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Evaluation of the Isbister nomogram and Rautaharju's method of QT correction for risk assessment in ICU patients acutely intoxicated with QT prolonging drugs

INTOXICATE-study

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Abstract

Achtergrond

Een lang QT-interval kan zorgen voor aritmieën. De meest voorkomende ventriculaire aritmie die kan ontstaan van een verlengd QT-interval is een torsade de pointes (TdP). Hoe langer het QT-interval, hoe groter de kans op TdP, voornamelijk een QT-interval >500ms is een marker voor het risico op TdP. Een belangrijke reden voor het ontstaan van een verlengd QT-interval is het gebruik van QT-verlengde (genees)middelen. Om te bepalen of een QT-interval verlengd is moet het gecorrigeerd worden voor hartslag, waardoor het gecorriceerde QT-interval (QTc) ontstaat. De meest gebruikte methode om het QT-interval te corrigeren is Bazett's methode, maar deze methode heeft zijn tekortkomingen. Het doel van dit onderzoeksproject is om de prestaties van het Isbister nomogram en Rautaharju's methode voor QT correctie te onderzoeken in IC-patiënten met een acute initoxicatie die ten minste één QT-verlengend (genees)middel hebben ingenomen.

Methode

Dit onderzoeksproject vindt plaats binnen de INTOXICATE-studie. De INTOXICATE-studie is een prospectief, multicenter, observationeel onderzoek naar de prognose en uitkomsten van patiënten met een intoxicatie op de Intensive Care Units (ICU's). Gegevens werden verzameld via Castor EDC met behulp van een elektronisch Case Report Form (eCRF). De gegevens werken op 15 maart 2022 om 10:49 in een SPSS formaat gedownload en daarna geanalyseerd om te bepalen welke patiënten ten minste één QT-verlengend (genees)middel hadden gebruikt, welke patiënten een QT-HR-paar boven het Isbister nomogram en Rautaharju's curve hadden en daarom QT-verlenging hadden en welke patiënten dit niet hadden, en welke patiënten de uitkomst TdP hadden.

Resultaten

In totaal waren 408 patiënten geïncludeerd van wie 205 (50,2%) waren blootgesteld aan een QT-verlengend (genees)middel. Van de 1009 blootstellingen waren er 319 afkomstig van QT-verlengende (genees)middelen. Quetiapine was het meest gebruikte QT-verlengende geneesmiddel (64 keer). In het Isbister nomogram hadden in totaal 68 patiënten (33,2%) die waren blootgesteld aan een QT-verlengend geneesmiddel een QT-HR-paar boven het nomogram. Met Rautaharju's methode hadden in totaal 75 patiënten (36,6%) die waren blootgesteld aan een QT-verlengend (genees)middel een QT-HR-paar boven de curve. De patiënten die boven de nomogram of Rautaharju's curve liggen hadden volgens die methode QT-verlenging. Van de in totaal 205 patiënten die waren blootgesteld aan een QT-verlengend (genees)middel had slechts 1 patiënt de uitkomst TdP.

Conclusie

Zowel het Isbister nomogram als Rautaharju's methode plaatste de patiënt met TdP goed. De patiënt werd met zijn QT-HR-paar boven de lijn van het nomogram en boven Rautaharju's curve geplaatst, waardoor de patiënt volgens de methodes QT-verlenging en risico op TdP had. Er moet wel meer onderzoek worden gedaan met grotere patiëntengroepen om het Isbister nomogram en Rautaharju's methode voor QT-correctie te evalueren.

Abstract

Background

A long QT interval can trigger arrhythmia. The most common ventricular arrhythmia that can occur from a prolonged QT interval is torsade de pointes (TdP). The longer the QT interval, the greater the likelihood of TdP, especially a corrected QT interval of >500ms is a marker for risk of TdP. One major reason a long QT interval can be acquired is by use of QT prolonging drugs. To determine if a QT interval is prolonged it needs to be corrected for heart rate, creating a correct QT interval (QTc). The most used correction for the QT interval is Bazett's correction, but this has his shortcomings. The aim of this research project is to examine the performance of the Isbister nomogram and Rautaharju's method for QT correction in acutely intoxicated ICU patients who ingested at least one QT prolonging drug.

Methods

This research takes place within the INTOXICATE study. The INTOXICATE study is a prospective, multicenter, observational study on the prognosis and outcomes of intoxicated patients in Intensive Care Units (ICU's). Data was collected via Castor EDC, using an electronic Case Report Form (eCRF). The data was downloaded into a SPSS format on March 15th 2022 at 10:49 and analyzed to determine which patients had used at least one QT prolonging drug, which patients had a QT-HR pair above the Isbister nomogram and Rautaharju's method for QT-correction, and therefore had QT prolongation and which patients did not, and which patients had the outcome TdP.

Results

In total 408 patients were included, of which 205 (50.2%) were exposed to a QT prolonging drug. Of the 1009 exposures, 319 were from QT-prolonging drugs. Quetiapine was the most used QT prolonging drug (64 times). In the Isbister nomogram a total of 68 patients (33.2%) who were exposed to a QT-prolonging drug had a QT-HR pair above the nomogram. In Rautaharju's method for QT correction a total of 75 patients (36.6%) of those exposed to a QT prolonging drug had a QT-HR pair above the curve, thus suggestion QT prolongation. Of the total of 205 patients who were exposed to a QT prolonging drug only 1 patient had the outcome of TdP.

Conclusion

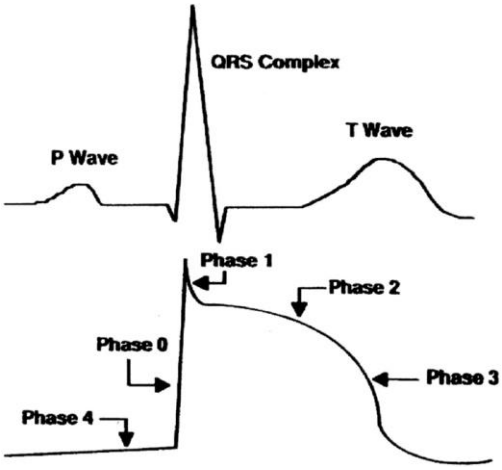
Both the Isbister nomogram and Rautaharju's method for QT correction placed the patient with TdP right. The patient was placed with its QT-HR pair above the line of the nomogram and above Rautaharju's curve and the patient therefore had QT prolongation and risk of TdP. More research should be done with larger patient groups to evaluate the Isbister nomogram and Rautaharju's method for QT correction.

Introduction

ECG, QT interval and torsades de pointes

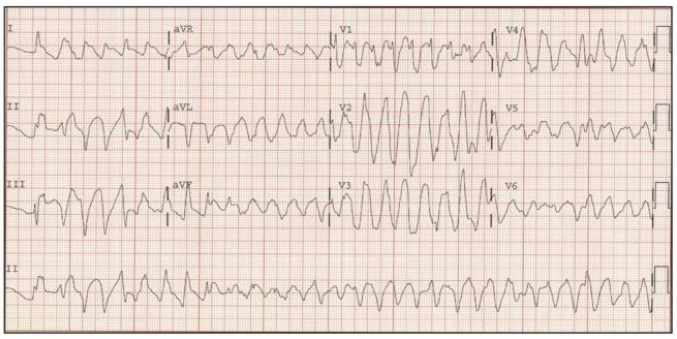
An electrocardiogram (ECG) is an non-invasive method to measure the activity of the heart. With an ECG different kinds of arrhythmia and other issues that are connected to the heart can be found. An example of an ECG can be found in Figure 1.

Figure 1: A normal ECG [1].



First is the P wave. This wave is needed to contract the atria and represents atrial depolarization. Next, is the QRS complex. This wave is needed to contract the ventricles and represents ventricular depolarization. Last, is the T wave, which represents the final part of ventricular repolarization. Repolarization is not only the T wave but starts as soon as the depolarization (phase 0) ends and starts at phase 1. The QT interval starts at phase 0 and ends at phase 3 and therefore is the depolarization and repolarization of the ventricle. A long phase 3, thus a longer QT interval can trigger arrhythmia [1]. This is because the ventricle becomes more susceptible to early electrical impulses, which are known as afterdepolarizations. If these afterdepolarizations reach a threshold these can cause unusual ventricular beats and therefore arrhythmia.

Figure 2: Torsade des pointes [2].



The most common arrhythmia that can occur from a prolonged QT interval is torsades de pointes (TdP). The longer the QT interval the greater the likelihood of TdP [3]. Especially a corrected QT interval of >500ms is a marker for the risk of TdP [4]. Torsades de pointes was first described in the 1960s by French cardiologist François Dessertenne. He described it as a ventricular tachycardia with 'twisting of the points', because the points of the QRS complex twist around the isoelectric baseline, as can be seen in Figure 2. [1, 2, 5]

Risk factors

A prolonged QT interval can be acquired or congenital. There are multiple reasons why a long QT interval can be acquired, which may result in TdP, these risk factors are [3, 6, 7]:

- QT prolonging drugs
- Electrolyte disturbances
    - Hypokalemia, hypomagnesemia, hypocalcemia
- Structural heart disease:
    - E.g. ventricular hypertrophy, cardiomyopathy, myocardial ischemia
- Bradycardia
- History of QTc-prolongation
- Female sex
- Advanced age

QT prolonging drugs

Many drugs can alter the QT interval. This is mainly done by blocking potassium channels [8]. Although there are many drugs that can alter the QT interval, not every drug does that to the same level. For some drugs it can happen at a normal, therapeutic dose, for other drugs QT prolongation can only happen at toxic dosages. A full list of QT prolonging drugs can be found on www.crediblemeds.org, which categorizes QT prolonging drugs into three different groups:

1. Known risk of TdP: drugs that prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended
2. Possible risk of TdP: drugs that can cause QT prolongation but currently lack evidence for a risk of TdP when taken as recommended
3. Conditional Risk of TdP: drugs that are associated with TdP but only under certain conditions for their use (excessive dose, in patients with hypokalemia, or when taken with interacting drugs).

Correction methods

A prolonged QT interval can cause TdP, but the QT interval depends on the heart rate. A lower heart rate is often associated with a longer QT interval, this is why the QT interval needs to be corrected for heart rate or cardiac cycle, which results in the corrected QT interval (QTc)[9].

The most common relationship for QT is the following: $QT = QT_c \cdot RR^{\alpha}$
The alpha is called the individual correction factor.
The RR is the length of the cardiac cycle.

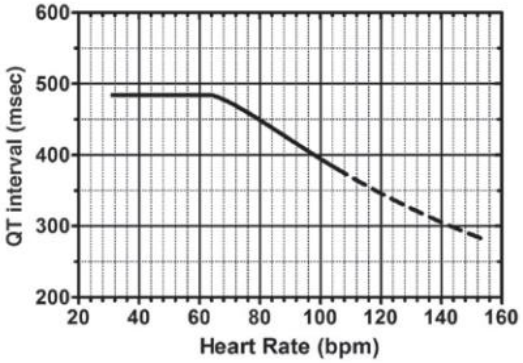
The most used correction to calculate the QTc is Bazett's correction ($QT_c = \frac{QT}{\sqrt{RR}}$) , but this correction has its shortcomings. Bazett's correction uses an alpha of 0.5 for everyone in the population, even though it is different for each person, ranging from 0.234 to 0.486 [10]. This causes the method to not be accurate and this is why it causes over-correction at slow heartrates and under-correction at higher heartrates.

Because of the shortcomings of Bazett's correction new methods were developed to better correct the QT and predict the risk of TdP. In this research the performance of the Isbister nomogram and Rautaharju's method for QT correction will be evaluated in intoxicated ICU patients, because previous research has shown that both the Isbister nomogram and Rautaharju's method for QT correction were better at predicting TdP than Bazett's method [11]. These patients were intoxicated, but were not necessarily admitted to the ICU. In this research will be looked at acutely intoxicated ICU patients.

Isbister nomogram

In Figure 3 the Isbister nomogram can be seen. The Isbister nomogram does not have a formula that can be used, but instead it uses heart rate and QT interval. The QT interval is plotted against the heart rate, creating a QT-HR pair in the nomogram. If this QT-HR pair is above the line, the patient has a prolonged QT interval [12].
The Isbister nomogram is derived from Fossa's diagram[13], but instead of the RR the HR has been taken to make it easier. Most of the time the HR is measured and not directly the RR. The line on the monogram is extrapolated to be able to look at patients with tachycardia as well [9].

Figure 3: The Isbister nomogram [12].



Rautaharju's method for QT correction

Another method to correct the QT interval is by Rautaharju's method. Rautaharju has developed a formula to correct the QT interval [14]. The formula is: $QT_c = QT \cdot \frac{(120+HR)}{180}$

Unlike Bazett's formula Rautaharju's method does not give a significant correlation between heart rate and QTc, which gives a more accurate QTc [11].

The aim of this research is to examine the performance of the Isbister nomogram and Rautaharju's method for QT correction in acutely intoxicated ICU patients who ingested at least one QT prolonging drug. The primary objective is to identify how many patients have a QT-HR pair above the nomogram and how many patients have a QT-HR pair above the Rautaharju-curve, and thus have QT prolongation according to these correction methods.

Method

Subjects

This research takes place within the INTOXICATE study. The INTOXICATE study is a prospective, multicenter, observational study on the prognosis and outcomes of intoxicated patients in Intensive Care Units (ICU's). The study focusses on patients with intoxications who have been admitted to a ICU or a High Dependency Unit (HDU). The patients can be entered in the study from all over the world if the hospital is enrolled in the INTOXICATE study. Enrolling in the INTOXICATE study can be done through the INTOXICATE website (www.toxicstudy.org). After the hospital is enrolled via the website, they will get a short questionnaire about the size and nature of the unit. If the questionnaire is completed, a local ethical approval is signed and a contract is signed, the unit can be added to the Castor EDC database. Castor is an electronic data capture (EDC) system in which data from multiple different sources can be put together. In Castor EDC the participating ICU's/HDU's can enroll acutely intoxicated patients by answering a questionnaire. For each patient an electronic Case Report Form (eCRF) was created and data was collected on age, height, weight, BMI, comorbidities, exposure(s), symptoms, vital functions, lab, ECG, treatment(s), vital status after discharge and after 30 days.

The inclusion criteria for the INTOXICATE-study are:

- The patient was admitted to the ICU/HDU directly from an ambulance or from the Emergency Room (ER), or was transferred from a medical or surgical ward to the ICU/HDU.
- Intoxication was the primary reason for ICU/HDU admission
- The patient stayed at least 4 hours at the ICU/HDU
- The patient is 18 years or older.

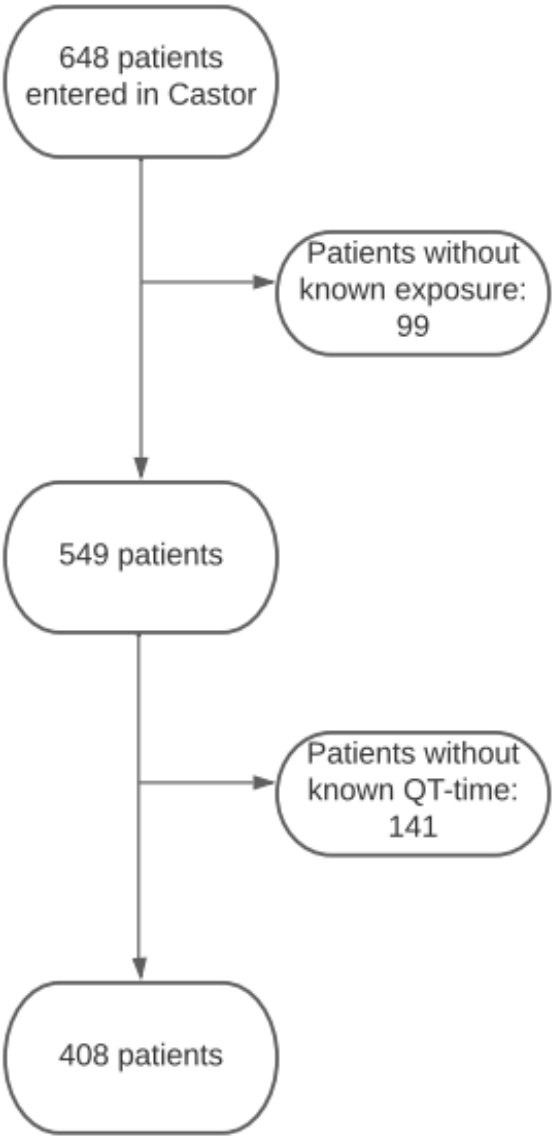
The exclusion criteria for this research project are:

- The patient was admitted to the ICU/HDU for another severe, concomitant condition (for example trauma due to a car accident while intoxicated)
- Patients who are missing the exposure in Castor EDC
- Patients who are missing the QT-time in Castor EDC

The database that was used for this research was downloaded from Castor EDC on 15-03-2022 10:49 in a SPSS format. More detailed information on for example the exposure and treatment details had to be downloaded separately. The detailed information was also downloaded in a SPSS format. Analyses and data cleaning were done using SPSS version 26. A full overview of data cleaning can be found in Appendix 1.

In total 648 patients from 57 different ICU's were in the database when downloaded from Castor EDC. From these patients 99 were excluded because the exposure was unknown. It could not be determined if these patients had taken a QT prolonging drug or not. Another important factor for analysis was QT-time. All patients without a known QT-time were excluded. This left the database with 408 patients. The excluded patients can be found in Figure 4.

Figure 4: Overview of excluded patients



Ethics

This research is an observational research only. No active interventions were given to the patients at any time. The data in the registry is coded and cannot be tracked back to the patient. The accredited Medical Research Ethics Committee of the University Medical Centre Utrecht decided that the *Dutch Medical Research Involving Human Subjects Act* did not apply to this study. The INTOXICATE study is conducted according to the principles of the Declaration of Helsinki (October 2013), the European General Data Protection Regulation (GDPR) (Regulation (EU) 2018/1725), and other local applicable regulations.

Data analysis

An independent samples T-test or a Mann-Whitney U test were used to determine if the group with QT prolonging drugs significantly different was than the group without QT prolonging drugs on the values age, BMI, SBP, HR, QT-time, depending on if the data was normally distributed. To test if the data normally was distributed the Kolmogrorov-Smirnov test was used with the hypothesis that the data is normally distributed by $p > 0.05$. A chi-square test was used to determine if there was an association between gender, vital status at hospital discharge or vital status 30 days after ICU admission and exposure to QT prolonging drugs. The same tests were done to compare patients with ECG results and without ECG results to see if patients without ECG results had the same demographics as patients with ECG results

To determine the performance of the Isbister nomogram and Rautaharju's QT correction a plotdigitizer was used to recreate the nomogram and Rautaharju's curve from a figure. This is a tool to get numerical data from figures. It is used before in some articles to get data, such as the research from Kaliszewska et al. [15]. According to Aydin et al. [16] the plotdigitizer gives reliable results. The exact coordinates of the nomogram and the curve could be determined and this could be used to determine if patients QT-HR pairs placed under or above the line. The patients QT-HR pairs were plotted in the figure and the estimation whether or not a patient had QT prolongation or not (above the curve/nomogram or not) was made based on the coordinates of the curve/nomogram provided by the plotdigitizer.

Results

Subjects

From November 1st 2020 until the moment of downloading the data from Castor EDC on March 15th 2022 at 10:49, the data of 408 patients who matched the inclusion criteria were used for analysis. The demographics of these patients are described in Table 1.

Table 1. Characteristics of included patients.

	Not exposed to QT-prolonging drugs	Exposed to QT-prolonging drugs	Total	P-value
Gender				0.001
Male (%)	111 (54.7%)	79 (38.5%)	190 (46.6%)	
Female (%)	92 (45.3%)	125 (61.0%)	217 (53.2%)	
Missing patients	-	1	1	
Total (%)	203 (49.8%)	205 (50.2%)	408	
Age				0.696
Median (IQR)	39 (28-58)	42 (30-56)	41 (29-56)	
BMI				0.031
Median (IQR)	25.51 (23.15-29.22)	24.44 (21.45-27.69)	24.77 (22.16-28.40)	
Missing patients	14	15	29	
Most deviant systolic blood pressure (SBP)				0.058
Median (IQR)	116 (96-145)	105 (90-135)	112 (92-140)	
Missing patients	1	-	1	
Heart Rate on ECG (HR)				0.012
Median (IQR)	86 (70-102)	94 (75-106)	90 (72-104)	
QT-time				0.565
Median (IQR)	400 (356-440)	404 (360-443)	400 (358-440)	
Vital status at discharge				0.015
Alive at discharge (%)	171 (84.2%)	188 (91.7%)	359 (88.0%)	
Deceased at ICU	17	6	23	
Deceased at ward following ICU discharge	0	0	0	
Missing patients	15	11	26	
Vital status after 30 days				0.049
Alive (%)	119 (76.3%)	136 (79.1%)	255 (77.7%)	
Deceased	4	0	4	
Missing patients (%)	33 (21.2%)	36 (20.9%)	69 (21.0%)	
Potentially fatal rhythm disturbance (TdP)				0.994
Yes	1	1	2	
No	202	204	406	

The patients were almost evenly distributed over the exposed and non-exposed group. There were more male than female patients in the non-exposed group and on the contrary, there were more females than males in the exposed group. Gender was significantly associated with exposure to QT prolonging drugs, according to the p-value of 0.001. The BMI of the patients was significantly different between the non-exposed and exposed group, with the exposed group having a BMI

significantly lower than the not-exposed group. The heart rate of patients exposed to QT prolonging drugs was significantly higher than patients who were not exposed to QT prolonging drugs. At last, both vital status at discharge and after 30 days were significantly associated with exposure to QT prolonging drugs. With the not-exposed group having more deaths both at discharge and after 30 days than the exposed group.

Exposure

Table 2: Overview of included patients per country.

Country	Number of units	Total patients (%)
The Netherlands	12	213 (52.2%)
Spain	9	79 (19.4%)
Turkey	6	17 (4.2%)
Jordan	3	17 (4.2%)
Libya	2	15 (3.7%)
Lithuania	1	31 (7.6%)
Germany	1	10 (2.5%)
Romania	1	6 (1.5%)
Egypt	1	6 (1.5%)
Brunei	1	4 (1.0%)
United States	1	2 (0.5%)
Belgium	1	2 (0.5%)
Australia	1	2 (0.5%)
Sudan	1	1 (0.25%)
Palestine	1	1 (0.25%)
United Kingdom	1	1 (0.25%)
Greece	1	1 (0.25%)
Total	44	408

In total, 1009 exposures were registered among 408 patients from 44 different units from 17 countries. The distribution of the different units and patients around the world can be found in Table 2. Most units and patients came from The Netherlands, with 12 units and 213 patients. This was more than 50% of the patients that were included. Followed by The Netherlands was Spain with 9 units and 79 patients, a total of 19.4% of the patients included were from Spain.

Of the 1009 exposures 319 were from QT prolonging drugs. In Appendix 2 all the different QT prolonging exposures are shown. In total 40 different QT prolonging exposures were identified in the included patients. From these 40 different QT prolonging exposures a top 10 could be made of the frequencies of the exposures, as seen in Table 3. Quetiapine was the most used QT prolonging drug with 64 exposures, followed by olanzapine with 29 exposures and cocaine with 27 exposures to make the top 3 complete.

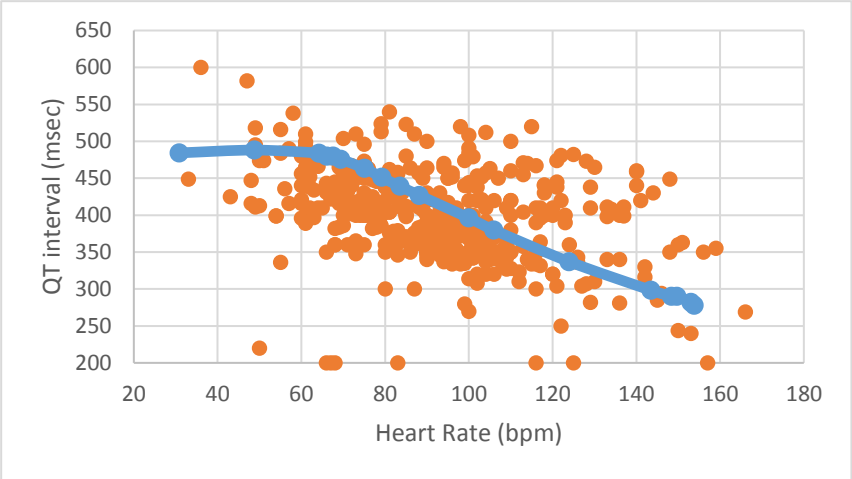
Table 3: Top 10 most used QT prolonging drugs.

Rank	Name (TdP risk grade)	Frequency
1	Quetiapine (3)	64
2	Olanzapine (3)	29
3	Cocaine (1)	27
4	Amitriptyline (3)	23
5	Tramadol (2)	15
5	Citalopram (1)	15
7	Clomipramine (3)	12
8	Methadone (1)	11
9	Lithium (2)	9
9	Mirtazapine (2)	9

Isbister nomogram

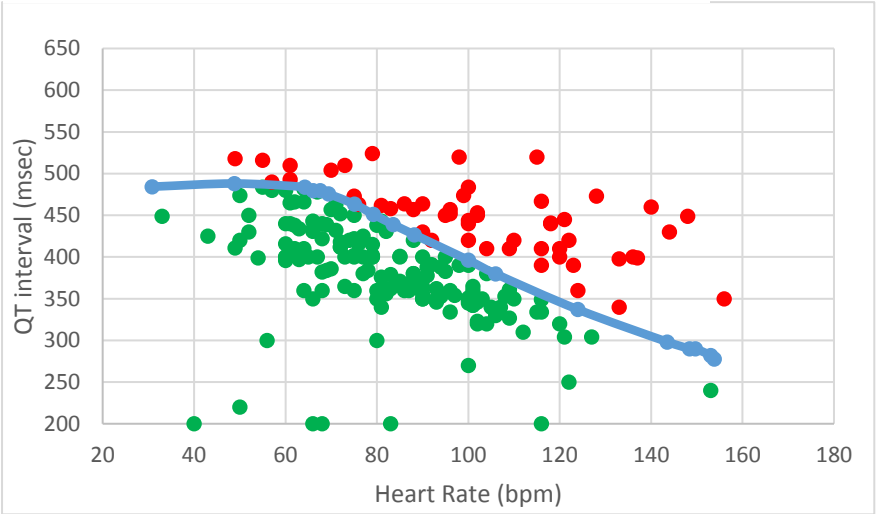
All the patients QT-HR pairs were plotted in the Isbister nomogram, as shown in Figure 5. Each dot represents a new QR-HR pair, one for every patient included in the research. The dots are scattered all over the figure, but the majority of them are underneath the Isbister nomogram.

Figure 5: QT-HR pairs of all patients in the Isbister nomogram.



The not-exposed and exposed group were also separately plotted in the Isbister nomogram. The red dots are QT-HR pairs above the nomogram and represent QT prolongation The green dots are QT-HR pairs underneath or on the nomogram and these patients do not have QT prolongation.

Figure 6: QT-HR pairs of the not-exposed patients in the Isbister nomogram.



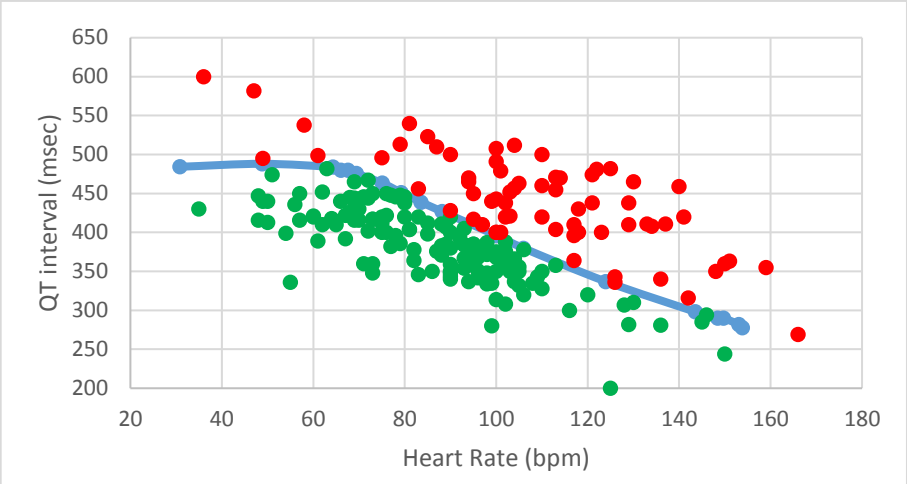
The QT-HR pairs from the not-exposed group can be seen in Figure 6. Already can been seen that most of the QT-HR pairs are underneath the nomogram. This is better displayed in Table 4. Of the not-exposed group a total of 150 patients, or 73.9% have a QT-HR pair underneath the nomogram and 53, or 26.1% have a QT-HR pair above the nomogram, of which one has the potentially fatal rhythm disturbance.

Table 4: Observed QT prolongation and potentially fatal rhythm disturbance in not-exposed patients in Isbister nomogram.

	Potentially fatal rhythm disturbance		
Observed QT prolongation in Isbister nomogram	Yes	No	Total
Yes	1	52	53 (26.1%)
No	-	150	150 (73.9%)
Total	1	204	203

The QT-HR pairs of the exposed group can be seen in Figure 7. A couple of the dots are outside the scope of the nomogram, which was further extrapolated to determine whether these patients had QT prolongation according to the nomogram or not.

Figure 7: QT-HR pairs of the exposed patients in the Isbister nomogram.



The details of Figure 7 can be found in Table 5, where can been seen how many patients have a QT-HR pair above and underneath the nomogram. Of the total of 205 patients 137 or 66.8% have a QT-HR pair underneath the nomogram and thereby do not have QT prolongation. A total of 68 or 33.2% have a QT-HR pair above the nomogram and do have QT prolongation according to the nomogram. Of the patients with a QT-HR pair above the nomogram one has the potentially fatal rhythm disturbance.

Table 5: Observed QT prolongation and potentially fatal rhythm disturbance in exposed patients in Isbister nomogram.

	Potentially fatal rhythm disturbance		
Observed QT-HR pair above Isbister nomogram	Yes	No	Total
Yes	1	67	68 (33.2%)
No	-	137	137 (66.8%)
Total	1	204	205

The total of QT-HR pairs underneath and above the nomogram, so the not-exposed and exposed group together, can be found in Table 6. Of the 408 patients 287 have a QT-HR pair underneath the nomogram and 121 patients have a QT-HR pair above the nomogram, a percentage of respectively 70.3% and 29.7%. In total 2 patients had the potentially fatal rhythm disturbance and they both had an observed QT-HR pair above the Isbister nomogram, which indicates that they had QT prolongation.

Table 6: Observed QT prolongation and potentially fatal rhythm disturbance in all included patients in Isbister nomogram.

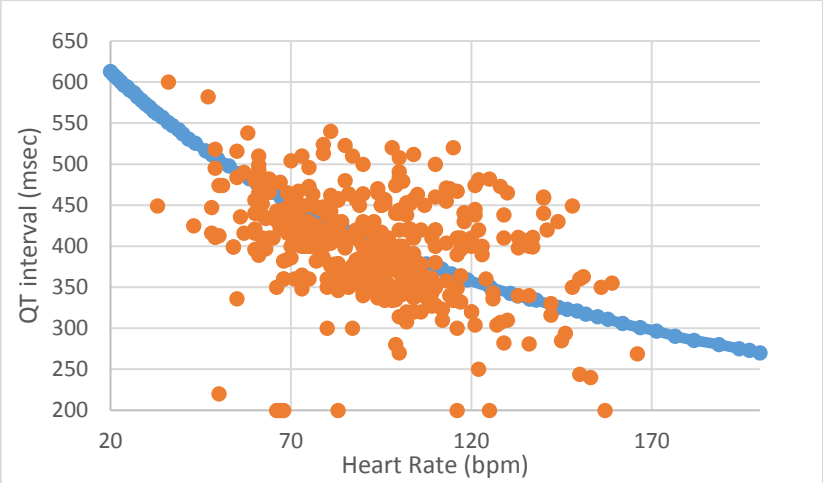
	Potentially fatal rhythm disturbance		
Observed QT-HR pair above Isbister nomogram	Yes	No	Total
Yes	2	119	121 (29.7%)
No	-	287	287 (70.3%)
Total	2	406	408

Rautaharju's method for QT correction

Even though Rautaharju has developed a formula to correct the QT interval. It can also be plotted as a curve. In this curve the QT-HR pairs of the patients can be plotted, without using the formula first. This makes it easier to see which patients have QT prolongation and which do not. The same patients are used that were used in the Isbister nomogram, so the QT-HR pairs are the same and the same two patients have a potentially fatal rhythm disturbance, but the curve is different, which makes a difference in patients with QT prolongation according to the different methods.

All the patients QT-HR pairs were plotted in Rautaharju's curve as can be seen in Figure 8. The figure shows that the majority of patients have a QT-HR pair under the curve, but with only this figure no conclusion can be drawn if these patient have taken a QT prolonging drug or not. That is what Figure 7 and Figure 8 show.

Figure 8: QT-HR pairs of all patients in the Isbister nomogram.



Just like the Isbister nomogram, the not-exposed and exposed group were separately plotted in the diagram of Rautaharju's curve for QT correction. The red dots are QT-HR pairs above the curve and represent QT prolongation The green dots are QT-HR pairs underneath or on the curve and these patients do not have QT prolongation.

Figure 9: QT-HR pairs of the not-exposed patients in Rautaharju's curve.

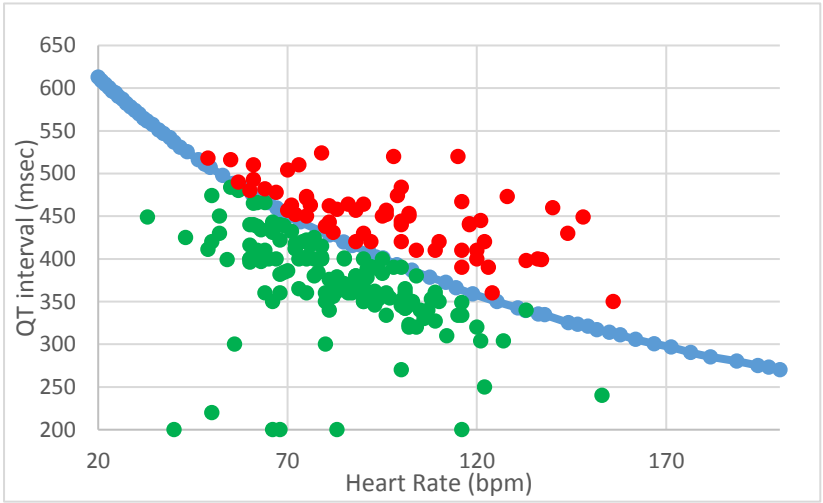


Figure 9 shows QT-pairs of patients in the not-exposed group. The details of the figure can be seen in Table 7, which states that a total of 63 patients have a QT-HR pair above the curve and 140 patients have a QT-HR pair below or on the curve, which respectively is a percentage of 31.0% and 69.0%. Of the 63 patients who have a QT-HR pair above the curve.

Table 7: Observed QT prolongation and potentially fatal rhythm disturbance in not-exposed patients in Rautaharju's curve.

	Potentially fatal rhythm disturbance		
Observed QT prolongation via Rautaharju's method	Yes	No	Total
Yes	1	62	63 (31.0%)
No	-	140	140 (69.0%)
Total	1	202	203

The same as in Figure 9 can be seen in Figure 10, but here the QT-HR pairs used are those from patients exposed to at least one QT prolonging drug. In Table 8 can be seen that 75 QT-HR pairs of patients in the exposed group are above the curve, which is a percentage of 36.6%. These patients do have QT prolongation according to Rautaharju's method of QT correction. Of the 205 patients in the exposed group, a total of 130 patients have a QT-HR pair underneath the curve, which amounts to a percentage of 63.4%.

Figure 10: QT-HR pairs of the exposed patients in Rautaharju's curve.

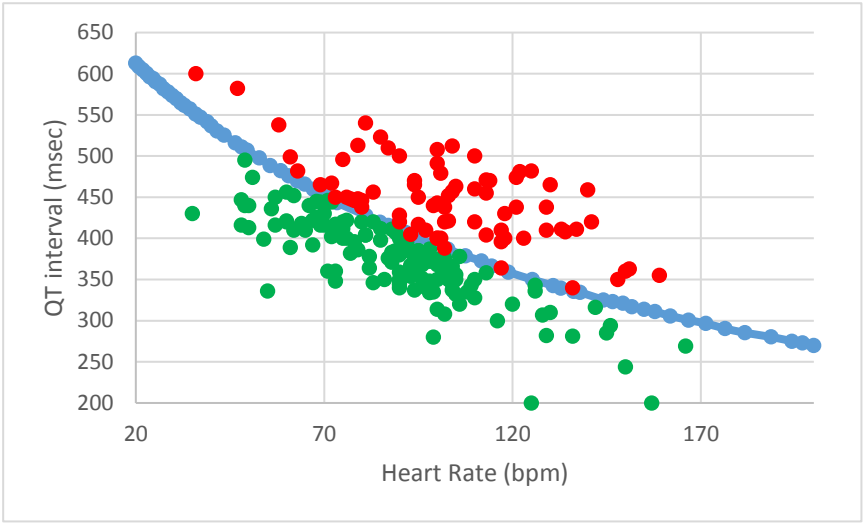


Table 8: Observed QT prolongation and potentially fatal rhythm disturbance in exposed patients in Rautaharju's curve.

	Potentially fatal rhythm disturbance		
Observed QT prolongation via Rautaharju's method	Yes	No	Total
Yes	1	74	75 (36.6%)
No	-	130	130 (63.4%)
Total	1	204	205

The total of QT-HR pairs underneath and above the curve, so the not-exposed and exposed group together, can be found in Table 9. In total 138 patients have a QT-HR pair above Rautaharju's curve, while 270 patients have a QT-HR pair underneath or on Rautaharju's curve. In total two patients have the outcome of potentially fatal rhythm disturbance, who both had an observed QT prolongation via Rautaharju's method.

Table 9: Observed QT prolongation and potentially fatal rhythm disturbance in all included patients in Rautaharju's curve.

	Potentially fatal rhythm disturbance		
Observed QT prolongation via Rautaharju's method	Yes	No	Total
Yes	2	136	138 (33.8%)
No	-	270	270 (66.2%)
Total	2	406	408

Isbister nomogram versus Rautaharju's method in exposed patients

In Table 10 the Isbister nomogram and Rautaharju's method for QT correction are put side to side to make a comparison. Rautaharju's method has more QT-HR pairs above the curve than the nomogram has.

Table 10: Difference in observed QT prolongation in Isbister and Rautaharju.

Observed QT-HR pair above curve/nomogram	Isbister	Rautaharju
Yes	68	75
No	137	130

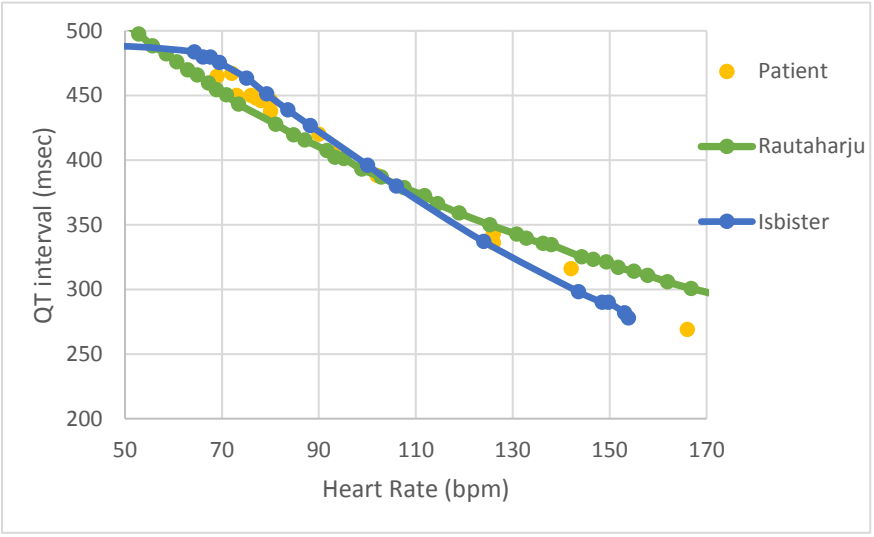
There is a difference in QT-HR pairs above Isbister nomogram and Rautaharju's curve. This means there is a difference in specificity. The sensitivity and specificity of the Isbister nomogram and Rautaharju's method can be found in Table 11. The sensitivity of the Isbister nomogram and Rautaharju's method is the same, 100%, but it has a wide confidence interval, because there is only one patient with TdP. If looked at specificity, there is a difference between the Isbister nomogram and Rautaharju's method. The specificity of Isbister is higher than Rautaharju's specificity, with respectively a percentage of 67.16% and 63.73%. This is due to the fact that more patients have a QT-HR pair above Rautharaju's curve than above the Isbister nomogram.

Table 11: Sensitivity and Specificity of Isbister nomogram and Rautaharju's method.

Method	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Isbister	100% (2.5-100%)	67.16% (60.25-73.55%)
Rautaharju	100% (2.5-100%)	63.73% (56.72-70.32%)

The patients who have a difference between Rautaharju and Isbister in the exposed group, for example in Rautaharju the QT-HR pair falls underneath the curve and in Isbister the QT-HR pair falls above the nomogram, can be found in Appendix 3.

Figure 11: Patients who differ between Isbister and Rautaharju.



In total there were 18 patients with a difference between the two methods of QT correction. In Figure 11, this is made clear, where the blue line is the Isbister nomogram, the green line is Rautaharju's curve and the yellow dots are the patients with a difference between Rautaharju and Isbister. The figure has been zoomed in, so not the whole nomogram and Rautaharju's curve are in the figure to better visualize the patients. As can be seen in the figure, these patients fall between Rautaharju's curve and the Isbister nomogram.

Difference in patients with/without ECG results

From the 648 patients who were in the dataset originally, a lot of patients did not have ECG results and were therefore excluded, because the QT-time of the patients was needed to perform the analysis. In Table 11 you can see the difference between the patients with ECG results and the patients without ECG results.

Table 11: Characteristics of patients with and without ECG results.

	Patients with ECG results	Patients without ECG results	Total	P-value
Gender				0.219
Male (%)	214 (47.1%)	77 (39.7%)	291 (44.9%)	
Female (%)	239 (52.6%)	68 (35.1%)	307 (47.4%)	
Missing patients (%)	1 (0.2%)	49 (25.3%)	50 (7.7%)	
Total (%)	454 (70.1%)	194 (29.9%)	648	
Age				0.509
Median (IQR)	41 (29-56)	41 (27-56)	41 (29-56)	
BMI				0.421
Median (IQR)	24.74 (21.85-28.07)	25.88 (21.78-29.39)	24.77 (21.80-28.41)	
Most deviant systolic blood pressure (SBP)				0.761
Median (IQR)	112 (92-140)	114 (91-137)	112 (92-140)	
Most deviant Heart Rate (HR)				0.464
Median (IQR)	96 (72-112)	90 (70-110)	95 (71-112)	
Vital status at discharge				0.000
Alive (%)	402 (88.5%)	103 (53.1%)	505 (77.9%)	
Deceased at ICU	24	25	49	
Deceased at ward following ICU discharge	0	2	2	
Missing patients	28	64	92	
Vital status after 30 days				0.007
Alive (%)	289 (67.2%)	89 (53.2%)	378 (63.3%)	
Dead	4	0	4	
Missing patients	137	78	215	

Most of the variables are not significantly different between the groups. Gender is not significantly associated with having ECG results. There is also no difference in age, BMI, SBP and HR between patients with and without ECG results. Vital status at discharge and vital status after 30 days is significantly associated with whether or not an ECG was taken, with an P-value of 0.000 and 0.007, respectively.

Discussion

The aim of this research project was to examine the performance of the Isbister nomogram and Rautaharju's QT correction in acutely intoxicated ICU patients who ingested at least one QT prolonging drug. From the 408 included patients, 205 were exposed to a QT prolonging drug. Of these 205 patients 68 had a QT-HR pair above the Isbister nomogram, which is a percentage of 33.2%, even though only 1 patient had the actual outcome of TdP. If looked at Rautaharju's method for QT correction, of the same 205 patients 75 had a QT-HR pair above Rautaharju's curve, which is 36.6% and thereby more patients have a QT-HR pair above Rautaharju's curve than they do above the Isbister nomogram.
The patient who was in the exposed group and did have the outcome TdP was in both Isbister and Rautaharju placed in the category of QT prolongation, because the QT-HR pair placed above the nomogram and the curve. This means that both the Isbister nomogram and Rautaharju's method for QT correction placed this patient correct in the group who are at risk of TdP.

There was also one patient with TdP in the not-exposed group. This patient did not take any QT prolonging drugs, but did have the outcome TdP. Even though the patient was not exposed to any QT-prolonging drugs, its QT-HR pair was placed correctly above the Isbister nomogram and above Rautaharju's curve, thus suggesting QT prolongation. The reason this patient had TdP and QT prolongation could be because not only taking a QT-prolonging drug can give a risk of QT prolongation and TdP, but there are also other risk factors. As said in the introduction these factors are electrolyte disturbances, structural heart disease, bradycardia, history of QT prolongation, female sex and an advanced age. Of these risk factors some can be ruled out, because these were asked in the questionnaire. The patient did not have any electrolyte disturbances, but did have a comorbidity of arrhythmia, which might have to do with the occurrence of the TdP. The patient did not have bradycardia, with a most deviant heart rate of 140 beats per minute, did not have the female sex and did not have an advanced age. The only thing we did not ask in the questionnaire is of the patient a history of QT prolongation had, which therefore could not be ruled out as a cause of the TdP.

In 2007, Chan et al. [9] performed a research to determine the sensitivity and specificity of the Isbister QT nomogram. The research showed a sensitivity of 98.3% without the extrapolation of the nomogram and a sensitivity of 96.6% with extrapolation. It also showed a specificity of 99.3% without the extrapolation and with the extrapolation a specificity of 98.7% was found. This suggests that the Isbister nomogram is a good risk assessment tool for QT prolongation and TdP.

In 2010, Waring et al. [17] performed a study to evaluate the Isbister nomogram in patients with an antidepressant overdose. The study concluded that the Isbister nomogram had a lower false-positive rate than the widely used Bazett's formula and that the Isbister nomogram offers potential advantages. Even though this research did not give a specificity or sensitivity it still suggested that the Isbister nomogram gives potential advantages. The study compared the Isbister nomogram to Bazett's formula, which is the most used method for QT correction. This is something that could have been done in the this research as well, because it can give the conclusion if Isbister nomogram or possibly Rautaharju's method for QT correction is better than the standard used QT correction formula, Bazett's formula.

In 2019, Othong et al. [11] performed a study to compare multiple QT correction methods with one another. The results were as followed: Rautaharju's method for QT correction had a sensitivity of 91.3% and a specificity of 87.33%. The Isbister nomogram was equally as good as Rautaharju's method for QT correction with exactly the same sensitivity and specificity. The accuracy of both Rautaharju and the Isbister nomogram was 89.08%.

Even though both the Isbister nomogram and Rautaharju's method placed the one patient with the outcome TdP who was exposed to a QT-prolonging drug both correctly, the methods do have another specificity, due to the different amount of patients they placed above the line, who did not have the outcome. The specificity of 67.16% of the Isbister nomogram is lower than can be found in previous research, where a specificity of 87.33% and 98.7% can be found.
The specificity of Rautaharju's method in this research was 63.73%, which is also lower than can be found in literature, where the specificity 87.33% was.
The sensitivity of both the Isbister nomogram and Rautaharju's method in this research was 100% with a very wide confidence interval of 2.5%-100%. The 'real' value could be practically everywhere, this makes it difficult to compare with previous research, which found that the sensitivity of both the Isbister nomogram and Rautaharju's method was in the 90%-range. With a sensitivity of Isbister of 96.6% and 91.3% and a sensitivity of Rautaharju of 91.3%.
De difference in specificity may be due to a small population and only one patient in the exposed group with the outcome of TdP. The same can be said about the wide confidence interval of the sensitivity, which also may be because of the small population. More research with a bigger population should be done to confirm the results.

There was also looked at the difference between patients with and without ECG results. It was important to see if the patients without ECG results and therefore excluded for the primary analysis had the same demographics. This is important to know, because it is important that the population taken for the primary analysis is the same as the general population in the study and that there is no selection bias. It can be seen that the population with and without ECG results are generally the same. There is no difference in gender, age, BMI, most deviant SBP and most deviant HR, so in these respects the populations are the same. Relatively more patients died at hospital discharge in the group where no ECG was made. There may be a reason for this. It could be that those patients were already really bad and no ECG was made, because they would probably die anyway. It is also possible that there was nog ECG made by accident or on purpose and afterwards that was the wrong decision, because something was wrong on the ECG and they missed it, which caused the patient to die. From a lot of patients it was not known whether or not they were dead at hospital discharge or 30 days after ICU discharge, especially in the group without an ECG, which may result in a distorted view of the results.

There are also some (other) limiting factors to this research. Torsade de pointes is often not recognized or reported[18]. This is why patients who had TdP can be missed and therefore some of the patients who had QT-prolongation according to the Isbister nomogram or Rautaharju's method of QT correction could have the outcome of TdP. For some of these patients the questionnaire states that these patient died due to other causes, such as respiratory failure, so a TdP is not very likely. Most of these patients, however, did not die. Some of these patients could have had unrecognized TdP and therefore were missed.

Furthermore it is important to state that some of the drugs that can cause QT-prolongation do not give TdP. One example of this is quetiapine. There is not one single case of a patient with an quetiapine overdose and torsade de pointes. Quetiapine can give QT-prolongation, especially in patients with a high heart rate, but this never caused a TdP. [19] Quetiapine is the most used QT prolonging drug in this research population, but is not associated with TdP.

In the questionnaire the QT-time is asked and not the QTc. Some ECG machines automatically give the QTc instead of the QT-time and therefore it can be that some local investigators entered the QTc-

time instead of the QT-time, which gives a double correction when making a QT-HR pair for determining QT prolongation. This may have influenced the outcome of the research.

This research was done with preliminary data, the INTOXICATE study is still ongoing, hoping to include 2000 patients. The conclusion therefore could differ from the final result, which maybe could evaluate the Isbister nomogram and Rautaharju's method for QT correction.

It is clear that some more research should be done to evaluate the Isbister nomogram and Rautaharju's method for QT prolongation. More patients should be included to give more TdP outcome and to confirm the results of the sensitivity and specificity of the Isbister nomogram and Rautaharju's method. Even though only one patient with an exposure to a QT prolonging drug had the outcome TdP, this patient was correctly placed above the line in both the Isbister nomogram and Rautharju's method for QT correction, and therefore had QT prolongation and was at risk of TdP. This result gives some hope that maybe one day Bazett's formula will be replaced by another QT-correction method for general use in clinical practice and maybe this new QT-correction method will be the Isbister nomogram or Rautaharju's formula.

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Appendix 1: Overview of data cleaning

Some of the data from entries were unrealistic and therefore deleted from the database. These data points could not be used for data analysis and were changed to 'missing'. The following data points were deleted:

Entry	Category	Original Value	Remark
025-0014	BMI	0	
074-0006	BMI	0	
024-0010	BMI	0	
001-0012	BMI	0	
025-0017	BMI	0	
146-0021	BMI	3.28	Very unlikely value
041-0001	SBP	0	Patient did have a heartbeat, but no blood pressure, very unlikely

Appendix 2: QT prolonging drugs

Amitriptyline
Aripiprazole
Chloroquine
Citalopram
Clomipramine
Clozapine
Cobimetinib
Cocaine
Diltiazem
Domperidone
Escitalopram
Flecainide
Fluoxetine
Flupentixol
Fluvoxamine
Galantamide
Haloperidol
Hydrochlorothiazide
Imipramine
Levomepromazine
Lithium
Methadone
Metoclopramide
Mirtazapine
Nortriptyline
Olanzapine
Omeprazole
Ondansetron
Pantoprazole
Paroxetine
Pipamperone
Promethazine
Quetiapine
Risperidone
Sertraline
Tiapride
Torsemide
Tramadol
Trazodone
Venlafaxine

Appendix 3: Difference between Rautaharju and Isbister

Record ID	Rautaharju	Isbister
009-0021	Under	Above
009-0028	Under	Above
008-0017	Under	Above
008-0005	Under	Above
040-0021	Under	Above
009-0010	Above	Under
041-0003	Above	Under
032-0015	Above	Under
014-0011	Above	Under
006-0016	Above	Under
102-0013	Above	Under
020-0002	Above	Under
005-0001	Above	Under
146-0015	Above	Under
040-0005	Above	Under
009-0004	Above	Under
012-0012	Above	Under
006-0020	Above	Under