Comparison of two algorithms to support medication surveillance for drug-drug interactions between QTc-prolonging drugs

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Comparison of two algorithms to support medication surveillance for drug-drug interactions between QTc-prolonging drugs

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ABSTRACT

Background: QTc-prolongation is an independent risk factor for developing life-threatening arrhythmias. Risk management of drug-induced QTc-prolongation is complex and digital support tools could be of assistance. Bindraban et al. and Berger et al. developed two algorithms to identify patients at risk for QTc-prolongation.
Objective: The main aim of this study was to compare the performances of these algorithms for managing QTc-prolonging drug-drug interactions (QT-DDIs).
Materials and Methods: A retrospective data analysis was performed. A dataset was created from QT-DDI alerts generated for in- and outpatients at a general teaching hospital between November 2016 and March 2018. ECGs recorded within 7 days of the QT-DDI alert were collected. Main outcomes were the performance characteristics of both algorithms. QTc-intervals of $>$ 500 ms on the first ECG after the alert were taken as outcome parameter, to which the performances were compared. Secondary outcome was the distribution of risk scores in the study cohort.
Results: In total, 10,870 QT-DDI alerts of 4987 patients were included. ECGs were recorded in 26.2 % of the QT-DDI alerts. Application of the algorithms resulted in area under the ROC-curves of 0.81 (95 % CI 0.79–0.84) for Bindraban et al. and 0.73 (0.70–0.75) for Berger et al. Cut-off values of $\geq$ 3 and $\geq$ 6 led to sensitivities of 85.7 % and 89.1 %, and specificities of 60.8 % and 44.3 % respectively.
Conclusions: Both algorithms showed good discriminative abilities to identify patients at risk for QTc-prolongation when using $\geq$ 2 QTc-prolonging drugs. Implementation of digital algorithms in clinical decision support systems could support the risk management of QT-DDIs.

1. Introduction

Several commonly used drugs prolong the QT or heart-rate corrected QT (QTc) interval. A prolonged QTc-interval is an independent risk factor for Torsade de Pointes (TdP), a potentially life-threatening arrhythmia that may result in ventricular fibrillation or sudden cardiac death (SCD) [1,2]. QTc-prolongation is also associated with an increase in hospital stay and overall mortality, which might be indirectly related to additional risk factors [3–5]. When QTc-intervals exceed 500 ms or increase by 60 ms or more from baseline after the initiation of a QTc-prolonging drug, the risk of ventricular arrhythmias increases. Haugaa et al. found that a QTc-interval $>$ 500 ms was a predictor for overall mortality [4]. QTc-prolonging drugs should not be prescribed to patients who are likely to develop QTc-intervals above this threshold [6,7]. Other risk factors such as electrolyte disturbances, cardiovascular diseases, genetic predisposition, increasing age and female gender have a substantial role in developing QTc-prolongation as well [2,8,9]. Heemskerk et al. showed that increasing numbers of risk factors for QTc-prolongation have an increasing effect on the QTc-interval [9]. This finding is in line with the theory of Roden et al. regarding the repolarization reserve: the more factors reducing the repolarization reserve, the higher the risk of QTc-prolongation and TdP [10,11]. The Arizona

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Table 1
Algorithms of (a) Bindraban et al. and (b) Berger et al. for predicting patients at risk for QTc-prolongation.

Risk factors	Score	Risk factors	Score
Age (in years)		Age (in years)	
≤ 70	0	51 - 75	1
> 70	1	≥ 76	2
Loop diuretics	3	Loop diuretics	2
eGFR < 60 mL/min	2	eGFR ≤ 50 mL/min	1
Serum potassium		Serum potassium	
≤ 2.9 mmol L^{-1}	7	≤ 2.5 mmol L^{-1}	2
3.0–3.4 mmol L^{-1}	3	3.0–3.4 mmol L^{-1}	1
Serum calcium		Female gender	1
≤ 2.14 mmol L^{-1}	3	Comorbidities	
Antiarrhythmic drugs	1	Cardiac comorbidities	2
Maximal QTc (in ms)		Hypertension	2
481–500	3	Diabetes Mellitus I/II	1
> 500	7	QTc-prolonging drugs[†]	1 per drug

[†]QTc-prolonging drugs with a known risk of TdP [12].
a Bindraban et al.
b Berger et al.

Centre for Education and Research on Therapeutics (AZCERT) composed a list of QTc-prolonging drugs and categorized them into drugs that have 'a conditional risk of TdP', 'a possible risk of TdP' and 'a known risk of TdP' [12]. The use of QTc-prolonging drugs itself will rarely result in a QTc-interval above 500 ms. As QTc-prolonging drugs rarely cause a prolongation of > 30 ms and normal QTc-intervals are usually < 470 ms, other risk factors must be present to develop QTc-intervals > 500 ms. Therefore, in patients with little or no risk factors, the additional risk of QTc-prolonging drugs on the QTc-interval is most likely negligible and the use of these combined drugs is acceptable in clinical practice [2,13–15]. However, the Dutch database for healthcare information system generates medication surveillance alerts if two or more QTc-prolonging drugs with 'a known risk of TdP' according to the AZCERT drug list are prescribed or dispensed [Table A1]. These alerts are shown to physicians and pharmacists as medication surveillance alerts. These QTc-prolonging drug-drug interaction (QT-DDI) alerts are generated by the support system based on the prescribed drugs, without taking other risk factors for developing QTc-prolongation or TdP into account. So, these alerts are non-specific and are also shown in patients who do not have (many) additional risk factors for QTc-prolongation and for whom these alerts will be redundant. With the rising number of QTc-prolonging drugs, these QT-DDI alerts can lead to so called alert fatigue: ignoring alerts even when they are relevant [16].

A clinical decision support system (CDSS) that generates patient-specific alerts incorporating other relevant risk factors, will support healthcare providers in selecting patients in whom additional ECG monitoring or substitution of one of the interacting QTc-prolonging drugs is required, and thereby increasing the relevance and reducing the number of alerts. Over the years, various algorithms have been introduced to identify patients at risk for QTc-prolongation [4,8,17]. Tisdale et al. showed that implementation of such an algorithm significantly reduced prescriptions for non-cardiac QTc-prolonging drugs. The number of patients with a prolonged QTc-interval (> 500 ms) at the cardiac critical care units were also significantly reduced due to implementation of such a model [8]. However, these models incorporated diagnoses and characteristics, such as sepsis and smoking status, that were not automatically extractable from electronic patients records and needed a person's perspective. Therefore these algorithms are not applicable to computerized CDSS. Two previous studies conducted by Bindraban et al. [18] and Berger et al. [19] developed algorithms to predict patients at risk for QTc-prolongation using characteristics that are automatically extractable from hospital information systems; both algorithms are shown in Table 1.

There were substantial differences in the methodology to develop these algorithms. Bindraban et al. developed their algorithm retrospectively in a patient population from a general teaching hospital for whom an ECG was recorded during use of one or more QTc-prolonging drugs, whereas Berger et al. developed their algorithm prospectively based on ECGs of patients admitted to a university medical center using two or more QTc-prolonging drugs. In the algorithm of Berger et al., additional risk factors were added based on a literature review due to a relatively small sample size. However, similar risk factors are included in both algorithms, which makes it interesting to compare the performances of the algorithms in a large dataset. Therefore, the main aim of this study was to evaluate the performance characteristics of these two previously developed algorithms for identifying patients at risk for QTc-prolongation when two or more QT prolonging drugs are prescribed. Secondary aim was to explore the distribution of risk scores in the study cohort.

2. Materials and methods

2.1. Study design

This retrospective observational study was conducted at the Spaarne Hospital, a general teaching hospital with locations in Haarlem and Hoofddorp, the Netherlands. A retrospective data collection and content analysis was performed to compare two previously developed algorithms for identifying patients at risk for QTc-prolongation in patients using two or more QTc-prolonging drugs. No approval of the Medical Ethics Committee was needed according to the Dutch Medical Research Involving Human Subjects Act because of the retrospective study design. All patient data were processed anonymously according to privacy legislation.

2.2. Study cohort

We selected all QT-DDI alerts that were generated in routine clinical practice of ambulatory and hospitalized patients between November 1st, 2016 and March 5th, 2018. All QT-DDI alerts of patients < 18 years old and QT-DDI alerts in which one of the QTc-prolonging drugs was temporarily stopped were excluded.

2.3. Data collection

Data were processed using Statistical Package for Social Science (SPSS, IBM SPSS Statistics version 24.0, Armonk, NY, United States). Data were extracted from the hospital information system Epic (Madison, WI, USA) using SAP Crystal Reports (Walldorf, Germany). QT-DDI alerts were generated based on the information from the Dutch drug database which supports the different pharmaceutical processes in healthcare, including medication surveillance [20].

The following variables were collected for all QT-DDI alerts: inpatient/outpatient status, ECGs recorded within 7 days after the QT-DDI alerts and ECGs with the longest QTc-interval recorded within a maximum of one year prior to the QT-DDI alerts, all active drug orders on QTc-prolonging drugs [Table A1] and the following drugs categories according the Anatomical Therapeutic Chemical (ATC) classification system: cardiac therapy (ATC C01), antihypertensive drugs (ATC C02, C03, C07–C09), antidiabetics (ATC A10) and loop diuretics (ATC C03CA). The Anatomical Therapeutic Chemical (ATC) classification system divides drugs into different groups according their therapeutic, pharmacological and chemical properties and to the organ or system on which they act. Because the diagnoses were not documented in such a way that we could use them in the CDSS or in the analyses of this study, these drug orders were used as a proxy for the comorbidities included in the algorithms [21]. Many healthcare information systems do not document diagnoses in such a way that they are assessable for CDSSs. Therefore, drug use associated with the diagnosis was included in the risk model.

For the corresponding patients: age, gender, renal function

(estimated Glomerular Filtration Rate, eGFR, based on the Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI), recent potassium and calcium levels (within 7 days before or after the QT-DDI alerts) were collected at time of the QT-DDI alerts. If data were missing, these values were categorized as being within the reference values. Patients were included multiple times in our dataset if multiple QT-DDIs were generated. QT-DDI alerts were excluded if they were generated within two minutes of a previous QT-DDI alert for identical drugs in the same patient, as it is likely the physician made an adjustment without changes in managing the risk of the QT prolongation. As the risk factors of patients could change over time, we evaluated each QT-DDI alert separate from the others.

All ECGs included in the database were standard 12-lead resting ECGs with automated analysis by the MUSE Cardiology Information System. The heart rate (RR), QT-interval and QRS-complex were automatically analyzed by the MUSE system and reported in the hospital information system Epic. For ECGs with QRS-complexes above $>$ 120 ms, the QT-intervals were corrected using the following equation: QT adjusted = QT–(QRS–120). The heart rate corrected QT intervals were then calculated using the Bazett formula ($QTc = QT/\sqrt{RR}$) [22]. When the QTc-interval was used as primary endpoint, the following ECGs were excluded: ECGs with a QTc-interval of $>$ 700 ms or $<$ 300 ms or a heart rate (HR) of $>$ 180 beats per minute (bpm) or $<$ 40 bpm. Deviant heart rates were excluded to minimize outliers influencing the analyses and deviant QTc-intervals were excluded, because they were most likely caused by misinterpretation of the QT-interval on the ECG.

2.4. Outcome and study variables

The main outcome measures of this study were the performance characteristics of the algorithms. Each patient was scored using both algorithms at the moment the QT-DDI alert was generated. A QTc-interval ($>$ 500 ms) as measured by the first ECG within 7 days after the alert using the Bazett formula was taken as gold standard, to which the performances of the algorithms were compared. If no ECG was recorded, the QTc-interval was considered not to be prolonged. We did not choose mortality or ventricular arrhythmia as outcome parameter due to lack of reliable data, therefore, we chose QTc-prolongation as a proxy for the risk on arrhythmia or sudden cardiac death. Secondary outcome measure was the distribution of the risk scores in the study cohort.

2.5. Statistical analysis

Data were analyzed using SPSS version 24.0. The clinical usefulness of both algorithms was assessed by their ability to distinguish patients with and without QTc-prolongation in our study cohort. The discriminative ability was quantified with receiver operating characteristics (ROC)-analyses, also known as concordance statistic (C-statistic). Cut-off points for the models were selected by maximizing the difference between sensitivity and 1 minus specificity. The following performance characteristics were obtained: specificity, sensitivity, positive and negative predictive value, Youden's index and accuracy. We used descriptive statistics to assess the distribution of the risk scores in the study cohort.

3. Results

3.1. Study cohort

Of the 16,285 QT-DDI alerts, we excluded 199 QT-DDI alerts of patients younger than 18 years old; 1604 QT-DDI alerts, because one of the QTc-prolonging drugs was temporarily stopped; 2657 QT-DDI alerts because the hospital information system erroneously identified two separate orders for the same drug as a QT-DDI; and 955 QT-DDI alerts, because the alerts were generated $\leq$ 2 min after identical QT-DDI alerts

Table 2
Characteristics of the QT-DDI alerts.

QT-IA characteristics	N = 10,870
Age (years), median (IQR)	70.0 (56–80)
≤ 50, n (%)	1,980 (18.2)
51–75, n (%)	4,739 (43.6)
≥ 76, n (%)	4,151 (38.2)
Female, n (%)	5,649 (52.0)
Outpatients, n (%)	880 (8.1)
Inpatients, n (%)	9990 (91.9)
Clinical departments	6117 (61.2)
Peri-operative departments	2770 (27.7)
Intensive Care Units	1103 (11.0)
Top 5 QT-DDIs, n (%)	
droperidol–ondansetron	1663 (15.3)
ciprofloxacin–ondansetron	1361 (12.5)
haloperidol–ondansetron	1142 (10.5)
propofol–ondansetron	1001 (9.2)
haloperidol–ciprofloxacin	892 (8.2)
No. of QT-DDI alerts/patient, mean ± SD	2.2 ± 1.9
No. QT-DDI alerts with ECG within 7 days after QT-DDI alert, n (%)	2846 (26.2)
No. QT-DDI alerts with ECG within 365 days prior to QT-DDI alert, n (%)	6586 (60.6)
eGFR (ml min^{-1}; CKD-EPI), mean ± SD	69.6 ± 28.8
Renal dysfunction (≤ 60 mL $min\ L^{-1}$), n (%)	2036 (18.7)
Potassium serum level (mmol L^{-1}) mean ± SD	4.10 ± 0.56
Hypokalemia (< 3.50 mmol L^{-1}), n (%)	548 (5.0)
Calcium serum level (mmol L^{-1}), mean ± SD	2.23 ± 0.21
Hypocalcemia (< 2.14 mmol L^{-1}), n (%)	660 (6.1)

Abbreviations: CKD-EPI, chronic kidney disease epidemiology collaboration; ECG, electrocardiogram; eGFR, estimated glomular filtration rate, IQR, interquartile range; No., number; QT-DDIs, QT drug-drug interactions; SD, standard deviation.
Missing values: CKD-EPI, n = 5215; potassium, n = 5327; calcium; n = 8,631.

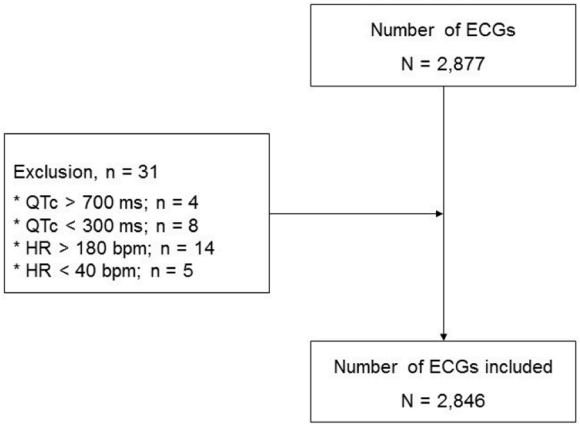

Fig. 1. Flowchart of inclusions of ECGs. *Abbreviations: ECG, electrocardiogram; bpm, beats per minute; HR, heart rate.*

Table 3
Characteristics of individual ECGs within 7 days of QT-DDI alerts.

Characteristics	n = 1796	SD	unit
Number of patients	1301		
Female	48.7		%
Age (mean ± SD)	73.9	13.5	years
Average number of ECGs/patient	1.4	0.9	
HR (mean ± SD)	89.6	24.0	bpm
QRS (mean ± SD)	100.2	27.7	ms
QT (mean ± SD)	380.3	55.9	ms
QTc Bazett (mean ± SD)	453.5	39.5	ms

Abbreviations: ECG, electrocardiogram; QT-DDI, QT drug-drug interaction; SD, standard deviation; HR, heart rate.

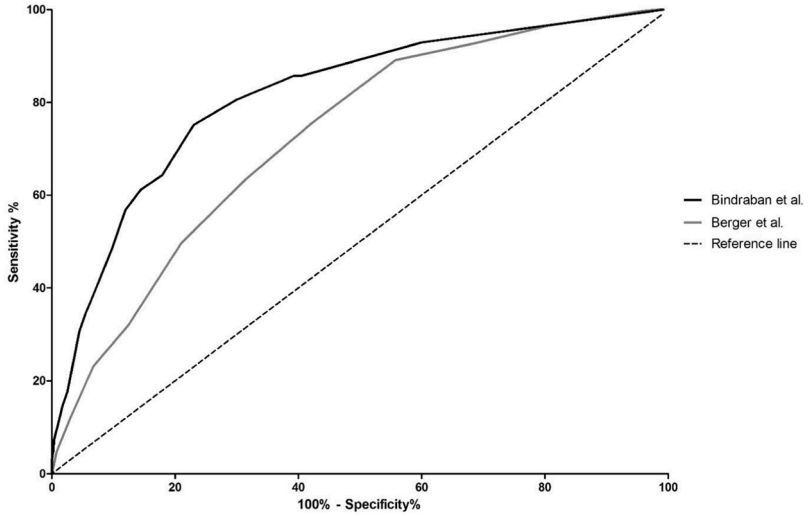

Fig. 2. ROC curves of the algorithms. Youden's index Bindraban et al. 0.521 and Berger et al. 0.334.

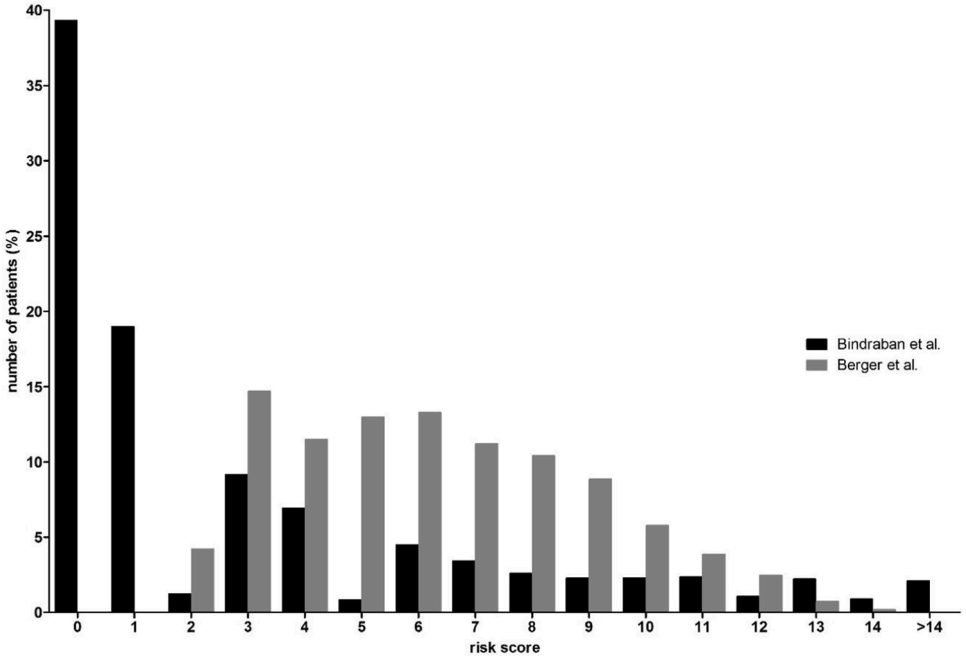

Fig. 3. Distribution of the risk scores using two different algorithms.

in the same patient. In total, 10,870 QT-DDI alerts were included that met the inclusion criteria, and these were generated in 4987 individual patients. The median patient age was 70 years (interquartile range, IQR: 24 years), and 52.0 % were female (Table 2, Table B1). For 2846 QT-DDI alerts (26.2 %), an ECG was recorded within 7 days of the alert.

Since multiple alerts can be generated in the 7 days before an ECG, a total of 1796 unique ECGs were recorded within 7 days after a QT-DDI alert (Fig. 1 and Table 3). The average QTc-interval was 453.5 ms. After 294 QT-DDI alerts (10.3 %) with an ECG within 7 days after the alert, the QTc interval was above 500 ms.

3.2. Main outcomes

The performance characteristics per cut-off value and ROC curves of both algorithms are shown in Fig. 2 or Table C1.

The areas under the ROC (AUROC) curve were 0.81 (95 % CI 0.79–0.84) and 0.73 (95 % CI 0.70–0.75) for respectively Bindraban et al. and Berger et al. The Youden's index was maximized at a cut-off value of $\geq$ 5 (0.521; Bindraban et al.) and $\geq$ 6 (0.334; Berger et al.) with sensitivities of 75.2 % and 89.1 %, and specificities of 77.0 % and 44.3 % respectively. As we were aiming for sensitivities $>$ 80 %, while maximizing specificities, the cut-off value for Bindraban et al. and Berger et al. were preferred at $\geq$ 3 and $\geq$ 6. These cut-off values led to sensitivities of 85.7 % and 89.1 % and specificities of 60.8 % and 44.3 % respectively. If a cut-off value of 3 was used in a clinical decision support system to generate alerts using the algorithm of Bindraban et al., 60.1 % of the alerts would not have shown, of which 0.6 % had a QTc-interval exceeding 500 ms. If a cut-off value of 6 was used to generate alerts using

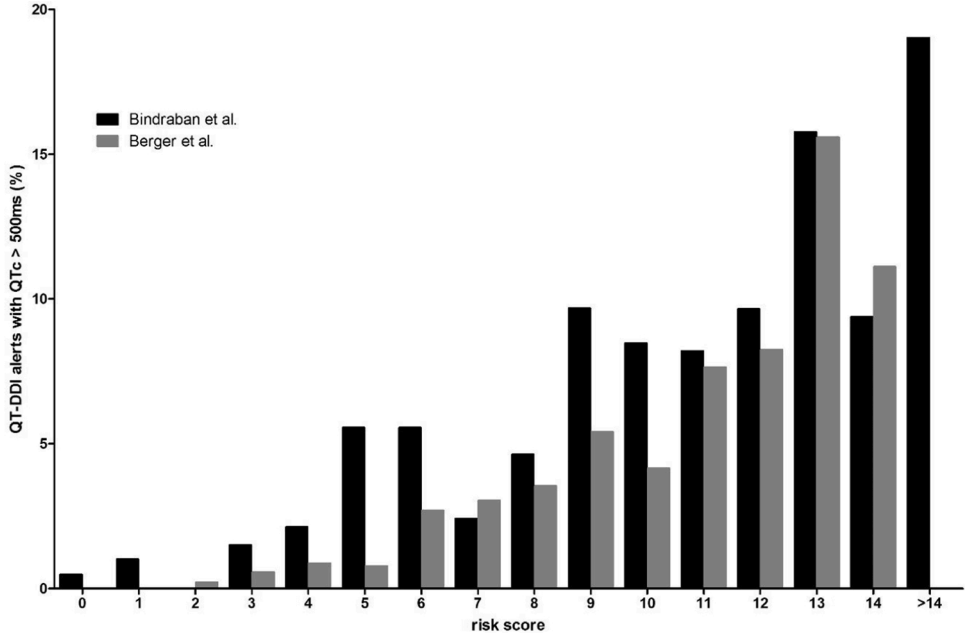

Fig. 4. Risk score versus proportion of QT-DDI alerts with QTc > 500 ms.

the algorithm of Berger et al., 43.4 % of the alerts would not have shown, of which 0.7 % had a QTc-interval exceeding 500 ms.

The distribution of the risk scores is shown in Fig. 3. The median (IQR) risk score of Bindraban et al. was 1.0 (0.0–4.0); 1.0 (0.0–4.0) in patients with no QTc-prolongation versus 9.0 (4.8–13.0) in patients with QTc-prolongation; and the median (IQR) risk score of Berger et al. was 6.0 (4.0–8.0); 6.0 (4.0–8.0) in patients with no QTc-prolongation versus 8.0 (7.0–10.0) in patients with QTc-prolongation.

In Fig. 4, QTc-intervals > 500 ms are plotted against the risk scores of the algorithms.

4. Discussion

The aim of this study was to compare two previously developed algorithms to support the medication surveillance of DDIs between QTc-prolonging drugs. Both algorithms applied weighted risk factors to determine if patients were at risk for QTc-prolongation (> 500 ms) when two or more QTc-prolonging drugs were prescribed. In our dataset, after 2.7 % of the alerts ECGs were recorded with QTc-intervals exceeding 500 ms. The algorithms showed good discriminative abilities as the AUROC curve were 0.81 (95 % CI 0.79–0.84) and 0.73 (95 % CI 0.70–0.75) for respectively Bindraban et al. and Berger et al. An AUROC over 0.7 indicates a good model [23]. The use of an algorithm will improve risk stratification in patients using QTc-prolonging drugs, resulting in less redundant ECG recordings and in a decrease of withholding first-line therapies by switching to non QT prolonging alternatives. These algorithms will also reduce the time-consuming manual evaluation in patient health records to ascertain if patients are at risk.

The Youden's index was maximized if respective cut-off values of ≥ 5 and ≥ 6 were used. These cut-off values led to sensitivities of 75.2 % and 89.1 %, and specificities of 77.0 % and 44.3 % as shown in Table 3. However, for the prevention of ventricular arrhythmia, a sensitivity below 80 % is not favored because sensitivity measures the proportion of actual positives that are correctly identified as such. Thus, a low sensitive test will overlook actual positives, resulting in false negatives. Limiting the likelihood of missing patients with QTc-prolongation is more important than incorrect classification of patients without QTc-prolongation [23,24]. Therefore, we decided to use acceptability criteria of sensitivities above 80 %, while keeping specificities at an acceptable level (> 40 %). Cut-off values of Bindraban et al. (≥ 3) and Berger et al. (≥ 6) could predict QTc-prolongation in patients using two or more QTc-prolonging drugs with sensitivities of 85.7 % and 89.1 % and specificities of 60.8 % and 44.3 % respectively. The positive predictive values of both algorithms were low (Table B1). Therefore, the tool needs further improvement, because the discriminative ability is insufficient.

The model of Bindraban et al. performed better than the model of Berger et al. One explanation is that Berger et al. developed their algorithm in a tertiary care population of a university medical center which is thus externally evaluated in this study, whereas Bindraban et al. developed their algorithm in the same population of the Spaarne Hospital, but used a different time span. External validations are important to determine the algorithms' performance and generalizability in different healthcare settings [24]. Another factor that may explain the differences in performance between the two algorithms is that Berger et al. did not take a previously observed prolonged QTc-interval into account. Results from previous ECGs are a reasonably effective marker to detect QTc-prolongation. When a patient has a prolonged QTc-interval within one year prior to the QT-DDI, the patient will have a higher chance of a prolonged QTc-interval after initiation of these drugs. The variety in the weighting of the risk factors between the algorithms and the number of variables included might also play a role.

Bindraban et al. [18] found a lower AUROC curve of 0.71 (95 % CI 0.68–0.73) during the original validation of the algorithm than the AUROC curve of 0.81 (95 % CI 0.79–0.84) found in this study. The validation of Bindraban et al. [18] differed in numerous aspects from this validation. First, their data extraction was based on ECGs recorded in patients using one or more QTc-prolonging drugs, while this study was based on QT-DDI alerts. Therefore, patients with a high risk of QTc prolongation will be overrepresented in their cohort, because ECGs are

mostly recorded in patients at risk for heart rhythm disturbances. Second, Bindraban et al. [18] developed their algorithm in patients using one or more QTc-prolonging drugs, whereas this study only included patients using two or more QTc-prolonging drugs. Nevertheless, similar sensitivities (> 80 %) were found in both validation studies when a cut-off value of ≥ 3 was used.

The variation in the AUROC curves of Berger et al. [19] 0.59 (95 % CI 0.54–0.63) versus 0.73 (95 % CI 0.70–0.75) is probably due to the fact that in the dataset of this study, patients with no ECG available were considered to have no QTc-prolongation, whereas Berger et al. [19] validated their algorithm in an external dataset in which only patients with ECGs available were included. Subsequently, high-risk patients were probably overrepresented in the original validation study of Berger et al [19]. A major strength of this study was the evaluation of two different algorithms in a large study cohort. We included both ambulatory and hospitalized patients, which makes the results more generalizable to various healthcare settings. As we included QT-DDI alerts of patients from all departments, selection bias was minimized.

Over the past years, several studies have introduced predicting models for QTc-prolongation and/or TdP. These models have similar discriminative abilities as the models compared in this study. Vandael et al. recently developed an optimized RISQ-PATH score to detect high-risk patients for developing QTc-prolongation with a sensitivity of 94.5 %, and a specificity of 22.1 % [25]. In 2013, Tisdale et al. developed a risk model in patients only admitted to cardiac care units, where they found a sensitivity of 74.0 % and a specificity of 77.0 % [8]. It remains a major challenge to develop clinical decision support applications that gains clarity on the risk of developing rare serious adverse events, such as QTc-prolongation or TdP.

Also, we need to address several limitations of this study. First of all, we did not manually measure the QT-interval, but relied on the automatically calculated QT-interval by the MUSE Cardiology Information System. There is still an ongoing debate whether or not QT-intervals should be measured manually. Manually measured QT-intervals are preferred to avoid misinterpretations by ECG devices [26] but Viskin et al. showed that the majority of physicians misinterpreted QT-intervals and less than 40 % of the physicians calculated the QTc-interval correctly [27]. Postema et al. showed that less than 25 % of the cardiologists and non-cardiologists interpreted the QTc-intervals correctly when these were manually measured [28]. At this moment, automatically calculated QT-intervals are widely used by physicians in clinical practice. We corrected the QT-interval for wide QRS-complexes to limit ECG exclusions. Secondly, QTc-prolongation may not be the perfect marker for predicting TdP, other effects that have impact on e.g. cardiac sodium channels can be extremely relevant as well [29]. However, other specific markers that are more predictive for ventricular arrhythmias than QTc-prolongation have not been discovered yet. Lastly, our analysis is limited by the assumption that patients for whom no ECG was recorded did not have QTc-prolongation. By excluding patients without ECGs available, selection bias is introduced and high-risk patients would be overrepresented. For example, the median age of patients in whom ECGs were recorded was higher than the median age of all patients (74 (14) years vs 70 (24) years). On the other hand, one could assume that patients to whom two or more QTc-prolonging drugs were prescribed, were probably not patients at risk for QTc-prolongation. However, several studies showed that QT-DDI alerts are frequently overridden and the current guidelines on ECG monitoring are frequently not adhered to [16,30]. We also observed several missing electrolyte values at time of the QT-DDI alerts (79 % of calcium values, 49 % of potassium values and 48 % of renal function values). These missing values were considered to be within the normal range, because we made the assumption that physicians would have measured electrolyte values if they were expected not to be within the normal range. Usually, in clinical practice, patients with missing values are common and these patients also need to be examined for the risk on developing arrhythmias. These algorithms are able to make an adequate estimation for these patients with missing values. Future studies using these type of risk models need to be conducted prosepectively to circumvent the disadvantages of retrospective study designs and to truly test clinical usefulness.

To conclude, both algorithms showed good discriminative abilities to predict QTc-prolongation in patients using two or more QTc-prolonging drugs. The algorithms could be implemented in electronic CDSSs to support the risk management of QT-DDIs, which will eventually reduce redundant ECG recordings, withholding of first-line therapies and the time-consuming manual evaluation in patient health records.

Authors' Contributions

MB and FB designed the research study. FB and MB contributed to the conduct of the study, where MB extracted data from the Spaarne Hospital. Data analysis was performed by FB. The results were analysed, interpreted and discussed by FB, HvdS, AK, PvdB, TvG and MB. FB drafted the manuscript and all co-authors revised and approved the final version of the manuscript.

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Authorship contributions

Please indicate the specific contributions made by each author. The name of each author must appear at least once in each of the three categories below.

Conception and design of study: M.L. Becker, F.A. Berger.

Summary Table

What was already known on the topic

- QTc-prolongation is an independent risk factor for developing life-threatening arrhythmias.
- Risk management of drug-induced QTc-prolongation when two or more QTc-prolonging drugs are used, is complex.

What this study added to our knowledge

- Two algorithms were developed that have shown good discriminative abilities to predict QTc-prolongation in patients using two or more QTc-prolonging drugs.
- These algorithms will eventually reduce redundant ECG recordings, withholding of first-line therapies and the time-consuming manual evaluation in patient health records.

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Declaration of Competing Interest

None.

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Appendix

Tables A1–C1.

Table A1
QT-DDI alerts are generated based the information in the 'G-standaard' including the following QTc-prolonging drugs.

ATC-code	Drugs
C01BD01	amiodarone
A02BD04	amoxicillin/clarithromycin/pantoprazole
L01XX35	anagrelide
L01XX27	arsenic trioxide
J01FA10	azithromycin
N05AA01	chlorpromazine
P01BA01	chloroquine
J01MA02	ciprofloxacin
N06AB04	citalopram
J01FA09	clarithromycin
C01BA03	disopyramide
A03FA03	domperidone
N06DA02	donepezil
N05AD08	droperidol
J01FA01	erythromycin
N06AB10	escitalopram
C01BC04	flecainide
J02AC01	fluconazole
N05AD01	haloperidol
C01BD05	ibutilide
C02KD01	ketanserin
C01BA01	quinidine
J01MA12	levofloxacin
N05AA02	levomepromazine
N07BC02	methadone
J01MA14	moxifloxacin
A04AA01	ondansetron
L01XA03	oxaliplatin
A03AD01	papaverine
G04BE30	papaverine/phentolamine
P01CX01	pentamidine
N05AG02	pimozide
C01BA02	procainamide
N01AX10	propofol
J01FA06	roxithromycin
N01AB08	sevoflurane
C07AA07	sotalol
N05AL01	sulpiride
H01BA04	terlipressin
L01XE12	vandetanib

Table B1
Characteristics of QT-DDI alerts stratified by recorded ECGs.

QT-IA characteristics	ECGs recorded N = 2877	No ECGs recorded N = 7933
Age (years), median (IQR)	77 (68–85)	67 (52–78)
≤ 50, n (%)	153 (5,3)	1828 (22.9)
51–75, n (%)	1102 (383)	3637 (455)
≥ 76, n (%)	1623 (564)	2528 (316)
Female, n (%)	1292 (44.9)	4357 (54.5)
Outpatients, n (%)	133 (4.6)	747 (9.3)
Inpatients, n (%)	2744 (94.7)	7214 (90.3)
Clinical departments	1865 (68.0)	4252 (58.7)
Peri-operative departments	327 (11.9)	2443 (337)
Intensive Care Units	552 (20.1)	551 (7,6)
Top 5 QT-DDIs, n (%)		
droperidol–ondansetron	117 (4.1)	1546 (19.3)
ciprofloxacin–ondansetron	138 (4.8)	1223 (15.3)
haloperidol–ondansetron	348 (12.1)	794 (9.9)
propofol–ondansetron	112 (3.9)	889 (11.1)
haloperidol–ciprofloxacin	484 (16.8)	408 (5.1)
No. QT-DDI alerts with ECG within 365 days prior to QT-DDI alert, n (%)	2464 (85.6)	4122 (51.6)
eGFR (ml min^{-1}; CKD-EPI), mean ± SD	63.9 ± 28.5	73.4 ± 28.4
Renal dysfunction (≤ 60 mL $min\ L^{-1}$), n (%)	997 (34.7)	1039 (13.0)
Potassium serum level (mmol L^{-1}) mean ± SD	4.12 ± 0.60	4.10 ± 0.53
Hypokalemia (< 3.5 mmol L^{-1}), n (%)	259 (9.0)	289 (3.6)
Calcium serum level (mmol L^{-1}), mean ± SD	2.19 ± 0.23	2.24 ± 0.20
Hypocalcemia (< 2.14 mmol L^{-1}), n (%)	316 (11.0)	344 (4.3)

Abbreviations: CKD-EPI, chronic kidney disease epidemiology collaboration; ECG, electrocardiogram; eGFR, estimated glomular filtration rate, IQR, inter-quartile range; No., number; QT-DDIs, QT drug-drug interactions; SD, standard deviation.

Missing values: CKD-EPI, n = 591 (ECG)/4624 (no ECG); potassium, n = 613 (ECG)/4714 (no ECG); calcium; n = 2945 (ECG)/6686 (no ECG).

Table C1
Performance characteristics of Bindraban et al. and Berger et al.

Cut-off value	Sensitivity	Specificity	Youden's index	NPV	PPV	Accuracy
Bindraban et al.						
≥ 1	92.9	40.2	0.331	99.5	4.1	0.42
≥ 2	85.7	59.5	0.452	99.3	5.6	0.60
≥ 3	85.7	60.8	0.465	99.4	5.7	0.61
≥ 4	80.6	70.0	0.506	99.2	7.0	0.70
≥ 5	75.2	77.0	0.521	99.1	8.3	0.77
≥ 6	73.5	77.8	0.512	99.1	8.4	0.78
Berger et al.						
≥ 4	96.6	19.3	0.159	99.5	3.2	0.21
≥ 5	92.9	31.0	0.239	99.4	3.6	0.33
≥ 6	89.1	44.3	0.334	99.3	4.3	0.45
≥ 7	75.9	57.5	0.334	98.8	4.7	0.58
≥ 8	63.3	68.7	0.319	98.5	5.3	0.69
≥ 9	49.7	79.0	0.287	98.3	6.2	0.78

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

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