patient stabilized on drug combination; monitoring effects	1	0.5
Intolerance not an allergy	1	0.5
Post-implementation custom alert	1,718	
Monitoring for signs of drug interaction/ordered combination	1,021	59.4
Assessed benefit is greater than risk	456	26.5
Patient stabilized on drug combination; monitoring effects	140	8.2
Other (document as comments)	101	5.9
Post-implementation additional DDI alert	180	
Will take recommended follow-up action	121	67.2
Benefit outweighs risk	38	21.1
Does not meet criteria	12	6.7
Other (document as comments)	7	3.9
See comments	2	1.1

Abbreviation: DDI, drug–drug interaction.
[a]Documentation was optional for the pre-implementation alert. The same override reasons were used for both pre- and post-implementation alerts.

significant decrease in the odds of QTc prolonging macrolides and QTc prolonging antifungals when compared with their respective drug categories which may indicate a shift in prescribing patterns due to the custom QTc prolongation alert.

Implementation of the custom QTc prolongation alert resulted in a statistically significant increase in the odds that there was an action taken on the alert at the time of order entry when compared with the traditional vendor-based DDI alert. This may have indicated a potential increase in the quality of the alert, showing the direct impact that the alert had on the patients it fired for. Our customized alert was able to incorporate more patient-specific information, communicate the criteria of the scoring tool and reason the alert fired, and provide users to the ability to order an ECG directly within the alert. When an action was not taken, ordering providers had to give a reason why they did not take an action. The reasons for overriding the alert were tailored specifically to this customize alert rather than a general override message and allowed more specific information gathering on ordering habits. A future area we are investigating to further enhance the utility of the BPA is to include alternative agents which can be ordered directly from the alert, particularly for antiemetics with less potential to prolong the QTc to facilitate ease of ordering.

While this study showed an increase in the odds of an action taken to reduce QTc prolongation medication prescribing post-implementation of the custom QTc prolongation alert, there was a net increase in total alerts. The additional increase in alert volume is attributed to the additional antiarrhythmic DDI alert for less than high-risk patients (risk score <11), which was continued post-implementation of the custom QTc prolongation alert. Current efforts are being made to examine the necessity of the antiarrhythmic DDI alert as well as incorporating it within the custom QTc prolongation alert, adjusting the firing threshold, or turning it off. A large increase in order verification alerts was also noticed in the study. The median times a unique alert fired increased from 1.5 to 3 and may indicate that a pharmacist or multiple pharmacists were viewing the alert multiple times. This may be attributed to the visually distinct design of the custom QTc prolongation alert. There was one person in the study who experienced TdP, and as noted, it does not appear to be drug induced.

Several limitations should be noted in our study. Patients with prolonged QRS intervals were not excluded. The custom alert fired regardless of the duration of the QRS interval. It should be noted that in Tisdale et al, patients with prolonged QRS intervals also were not excluded in the creation and validation of the risk score. There is a potential limitation of the risk score as patients with prolonged QRS intervals may have inaccurate QT intervals. Other limitations of the study include the short time period of the study, difficulty and inability to easily capture actions or pharmacists interventions made outside of the alert time frame given that pharmacist–provider communication is frequently not documented, and the potential for temporal bias due to the study design.

Conclusion

In summary, we implemented a customized QTc CDS alert strategy in our EHR for hospitalized patients aimed at providers. We were able to decrease patient exposure to QTc prolonging medications while not increasing the rate of QTc prolongation. Our results illustrate the benefit of using a validated risk score with a higher quality customized CDS approach compared with a traditional vendor-based strategy which further resulted in a significantly improved alert acceptance and action rate. Further research is needed to confirm if an approach such as ours can decrease QTc prolongation rates as well as the applicability of the scoring tool for non-cardiac care patients.

Clinical Relevance Statement

Drug–drug CDS within the EHR are typically based on data provided by medication knowledge vendors and are not patient-specific which can promote alert fatigue and negate their relevance and cause suboptimal outcomes through ignoring clinically important alerts. QTc prolonging medications are frequently prescribed and have numerous drug–drug interactions, particularly based on the presence of patient-specific risk factors. This research provides a pragmatic evaluation where replacing non-patient-specific CDS with a more patient-focused and information-rich approach can improve behavior around CDS alerts and medication prescribing related to QTc prolonging medications.

Multiple Choice Questions

1. You are tasked with implementing a clinical decision tool to enhance medication dose checking across a health system. Which of the below options would you pick to ensure patient safety and reduce alert fatigue?
   a. Commercial database driven alerts that cannot be modified once implemented.
   b. Customized, rule-based alerts that can utilize patient-specific information.
   c. Non-interruptive in basket message notifying users of potential inappropriate medication doses.
   d. None of the above.

   Correct Answer: The correct answer is option b. Clinical decision support based on patient-specific information provides the best opportunity to maximize effectiveness, alert relevance, and minimize alert fatigue.

2. Which of the following were risk factors for developing QTc prolongation based on a validated QTc prolongation risk scoring tool?
   a. Loop diuretic.
   b. Age $\geq$68 years.
   c. Serum potassium $\leq$3.5 mmol/L.
   d. Active QTc prolonging medication.
   e. All of the above.

Correct Answer: The correct answer is option e. All the risk factors indicated have been found to be significantly associated with QTc-risk prolongation based on the work by Tisdale et al.[9,10]

Protection of Human and Animal Subjects

The study was performed in compliance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and was reviewed by the University of Michigan Institutional Review Board. It was determined that this study was not regulated.

Conflict of Interest

None declared.

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Appendix A QTc Prolonging and non-QTc prolonging medications

Medication class	QTc Prolonging[a]	Non-QTc prolonging
Antiarrhythmics	Amiodarone, disopyramide, dofetilide, dronedarone, flecainide, ibutilide, and quinidine	Adenosine, lidocaine, mexiletine, and propafenone
Fluoroquinolones	Ciprofloxacin, levofloxacin, and moxifloxacin	N/A
Macrolides	Azithromycin, erythromycin, and clarithromycin	Fidaxomicin
Azole-antifungals	Fluconazole	Isavuconazonium, itraconazole, posaconazole, and voriconazole
Antipsychotics	Aripiprazole, asenapine, chlorpromazine, clozapine, haloperidol, lurasidone, paliperidone, quetiapine, risperidone, ziprasidone	Brexipiprazole, fluphenazine, and olanzapine
Antiemetics	Granisetron, ondansetron, and promethazine	Aprepitant, fosaprepitant, meclizine, prochlorperazine, scopolamine, and trimethobenzamide

[a]CredibleMeds was used to determine QTc prolonging medications.