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PHARMACODYNAMICS

Risk factors for QTc interval prolongation

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Abstract

Purpose Prolongation of the QTc interval may result in Torsade de Pointes, a ventricular arrhythmia. Numerous risk factors for QTc interval prolongation have been described, including the use of certain drugs. In clinical practice, there is much debate about the management of the risks involved. In this study, we quantified the effect of these risk factors on the length of the QTc interval.
Methods We analyzed all ECGs that were taken during routine practice between January 2013 and October 2016 in the Spaarne Gasthuis, a general teaching hospital in the Netherlands. We collected laboratory values in the week before the ECG recording and the drugs prescribed. For the identification of risk factors, we used multilevel linear regression analysis to correct for multiple ECG recordings per patient.
Results We included 133,359 ECGs in our study, taken in 40,037 patients. Patients using one QT-prolonging drug had a 11.08 ms (95% CI 10.63–11.52; $p < 0.001$) longer QTc interval. Patients using two QT-prolonging drugs had a 3.04 ms (95% CI 2.06–4.02; $p < 0.001$) increase in the QTc interval compared to patients using one QT-prolonging drug. Women had a longer QTc interval compared to men (16.30 ms 95% CI 14.59–18.01; $p < 0.001$). The QTc interval increased with increasing age, but the difference between men and women diminished. Other independent risk factors that significantly prolonged the QTc interval with at least 10 ms were hypokalemia, hypocalcemia, and the use of loop diuretics.
Conclusion We identified and quantified various risk factors for QTc interval prolongation.

Keywords Long QT syndrome/chemically induced · Electrocardiography · Risk assessment · Drug-related side effects and adverse reactions · Hospital information systems

Introduction

Prolongation of the QTc interval on the ECG is associated with Torsade de Pointes (TdP), potentially fatal ventricular arrhythmias [1]. Numerous risk factors have been identified that prolong the QTc interval, including an increasing age, female gender, genetic variants, cardiovascular diseases, and electrolyte disturbances [2–8]. Besides these risk factors, various drugs prolong the QTc interval, including antimicrobial drugs, psychotropic drugs, and cardiovascular drugs [9, 10]. These drugs have been associated with an increased risk of cardiac events [11, 12]. The list of QT-prolonging drugs, composed by CredibleMeds (Arizona Center for Education and Research on Therapeutics), now contains over 100 drugs associated with TdP [13]. This list is divided in three categories, drugs with a conditional risk of TdP, drugs with a possible risk of TdP, and drugs with a known risk of TdP, based on whether each can cause QTc interval prolongation or TdP.

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Notwithstanding the increased risk of TdP, these drugs are frequently used in clinical practice.

The QT interval is affected by heart rate. Various formulas are used to correct for the heart rate, among which the Bazett's formula ($QTc = QT / RR^{1/2}$) is most frequently used [14]. For women, the cutoff point for a prolonged QTc interval, corrected with the Bazett's formula, is 470 ms, while in men, the cutoff is 450 ms [15]. However, it is suggested that the Bazett's formula overestimates the QTc interval at higher heart rates. The Fridericia's formula ($QTc = QT / RR^{1/3}$) is described as a superior formula to correct for heart rate and to better predict mortality [16, 17].

In clinical practice, there is much debate about the management of the risk associated with QT-prolonging drugs. Many risk factors have been described, although the actual degree of QTc interval prolongation and whether the effect is independent or not is often unknown. Overestimating the risks implies unnecessary safety measures, such as withholding primary therapies. On the other hand, cases of TdP may result in death, especially outside the hospital. For a proper weighing of risk and benefits, it is important to consider the presence of risk factors. In patients without risk factors for QTc prolongation, the risk of QT-prolonging drugs will most likely be acceptable and vice versa [18]. Better knowledge of the QTc prolonging effect of drugs in relation to the effect of other risk factors is needed to improve decision-making.

In this study, we quantified the effect of the risk factors on the length of the QTc interval in a hospital population. Besides the use of drugs that are known to prolong the QTc interval, we analyzed the effect of the following risk factors on the QTc interval: age, female gender, hypokalemia and hyperkalemia, hypocalcemia and hypercalcemia, hypomagnesemia and hypermagnesemia, impaired renal function, the use of antidiabetic drugs, the use of loop diuretics, and the use of low-dose acetylsalicylic acid. These drug groups were included as proxy for diabetes mellitus, cardiovascular diseases including heart failure, and a history of thrombotic diseases including myocardial infarctions, respectively. Diabetes mellitus, heart failure, and a history of myocardial infarction are risk factors for QTc interval prolongation.

Methods

Setting

This study was performed in the Spaarne Gasthuis (Haarlem/Hoofddorp, the Netherlands), a general teaching hospital.

Study cohort

We performed a retrospective observational study. We selected all ECGs that were taken in routine clinical practice of inpatients and outpatients between 21 January 2013 and 10 October 2016. ECGs from patients under 18 years of age, with a heart rate under 50 bpm or over 180 bpm, with a QRS interval above 120 ms, or with a QTc (Bazett) interval under 300 ms or over 750 ms were excluded. A prolonged QRS interval was excluded, because a prolonged QRS interval will also result in a prolonged QT interval. Deviant heart rates and QTc intervals were excluded to minimize outliers influencing the analyses. The deviant heart rates will result in underestimation or overestimation of the QTc interval when correcting the QT interval for the heart rate. Deviant QTc intervals will most likely be caused by misinterpretation of the QT interval on the ECG. Moreover, we excluded all patients of whom no drug ordering data were available at the time of the ECG recording, because it is uncertain whether these patients did not use drugs or data was missing.

Data collection

Data were collected from the hospital information system EPIC (Madison, WI, USA). All ECGs were standard 12-lead resting ECGs with automated analysis by the MUSE Cardiology Information System. The heart rate (RR), QT, and QRS interval, analyzed by the MUSE system, were recorded in the hospital information system EPIC. For each ECG, we collected the last measured serum creatinine, potassium, calcium, and magnesium levels in the 7 days before the ECG recording. Renal function was analyzed as the estimated glomerular filtration rate (eGFR) calculated with the MDRD formula. We analyzed whether antidiabetic drugs, loop diuretics, or acetylsalicylic acid as platelet aggregation inhibitor were prescribed at the time of the ECG recording. We counted the number of drugs prescribed and the number of drugs prescribed with a known risk of TdP according to the CredibleMeds list (October 2015) [13]. We only included drugs with a known risk of TdP, because for these drugs, there is obvious evidence that they substantially prolong the QT interval or increase the risk of TdP [19].

Outcome and study variables

The QTc interval was calculated from the QT interval by correcting for heart rate using both the Bazett's and Fridericia's formula. We investigated the effect of the following risk factors on the length of the QTc interval: age, female gender, the use of QT-prolonging drugs (one, two, or three or more) versus no use, serum potassium level (≤ 3.0, 3.1–3.4, ≥ 5.1 versus 3.5–5.0 mmol/l), serum magnesium levels (≤ 0.69 and > 1.00 versus 0.70–1.00 mmol/l), serum calcium level (≤ 1.69, 1.70–2.14, and > 2.55 versus 2.15–2.55 mmol/l), eGFR (≤ 29 and 30–60 versus > 60 ml/min), and the use of antidiabetic drugs versus no use, the use of high-ceiling diuretics versus no use, and the use of acetylsalicylic acid versus no

use. If electrolyte values were missing, these values were categorized as being the reference value, which is the normal value used by our laboratory.

Statistical analysis

We used multilevel linear regression analyses, with a repeated effect for time between measurements. Variables were analyzed both with univariate analyses and multivariate analysis. In the multivariate analysis, we adjusted for the other variables in our study and included the interaction term between age and gender. We analyzed the association between the number of risk factors that prolong the QTc interval with at least 10 ms and the QTc interval. Risk factors that prolonged the QTc interval with at least 20 ms were counted twice. We also analyzed whether drug-induced QTc prolongation differed with the number of risk factors other than the use of QT-prolonging drugs. p value for statistical significance was set at 0.05. Statistical analyses were performed using SAS (version 9.3).

Ethics

Since this is a retrospective observational study, no approval of a Medical Ethical Committee was needed according to the Dutch Medical Research Involving Human Subjects Act. All patient data were processed anonymously, according to privacy legislation.

Results

Of the 196,086 ECGs taken in the study period, we excluded 3455 ECGs for age below 18 years, 6884 ECGs for heart rate below 50 or above 180, 28,806 ECGs for QRS interval above 120 ms, 160 ECGs for QTc interval below 300 ms or above 750 ms, and 23,422 ECGs because no drug prescription data were available. We included 133,359 ECGs from 40,037 patients in our analyses (Table 1). Patients had a mean age of 65.3 years (SD 16.0), and 48.6% was male. The mean QTc interval was 437.9 ms (SD 34.1) if calculated with the Bazett's formula, or 418.3 ms (SD 31.6) if calculated with the Fridericia's formula.

The QTc interval was longer in patients who used one QT-prolonging drug, than in patients who used no QT-prolonging drugs (Table 2). This was independent whether we corrected with the Bazett's formula (difference 11.08 ms; 95% CI 10.63–11.52; $p < 0.001$) or the Fridericia's formula (difference 6.35 ms; 95% CI 5.93–6.78; $p < 0.001$). In patients who used two QT-prolonging drugs, there was a 3.04 ms (95% CI 2.06–4.02; $p < 0.001$) increase in the QTc interval compared to patients who used one QT-prolonging drug, if we used the Bazett's formula and adjusted for the other variables in the study (Fig. 1). In patients who used two or more QT-prolonging drugs, the heart rate was higher. If we adjusted with the Fridericia's formula, the QTc interval was 3.74 ms shorter (95% CI 2.71–4.76; $p < 0.001$) in patients who used two QT-prolonging drugs, compared to patients who used one QT-prolonging drug (Fig. 2).

Table 1 Baseline characteristics

Number of ECGs	133,359		
Number of patients	40,037		
Gender (male)	48.6%		
Age (mean, SD)	65.3	16.0	years
Average number of ECGs per patient	3.33		
RR (mean, SD)	81.4	21.7	bpm
QRS (mean, SD)	91.3	12.2	ms
QT (mean, SD)	383.6	46.1	ms
QTc Bazett (mean, SD)	437.9	34.1	ms
QTc Fridericia (mean, SD)	418.3	31.6	ms

In female patients, the QTc interval was on average 13.91 ms (95% CI 12.28–15.55; $p < 0.001$) longer than in male patients. In both male and female patients, the QTc interval increased with increasing age (Fig. 3, supplemental Fig. 1). In male patients, this increase was larger than in female patients, and the difference in length of the QTc interval between male and female patients diminished with increasing age.

Besides the use of QT-prolonging drugs, an increasing age, and gender, independent risk factors with an effect of 10 ms or more on the QTc interval were hypokalemia, hypocalcemia, and the use of loop diuretics (Table 2). In patients with a potassium level below 3.0 mmol/l, the average potassium level was 2.8 mmol/l and the increase in QTc interval was 24.09 ms (95% CI 22.51–25.66; $p < 0.001$). In patients with a potassium level above 5.0 mmol/l, the average potassium level was 5.6 mmol/l and these patients had a QTc interval that was 3.19 ms shorter (95% CI 1.79–4.58; $p < 0.001$) compared to patients with a normal potassium level. If we corrected the QT interval using the Fridericia's formula, hypokalemia and hypocalcemia were independent risk factors with an effect of at least 10 ms (supplemental Table 1).

Increasing numbers of risk factors for QTc prolongation had an additive effect on the QTc interval (Fig. 4, supplemental Fig. 2). We included the following risk factors that prolong the QTc interval with at least 10 ms: age above 70 years, female gender, the use of QT-prolonging drugs, hypokalemia below 3.5 mmol/l, hypokalemia below 3 mmol/l, hypocalcemia below 1.69 mmol/l, and the use of loop diuretics. We counted a potassium level below 3 mmol/l as two risk factors, because the QTc interval was prolonged with more than 20 ms. The addition of a risk factor resulted on average in a mean increase of the QTc interval by 8 ms, independent of the number of risk factors already present. In patients with no

Table 2 Risk factors associated with QT prolongation and the QTc interval adjusted with the Bazett's formula

		Number	RR	QTc (Bazett)	Univariate		Multivariate	
			Mean	Mean	Change	95% CI	Change	95% CI
Age (years)		NA	NA	NA	0.31	0.30–0.32*	0.24	0.23–0.26*
Gender	Male	69,599	80.0	434.9	Ref.		ref.	
	Female	63,760	83.1	441.2	6.35	5.99–6.72*	16.30	14.59–18.01*
Age × gender		NA	NA	NA	NA		− 0.17	− 0.19–0.14*
Number of QT-prolonging drugs	0	102,277	79.6	434.6	Ref.		Ref.	
	1	26,162	86.6	448.0	13.42	12.97–13.88*	11.08	10.63–11.52*
	2	4476	92.4	453.0	18.40	17.39–19.40*	14.12	13.14–15.10*
	≥ 3	444	95.2	453.4	18.77	15.64–21.89*	14.70	11.68–17.73*
Potassium level (mmol/l)	≤ 3.0	1630	87.3	465.1	28.61	26.99–30.24*	24.09	22.51–25.66*
	3.1–3.4	4439	87.2	453.2	16.70	15.93–17.47*	13.83	13.09–14.58*
	Normal K level[a]	51,324	81.0	436.5	Ref.		Ref.	
	Missing K level[a]	73,427						
	> 5.0	2539	89.3	441.5	4.99	3.58–6.40*	− 3.19	− 4.58–1.79*
Magnesium level (mmol/l)	< 0.70	2058	96.8	456.4	18.89	17.45–20.33*	4.38	2.92–5.84*
	Normal Mg level[a]	4537	81.2	437.5	Ref.		Ref.	
	Missing Mg level[a]	126,409						
	> 1.00	355	93.8	458.0	20.48	16.90–24.06*	7.72	4.26–11.18*
Calcium level (mmol/l)	≤ 1.69	211	99.7	469.1	31.72	27.70–35.70*	20.36	16.47–24.26*
	1.70–2.14	2902	95.2	456.6	19.30	18.12–20.47*	8.10	6.90–9.29*
	Normal Ca level[a]	7792	81.1	437.3	Ref.		Ref.	
	Missing Ca level[a]	121,826						
	> 2.55	628	89.4	442.3	4.94	2.18–7.41*	− 1.33	− 3.70–1.04
eGFR (MDRD) (ml/min)	< 30	4918	87.6	451.7	16.10	15.16–17.04*	6.81	5.85–7.77*
	30–59	15,801	85.7	446.7	11.11	10.60–11.62*	5.18	4.66–5.71*
	≥ 60[a]	39,344	80.6	435.6	Ref.		Ref.	
	Missing data[a]	73,296						
Antidiabetic drugs	No antidiabetics	116,159	80.8	436.8	Ref.		Ref.	
	Antidiabetics	17,200	86.0	445.3	8.46	7.91–9.00*	3.77	3.23–4.30*
Loop diuretics	No loop diuretics	111,470	80.3	435.4	Ref.		Ref.	
	Loop diuretics	21,889	87.3	450.5	15.07	14.58–15.56*	10.10	9.60–10.60*
Acetylsalicylic acid (low dose)	No acetylsalicylic acid	124,874	81.6	437.8	Ref.		Ref.	
	Acetylsalicylic acid	8485	79.0	439.7	1.89	1.14–2.63*	− 0.83	− 1.55– − 0.11**

[a] If electrolyte values were missing, these values were categorized as being the reference value

*$p < 0.001$; **$p < 0.05$

other risk factors, the use of QT-prolonging drugs resulted in a QTc interval prolongation of 15.92 ms (95% CI 15.01–16.83; $p < 0.001$) (Fig. 5, supplemental Fig. 3). In patients with multiple risk factors other than the use of QT-prolonging drugs, the drug-induced QT prolongation was smaller than in patients with no other risk factors.

Discussion

We identified risk factors that were associated with QTc interval prolongation. Besides age, independent risk factors that significantly prolonged the QTc interval with at least 10 ms were hypokalemia, hypocalcemia, gender, the use of QT-prolonging drugs, and the use of loop diuretics. The risk factors hypomagnesemia, hypermagnesemia, renal failure, and the use of antidiabetic drugs significantly prolonged the QTc interval with less than 10 ms. In the multivariate analyses, we adjusted for the other variables included in our study. For example, the association between loop diuretics and QTc was independent of the potassium level.

In patients who used two or more QT-prolonging drugs, there was only a minor increase in QTc interval adjusted with the Bazett's formula compared to patients who used one QT-prolonging drug. However, the heart rate increased with the number of QTc prolonging drugs, and it is suggested that the

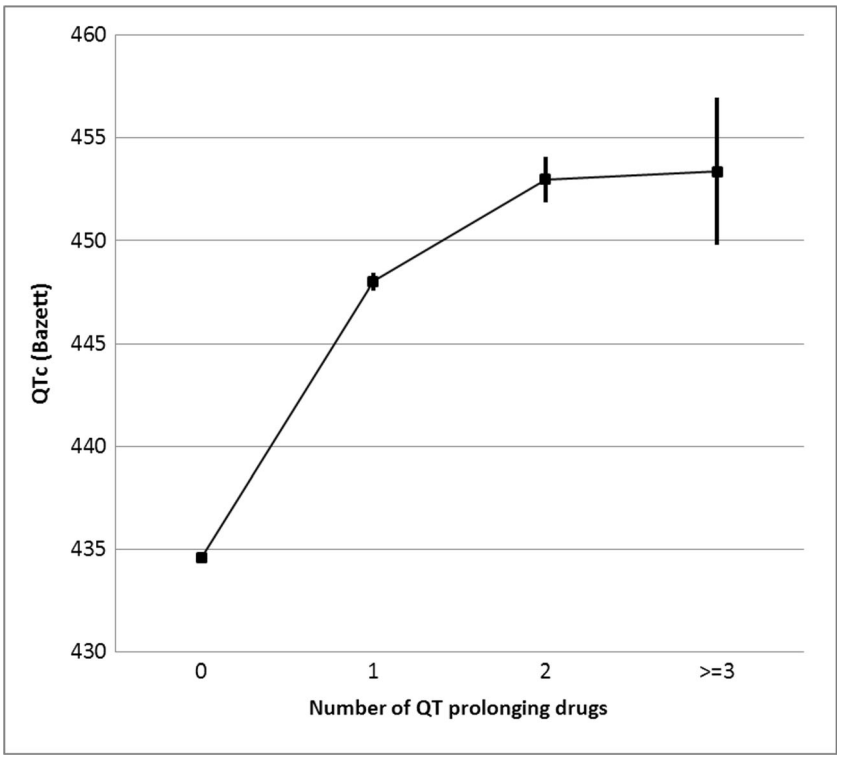

Fig. 1 The number of QT-prolonging drugs and the QTc interval corrected with the Bazett's formula (bars are 95% CI)

Bazett's formula overestimates the QTc interval in patients with a higher heart rate [17]. If we adjusted with the Fridericia's formula, there was indeed no further increase in QTc interval in patients who used two or more QT-prolonging drugs. The study by Tisdale et al. also found similar odds ratios for the risk of QTc interval prolongation in patients who used one QT-prolonging drugs or two or more (OR 2.8; 95% CI 2.0–4.0 and 2.6; 95% CI 1.9–5.6) [2]. Similarly, a study in patients hospitalized for ventricular arrhythmia did not demonstrate a significantly increased risk of two or more

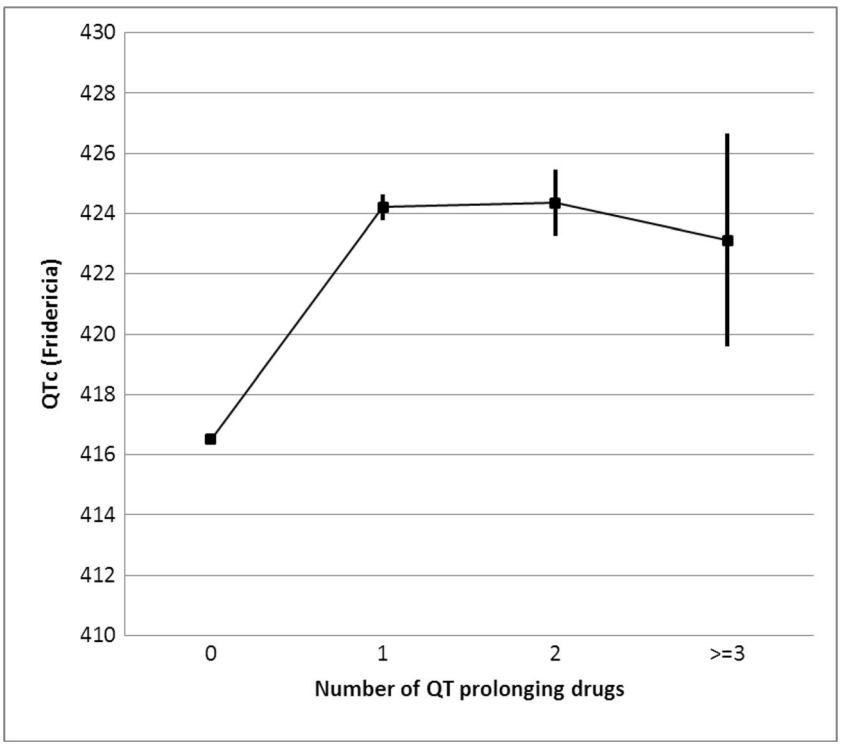

Fig. 2 The number of QT-prolonging drugs and the QTc interval corrected with the Fridericia's formula (bars are 95% CI)

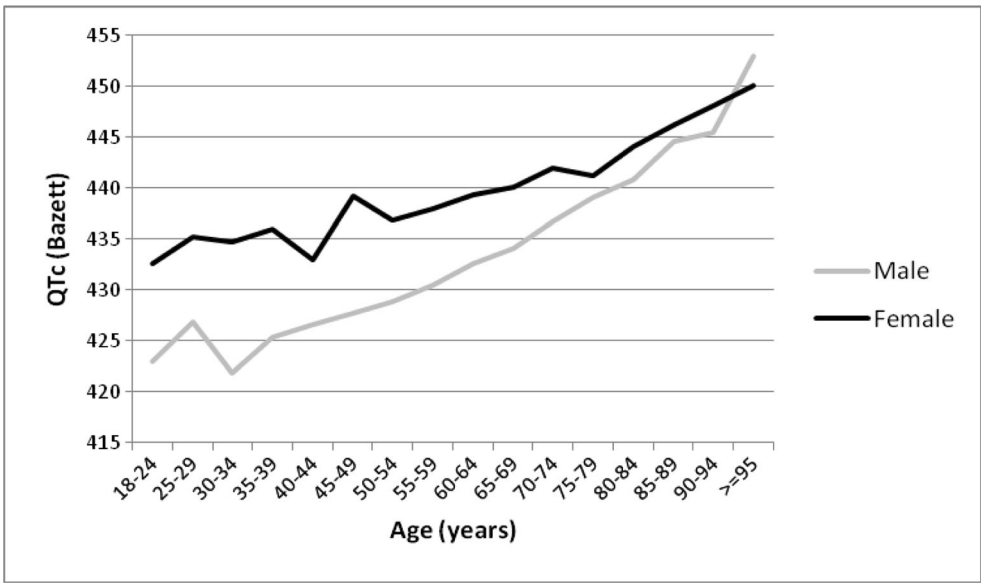

Fig. 3 The association between age and gender and the QTc interval corrected with the Bazett's formula

QT-prolonging drugs with a possible or known risk of TdP compared with one drug, although this study did find an additive effect for QT-prolonging drugs with a known risk of TdP not being a supra-additive or synergistic effect [19]. Drug interactions between QT-prolonging drugs have been recognized as an independent risk factor for QTc interval prolongation and torsade de pointes [18, 20]. Many healthcare information systems do warn if two or more QT-prolonging drugs are prescribed or dispensed. However, our results suggest that the QTc prolonging effect does not further increase if more than one QT-prolonging drugs are prescribed.

Another generally accepted risk factor for QTc prolongation is female gender. The cutoff point for QTc prolongation differs for men (450 ms) and women (470 ms) [15]. In our study, however, we identified that this difference diminishes with increasing age. These results remained significant in the multivariate analyses, in which we adjusted for the other variables included in our study. This is in line with the suggestion that sex hormones regulate the QTc interval by an effect on cardiac ion channels [21, 22]. Androgens most likely shorten the QTc interval, while the effect of estrogen and progesterone on the QTc interval is less clear. The diminishing difference in QTc interval with increasing age has been described before [23], and is most likely due to a decrease in levels of sex hormones over age. This may suggest that the difference in cutoff point between men and women is less relevant in elderly people.

Hypokalemia and hypocalcemia were the strongest independent risk factors for QTc prolongation. Hypokalemia was previously identified as a risk factor in other studies [2, 5, 6]. In our study, we differentiated between patients with a mild hypokalemia (3.0–3.5 mmol/l) and severe hypokalemia (<

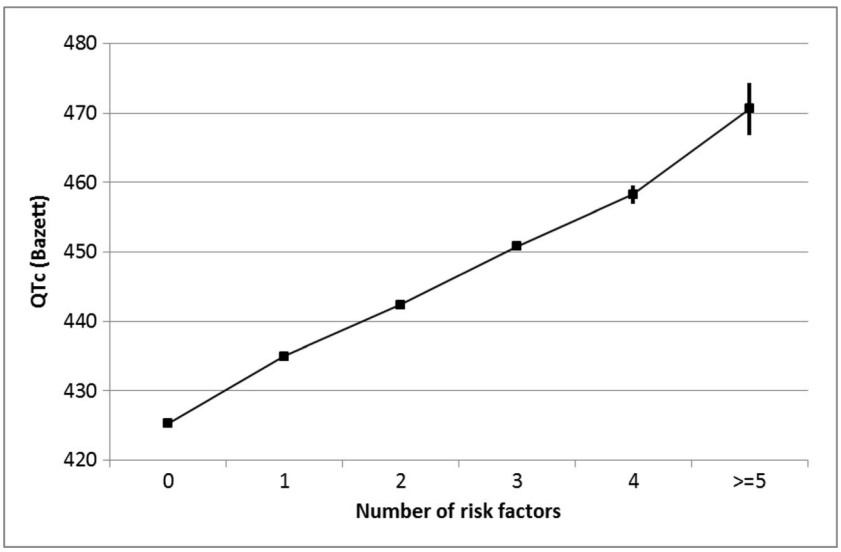

Fig. 4 The number of QT-prolonging risk factors and the QTc interval adjusted with the Bazett's formula (bars are 95% CI)

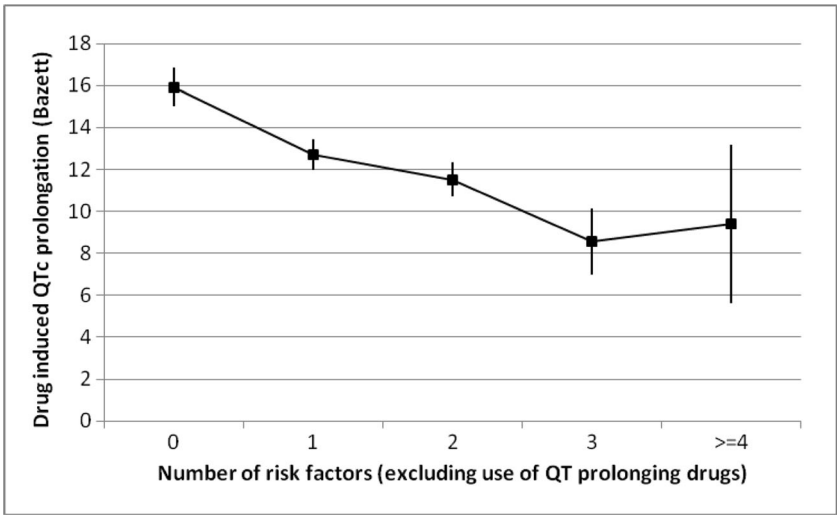

Fig. 5 Drug-induced QTc prolongation (adjusted with the Bazett's formula) per number of risk factors present. In this analysis, the use of QT-prolonging drugs was not counted as risk factor

3.0 mmol/l). A mild hypokalemia prolongs the QTc interval with 13.8 ms, and a severe hypokalemia further prolongs the QTc interval with another 10.3 ms. In patients with a hyperkalemia, the QTc interval was on average 3 ms shorter. However, we could not differentiate hyperkalemia levels that are erroneously elevated due to hemolysis. Therefore, this association was most likely an underestimation. Three studies analyzed whether hypocalcemia is an independent risk factor for QTc interval prolongation [2, 4, 5]. Two studies [4, 5] did find an association, while the third study [2] did not. In our study, we identified that especially calcium levels below 1.69 mmol/l were associated with a 20.4-ms prolonged QTc interval.

We identified the use of loop diuretics as an independent risk factor. Loop diuretics do not prolong the QTc interval themselves, but the morbidities treated with loop diuretics do. Patients who used loop diuretics have a QTc interval that is on average 10.1 ms longer. This is in line with the results of Tisdale et al., who also identified that the use of loop diuretics was an independent risk factor for QTc interval prolongation in a population of patients admitted to the cardiac care unit [2]. Furosemide is often used for congestive heart failure, and congestive heart failure is a risk factor for QTc interval prolongation [24].

We analyzed the effect of multiple risk factors on the QTc interval and found an additive effect. In patients with multiple risk factors, the addition of another risk factor had a similar QTc prolonging effect compared to patients with no risk factors. With the number of risk factors other than the use of QTc prolonging drugs, the drug-induced QTc prolonging effect diminished. This may suggest that patients with multiple risk factors are not more vulnerable for the effect of the addition of another risk factor and not more vulnerable for drug-induced QTc prolongation, although any increase in QTc interval may result in a higher risk of TdP.

Many drugs do prolong the QTc interval and imply a small increased risk of TdP. Decisions whether these drugs can be prescribed and dispensed safely to patients are part of daily clinical practice. In this study, we quantified the QTc interval prolonging effect, and this knowledge may contribute to improved risk management. This is particularly useful in the management of the risks involved with the prescription of QT-prolonging drugs.

Our study has some potential strengths and limitations. We analyzed a set of previously identified risk factors on the length of the QTc interval. By using multilevel multivariate analysis, we could identify whether these risk factors were independent and correct for repeated ECG measurements within the same patient. We included ECGs that were taken as part of routine clinical practice. The advantage is that a substantial number of patients used QT-prolonging drugs or had deviant laboratory values, improving the power to study these associations. However, the disadvantage is that for these patients, deviations in the ECG were expected and that patients without cardiac diseases were underrepresented in our study. In our study, we used the QTc interval as the outcome parameter, although the occurrence of TdP is the clinically relevant outcome. The incidence of TdP was too low to study as an outcome parameter in our study. For QTc prolonging drugs, the association between the degree of QTc prolongation and the risk of TdP may differ. Some drugs do prolong the QTc interval, without causing a substantially increased risk of TdP. We had to deal with missing electrolyte values, if they were not measured before the ECG measurement. We decided to analyze them as having a normal value, because analyzing them as missing would exclude them from the multivariate analysis and the analyses would only include a selected population of patients for whom all electrolyte values were measured. If there was no reason to measure the

electrolyte values, most likely these were within normal range. We analyzed all QTc prolonging drugs with a known risk of TdP as one group, assuming a similar effect on the QTc interval. However, the pharmacologic pathway for the QTc prolongation differs between drugs, such as interaction with the hERG-related potassium channel and mechanisms involving sodium and calcium currents [19]. It is suggested that combining drugs with different pharmacological pathways for QTc prolongation results in greater additive effect than combining drugs with similar pharmacological pathways. In our study, we could not take this differentiation into account, possibly underestimating the effect of combinations of QTc prolonging drugs that have different pharmacologic pathways for the QTc prolongation. In our study, we analyzed risk factors but could not analyze a cause-effect relationship. For example, QT-prolonging drugs may be used for conditions that do prolong the QTc interval independent of the drug use. In these cases, we could not differentiate between the effect of the QT-prolonging drug and the underlying condition. In our study, we could not differentiate whether cardiac diseases were present. Therefore, we used strict inclusion criteria for the QRS interval and excluded a small number of ECGs with deviant QTc values. ECGs with a prolonged QRS were also excluded, because prolongation of the QRS interval does result in prolongation of the QT interval. The QT interval was automatically analyzed by the MUSE system. It is matter of debate whether manual or automatic determination of the QT interval is superior [25, 26]. A previous study on the performance of the MUSE systems shows that misinterpretation of the ECG is particularly present in patients with a non-sinus rhythm [27].

To conclude, we identified that age, female gender, hypokalemia, hypocalcemia, the use of QT-prolonging drugs, and the use of loop diuretics were independent risk factors that prolong the QTc interval with at least 10 ms. In patients who used more than one QT-prolonging drug, the QTc interval was not substantially longer than in patients who used one QT-prolonging drug, and if we adjusted with the Fridericia's formula, these QTc intervals were similar. The QTc interval increases with increasing age, and the difference between men and women diminishes with increasing age.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study, formal consent is not required.

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