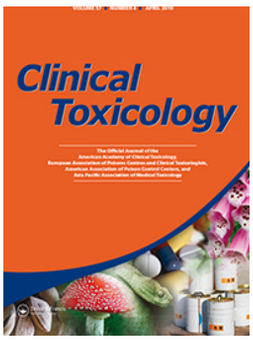

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

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To cite this article: Rittirak Othong, Suttisak Wattanasansomboon, Thanakorn Kruutsaha, Douglas Chesson, Sakda Arj-Ong Vallibhakara & Ziad Kazzi (2019) Utility of QT interval corrected by Rautaharju method to predict drug-induced torsade de pointes, Clinical Toxicology, 57:4, 234-239, DOI: 10.1080/15563650.2018.1510501

To link to this article: https://doi.org/10.1080/15563650.2018.1510501

CLINICAL TOXICOLOGY
2019, VOL. 57, NO. 4, 234–239
https://doi.org/10.1080/15563650.2018.1510501

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CLINICAL RESEARCH

Utility of QT interval corrected by Rautaharju method to predict drug-induced torsade de pointes

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ABSTRACT

Introduction: New QT correction formulae derived from large populations are available such as Rautaharju's [QTcRTH = QT * (120 + HR)/180] and Dmitrienko's [QTcDMT = QT/RR$^{0.413}$]. These formulae were derived from 57,595 and 13,039 cases, respectively. Recently, a study has shown that they did not experience errors across a wide range of heart rates compared to others.

Objectives: (1) To determine the best cut-off value of QTcRTH and QTcDMT as a predictor of torsade de pointes (TdP) and (2) to compare the sensitivity and specificity using the cut-off value of QTcRTH with those of the QTcBazett (QTcBZT), QTcFridericia (QTcFRD), and QT nomogram.

Methods: Data were derived from two data sets. All cases aged over 18 years with an exposure to QT-prolonging drugs. Group-1, all cases developed TdP. Data in Group-1 were obtained from systematic review of reported cases from Medline since its establishment until 10 December 2015. Group-2 is composed of those who overdosed on QT prolonging drugs but did not develop TdP. This data set was previously extracted from a chart review of three medical centers from January 2008 to December 2010. Data from both groups were used to calculate QTcRTH and QTcDMT. The cut-off values from QTcRTH and QTcDMT that provided the best sensitivity and specificity to predict TdP were then selected. The same method was applied to find those values from QTcBZT, QTcFRD, and QT nomogram. The receiver operating characteristic curve (ROC) was applied where appropriate.

Results: Group-1, 230 cases of drug-induced TdP were included from the systematic review of Medline. Group-2 (control group), which did not develop TdP, consisted of 292 cases. After applying all of the correction methods to the two datasets, the best cut-off values that provided the best accuracy (Ac) with the best sensitivity (Sn) and specificity (Sp) for each formula were as follows: **QTcRTH** at 477 milliseconds (ms), Ac = 89.08%, Sn = 91.30% (95%CI = 86.89–94.61), Sp = 87.33% (95% CI = 82.96–90.92); **QTcDMT** at 475 ms, Ac = 88.31%, Sn =91.30% (95%CI = 86.89–94.61), Sp = 85.96% (95%CI = 81.44–89.73); **QTcBZT** at 490 ms, Ac = 86.97%, Sn = 88.26% (95%CI = 83.38–92.12), Sp = 85.96% (95%CI = 81.44–89.73); **QTcFRD** at 473 ms, Ac = 88.89%, Sn = 89.13% (95%CI = 84.37–92.84), Sp =88.70% (95%CI = 84.50–92.09). We found a significant difference (*p*-value = 0.0020) between area under the ROC of the QTcRTH (0.9433) and QTcBZT (0.9225) but not QTcFRD (0.9338). The Ac, Sn, and Sp of the **QT nomogram** were 89.08%, 91.30% (95%CI = 86.89–94.61), and 87.33% (95%CI = 82.96–90.92), respectively, and they were all equal to those of QTcRTH.

Conclusion: Rautaharju method not only produced minimal errors for QT interval correction but also at QTcRTH 477 ms, it could predict TdP as accurately as QT nomogram and was better than the QTcBZT.

ARTICLE HISTORY
Received 13 March 2018
Revised 4 August 2018
Accepted 6 August 2018
Published online 24 September 2018

KEYWORDS
QT prolongation; QT correction; Dmitrienko; risk assessment

Introduction

Evaluation of QT intervals on the 12-lead electrocardiogram (ECG) is of value for drug-induced QT prolongation. One of the worst outcomes in those with QT prolongation is the occurrence of torsade de pointes (TdP) [1]. Because the QT interval varies with the heart rate, it is recommended that clinicians use corrected QT intervals (QTc) instead [2]. The Bazett formula (QTcBZT) is the most widely used correction method worldwide [3] although it has been criticized for causing both over-correction and under-correction at faster and slower heart rates, respectively [4].

In 2015, Rabkin and Cheng published a study that evaluated the correlation between 107 pairs of QTc of each formula and heart rates from 107 ECGs obtained from their hospital. Those eight formulae evaluated were Bazett (QTcBZT), Fridericia (QTcFRD), Hodges (QTcHDG), Framingham (QTcFRM), Rautaharju (QTcRTH), Dmitrienko (QTcDMT), Goto (QTcGOT), and Mayeda (QTcMYD). The study

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Supplemental data for this article can be accessed here.

demonstrated that only the QTcRTH and QTcDMT did not produce a significant correlation between the QTc and heart rates. As a result, these two formulae would provide the most accurate QTc. The other six QT correction formulae were significantly dependent on heart rates [5].

QTcRTH [6] and QTcDMT [7] (Box 1) were derived in 2014 and 2005 from 57,595 and 13,039 cases, respectively. In contrast, both the QTcBZT and QTcFRD that have been widely used were derived in 1920 from just 39 and 50 cases, respectively [5]. However, both QTcRTH and QTcDMT have never been used as risk assessment tools for TdP before.

Box 1 . QT correction formulae in this study

1. Rautaharju (2014): $QTcRTH = QT * (120 + \text{heart rate})/180$
2. Dmitrienko (2005): $QTcDMT = QT/RR^{0.413}$
3. Bazett (1920): $QTcBZT = QT/RR^{0.5}$
4. Fridericia (1920): $QTcFRD = QT/RR^{0.33}$

Another available risk assessment tool for drug-induced TdP is the QT nomogram. It provided a very high sensitivity (96.9%) and specificity (98.7%) to predict drug-induced TdP [8]. However, subsequent studies did not reveal consistency of both its sensitivity and specificity, for example: van Gorp's study: sensitivity = Infinity (no TdP cases), specificity = 86% [8]; Berling's study: sensitivity = 100%, specificity 90.3% [9]; Isbister's study: sensitivity = 100%, specificity = 28% [10].

Objectives

The primary objective of this study was to determine the best cut-off value of the QTcRTH and QTcDMT as a predictor of TdP. The secondary objectives were to compare the sensitivity and specificity from the best cut-off value of QTcRTH and QTcDMT with those of the QT nomogram, QTcFRD, and QTcBZT and to compare performance among those methods as risk assessment tools for TdP.

Study design and methods

This was a prognostic study using a case-control design. Data for this study were derived from two datasets. One was for the case group, and the other was for the control group.

Group 1: case group

Data in the case group were obtained from a systematic search of Medline using the search term "Torsades de Pointes" [MeSH] from the establishment of Medline to 10 December 2015. All cases in this group must have had TdP after they were exposed to any substances that can cause QT prolongation. We used the database on the Crediblemeds.org [11] as the source to identify any QT prolonging substances. The inclusion and exclusion criteria for the case group were as follows:

Inclusion criteria for the case group

1. Age $\geq$18 years
2. At least the following data are available: QT or QTc, heart rate (HR) or RR interval, so that QT, HR, or RR interval could be extracted.
3. Those who had prolonged QT progressing to TdP and the cause of QT prolongation was from drug(s) or substance(s).

Exclusion criteria for the case group

1. TdP was known to be from other etiologies such as congenital long QT syndrome alone and was not from drugs, acute myocardial infarction, or cardiomyopathy. Cases with hypokalemia, hypomagnesemia, or hypocalcemia if those factors were determined not to be from drugs/substances.
2. Non-English literature
3. No access to full-text papers

After searching, we had two trained data abstractors who manually reviewed all of the literature obtained from the Medline database and applied the inclusion and the exclusion criteria above to include those eligible cases to this case group. They further extracted the following data to our standardized data extraction sheet: age, sex, substances exposed, QT interval, RR interval, and HR.

Thirty-five articles were used to test for the inter-rater reliability between the two abstractors, and the Cohen's Kappa coefficient was 0.894. All of the excluded papers were reviewed once again by the principle investigator.

Group 2: control group

Data from this group were derived from a previous retrospective chart review study done in three hospitals in Atlanta, Georgia, USA. We identified those patients at the three hospitals through the Georgia Poison Center Database from 1 January 2008 to 31 December 2010. Those patients overdosed on QT prolonging drugs and were older than 18 years of age. We then manually reviewed all eligible medical records using the following inclusion and exclusion criteria.

Inclusion criteria for the control group

1. Age $\geq$18 years
2. At least one 12-lead-ECG was available
3. At least one of the medications the patient overdosed on was known to increase risk of QT prolongation and/or TdP based on the AzCERT QT drug list which was previously available at www.qtdrugs.org (accessed on March 21, 2011) (Currently, it is available at https://www.crediblemeds.org [8].)
4. Had no TdP

Exclusion criteria for the control group

1. Known history of congenital long QT syndrome

The eligible medical records between 1 January 2008 and 31 December 2010 from Emory University Hospital (EUH) (38,000 annual visits) and Emory University Hospital Midtown

(EUHM) (61,000 annual visits), and between 1 January 2008 and 31 December 2009 from Grady Memorial Hospital (GMH) (125,000 annual visits) [8] were reviewed.

Two investigators were trained, and a standard operating procedure was developed as a memorandum of understanding between the two. Any disagreement or issues during chart abstraction between the two were discussed and resolved together.

Interval measurement

On each ECG, QT intervals were measured manually in lead II, as suggested by multiple investigators [12–15], from the beginning of the Q wave to the end of T wave. This was done in three consecutive complexes. The average was taken. We used the threshold method to identify the end of the T wave even though the tangent method has been introduced for better inter-rater reliability among ECG readers, but it could give shorter QT intervals [16]. In case we could not separate between the T and U wave, the end point was the one from the U wave. RR intervals were measured from R to R of the corresponding complexes that were used to measure the QT intervals. The average was taken.

QT intervals were measured by the two investigators (RO and DC) from the same 45 ECGs to calculate the concordance correlation coefficient (CCC) for inter-rater reliability test of continuous data and the CCC was 0.943 (excellent).

Data analysis

QT and HR or RR intervals, where appropriate, were applied from both groups to each of the following formulae: Bazett, Fridericia, Rautaharju, and Dmitrienko. Sensitivity, specificity, accuracy, and Youden index were calculated at different corrected QT intervals as a predictor for TdP. QT-HR pairs from both groups were plotted on the QT nomogram to calculate the sensitivity, specificity, and accuracy to predict TdP.

Cut-off value selection for QT correction formulae: the best cut-off value of each formula that provided the greatest sensitivity and specificity that gave the highest accuracy with the highest Youden index [17] was selected.

Results

In the case group (all with TdP), after applying the search term "Torsades de Pointes" [MeSH] to Medline and limiting the search by ages 18 years old or older, English language, and human, up until 10 December 2015, 570 articles were discovered. Furthermore, 379 articles were excluded because TdP was not drug-induced, there were no adequate data to calculate QTc and no access to full-text papers. Finally, 191 articles were included and they contained 230 TdP cases for the analysis of both objectives (Figure 1).

In the control group (no TdP), all of the 292 cases from our previous study were eligible and included. Demographic data of both groups are presented in Table 1. The TdP patients were significantly older and with more females than the control group.

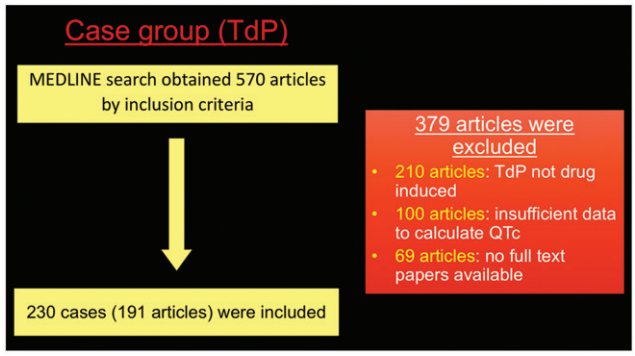

Figure 1. Flow chart for case selection in the case group.

Table 1. Demographic data of both groups.

	Control (no TdP) $N = 292$	Case (TdP) $N = 230$	p-Value
Age (years)			
Median (IQR)	37.0 (27.3–48.0)	60.5 (43.0–73.0)	<.001*
Min	18	18	
Max	75	97	
Gender (%)			
Male	164 (56.2)	71 (30.9)	<.001**
Female	128 (43.8)	159 (69.1)	

*Mann–Whitney U test.
**Pearson Chi-square.

After applying QT and HR or RR intervals, where they were appropriate, from both groups to each formula, the best selected cut-off value of each formula with its best corresponding sensitivity, specificity, and accuracy is presented in Table 2. The sensitivity, specificity, and accuracy calculated for the QT nomogram after applying QT-HR pairs from both groups are also presented in Table 2 to compare the sensitivity, specificity, and accuracy from those four formulae. It revealed that the accuracy and the sensitivity were equal between the QT nomogram and the QTcRTH at the cut-off of 477 ms, and they were the highest among other methods.

Figure 2 shows the QT-HR pairs from both groups plotted on the QT nomogram. Lines from individual cut-off value of the four QT correction formulae were also applied to the nomogram for comparison.

The four QTc formulae's (Figure 3, Table 3) capability of predicting TdP was tested, and it was found that the Rautaharju's formula provided the largest area under the receiver operating characteristic curve (ROC curve; AUC = 0.9433) and that was significantly larger than the respective areas of other formulae, except one of the QTcFRD (Table 4).

Discussion

In this case-control study, cases with drug-induced TdP were significantly older and more of them were females (69.1% vs. 43.8%) compared with controls. Older age and female sex are known for TdP in the setting of drug-induced QT prolongation [18].

Best cut-off value from each formula

With the selected cut-off value from each formula shown in Table 2 with its corresponding sensitivity, specificity, and

Table 2. Selected cut-off point, sensitivity, specificity, and accuracy from each formula.

	Cut-off point (ms)	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	Accuracy (%)
QTcRTH	477	91.30 [86.89–94.61]	87.33 [82.96–90.92]	89.08
QT nomogram	–	91.30 [86.89–94.61]	87.33 [82.96–90.92]	89.08
QTcDMT	475	91.30 [86.89–94.61]	85.96 [81.44–89.73]	88.31
QTcFRD	473	89.13 [84.37–92.84]	88.70 [84.50–92.09]	88.89
QTcBZT	490	88.26 [83.38–92.12]	85.96 [81.44–89.73]	86.97

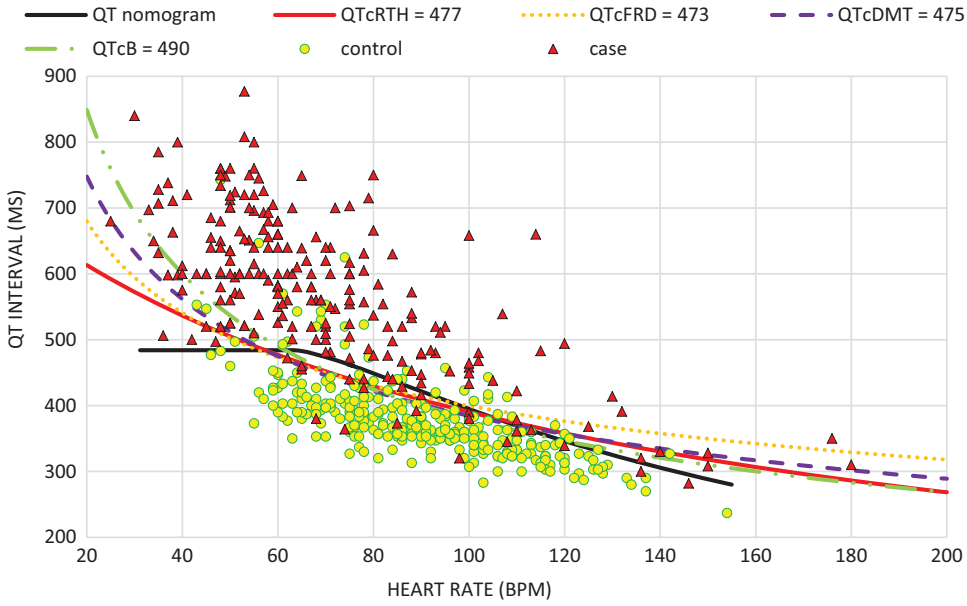

Figure 2. QTcRTH vs. QTcFRD vs. QTcDMT vs. QTcBZT vs. nomogram.

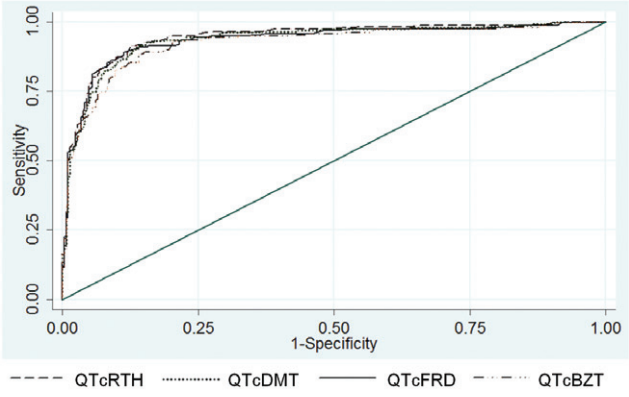

Figure 3. ROC curves of QTcRTH, QTcDMT, QTcFRD, and QTcBZT.

Table 3. Area under the ROC curves from the four formulae.

	AUC	95% CI
QTcRTH	0.9433	0.9225–0.9642
QTcFRD	0.9338	0.9102–0.9575
QTcDMT	0.9326	0.9089–0.9562
QTcBZT	0.9225	0.8973–0.9476

Table 4. Comparing area under the ROC curves (AUC-ROC) from different formulae.

AUC-ROC: 1	AUC-ROC: 2	*p*-Value
QTcRTH: 0.9433	QTcFRD: 0.9338	.0630
QTcRTH: 0.9433	QTcDMT: 0.9326	.0261*
QTcRTH: 0.9433	QTcBZT: 0.9225	.0020*
QTcFRD: 0.9338	QTcDMT: 0.9326	.6825
QTcFRD: 0.9338	QTcBZT: 0.9225	.0868
QTcDMT: 0.9326	QTcBZT: 0.9225	.0108*

accuracy, the QTcRTH at 477 ms provided the highest Youden index, highest accuracy with the greatest sensitivity among all the QTc formulae tested. But, the specificity from the cut-off value of QTcFRD was minimally higher than that of the QTcRTH.

Best cut-off value of Bazett's formula

The cut-off value that provided the highest accuracy and sensitivity for the QTcBZT to predict TdP was 490 ms. A 2010 Scientific Statement from the American Heart Association (AHA) and the American College of Cardiology (ACC) states that there is "no threshold of QTc prolongation at which TdP is certain to occur", but suggests that QTc >500 ms increases risk for TdP considerably [18]. Other sources frequently list QTc >500 ms as an important threshold for TdP as well, either for clinical study or practice [19,20]. In this study using the 500 ms cut-off point, the sensitivity, specificity, and accuracy were 84.78%, 88.01%, and 86.59%, respectively. Even though using 500 ms of QTcBZT as a threshold increased specificity minimally, it will compromise both the sensitivity and accuracy of the test where sensitivity is more important for this type of screening test because misclassification of patients at risk may lead to serious adverse events such as TdP and death. On the other hand, specificity of the test is less important because most medical care for drug-induced QT prolongation is observation and support which are not harmful. Thus, because sensitivity is more important than specificity, with the highest accuracy, we propose physicians

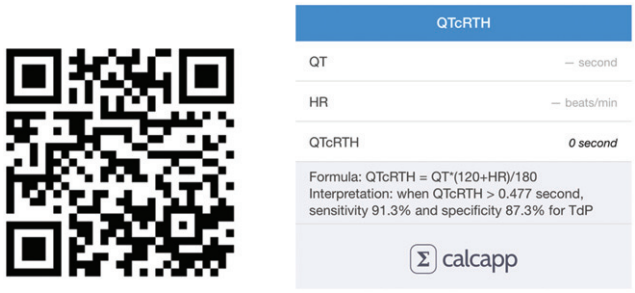

Figure 4. Free QR code for the QTcRTH calculation.

use 490 ms as a threshold for TdP based on our study if they still wish to continue using QTcBZT.

Among the four QTc formulae, which one should be used?

Among the four QTc formulae, the QTcRTH at 477 ms provided the highest accuracy with the highest sensitivity. The ROC curves demonstrated that area under the curve (AUC) of the QTcRTH was the largest, which means it performed the best in predicting TdP. Although it was not significantly larger than the AUC from the QTcFRD (p-value = 0.0630), it was larger than the AUC of QTcDMT and QTcBZT. Rabkin et al. demonstrated that the QTcRTH formula produced minimal errors from QT-HR correction (QTc was independent of heart rates) but the QTcFRD produced significant errors especially at abnormal heart rates (>100 or <60 beats/min) [5]. Thus, we recommend using QTcRTH formula instead of the others including QTcFRD.

QT nomogram

The original study that evaluated the QT nomogram by Chan et al. showed that the sensitivity (96.9%) and specificity (98.7%) of the QT nomogram were higher than the sensitivity (91.3%) and specificity (87.3%) in this study [19]. This may be due to the differences of the control groups of the two studies. The control group in Chan's study enrolled those who overdosed on non-QT prolonging drugs such as paracetamol and benzodiazepines (they had no risk of TdP at all). In contrast, everyone in our control group overdosed on QT prolonging drugs, and they were actually truly reflective of those who were at risk for TdP in real life.

QTcRTH vs. QT nomogram, which to use?

QTcRTH at 477 ms provided the same sensitivity, specificity, and accuracy compared with the QT nomogram (Table 2). However, QT nomogram could only tell us if those patients were at risk or not for TdP. On the other hand, the QTcRTH is available in continuous manner. This will allow us to see more information on diagnostic tests with continuous values (like blood pressure, e.g., not just hypertension; it can also tell us severity) [21]. As a result, the likelihood ratio (LR) can be calculated for the QTcRTH at different thresholds (data provided in the supplement), and it can be used to quantify the probability of the outcome for any individual case [21]. For example, when a patient has a QTcRTH at 477 ms, the patient is at risk for TdP (LR+ = 7.2). When the same patient's QTcRTH becomes 525 ms, the LR + increases to 15.7. The pre-test probability does not change because it is the same patient with the same drug, but the post-test probability of the outcome increases. Clearly, we know the patient is not improving but getting worse, and we may need to move the patient to a critical care area and prepare for dysrhythmia management, not just observing him as usual. In contrast, the QT nomogram could not provide the same sense as the QTcRTH does (once the QT-HR pair is above the line, all it can do is that it only tells you your patient is at risk no matter what how far it is from the line). As a result, QTcRTH is not only as a good risk assessment tool as the QT nomogram, but it can also stratify the acuity of the risk and direction of the condition (better or worse) which the QT nomogram cannot.

There were 115 TdP cases with an HR between 60 and 100 beats/min, and the other 115 TdP cases had an HR either below 60 or above 100 beats/min. From Figure 2 (QTcRTH 477-ms line vs. QT nomogram line), even though the two methods provided the same prediction parameters, QTcRTH at 477 ms failed more often to detect TdP cases when the heart rates were below 60 and above 100 beats/min (misclassified 11 out of 115 TdP cases as no TdP) compared with the QT nomogram (misclassified 5 out of 115 TdP cases as no TdP). On the other hand, QT nomogram misclassified TdP cases (15/115 cases) as low risk more than the QTcRTH at 477 ms (9/115 cases) when the heart rates were in a normal range (60–100 beats/min). However, in total, each tool misclassified 20 out of 230 TdP cases equally. Thus, one may wish to select one tool above the other based on the patient's heart rate at the time to assess risk for TdP. In this way, we could benefit best from both tools.

Ease of use for the QTcRTH vs. QT nomogram

The factors needed to calculate the QTcRTH (Box 1) are the QT interval and the heart rate, which are the same requirements as for when using the QT nomogram. Even though there is no calculation for the QT nomogram, the nomogram itself is still required. On the other hand, the equation to calculate the QTcRTH is simple and not time-consuming, even without a calculator (Box 1). In addition, with current technology, one can access and use an app to aid the QTcRTH calculation easily (QR code provided here for free: Figure 4).

Limitation

Prognostic information is best derived from studying a cohort group [22,23], but because of the rarity of TdP in clinical practice, instead, we chose the case-control design. QT/QTc and RR/HR in the case group were taken from what had been reported in the literature from the Medline search. Occasionally, when ECGs were provided in the literature, the QT and RR/HR were manually measured. For those cases with hypokalemia, hypomagnesemia, and hypocalcemia,

those cases were included in this study only if those risk factors were determined to be from drugs. Those factors can all cause/exacerbate prolongation of the QTc. It is unclear if the cardiac event (TdP) was secondary to drug effect alone, drug-induced electrolyte abnormalities, synergistic drug/electrolyte abnormality effect, or electrolyte abnormality alone that caused the event.

A few studies demonstrated that Framingham's formula provided accurate QT correction, which may be true but only when heart rates were within the normal range [24]. However, when ECGs with a wider range of heart rates (e.g., >100 beats/min) were included, it caused errors similarly to most formulae, such as Fridericia and Bazett [5,25]. We did not assess its utility, in this study; as a result, it is unclear how it performs in our patient population as compared to the other formulae.

Conclusions

Rautaharju QT correction method not only produced minimal errors for QT interval correction but also at the QTcRTH 477 ms, it could predict TdP as accurately as the QT nomogram and was better than the QTcBZT. We believe this tool is worth exploring for its clinical use among physicians who deal with drug-induced QT prolongation. However, this study was a development study of the tool, and it should be further validated for its high performance in a prospective clinical study.

Disclosure statement

No potential conflict of interest was reported by the authors.

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