DRUG INDUCED QTC-PROLONGATION:
Towards a better understanding of potential risks

Florine Anne Berger

COLOFON

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GENEESMIDDEL GEINDUCEERDE QTC-VERLENGING:
Naar een beter begrip van de potentiële risico's

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Towards a better understanding of potential risks

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'The best view comes after the hardest climb'

Voor mijn broer en zussen

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GENERAL INTRODUCTION

1

GENERAL INTRODUCTION

Health care professionals using electronic prescription programs are often confronted with drug safety alerts when combinations of two or more QTc-prolonging drugs are prescribed. An example of a warning presented to the prescriber is: *"Both drugs can prolong the QTc-interval, with serious arrhythmias (Torsades de Pointes, among others) as possible result"*.[1] Typically such warnings are ignored by both the prescribing physician and the dispensing pharmacist, and thus the prescriptions are continued.[2-4] In general, important reasons for overriding drug-drug interaction alerts are the difficulty of quantifying the risks, a limited understanding of the clinical importance of drug-drug interactions and alert fatigue due to high exposure to (redundant) alerts and reminders in the electronic prescribing system.[3] In assessing the relevance of QTc- prolonging drug-drug interactions, especially the first reason may apply. The risk of QTc-prolongation is documented for single drug use. For example, The Arizona Center for Education and Research on Therapeutics (AzCERT) maintains the CredibleMeds® database that contains a list of drugs categorized by their potential to cause QTc-prolongation and/or Torsades de Pointes (TdP).[5, 6] Nevertheless, this QT drug list does not provide sufficient guidance for the majority of the health care professionals. Combining drugs that prolong the QTc-interval may further increase the risk of adverse events. But very few studies have addressed the risk of combining two or more QTc-prolonging drugs.[7-9] In this introduction, the difficulties of understanding the risk of developing life-threatening arrhythmias because of the use of QTc-prolonging drugs are reviewed.

Pro-arrhythmic side-effects of drugs, such as QTc-prolongation or Torsade des Pointes (TdP), have been a major safety concern in patient health care for many years. In 1997 terfenadine was removed from the market because of its association with life-threatening ventricular arrhythmias. Since then the attention to the potential pro-arrhythmic effects of drugs was drawn.[10] Subsequently, other drugs were withdrawn (e.g. cisapride) or restricted in use (e.g. domperidone, (es)citalopram) due to the risk of cardiotoxicity.[11, 12] These withdrawals and restrictions were accompanied with considerable attention of the media, creating an ongoing debate between health care professionals.[12-14] More and more drugs were added to the list of QTc-prolonging drugs. However, the risk of pro-arrhythmic effects of often widely used drugs in a general patient population is extremely difficult to determine. QTc-prolongation is a surrogate marker for the development of ventricular arrhythmia such as TdP, which can ultimately lead to sudden cardiac death (SCD).[15] A correlation has been found between TdP and an increase of the QTc-interval of only 10 milliseconds (ms).[16, 17] Although several drugs are well known for prolonging the QTc-interval with 10 ms, the occurrence of TdP while using these drugs is extremely rare, because even in a situation of an elevated relative risk the absolute risk of developing serious drug induced cardiac arrhythmias is low.[18, 19]

Understanding the underlying mechanisms of QTc-prolongation and TdP is needed to assess the risk of developing arrhythmias while combining multiple QTc-prolonging drugs. Also, knowledge on the prevalence of QTc-prolongation when combining these drugs and knowledge on other contributing factors in developing QTc-prolongation is needed for further understanding of this safety concern.

The ECG and the QTc-interval

The electric activity of the heart can be recorded with an electrocardiogram (ECG). The ECG shows the different phases of cardiac action potentials representing the transmembrane voltage pattern that occurs within each heartbeat. These phases are induced by an interactive flow of ion currents across the membranes of the myocytes.[20]

Phase 0 represents the inward current of sodium ions conducting a rapid depolarization, followed by phase 1, a rapid inactivation of the sodium current and a transient efflux of potassium. Phase 2, the plateau phase, represents a balance between the calcium influx and potassium efflux. During Phase 3, the calcium influx is stopped, while the slow delayed rectifier potassium channels remain open, which results in opening of the rapid delayed rectifier potassium channels, inducing repolarization. The potassium efflux is stopped when the membrane potential is restored and the resting potential is maintained by an inward rectifier potassium current (phase 4).[20, 21]

These phases conduct an action potential that is shown on a surface ECG, where the P-wave represents atrial depolarization. During the PR interval, the electrical activity moves from the atria to the ventricles inducing ventricular depolarization, presented as the QRS complex on the ECG. The QRS complex is followed by the T-wave representing ventricular repolarization. The QTc-interval starts at the beginning of the QRS complex until the end of the T-wave, representing ventricular de- and repolarization. [22, 23]

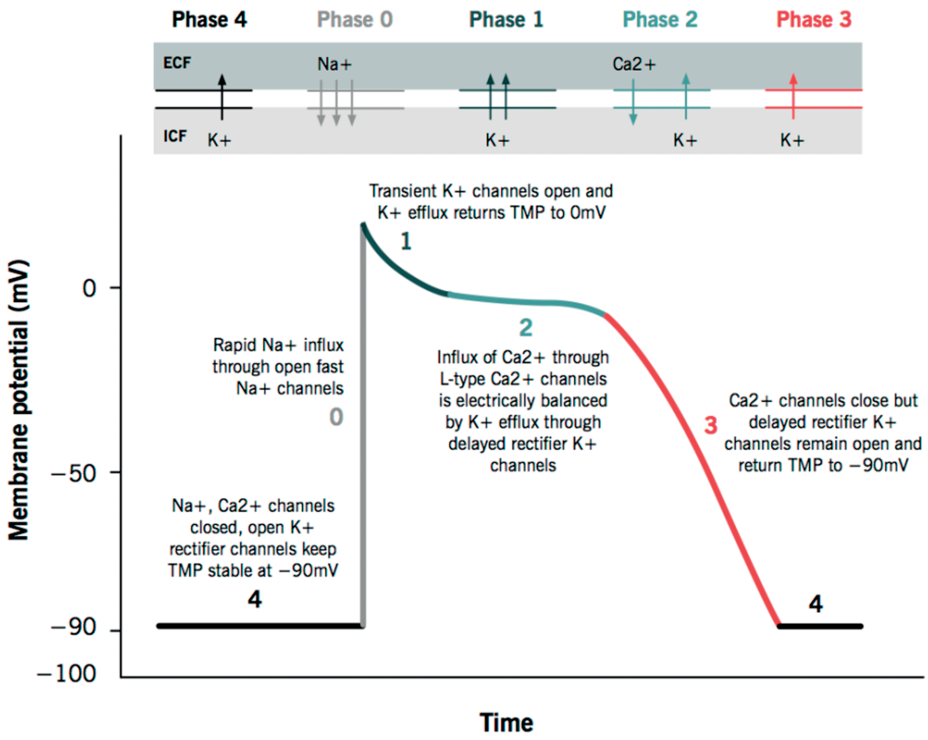

Figure 1. Action potential of cardiac myocytes. [*Source: Ikonnikov G and Wong E*]

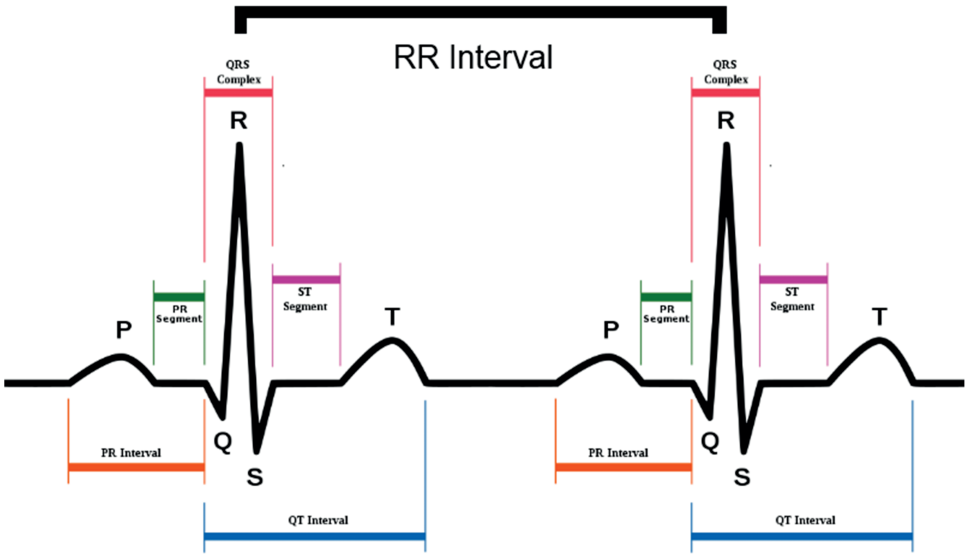

Figure 2. ECG sinus rhythm [*Source: Tawakal I, Suryana E, Noviyanto A, et al. Analysis of multi codebook GLVQ versus standard GLVQ in discriminating sleep stages 2012]*

In case of a prolonged QTc-interval, the ventricular repolarization is delayed. In healthy individuals the QTc-interval ranges from 360 to 450 milliseconds (ms).[25, 26] A QTc-interval above 450 ms in males and above 470 ms in females is considered to be prolonged according to the European Medicine Agency (EMA) guidelines.[27, 28] However, several other authorities consider QTc-intervals to be prolonged when they exceed 450 ms according to the Food and Drug Administration (FDA) or ≥ 470 ms in males and ≥ 480 ms in females according to the American Heart Association (AHA).[29] All authorities state that a QTc-interval > 500 ms is abnormally prolonged and poses a clear risk of developing TdP. They also agree on the fact that an increase of > 60 ms from baseline (delta QTc) poses a serious risk for developing TdP.[29,30] In general, the term QTc (QT-corrected) interval is used. The QT-interval measured on the ECG should be corrected for heart rate, because time-duration intervals are influenced by heart rate (RR cycle length). QT-intervals are preferably manually measured from lead II, from the beginning of the onset of the QRS complex to the end of the T-wave.[31-33] Viskin *et al.* found that QT-intervals are frequently misinterpreted and a long QT could not be correctly identified by the majority of physicians.[34] Also, the inter-observer agreement was low among the physicians.[34] Postema *et al.*, however, performed a proof-of-principle study in which inexperienced ECG readers were able to accurately and reproducibly diagnose prolonged and normal QTc-intervals by using the tangent method.[32, 35]

Various heart rate correction formulae have been developed in order to determine if a QTc-interval is prolonged compared to its predicted value at a reference heart rate of 60 beats/min using resting ECGs.[36-39] For the perfect prediction, stable sinus rhythm resting ECGs are required without fluctuations in the RR-interval.[27, 39-41] The most frequently used formula is the Bazett square root formula ($\mathrm{QTcB} = \mathrm{QT}/\sqrt{\mathrm{RR}}$), however this formula is

known for overestimating the QTc-interval at higher heart rates and underestimating the QTc-interval at lower heart rates.[36, 42] Another well-known formula is the Fridericia formula ($QTcF = QT/\sqrt[3]{RR}$).[37] This formula is known to give a better prediction at higher heart rates.[27, 43] According to Vandenberck *et al.,* this formula has the best rate correction along with the linear Framingham formula.[41] Still, there is no clear consensus on the best formula that should be used in clinical practice.

Usually, two different types of QTc-prolongation are discerned: the inherited or congenital long QT syndrome (cLQTS) and the acquired long QT syndrome (aLQTS). The cLQTS is caused by genetic abnormalities. Mutations in at least 17 genes have been identified thus far in patients with cLQTS encoding for cardiac ion channel subunits of proteins involved in modulation of ion currents causing a delayed ventricular repolarization.[44, 45] The prevalence of cLQTS is approximately 1:2000-5000.[45, 46] The aLQTS is most frequently caused by drugs that prolong the QTc-interval combined with several risk factors for TdP.[16, 26, 47, 48] In this thesis, we primarily focus on the acquired LQTS.

QTc-prolongation and the risk of TdP

The French cardiologist Desertenne first described TdP in 1966.[49] Torsade de Pointes, or "*twisting points*", is a ventricular polymorphic tachycardia, characterized by a short polymorphic ventricular arrhythmia with twisting QRS complexes around the isoelectric line of the ECG.[33] The combination of several pause-dependent non-sustained ventricular tachycardias with a prolonged QT-interval is frequently diagnosed as TdP. TdP can either be self-limiting or can degenerate into ventricular fibrillation.[15] Symptoms of TdP are syncope and palpitations, because of the sudden drop in arterial blood pressure and the elevated heart rates.[15, 50] In case of a non-self-limiting TdP, Dutch guidelines describe to treat bradycardia by directly administering intravenous magnesium sulfate 1-2 g and to normalize electrolyte disturbances, followed by cardioversion if necessary or administering isoprenaline 2 microg kg^{-1}, a non-selective β adrenoreceptor agonist.

The exact risk of developing TdP due to drug induced QTc-prolongation is extremely difficult to determine, because of its rare occurrence. A QTc-interval above 500 ms is associated with a 2- to 3 fold higher risk of TdP, and the more the QTc-interval is prolonged, the higher the risk of developing TdP.[51-53] However, data on the exact incidence of drug induced TdP are limited, mainly because TdP is not recognized nor registered on the ECG, when TdP results in ventricular fibrillation, or an out-of-hospital cardiac arrest. Therefore, reporting bias should always be considered. [54] According to pharmacovigilance data, the annual reporting rates of drug induced LQTS/TdP per million population vary between 1.2 in Sweden, 0.26 in Germany, and 0.08 in Italy.[54-56] Saraganas *et al.* reported a higher incidence of drug induced LQTS/TdP-cases of 2.5 per million year in males and 4.0 per million years in females when an active surveillance program was applied.[56] Several studies have reported an increased incidence of sudden cardiac death (SCD) in patients treated with (non-cardiac) QTc-prolonging drugs. Straus *et al.* found a three-fold increased risk of SCD in patients using non-cardiac QTc-prolonging drugs (adjusted odds ratio 2.7 (95% CI 1.6 – 4.7). The authors also estimated that yearly 320 cases of SCD in the Netherlands are caused by non-cardiac QTc-prolonging drugs. [57]

QTc-prolonging drugs and other risk factors

Many drugs, both cardiac and non-cardiac, are known for delaying the ventricular repolarization. Non-cardiac drugs vary from antibiotics to antipsychotics, antidepressants and oncolytic agents. Currently, over 190 drugs are associated with QTc-prolongation according to the CredibleMeds® QT drug lists of the Arizona Center for Education and Research on Therapeutics (AzCERT). AzCERT categorizes QTc-prolonging drugs into three categories representing the level of certainty on the risk of TdP. More than 50 drugs are categorized as drugs with a *known risk of TdP*.[5, 6] Many of these drugs such as antibiotics and psychotropic drugs are widely used in clinical practice. The reason for these drugs to prolong the QTc-interval is still not fully unfolded. The suggested mechanism of drug induced QTc-interval prolongation is inhibition or reduced expression of the human ether-a-go-go related (hERG) gene that encodes a potassium channel that regulates repolarizing currents (I_{kr}) in the cardiomyocytes or inhibition of late sodium currents.[33, 58] Inhibition of these I_{kr} results in a delay in the ventricular repolarization causing prolongation of the QT-interval. The QTc-prolonging potential might be explained by the different mechanisms of inhibition of, or affinity to the hERG channels. QT drug-drug interactions might enlarge this effect pharmacokinetically by increasing the plasma concentration of a QTc-prolonging drug (usually by inducing or inhibiting cytochrome P450 enzymes), or pharmacodynamically by causing a synergistic effect on QTc-prolongation. However, the synergistic effects of combining QTc-prolonging drugs still remain unclear.[59]

Beside the use of QTc-prolonging drugs, several other risk factors are associated with QTc-prolongation and TdP such as hypokalaemia, hypomagnesemia, heart diseases (i.e. ischemic heart diseases, heart failure, and arrhythmia such as atrial fibrillation), and renal impairment. Also, demographic risk factors such as an older age, female sex and genetic predisposition are associated with QTc-prolongation. However, the impact of these risk factors on the extent of QTc-prolongation is largely unknown, which makes it challenging to identify patients at risk for QTc-prolongation.[9, 33, 44, 60-67]

Risk management

The aforementioned issues make it extremely difficult for health care professionals to perform a decent risk-benefit assessment when combining QTc-prolonging drugs. Currently, in the Netherlands, clinical decision support systems (CDS systems) in primary and secondary care generate QT drug-drug interaction alerts when two or more QTc-prolonging drugs with a *known risk of TdP* are combined.[1, 5] More than 40% of the processed drug prescriptions lead to drug safety alerts which leads to alert fatigue in both physicians and pharmacists.[68] It should be questioned if this zero-risk policy is preferred and if we want to completely eliminate risks (at the cost of huge numbers of non-specific alerts) instead of trying to mitigate these risks. The specificity of the QT drug-drug interaction alerts generated by CDS systems is close to zero, because there is a complete lack of discrimination in high- and low-risk patients. These non-specific alerts result in a low number of interventions and noncompliance with current guidelines.[69-73] The management of drug induced QTc-prolongation includes a balance between the extremely small risk of TdP and sudden cardiac death, and the risk of withholding first-line therapies and switching to non QTc-

prolonging alternatives. In patients with no risk factors for QTc-prolongation, the risk of drug induced TdP will be minor and withholding these therapies will result in a higher risk of adverse outcomes.[15, 67] Moreover, in these low-risk patients frequent recording of ECGs following an alert of potential risk for QTc-prolonging will be of no added value. To solve this problem, physicians and pharmacists need decision support systems that identify those patients in whom a clinically significant risk is present, based on patient characteristics, laboratory values and/or the specific drugs and dosages involved. To decrease the alert burden, more advanced clinical rules are needed to improve the specificity of the alerts and decrease the alert rate. Subsequently, valuable tools to balance the risks and benefits should be explored.

Yet another way of risk management is the communication of potential risks by the regulatory authorities. Frequently, these risk communications are picked up by the popular media, increasing attention to the potential risks. However, little is known on the effect this attention has on the risk management by healthcare professionals, e.g. on monitoring (such as ECG recording) and on prescribing.

AIMS AND OUTLINE OF THIS THESIS

The overall aim of this thesis is to gain more insight into the prevalence and associated risk factors of QTc-prolongation in patients using QTc-prolonging drugs, and to provide more guidance on safe prescription practices in high-risk patients. The following research questions were studied:

- What is the prevalence of QTc-prolongation when patients are treated with QTc-prolonging drugs and which risk factors are associated with this QTc-prolongation?
- Can algorithms be developed that are able to identify high-risk patients who are more prone to developing QTc-prolongation?
- Are a prediction model or risk communication through media attention, potentially valuable tools for risk management of drug induced QTc-prolongation?

The work presented in this thesis is subdivided into four sections. The first section describes the incidence of patients with a prolonged QTc-interval when several QTc-prolonging drugs are used or combined, and potential risk factors of QTc-prolongation are reported. In the second section, we focus on the development of two prognostic prediction models to optimize individualized patient care. The third section describes two examples of risk management of QTc-prolonging drug-drug interactions: implementation of a prediction model in community pharmacies and the use of media attention to influence prescribing and monitoring behavior of healthcare professionals. Finally, the fourth section provides a general discussion that addresses our main findings and future perspectives for optimizing the risk management of drug induced QTc-prolongation.

Part I: In **Chapter 2**, we report on the risk of QTc-prolongation in hematological patients using fluconazole and ciprofloxacin. In this study, fluconazole and ciprofloxacin are mainly orally administered. **Chapter 3** shows the effect of intravenous ciprofloxacin and low-dose erythromycin on the course of the QTc-interval and is performed in ICU patients. In **Chapter 4**, we focus on

the risk of QTc-prolongation in breast cancer patients treated with tamoxifen in combination with serotonin reuptake inhibitors. **Chapter 5** describes the QTc-prolonging effect of chloroquine when used in COVID-19 patients.

Part II: Chapter 6 describes the development of a prognostic prediction model for a general teaching hospital setting. **Chapter 7** describes the development of a prognostic prediction model for a tertiary care hospital setting. In **Chapter 8**, the performances of both prediction models are compared using a large independent retrospective dataset.

Part III: Chapter 9 shows the effect of implementing a prediction model on the handling of drug-drug interactions regarding QTc-prolongation in community pharmacies. Finally, in **Chapter 10** we report on the impact of media attention regarding the cardiotoxicity of domperidone on the prescribing behavior and the frequency of ECG monitoring.

Finally, **Part IV: Chapter 11** provides a general discussion that addresses our main findings, a section on future perspectives and concluding remarks; followed by a summary (English and Dutch, **Chapter 12**) of the outcomes of this thesis.

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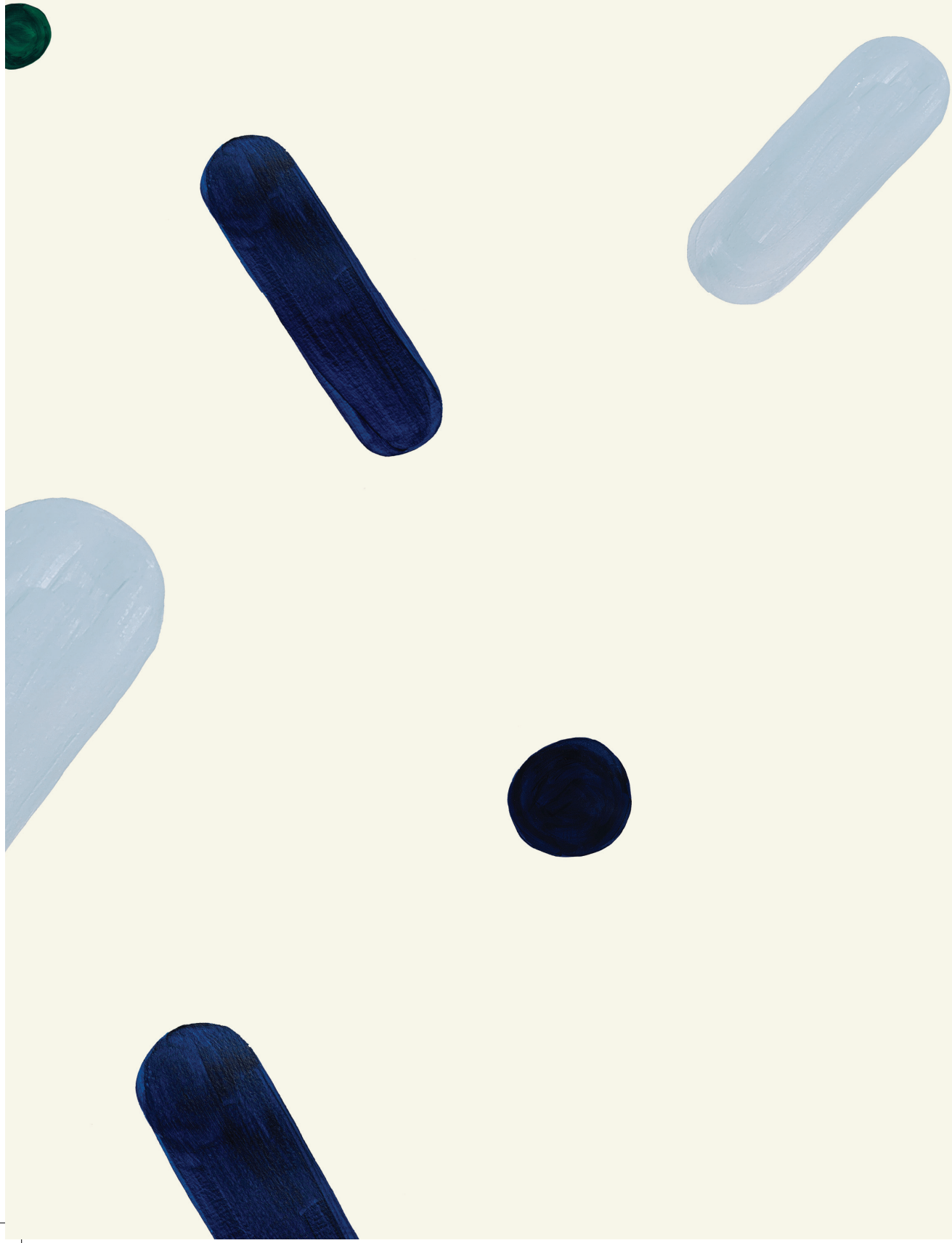
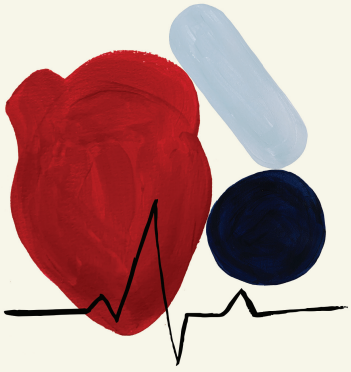


PART I

QTC-PROLONGATION IN CLINICAL PRACTICE



CHAPTER 2

QTC-PROLONGATION DURING CIPROFLOXACIN AND FLUCONAZOLE COMBINATION THERAPY: PREVALENCE AND ASSOCIATED RISK FACTORS

Florine A. Berger
Nico Monadian
Natasja M. S. de Groot
Bart Santbergen
Heleen van der Sijs
Matthijs L. Becker
Annoek E. C. Broers
Teun van Gelder
Patricia M. L. A. van den Bemt

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ABSTRACT

Aim: Ciprofloxacin and fluconazole combination therapy is frequently used as prophylaxis for and treatment of infections in patients with haematological malignancies. However, both drugs are known to prolong the QTc-interval, which is a serious risk factor for Torsade de Pointes (TdP). Therefore, the aim of this study was to assess the prevalence of QTc-prolongation during ciprofloxacin and fluconazole use. The secondary objective was to determine associated risk factors of QTc-prolongation in these patients.

Methods: A prospective observational study was performed in patients admitted to the Erasmus University Medical Centre and treated with ciprofloxacin and fluconazole. A twelve-lead electrocardiogram (ECG) was recorded at the T_{max} of the lastly added drug. Main outcome was the proportion of patients with QTc-prolongation during treatment. The following potential risk factors were collected: patient characteristics, serum electrolyte levels, dosage of ciprofloxacin and fluconazole, renal and liver function and concomitant use of other QTc-prolonging drugs and CYP3A4-inhibitors.

Results: 170 patients were included, of which 149 (87.6%) were treated for haematological malignancies. The prevalence of QTc-prolongation was 4.7%. No risk factors were found to be associated with QTc-prolongation. The QTc-interval increased with 10.7 ms (95% confidence interval (CI) 7.2 – 14.1 ms) during ciprofloxacin – fluconazole therapy.

Conclusion: The prevalence of QTc-prolongation in patients using ciprofloxacin and fluconazole is low compared to the prevalence in the general population which is varying from 5 – 11%. Also, no risk factors were found. Given the low prevalence, routine ECG monitoring in patients on this therapy should be reconsidered.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Ciprofloxacin and fluconazole are both known to prolong the QTc-interval and are listed on the CredibleMeds® QT drug list with a known risk of TdP by Arizona Centre for Education and Research on Therapeutics (AZCERT).
- The current guidelines of the American Heart Association and the American College of Cardiology Foundation require routine ECG monitoring for patients using drugs with a known risk of TdP.
- The exact risk of this drug-drug interaction (DDI) on developing QTc-prolongation or TdP is not known.

WHAT THIS STUDY ADDS

- The prevalence of QTc-prolongation in patients using ciprofloxacin and fluconazole combination therapy is low (4.7%) and in none of these patients the QTc-interval rose to abnormal levels above 500 ms.
- No risk factors were found to be associated with QTc-prolongation in these patients.
- Routine ECG monitoring in patients using ciprofloxacin and fluconazole combination therapy should be reconsidered.

INTRODUCTION

A combination of ciprofloxacin and fluconazole is frequently used as prophylaxis for and treatment of infections in patients with haematological malignancies. This drug combination decreases both bacterial and fungal infections and is incorporated in the guidelines on the use of antimicrobial agents in neutropenic cancer patients.[1-5] Both drugs are also known for prolonging the QT-interval.[6-8] QT or heart rate corrected QT (QTc) interval prolongation is a serious risk factor for the development of ventricular tachyarrhythmia such as TdP, which may lead to sudden cardiac death.[9-12] Several other risk factors play a key role in developing QTc-prolongation, for example, hypokalaemia, hypomagnesemia, heart diseases, renal impairment and unchangeable risk factors such as an older age and female gender.[10, 13-16] As haematological patients frequently encounter these comorbidities during chemotherapy, they might be at increased risk.

Ciprofloxacin, a broad-spectrum second generation fluoroquinolone antibiotic, blocks the outward potassium current (I_{kr}) in the cardiac myocyte. A delay in the efflux of potassium in the myocyte will delay the ventricular repolarization, which ultimately leads to a prolonged QTc-interval.[8, 17, 18] Fluconazole, a triazole antifungal agent, seems to prolong the QTc-interval via the same mechanism. In addition, fluconazole inhibits the Cytochrome P450 3A4 (CYP3A4) enzyme, which results in increased levels of QTc-prolonging drugs that are metabolized by CYP3A4.[8, 19]

The actual QTc-prolonging effect and risk of TdP of these drugs have not been extensively studied, apart from several case reports.[20-26] Furthermore, most studies on drug-induced QTc-prolongation have focused on the risk of QTc-prolongation and TdP, when using only one QTc-prolonging drug. Whether combining two or more QTc-prolonging drugs leads to a cumulative or perhaps even synergistic prolongation of the QTc-interval is unknown.[13, 27, 28]

Zeuli *et al*. studied the effect of fluoroquinolone and azole therapy on QTc-prolongation in 94 haematological patients. In this retrospective study, twenty-one (22%) patients had clinically significant changes in QTc-interval from baseline and several associated risk factors were found, such as hypokalaemia ($p = 0.03$) and a left-ventricular ejection fraction of < 55% ($p = 0.02$). Zeuli *et al*. recommended to monitor these haematological patients extensively.[29] In line with this study, ciprofloxacin has recently been added to the list of QTc-prolonging drugs with a *known risk of TdP* according to CredibleMeds® QT drug list by AzCERT.[7] On the other hand, several studies have shown that ciprofloxacin seemed to be the least '*torsadogenic*' of all fluoroquinolones, as indicated by very few reported TdP cases and its high hERG IC_{50} values. High hERG IC_{50} values illustrate a low association with clinical QTc-prolongation.[8, 21, 30] Frothingham has shown in a retrospective database analysis that the occurrence of TdP was lowest in ciprofloxacin use (0.3 cases/10 million prescriptions) compared to other fluoroquinolones. Additionally, a large bi-national cohort study have shown that an increased risk of serious arrhythmia in the general adult population was not associated with the use of oral fluoroquinolones. Ciprofloxacin was the most commonly used oral fluoroquinolone (82.6%). This raises the question if the medication safety alerts generated by the electronic prescribing system should lead to ECG monitoring in patients on treatment with ciprofloxacin and fluconazole therapy, as a pathophysiological association might not even be present. If not, these alerts only contribute to alert fatigue potentially resulting in unsafe prescribing.[31, 32]

Therefore, the aim of this study was to assess the prevalence of QTc-prolongation in hospitalized patients treated with ciprofloxacin and fluconazole as part of their usual care. The secondary objective was to assess the association of QTc-prolongation with possible risk factors such as patient characteristics, electrolyte parameters, dosage of the interacting drugs and concomitant medication.

METHODS

Study design

This prospective observational cohort study was conducted at the Erasmus University Medical Centre in Rotterdam, the Netherlands as part of the QT-INTERACT study. This study has focused on the prevalence and associated risk factors of patients using two or more QTc-prolonging drugs. These drugs are listed in the CredibleMeds® QT drug list with a *known risk of TdP*.[7] An observational study design was chosen as the main objective of this study was to assess the prevalence of QTc-prolongation in patients using two or more QTc-prolonging drugs as part of their usual care. However, it is important to mention that we only included patients treated with ciprofloxacin and fluconazole for this analysis, as this DDI encompassed the largest group of patients. Permission of the medical ethics committee of the Erasmus University Medical Centre in Rotterdam was obtained (MEC-2015-364), and written informed consent was obtained from all individual participants included in the study after full explanation of what was involved. The study was conducted according to the principles of the Declaration of Helsinki.

Study population

All adult patients (≥ 18 years) admitted to the Erasmus University Medical Centre using two or more QTc-prolonging drugs were eligible for participation during a twelve month study period (September 2015 – September 2016) according to the protocol of the QT-INTERACT study.

Patients with a diagnosis of congenital long QT syndrome, an implantable cardioverter-defibrillator (ICD) or a pacemaker were excluded. Patients who had ECGs with a left or right bundle branch block (LBBB/RBBB), atrial fibrillation or other ECG abnormalities due to cerebral pathology, ischemia or bigeminy, were excluded from further analysis due to interference with the QTc-interval. ECGs with a QRS complex > 120 ms, RR-intervals > 1800 ms or < 500 ms, or ECGs with a QTc-interval > 700 ms or < 300 ms were excluded as these ECGs do not represent reliable QTc-intervals.

Outcome measures

The primary outcome measure of this study was the proportion of patients with QTc-prolongation during combined treatment with ciprofloxacin and fluconazole. QTc-prolongation was defined as > 450 ms in males and > 470 ms in females based on the European Society of Cardiology guidelines. However, a QTc-interval of ≥ 500 ms or an increase of ≥ 60 ms from baseline were considered to be clinically relevant.[33] Twelve-lead ECGs were recorded with the Mortara® ELI-350 ECG device (Milwaukee, Wisconsin, USA). QT-intervals were manually measured, preferably from lead II, from the beginning of the onset of the QRS complex to the end of the T-wave.[34, 35] The measured QT-

intervals were corrected for heart rate using the Fridericia formula as this formula ($QTcF = QT/\sqrt[3]{RR}$) has the best rate correction along with the Framingham formula according to Vandenberk *et al*.[36]

Secondary outcome measures were the potential risk factors associated with QTc-prolongation, such as age, gender, race, body mass index (BMI), serum electrolyte parameters, dosage of interacting drugs, comorbidities, renal and liver function parameters and the concomitant use of other QTc-prolonging drugs and CYP3A4-inhibitors.

Data collection

The hospital pharmacy uses a medication surveillance system to identify DDIs. All patients on treatment with two or more QTc-prolonging drugs were identified using the medication surveillance system from September 2015 until September 2016. If patients were eligible for inclusion, informed consent was obtained. Subsequently, a twelve-lead ECG was recorded at the estimated time to peak concentration (T_{max}) of the lastly added drug, or at the longest T_{max} in case both drugs were started at the same time. Ciprofloxacin and fluconazole have a T_{max} of respectively 60 – 120 minutes and 30 – 90 minutes. Most patients (91.2%) received 500 mg ciprofloxacin twice daily at 08h00 and 18h00, and 400 mg fluconazole at 12h00. Of each patient, the following characteristics were collected from the electronic patient records: age, gender, race, BMI, medical history and the medical condition at time of the ECG recording as well as the given dose of the interacting drugs. The serum sodium, potassium, magnesium and calcium concentrations were collected within 5 days before or after the ECG recording, using the measurement closest to the ECG recording. Calcium levels were corrected for albumin levels using the following formula:

Corrected calcium in mmol L-1 = [measured calcium in mmol L-1] + (0.025 × (40-[albumin in g L-1])).[37]

The estimated glomerular filtration rate (eGFR), creatinine, aspartate transaminase (ASAT), alanine aminotransferase (ALAT) and bilirubin were also obtained within 5 days before or after the ECG recording. Concomitant medication data were collected from the electronic medication prescription system *Medicator* (Computer Sciences Corporation (CSC) Healthcare Group, Leiden, the Netherlands) within 8 hours prior to the ECG recording. A sub classification was made into concomitant QTc-prolonging drugs with a *possible* or *conditional risk of TdP* according to the CredibleMeds® QT drug lists, and CYP3A4 inhibiting drugs.[38] Baseline ECGs were selected within a maximum of 90 days prior to the ECG recording and with no use of QTc-prolonging drugs with a *known risk of TdP* according to the CredibleMeds QT drug list.[7]

All data were captured in an electronic clinical data management system (OpenClinica, LLC, Waltham, United States). Data were handled confidentially according to the Dutch Personal Data Protection Art (Wbp). This study was audited to evaluate and improve the effectiveness of processes and related controls. Data monitoring was performed by an independent data monitor to ensure completeness and plausibility.

Statistical analysis

A sample size calculation could not be made because the exact prevalence of QTc-prolongation in ciprofloxacin – fluconazole treatment was unknown. Data were analysed using Statistical Package for the Social Sciences (SPSS, IBM SPSS statistics version 21.0, USA). The primary outcome was determined by dividing the number of patients with QTc-prolongation by the total number of patients included in the study. The QTc-interval was dichotomized as either prolonged or not prolonged according to the ESC guidelines (> 450 ms for males and > 470 ms for females). Univariate logistic regression analysis was performed to determine associated risk factors. Factors that were associated with a $p < 0.05$ in the univariate analyses were entered into multivariate models to adjust for confounding. Effect sizes were presented in odds ratios (OR) with their corresponding 95% confidence intervals (95% CI). Additionally, a post hoc analysis was performed in patients with available baseline ECGs to study the change in QTc-interval during treatment using a paired t-test.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY[39], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16.[40]

RESULTS

Study design

Of the 849 screened patients, 567 patients were excluded according to the exclusion criteria as shown in Figure 1. A total of 282 patients provided informed consent, and in these patients an ECG was recorded. For this analysis, only patients on combined treatment with ciprofloxacin and fluconazole were taken into account. After exclusion of patients with ECG abnormalities, a total of 170 patients using ciprofloxacin and fluconazole were included in the analysis. The mean age of this cohort was 56 years. Most patients were male (64.1%) and had haematological malignancies (87.6%). A detailed overview of the baseline patient characteristics is presented in Table 1.

Primary outcomes

Eight patients had QTc-prolongation during ciprofloxacin – fluconazole therapy (mean ± standard deviation (SD) QTc-interval 461.1 ± 10.8 ms) when the Fridericia formula was used. This resulted in a prevalence of 4.7%. In none of these patients the QTc-interval rose to abnormal levels above 500 ms. Seven out of 8 patients (87.5%) with QTc-prolongation were men.

A baseline ECG was available in 137 patients. The mean ± SD QTc-interval at baseline was 400.3 ± 19.6 ms compared to a mean ± SD QTc-interval of 411.4 ± 21.7 ms during treatment. The overall mean QTc change from baseline was 10.7 ms (95% CI 7.2 – 14.1; $p < 0.01$) as shown in Figure 2.

In two patients the QTc-intervals increased with ≥ 60 ms during treatment (63 ms; 98 ms); both patients had a prolonged QTc-interval after administration of ciprofloxacin and fluconazole (451 ms; 483 ms, ECGs are included in Supplementary Figure S1). A baseline ECG was available in 7

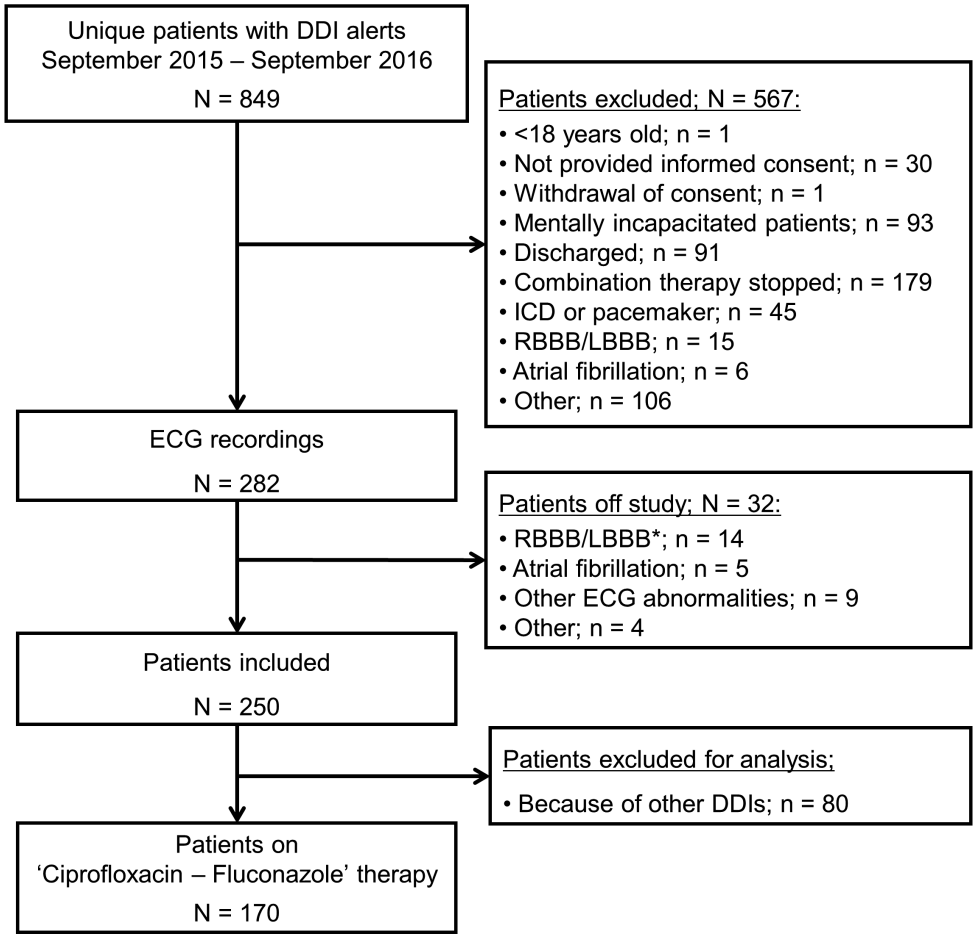

Figure 1. Flowchart of patient inclusion. DDI (drug–drug interaction), ECG (electrocardiogram), ICD (implantable cardioverter defibrillator), LBBB (left bundle branch block), RBBB (right bundle branch block)

out of 8 patients with QTc-prolongation during treatment. One of these patients had a prolonged QTc-interval at baseline (464 ms); the prolonged QTc-interval was pre-existent and apparently not caused by the DDI. Thus, with regard to patients with baseline ECGs (n = 137), six patients had a prolonged QTc-interval presumably caused by ciprofloxacin – fluconazole therapy (4.4%).

Most patients (91.2%) received oral ciprofloxacin 500 mg bid and fluconazole 400 mg once daily. The deviating dose regimens are listed in Table 2. One out of three patients who received ciprofloxacin and/or fluconazole intravenously had a prolonged QTc-interval (465 ms). This patient also received 1mg haloperidol, a third QTc-prolonging drug with a *known risk of TdP*.[7]

On top of the ciprofloxacin and fluconazole treatment, 6.5% of the cohort was exposed to concomitant treatment with a third QTc-prolonging drug with a *known risk of TdP* (Table 3). Two of these patients (18.2%) had a prolonged QTc-interval, using respectively flecainide 200 mg and haloperidol 1 mg daily. During our study period no cases of TdP occurred.

Table 1. Patient characteristics of ciprofloxacin – fluconazole users

Patient characteristics	**Total, n = 170**
Age (year), median; IQR	56.0; 18.0
≤50, n (%)	61 (35.9)
51 – 75, n (%)	106 (62.4)
≥76, n (%)	3 (1.8)
Female gender, n (%)	61 (35.9)
Caucasian race, n (%)	154 (90.6)
BMI, median; IQR	25.2; 6.13
Comorbidities, n (%)	
Myocardial infarction	6 (3.5)
Heart failure	-
Arrhythmia [a]	3 (1.8)
Bradycardia	-
Hypertension	36 (21.2)
Diabetes Mellitus	13 (7.6)
COPD/Asthma	11 (6.5)
Hematological malignancies	149 (87.6)
Hepatic dysfunction, n (%) *	
Increased ASAT (> 170 U L^{-1} for males; > 150 U L^{-1} for females)	3 (1.8)
Increased ALAT (> 220 U L^{-1} for males; > 165 U L^{-1} for females)	3 (1.8)
Increased bilirubin (> 16 µmol L^{-1})	36 (21.2)
Renal dysfunction, n (%)	
Increased creatinine (> 115 µmol L^{-1} for males; > 90 µmol L^{-1} for females)	9 (5.3)
eGFR < 50 ml min^{-1}	7 (4.1)
Electrolyte disturbances, n (%) **	
Hyponatremia (Na^+ < 136 mmol L^{-1})	19 (11.2)
Hypokalaemia (K^+ < 3.5mmol L^{-1})	5 (2.9)
Hypocalcaemia (Ca^{2+} < 2.2mmol L^{-1})	45 (26.5)
Hypomagnesemia (Mg^{2+} < 0.7mmol L^{-1})	15 (8.8)
> 2 'known' QTc-prolonging drugs, n (%) [b]	11 (6.5)
Concomitant medication	
Total number, median; IQR	8.0; 3.0
Loop diuretics, n (%)	51 (30.0)
Concomitant QTc-prolonging drugs, n (%) [c]	
0	13 (7.6)
1	50 (29.4)
≥ 2	107 (62.9)
CYP3A4-inhibitors, n (%) [d]	2 (1.1)

IQR (interquartile range), BMI (body mass index), eGFR (estimated glomerular filtration rate)

* Missing values: ASAT (n = 2), ALAT (n = 2), bilirubin (n = 4)

** Missing values: Ca^{2+} (n = 53), Mg^{2+} (n = 60)

[a] A history of supraventricular tachycardia (n = 3), including atrial fibrillation (n = 2)

[b] QTc-prolonging drugs with a *known risk of TdP*

[c] QTc-prolonging drugs with a *possible* and a *conditional risk of TdP* on top of ciprofloxacin – fluconazole therapy[7]

[d] Ciprofloxacin and fluconazole were excluded as CYP3A4-inhibitors

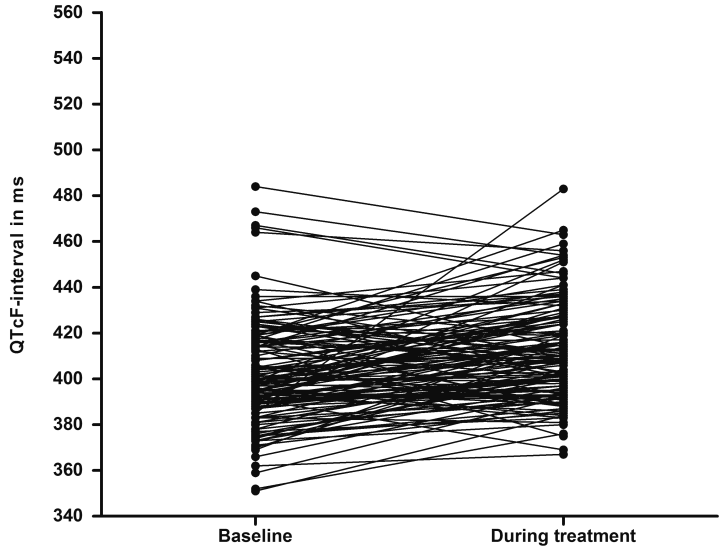

Figure 2. QTcF-intervals at baseline and during treatment (n = 137)

Table 2. Daily dose of the deviating dose regimens (n = 15)

Ciprofloxacin (mg)		Fluconazole (mg)		Patients, n
1200	iv	**400**	iv	1
800	iv	**400**	iv	1
800	iv	**400**	po	1
1000	po	**200**	po	6
1000	po	**150**	po	1
500	po	**200**	po	4
250	po	**200**	po	1

Iv (intravenously), po,(per os: oral administration)

Secondary outcomes

The association between various potential risk factors and QTc-prolongation is shown in Table 4. Due to the low number of patients with QTc-prolongation, univariate logistic regression was not feasible for each determinant. We found an association with age and QTc-prolongation (OR 1.08; 95% CI 1.00 – 1.17), as well as with the use of three QTc-prolonging drugs with a *known risk of TdP* (5.67; 1.00 – 32.15). After multivariate regression analysis no risk factors were statistically significantly associated with QTc-prolongation.

Most patients (62.9%) were exposed to concomitant treatment with two or more other QTc-prolonging drugs with a *possible* or *conditional risk of TdP*. However, these QTc-prolonging drugs were not significantly associated with QTc-prolongation (Table 4). These drugs included anti-emetics (89.9%), diuretics (33.8%) and proton pump inhibitors (9.5%).

Table 3. Patients using > 2 QTc-prolonging drugs with a *known risk of TdP* (n = 11)[7]

3rd QTc-prolonging drug (daily dose)	Patients, n = 11	Baseline QTc (ms)	Follow-up QTc (ms)
Citalopram (30 mg)	1	426	410
Flecainide (200 mg)	**1**		**468**
Haloperidol (0.5 mg)	1	421	419
Haloperidol (1 mg p.r.n.)	**1**	**419**	**465**
Haloperidol (2 mg)	1	-	377
Haloperidol (2 mg)	1	397	415
Haloperidol (2 mg)	1	399	452
Methadone (10 mg)	1	418	407
Sotalol (120 mg)	1	420	453
Sotalol (120 mg)	1	-	407
Sotalol (80 mg)	1	-	436

P.r.n (pro re nata: as needed)
Bold: patients with QTc-prolongation

DISCUSSION

To our knowledge, this is the first prospective study exploring the prevalence and associated risk factors of QTc-prolongation in patients treated with ciprofloxacin and fluconazole. In this observational study, 4.7% of the patients showed a prolonged QTc-interval during treatment when the Fridericia formula was used. We did not found risk factors that were associated with QTc-prolongation in this population. These results contribute to a better insight into the prevalence and magnitude of QTc-interval prolongation in patients using two or more QTc-prolonging drugs.

According to the American Heart Association/American College of Cardiology (AHA/ACC) consensus statement on prevention of TdP in hospital settings, a prolonged QTc-interval of more than 500 ms or an increase in QTc-interval of at least 60 ms from baseline are considered to be clinically relevant.[15] Eight patients in our cohort had a prolonged QTc-interval according to the cut-off value of 450 ms for males and 470 ms for females, however, none of these patients had a QTc-interval above 500 ms. Only two patients showed an increase in QTc-interval of ≥ 60 ms from baseline. Additionally, the post hoc analysis showed a significant mean increase in QTc-interval of 10.7 ms during treatment. Most baseline ECGs, however, were recorded before start of chemotherapy as standard care. It is most likely that the patients were in a better medical condition at baseline than when the ECGs were recorded during treatment. Since Holter monitoring studies have revealed substantial daily QTc variability (hourly mean QTc range of 38 ± 6 ms), this increase could even be considered as negligible.[41, 42]

Patients with QTc-prolongation continued treatment and did not have any complications. Also, no cases of TdP occurred during our study period. As previously mentioned, Zeuli *et al.* found a prevalence of 22% of clinically relevant significant change in QTc from baseline when fluoroquinolones and azoles were combined. However, only three patients (3.2%) of the total cohort received ciprofloxacin – fluconazole therapy. They also found a small mean QTc change

Table 4. Association of potential risk factors with QTc (Fridericia) -prolongation (n = 170)

Potential determinants	QTcF prolongation n = 8	No QTcF prolongation n = 162	OR	95% CI	Multivariate Regression OR_{adj}	95% CI	Adj.
Age (years), median; IQR	66.0; 11.0	55.0; 18.0	1.08	1.00 – 1.17	1.07	0.99 – 1.16	QTc-drugs
≤ 50, n (%)	1 (12.5)	60 (37.0)	Ref.	Ref.			
51 – 75, n (%)	7 (87.5)	99 (61.1)	4.24	0.51 – 35.3			
≥ 76, n (%)	-	3 (1.9)	-	-			
Female gender, n (%)	1 (12.5)	60 (37.0)	0.24	0.03 – 2.02			
Caucasian race, n (%)	6 (75.0)	148 (91.4)	0.28	0.05 – 1.54			
BMI, median; IQR	25.3; 4.9	25.2; 6.3	0.95	0.80 – 1.13			
Comorbidities, n (%)							
Myocardial infection	-	6 (3.7)	-	-			
Arrhythmia [a]	-	3 (1.9)	-	-			
Hypertension	3 (37.5)	33 (20.4)	2.35	0.53 – 10.31			
Diabetes Mellitus	-	13 (8.0)	-	-			
COPD/Asthma	-	11 (6.8)	-	-			
Hematological malignancies	6 (75.0)	143 (88.3)	0.40	0.08 – 2.12			
Organ failure							
Hepatic dysfunction, n (%) [*]							
Increased ASAT	-	3 (1.9)	-	-			
Increased ALAT	-	3 (1.9)	-	-			
Increased bilirubin	4 (50.0)	32 (19.8)	3.94	0.94 – 16.06			
Renal dysfunction, n (%)							
Increased creatinine	-	9 (5.6)	-	-			
eGFR < 50 ml min^{-1}	-	7 (4.3)	-	-			
Electrolyte disturbances, n (%) [**]							
Hyponatremia	-	19 (11.7)	-	-			
Hypokalaemia	-	5 (3.1)	-	-			
Hypocalcaemia	2 (250)	43 (26.5)	0.79	0.14 – 4.50			
Hypomagnesemia	1 (12.5)	14 (8.6)	1.29	0.14 – 11.83			
>2 QTc-prolonging drugs, n(%) [b]	2 (25.0)	9 (5.6)	5.67	1.00 – 32.15	4.35	0.73 – 25.82	Age
Concomitant medication							
Total number, median; IQR	9.0; 2.0	8.0; 4.0	1.10	0.86 – 1.42			
Loop diuretics, n (%)	4 (50.0)	47 (29.0)	2.45	0.59 – 10.19			
Co QTc-prolonging drugs, n (%) [c]							
0	-	13 (8.0)	-	-			
1	2 (25.0)	48 (29.6)	-	-			
≥ 2	6 (75.0)	101 (62.3)	-	-			
CYP3A4-inhibitors, n (%) [d]	-	2 (1.2)	-	-			

IQR (interquartile range), BMI (body mass index), OR (odds ratio), CI (confidence interval)

[*] Missing values: no QTc: ASAT (n = 2), ALAT (n = 2), bilirubin (n = 4)

[**] Missing values: QTc: Ca^{2+} (n = 2), Mg^{2+} (n = 2); no QTc: Ca^{2+} (n = 51), Mg^{2+} (n = 58)

[a] A history of atrial fibrillation (n = 2, QTc-prolongation); supraventricular tachycardia (n = 1, no QTc-prolongation)

[b] QTc-prolonging drugs with a known risk of TdP

[c] QTc-prolonging drugs with a possible and a conditional risk of TdP on top of ciprofloxacin – fluconazole therapy[7]

[d] Ciprofloxacin and fluconazole were excluded as CYP3A4-inhibitors

from baseline of 6.1 ms (95% CI 0.2 – 11.9 ms) during treatment. According to our results, we think that the QTc-prolonging effect of ciprofloxacin and fluconazole therapy is not clinically relevant in this population. It must be noted that most patients (91.2%) received 1000 mg of ciprofloxacin and 400 mg of fluconazole orally per day. One of the three patients receiving intravenous ciprofloxacin and fluconazole developed QTc-prolongation, which may imply that more caution is needed when these drugs are administered intravenously.

Many patients (92.3%) were co-treated with additional QTc-prolonging drugs with a *possible* or *conditional risk of TdP* according to the CredibleMeds® QT drug list.[7] However, these additional QTc-prolonging drugs did not affect the prevalence of QTc-prolongation. Also, a third QTc-prolonging drug with a *known risk of TdP* was not associated with QTc-prolongation. Even three patients who received sotalol (daily dose 120mg) on top of the DDI did not show QTc-prolongation (407 ms; 436 ms; 453 ms). Sotalol is one of the most powerful I_{kr} potassium-channel blockers. This indicates that there might not be a synergistic QTc-prolonging effect when two or more QTc-prolonging drugs with a *known risk of TdP* are combined. Meid *et al.*, supported this hypothesis in a retrospective study on additive QTc-prolonging drugs in older people with ventricular tachyarrhythmia claims. They did not find a supra-additive or synergistic risk of ventricular tachyarrhythmia when more than one QTc-prolonging drug was used.[27] Therefore, the validity of the CredibleMeds® QT drug lists should be questioned. AzCERT has developed a process to place drugs in risk categories for their clinical ability to cause TdP and QTc-prolongation. AzCERT collects its data from different sources including the FDA adverse event reporting system (FEARS), the WHO adverse events database, case reports and reports in medical literature. However, the evaluation of causality is often difficult and evidence is frequently incomplete. Still, there is a growing number of drugs that have been added to the lists since 1999 when it was established. Thereby, the lists lack quantification of relative risks, which makes it difficult for doctors to interpret these risk alerts.[43, 44]

With the increasing number of QTc-prolonging drugs, alert fatigue could be imposed on physicians who might not react anymore to truly relevant alerts. There should be a balance between the amount of alerts generated by the Clinical Decision Support Systems (CDSS) and its effect on patient care. This study implies that the recommendation to routinely monitor ECGs of patients using ciprofloxacin and fluconazole should be reconsidered.

Because of the prospective study design, we could adjust for many variables. Most ECGs were recorded at the T_{max} of ciprofloxacin as the dose regimens were equal in most patients; in 15 patients, the dose regimen deviated (Table 2). Also, ECGs were recorded using the same Mortara® Eli-350 device and performed by three trained investigators. Limitations of this study include, at first, the fact that the mean age of our population was relatively low (56 years old). Older patients treated with ciprofloxacin and fluconazole may have a higher risk of QTc-prolongation, as well as a higher risk of developing arrhythmias, since increasing age is a known risk factor for QTc-prolongation and TdP.[10, 13-16] Nevertheless, we did not found an increasing age to be associated with QTc-prolongation when ciprofloxacin and fluconazole were used. Second, a baseline ECG was only available when the physician ordered an ECG before treatment as part of routine care because the medication surveillance system could not report real-time DDIs. Therefore, in the patient with QTc-prolongation and without a baseline ECG available, the prolonged QTc-interval could have

been pre-existent. If that was the case, the prevalence of a prolonged QTc-interval caused by ciprofloxacin and fluconazole would even be less.

Several determinants, such as a female gender, hypokalaemia, hypomagnesemia, heart diseases and renal impairment are known risk factors for QTc-prolongation.[10, 13-16] However, in our analyses, all known risk factors failed to achieve statistical significance, possibly due to the low number of QTc-prolongation events. Additionally, several serum electrolyte parameters were missing. Most patients with QTc-prolongation (87.5%) were male, which is in contrast to previous studies that have identified female gender as a risk factor for developing QTc-prolongation.[10, 13-16]

A review of Montanez *et al*. identified seven large population-based cohort studies evaluating the association between QTc-prolongation and cardiovascular mortality. Of the 36031 individuals included in these cohort studies, 2,677 individuals had a prolonged QTc-interval (≥ 440 ms) representing 8.7% of the general population.[45] Straus *et al*. found a prevalence of 11.1% in a population of older adults, using > 450 ms for men and > 470 ms for women as cut off values for QTc-prolongation.[11] Therefore, it could be stated that the prevalence of QTc-prolongation in patients using this combination is rather low (4.7%).

To conclude, our study confirms that ciprofloxacin and fluconazole combination therapy prolongs the QTc-interval. However, our study also shows that this increase is negligible in relation to the daily QTc-variability. No risk factors were found to be associated with QTc-prolongation during this treatment. Given the low prevalence and slight increase of the QTc-interval, routine ECG monitoring in haematological patients using ciprofloxacin and fluconazole should be reconsidered. Caution is needed when ciprofloxacin and fluconazole are administered intravenously.

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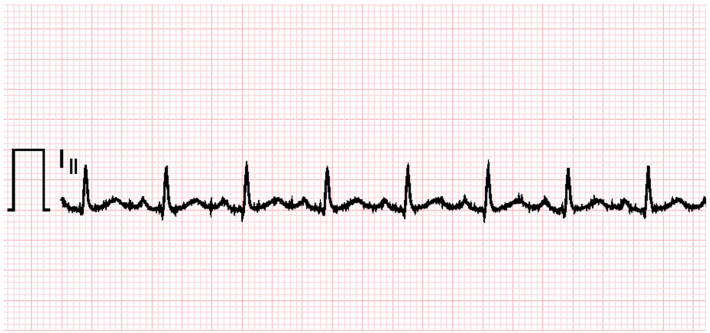
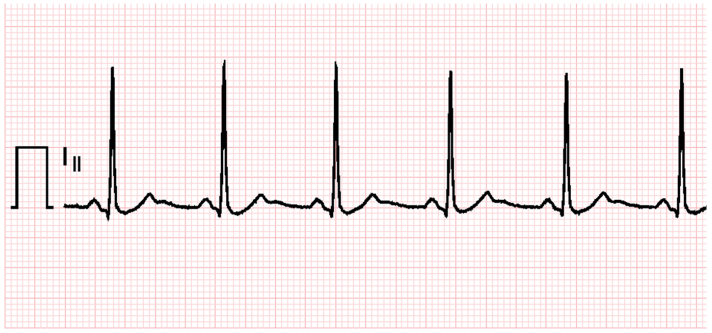
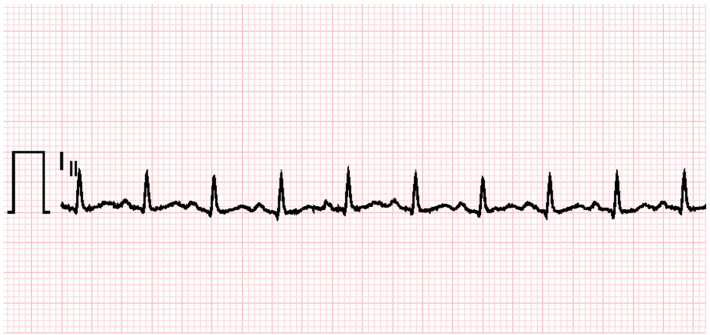


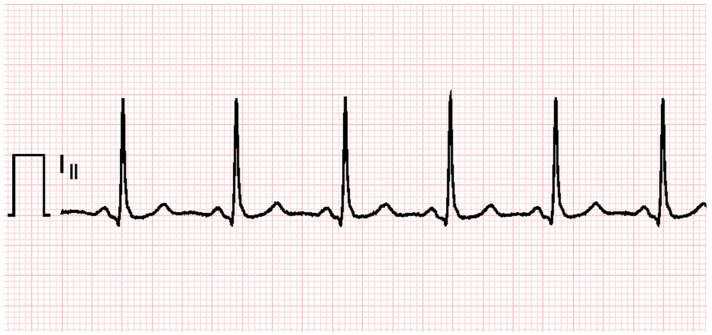
(a) QTcF-interval of 385 ms at baseline



(c) QTcF-interval of 388 ms at baseline



(b) QTcF-interval of 483 ms during treatment



(d) QTcF-interval of 451 ms during treatment

Figure S1. (a) baseline ECG of patient A, **(b)** ECG during treatment of patient A, **(c)** baseline ECG of patient B, **(d)** ECG during treatment of patient B. In both patients, the QTc interval increased by ≥ 60 ms.

CHAPTER 3

DYNAMICS OF THE QTC-INTERVAL OVER A 24-HOUR DOSE INTERVAL OF INTRAVENOUS CIPROFLOXACIN AND LOW-DOSE ERYTHROMYCIN IN ICU PATIENTS

Florine A. Berger
Willem van Weteringen
Heleen van der Sijs
Nicole G. M. Hunfeld
Jeroen J. H. Bunge
Natasja M. S. de Groot
Patricia M. L. A. van den Bemt
Teun van Gelder

Submitted

ABSTRACT

QTc-interval prolongation is an adverse effect associated with use of fluoroquinolones and macrolides. Ciprofloxacin and erythromycin are both frequently prescribed QTc-prolonging drugs in critically ill patients. Critically ill patients may be more vulnerable to developing QTc-prolongation as several risk factors can be present at the same time. Therefore, it is important to know the QTc-prolonging potential of these drugs in the Intensive Care Unit (ICU) population. The aim of this study was to assess the dynamics of the QTc-interval over a 24-hour dose interval during intravenous ciprofloxacin and low-dose erythromycin treatment. Therefore, an observational study was performed in ICU patients (≥ 18 years) receiving ciprofloxacin 400 mg t.i.d. or erythromycin 100 mg b.i.d. intravenously. Continuous ECG data were collected from 2 hours before to 24 hours after the first administration. QT-analyses were performed using high-end holter software. The effect was determined with a two-sample t-test for clustered data on all QTc values. A linear mixed model by maximum likelihood was applied, for which QTc values were assessed for the available time intervals and therapy. No evident effect over time on therapy with ciprofloxacin and erythromycin was observed on QTc-time. There was no significant difference (p = 0.22) in QTc values between the ciprofloxacin group (mean 393 ms) and ciprofloxacin control group (mean 386 ms). The erythromycin group (mean 405 ms) and erythromycin control group (mean 404 ms) neither showed a significant difference (p = 0.80). In 0.6% of the registrations (1.138 out of 198.270 samples) the duration of the QTc-interval was longer than 500 ms. The index groups showed slightly more recorded QTc-intervals over 500 ms. To conclude, this study showed no changes in the duration of the QTc-interval in patients in whom ciprofloxacin (400 mg t.i.d.) or erythromycin (100 mg b.i.d.) was administered.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Fluoroquinolones and macrolides are both known to prolong the QTc-interval and are listed on the CredibleMeds® QT drug list with a known risk of TdP by Arizona Centre for Education and Research on Therapeutics (AzCERT).
- It seems that ICU patients are prone to developing QTc-interval prolongation.
- The association between the occurrence of the maximum mean QTc increase from baseline and time after administration of the QTc-prolonging drug has not been extensively studied for many of the QTc-prolonging drugs.

WHAT THIS STUDY ADDS

- Intravenous ciprofloxacin and low-dose erythromycin do not have a significant effect on the QTc-interval over a 24-hour time interval in ICU patients.
- The QTc-interval of ICU patients is highly variable over time.
- No recommendations as to timing of ECGs after initiation for one or more QTc-prolonging drugs can be provided as substantial changes in the QTc-interval over a dose interval were not found.

INTRODUCTION

To date, more than 60 drugs are known for their QTc-prolonging effects with a known risk of Torsade de Pointes (TdP), a rare, but potentially fatal ventricular tachycardia.[1] According to the European Medicine Agency (EMA) guidelines, a QTc-interval is prolonged when it exceeds 450 ms in males and 470 ms in females. A QTc-interval of > 500 ms or an increase of 60 ms or more from baseline is associated with a higher occurrence of TdP and is, therefore, considered to be clinically relevant. When two or more QTc prolonging drugs are prescribed, medication surveillance in terms of ECG monitoring before and after drug administration is warranted.[2] Before drug approval and registration by the EMA, clinical evaluation of QT/QTc-prolongation and pro-arrhythmic potential for non-arrhythmic drugs is usually performed following the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 14 guidelines. These thorough QT studies exclude patients with additional risk factors or a prolonged baseline QTc-interval, so the QTc-prolonging effect of these drugs in critically ill patients with multiple risk factors is not studied. Additionally, according to these guidelines, ECG recordings are taken on specific time-points around the T_{max}. However, the association between the occurrence of the maximum mean QTc increase from baseline and time after administration of the QTc-prolonging drug has not been extensively studied for many of the QTc-prolonging drugs. Drug effects are generally related to plasma concentrations with a maximum effect (E_{max}) on the T_{max} of the drug. The QTc-interval may thus be maximally prolonged at the T_{max}, but there might also be a lag phase between peak plasma concentrations and maximum QTc-prolongation.[3] Continuous analyses of high-frequency monitor data are needed to measure such drug effects and to provide a more solid basis for the timing of ECG monitoring.

QTc-prolongation may not only be caused by QTc-prolonging drugs, but also by older age, female sex, heart diseases such as bradycardia, chronic heart failure, electrolyte disturbances such as hypokalaemia and hypomagnesemia, and renal dysfunction.[4-6] TdP mainly occurs when multiple risk factors inducing QTc-prolongation are present. Risk factors for developing QTc-prolongation and TdP in critically ill patients seem to be similar to those in the ambulatory population.[7-9] However, critically ill patients may be more vulnerable as several risk factors can be present at the same time. Therefore, it is important to know the prevalence of drug induced QTc-prolongation in the Intensive Care Unit (ICU) population.[10]

Ciprofloxacin and erythromycin are both frequently used QTc-prolonging antibiotics in critically ill patients. Ciprofloxacin is a broad-spectrum second-generation fluoroquinolone and is mainly used intravenously (IV) in ICU patients to treat a number of bacterial infections. Ciprofloxacin was added to the QT drugs list in March 2015 resulting in many QT drug-drug interaction alerts. However, the QTc-prolonging effect of ciprofloxacin seems minimal when administered orally.[11-15] IV administration of ciprofloxacin, especially in critically ill patients, might increase the QTc-prolonging potential of ciprofloxacin. Erythromycin is a macrolide antibiotic and well-known for its QTc-prolonging effect.[16] However, in ICU patients it is commonly administered in low dosages to treat delayed gastric emptying.[17] The QTc-prolonging effect of low-dose erythromycin is relatively unknown.[7,18,19]

To address these knowledge gaps, the primary objective of this study was to assess the time course of the QTc-interval for at least 24 hours during the use of IV ciprofloxacin and low-dose erythromycin in ICU patients. The secondary aim was to assess the characteristics of QTc-interval dynamics, such as the association of the time to the longest QTc-interval with the T_{max} of both drugs.

METHODS

Study design and setting

The study was designed as an observational cohort study, in which a cohort of patients using ciprofloxacin or erythromycin IV (index group) was compared to a cohort of patients using no QTc-prolonging drugs (control group). Ciprofloxacin and erythromycin IV were only given as part of routine clinical care. The study was performed at the Intensive Care Units of Erasmus University Medical Centre in Rotterdam, the Netherlands. The medical ethics review board of the Erasmus MC approved the protocol (MEC-2016-407) and written informed consent was obtained from all individual participants/legal representatives prior to study initiation. The study was conducted according to the principles of the Declaration of Helsinki.

Study population

Patients aged 18 years or older using only ciprofloxacin or erythromycin IV as a potentially QTc-prolonging drug were eligible for inclusion in the index group. Patients without the use of QTc-prolonging drugs, according to QT drugs list of drugs with a known risk of TdP of the Arizona Centre for Education and Research on Therapeutics[1], were eligible for inclusion in the control group. If QTc-prolonging drugs with a known risk of TdP[1] were used before the study period, the QTc-prolonging drugs had to be fully eliminated before the patient was eligible for inclusion. A drug was considered to be fully eliminated after 5 times the elimination half-life ($T_{½}$) of the drug.

Patients were excluded if one of the following conditions were present: congenital prolonged QTc syndrome, a (bi)ventricular implantable cardioverter defibrillator (ICD) or pacemaker, the presence of atrial fibrillation or other ECG abnormalities interfering with the QTc-interval at baseline; for example, left and right bundle branch block. Patients were also excluded if they used QTc-prolonging drugs with a known risk of TdP. However, low-dose haloperidol IV of less than 5 mg per day was allowed in all groups, as haloperidol has no significant effect on QTc-prolongation in low dosages.[20] Propofol was allowed in the erythromycin and erythromycin control group, as erythromycin was only prescribed in patients sedated with propofol.

Outcome measures

The primary outcome measure of this study was the course of the QTc-interval during a 24-hour dose interval of IV ciprofloxacin and low-dose erythromycin in ICU patients reported as 25th to 75th percentiles. The secondary outcome measure was the effect of administration of ciprofloxacin and erythromycin IV determined by comparing an hour before the first administration (baseline) and an hour after the first, second and third administration. A QTc-interval of 500 ms was used as threshold

to indicate clinically relevant QTc-prolongation. Lastly, we studied the overall variability of the QTc-intervals during 24 hours in both groups.

Data collection

Ciprofloxacin and erythromycin IV were prescribed by physicians in the ICU according to standard institutional protocol. The dose regimen of ciprofloxacin IV was 400 mg three times daily with an infusion time of 30 – 60 minutes. The dose regimen of erythromycin IV was 100 mg twice daily with an infusion time of 30 – 60 minutes.

The following data were prospectively collected from the electronic Patient Data Management System (version 8.3.2., PICIS, Wakefield, MA, used in the hospital until the 21st of June, 2017) or the patient's electronic medical record HiX (Chipsoft B.V., the Netherlands, used in the hospital from the 23rd of June, 2017) depending on the inclusion period: general patient characteristics, liver and renal function parameters, serum electrolyte levels, acute physiology and chronic health evaluation (APACHE) scores, sequential organ failure assessment (SOFA) scores, concomitant medication and dosages. Seventy-two hours of 200 Hz ECG telemetry data were collected from bedside monitors (Infinity M540, Drägerwerk AG & Co. KGaA, Lübeck, Germany) and converted to SynescopeTM (version 3.10, ELA Medical; a sorin group company, Italy), a high-end ECG Holter analysis software including a QT-analysis module. The Dräger Infinity system that was used is validated for the determination of QTc-intervals. This module applied a 30-second averaging time for the waveform complexes. The QT-interval was measured from the beginning of the QRS complex to the end of the T wave. The QRS intervals were averaged by synchronizing the start of the QRS complexes. Based on those mean waveforms, the software calculated the peak of the T wave using the parabola method. The end of the T wave was calculated by determining the intersection between the maximum decreasing tangent and the isoelectric line.[21,22] The analysis was performed automatically for all available leads. For the QT correction the QT/RR linear regression analysis was conducted after precise manual beat classification and template correction with calculation of slopes and correlation coefficients (QT/RRcorr). Data points where no QTc value was registered due to low signal strength, were excluded from the analysis. All values were manually checked for artefactual data.

Additionally, from the patient monitoring system heart rate data were registered at a rate of 1 Hz from 2 hours before until 24 hours after the start of ciprofloxacin and erythromycin therapy. Data averaging was 10 seconds for ECG-derived heart rate. A software tool was constructed in LabVIEW (version 2017 SP1, National Instruments, Austin, TX, USA) for time-based data stratification. All data were handled confidentially and stored in the Electronic Data Capture (EDC) OpenClinica (OpenClinica©, LLC and collaborators, version 3.12.2).

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS, IBM SPSS statistics version 24.0, USA) and R Software (R Foundation for Statistical Computing). For both groups standard statistical methods were used to calculate means, and standard deviations (SD)

(for normally distributed variables), and medians and interquartile ranges (IQR) (for not normally distributed variables), as well as independent *t*-tests. The independent *t*-test was used to compare continuous variables, assuming equal or unequal variances between the two cohorts, and Chi-Square test or Fisher's Exact test, as appropriate, was used for categorical variables.

Collected physiological data (per second) and the QTc values (per 30 seconds) were grouped in 60 minute timeframes. To provide an estimate of the effects of the therapy on the QTc values over time, several time intervals were included of which; an hour before the first administration (baseline) and an hour after the first, second and third administration. A QTc-interval of 500 ms was used as threshold to indicate clinically relevant QTc-prolongation. The effect of administration of ciprofloxacin and erythromycin IV on the QTc-interval was determined with a two-sample *t*-test for clustered data on all QTc values that were registered during the 26 hour study period. A linear mixed model by maximum likelihood was applied to adjust for the repeated measurements of QTc values. The fixed and random effects of the available time intervals and therapy on the QTc values were assessed. In accordance with pharmacokinetic studies, we estimated that 20 patients for the index group and 20 patients for the control group would be sufficient to study whether changes in the QTc-interval prolongation follow the course of drug concentrations throughout a 26-hour time interval. Mean QTc-intervals > 500 ms were calculated per patient and tested between therapy and control groups using a Wilcoxon rank sum test.

RESULTS

Study population

In total, 71 patients were included for analysis; 14 patients were included in the ciprofloxacin group and 17 patients in the erythromycin group. In both control groups 20 patients were included. The flowchart with reasons for exclusion is shown in Figure 1. Patient characteristics of the different subgroups are shown in Table 1. The mean age of all patients was 54 years old. Most patients in the erythromycin groups were male (85% and 77% respectively). The APACHE II scores of the patients in the ciprofloxacin group were significantly higher than in the ciprofloxacin control group.

Ciprofloxacin

Figures 2a and 2b show the trends in heart rate and QTc-interval during a 2-hour baseline period and throughout the 24-hour period in which ciprofloxacin was administered in the index group, plotted together with the control group. A linear mixed model was fit with QTc values as the response variable, with fixed effects of therapy and the time intervals, and their relation to the individual patient. The model was fit by maximum likelihood, including random intercepts for the individual patient and random slopes for therapy and their interaction with the patient. The results are shown in table 2. No evident effect over time on therapy was observed on the QTc-intervals.

Erythromycin

Figures 3a and 3b show the heart rate and QTc-interval during 26 hours in the erythromycin index and control groups. As with ciprofloxacin there was no change in heart rate or increase in the QTc-

Table 1. Baseline demographics

Demographics	Ciprofloxacin n = 14	Control ciprofloxacin n = 20	Erythromycin *p*-value	n = 17	Control erythromycin n = 20	*p*-value
Age (years), mean ± SD	54.6 ± 15.8	53.7 ± 13.7	0.85 [a]	50.1 ± 16.6	47.9 ± 20.0	0.72 [a]
≤ 50, n (%)	5 (35.7)	6 (30.0)	0.73 [b]	8 (47.1)	10 (50.0)	0.86 [b]
> 50, n (%)	9 (64.3)	14 (70.0)		9 (52.9)	10 (50.0)	
Female sex, n (%)	7 (50.0)	8 (40.0)	0.56 [b]	4 (23.5)	3 (15.0)	0.68 [b*]
BMI (kg/m^2), mean ± SD	26.7 ± 4.3	26.2 ± 4.8	0.75 [a]	24.7 ± 3.2	25.3 ± 2.4	0.55 [a]
Race, Caucasian, n (%)	10 (71.4)	17 (85.0)	0.41 [b]	13 (76.5)	18 (90.0)	0.38 [b*]
Reason for admission, n (%)						
General medical	11 (78.6)	12 (60.0)	0.26 [b]	8 (47.1)	9 (45.0)	0.90 [b]
Surgical	2 (14.3)	5 (25.0)	0.67 [b*]	1 (5.9)	-	-
Emergency surgical	1 (7.1)	2 (10.0)	1.00 [b*]	6 (35.3)	10 (50.0)	0.37 [b]
SAH	-	1 (5.0)	-	2 (11.8)	1 (5.0)	0.58 [b*]
Comorbidities,n (%)						
Hypertension	6 (42.9)	3 (15.0)	0.07 [b]	4 (23.5)	3 (15.0)	0.68 [b*]
Diabetes Mellitus	2 (14.3)	2 (10.0)	0.55 [b*]	2 (11.8)	1 (5.0)	0.58 [b*]
Myocardial Infarction	-	1 (5.0)	-	-	1 (5.0)	-
Serum electrolyte parameters, n (%)						
Hypokalaemia (< 3.5 mmol L^{-1})	-	1 (5.0)	-	1 (5.9)	-	-
Hyponatremia (< 136 mmol L^{-1})	2 (14.3)	3 (15.0)	0.67 [b*]	3 (17.6)	-	-
Hypomagnesemia[c] (< 0.7 mmol L^{-1})	2 (14.3)	3 (15.0)	0.62 [b*]	1 (5.9)	2 (10.0)	0.56 [b*]
CRP*, median (IQR)	103.8 (141.3)	93.0 (111.0)	0.55 [a]	88 (124)	43.9 (78.7)	0.43 [a]
Renal dysfunction[c], n (%)	3 (21.4)	-	-	4 (23.5)	2 (10.0)	0.38 [b*]
ICU length of stay until inclusion (in days), median (IQR)	1 (15.3)	2.5 (10.0)	0.32 [a]	3.0 (4.0)	0 (1.0)	0.08 [a]
APACHE II[c]	23.1 ± 7.2	16.8 ± 5.8	0.02 [a]	20.4 ± 6.3	19.5 ± 6.0	0.72 [a]

BMI (body mass index), CRP (C-reactive protein), ICU (intensive care unit), APACHE (acute physiology and chronic health evaluation), IQR (interquartile range), SAH (subarachnoidal haemorrhage), SD (standard deviation)

[a] Independent *t*-test

[b] Chi-square test / * Fisher's Exact Test

[c] Missing values: APACHE II: ciprofloxacin (n = 5), ciprofloxacin control (n = 4), erythromycin (n = 4), erythromycin control (n = 8); CRP: ciprofloxacin control (n = 1); Hypomagnesemia: ciprofloxacin control (n = 2); Renal dysfunction: ciprofloxacin control (n = 1)

Table 2. Estimated fixed effects of the maximum likelihood linear mixed model.

(a)	Fixed effect	Estimate	95% CI	Std.Error	t
Ciprofloxacin	Intercept	387.64	377.86 – 397.43	4.85	79.92
	Time interval	0.10	0.06 – 0.14	0.02	4.56
	Therapy	2.05	-4.38 – 8.52	3.07	0.67
Erythromycin	Intercept	398.82	389.36 – 408.28	4.70	84.83
	Time interval	0.40	0.36 – 0.44	0.02	19.07
	Therapy	2.27	-5.86 – 10.39	3.91	0.58
(b)	**Random effect**	**Type of effect**		**Variance**	**Std.Dev.**
Ciprofloxacin	Individuals	random intercept		797.2	28.23
	Therapy	random slope		125.6	11.21
	Residuals			254.1	15.94
Erythromycin	Individuals	random intercept		815.7	28.56
	Therapy	random slope		256.4	16.01
	Residuals			277.4	16.65

CI (Confidence Interval), Std.Error (Standard Error), Std.Dev. (Standard Deviation)

interval following the administration of erythromycin. A linear mixed mode was applied as described above, the results are reported in Table 2. Erythromycin had no clear effect on QTc-intervals over time.

Variability

In this heterogeneous study population the QTc-interval was highly variable within each of the groups, but did not vary between the groups, as is shown in Figure 4. There was no significant difference ($p = 0.22$) in QTc values between the ciprofloxacin group (mean 393 ms) and ciprofloxacin control group (mean 386 ms). The erythromycin group (mean 405 ms) and erythromycin control group (mean 404 ms) neither showed a significant difference ($p = 0.80$). In 0.6% of the registrations (1.138 out of 198.270 samples) the duration of the QTc-interval was longer than 500 ms. The index groups showed slightly more recorded QTc-intervals over 500 ms (ciprofloxacin 1.2%, erythromycin 0.8%) than the control groups (ciprofloxacin control 0.2%, erythromycin control 0.3%). However, QTc-intervals > 500 ms were not significant between therapy and control groups: ciprofloxacin therapy group (n = 7), median 531 (IQR 518 – 540) ms *versus* control group (n = 14), median 524 (IQR 515 – 531) ms; $p = 0.36$ and erythromycin therapy group (n = 13), median 525 (IQR 516 – 545) ms *versus* control group (n = 16), median 521 (IQR 516 – 544) ms; $p = 0.71$.

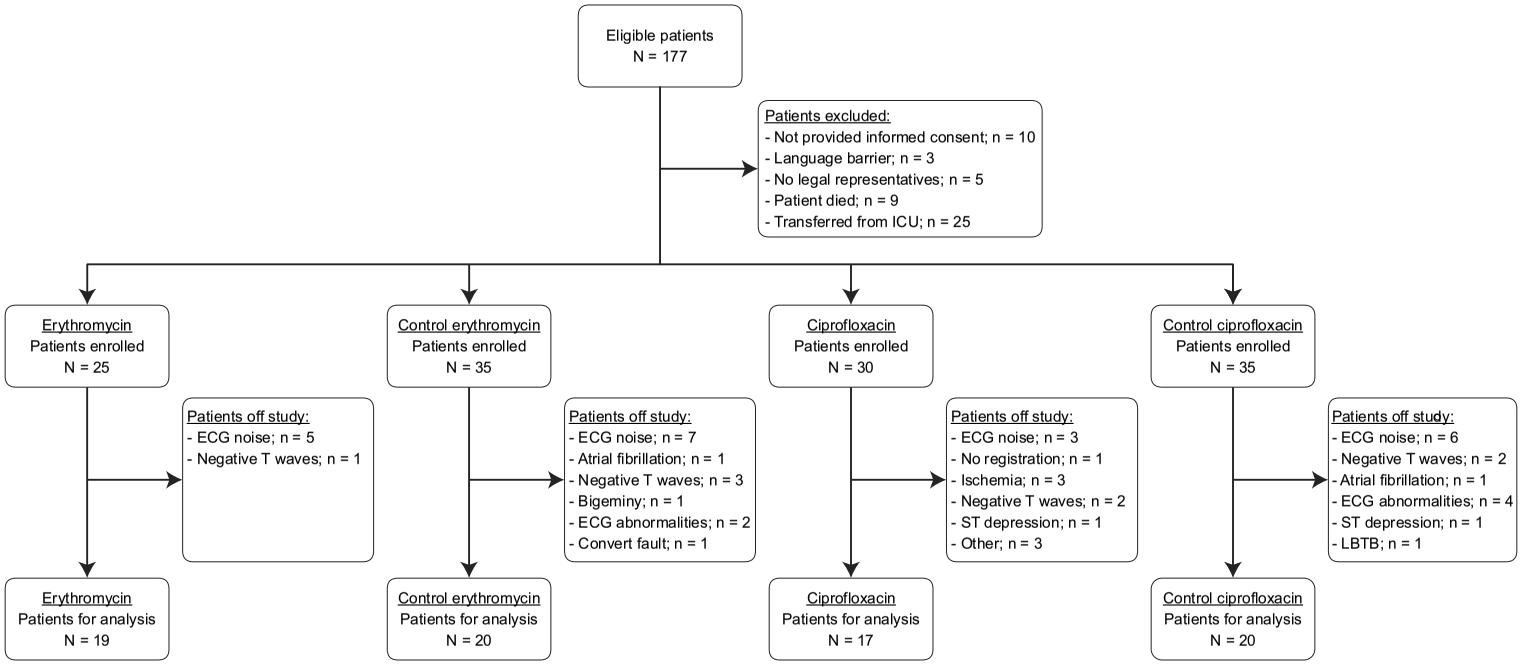


Figure 1. Flowchart of the results of inclusion and exclusion in the ciprofloxacin and erythromycin index and control groups

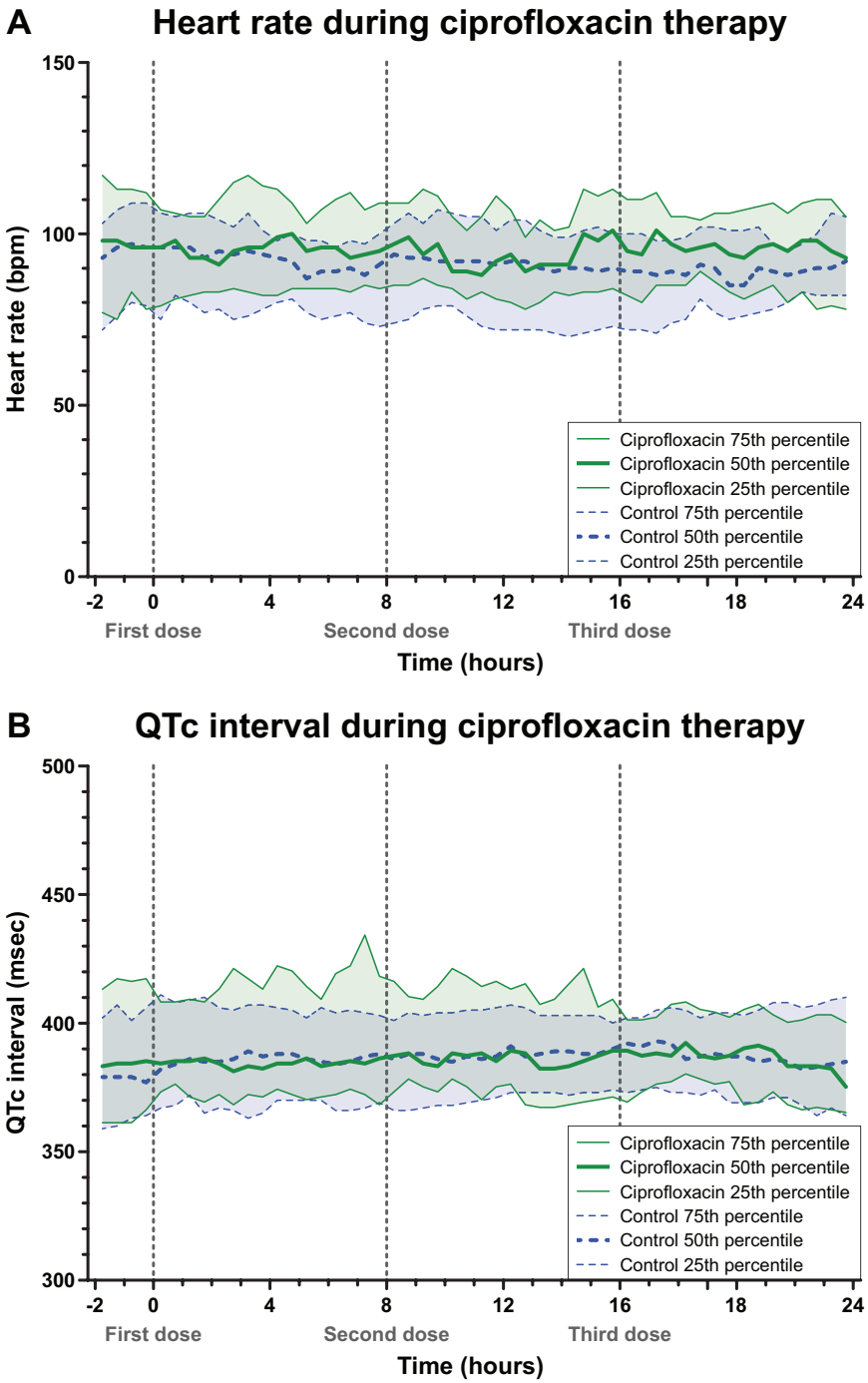


Figure 2. (a) Heart rate and, **(b)** QTc-intervals of ciprofloxacin index (n = 14) and matched control (n = 20) group during a 2-hour baseline period, followed by 24 hours of ciprofloxacin therapy with three intravenous administrations of ciprofloxacin as indicated by the vertical dotted lines. Trend lines indicate the 25th, 50th and 75th percentile.

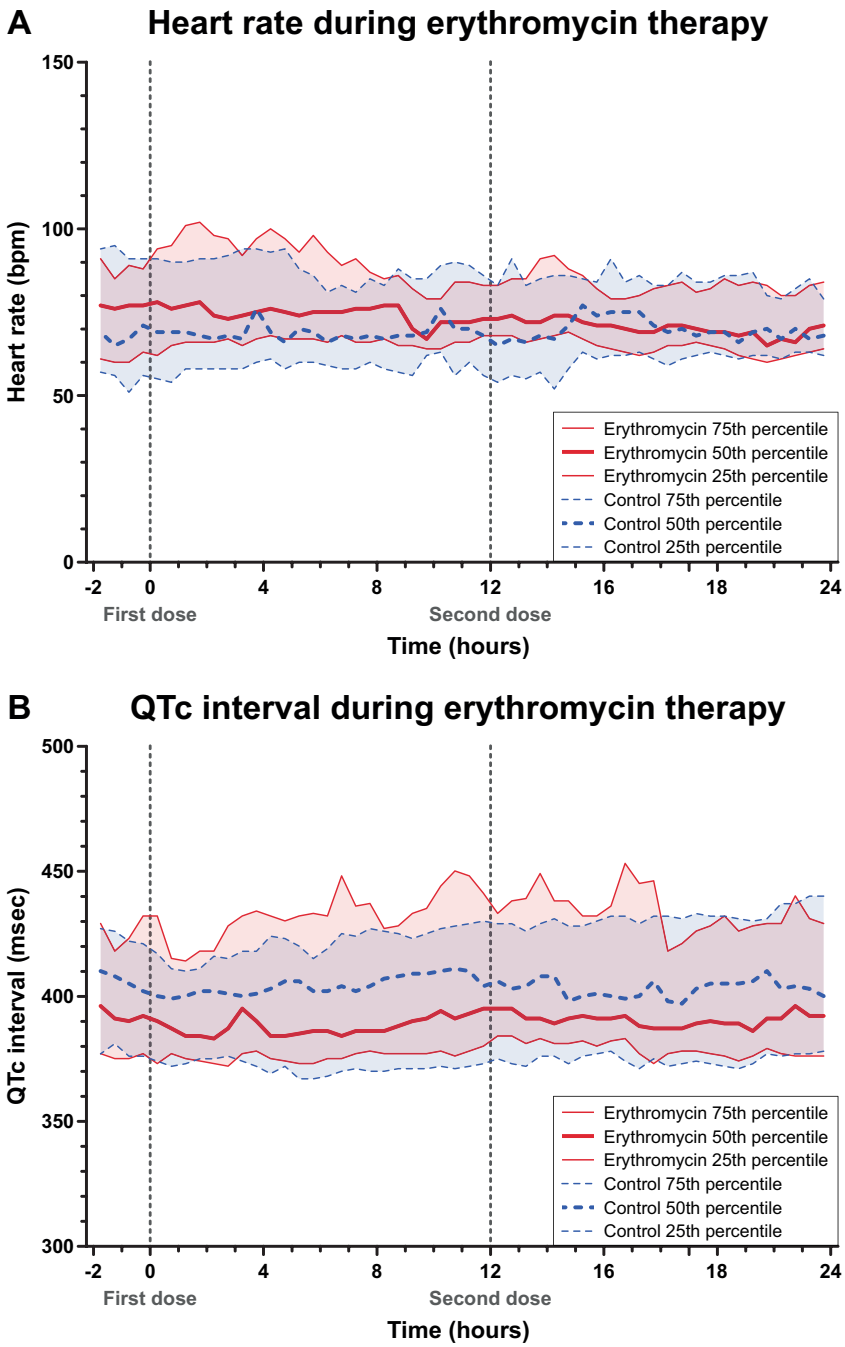


Figure 3. (a) Heart rate and, **(b)** QTc-intervals of erythromycin index (n = 17) and matched control (n =2 0) group during a 2-hour baseline period, followed by 24 hours of erythromycin therapy with three intravenous administrations of ciprofloxacin as indicated by the vertical dotted lines. Trend lines indicate the 25th, 50th and 75th percentile.

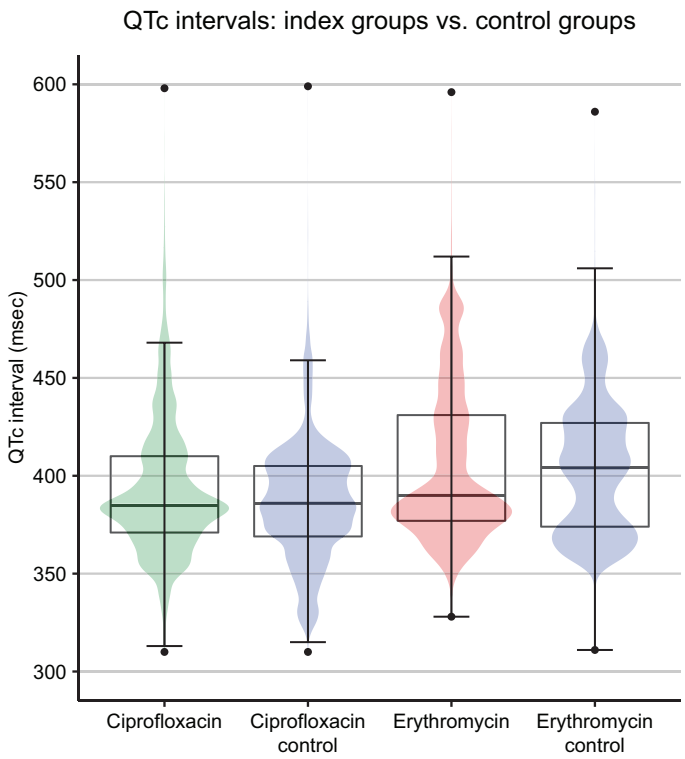


Figure 4. Violin plot of QTc-intervals (in ms) in the ciprofloxacin (n = 36.989 samples) and erythromycin (n = 47.754 samples) index groups and their respective control groups (n = 55.511 and n = 58.016 samples). Boxes indicate the median and interquartile range, whiskers indicate the standard error. Dots indicate the minimum and maximum values of the range. No significant differences were found between the index and control groups.

DISCUSSION

This study showed no changes in the duration of the QTc-interval in patients in whom ciprofloxacin or erythromycin was administered intravenously. Despite the fact that ECG was continuously recorded and the administration of both antibiotics carefully timed, no changes were observed. The index groups showed slightly more recorded QTc-intervals over 500 ms (ciprofloxacin 1.2%, erythromycin 0.8%) than the control groups (ciprofloxacin control 0.2%, erythromycin control 0.3%).

For ciprofloxacin it was expected that some changes would be observed, as this antibiotic has been mentioned to be associated with QTc-prolongation.[23] In line with our data also Heemskerk *et al*. could not find a QTc-prolonging effect of ciprofloxacin and they concluded that it is unlikely that ciprofloxacin has a clinically relevant QTc-prolonging effect or an increased risk of TdP.[15] Also in a recent drug-drug interaction study performed by our group we found that the prevalence of QTc-prolongation in patients using a combination of ciprofloxacin with fluconazole was low.[24] As a consequence ciprofloxacin can be removed from lists used for medication surveillance. ECG monitoring does not seem to be necessary for ciprofloxacin.

Erythromycin is a macrolide antibiotic, often used as a prokinetic in ICU patients. Like the other macrolides, erythromycin has been associated with severe QTc-interval prolongation. Especially when erythromycin is co-administered with other drugs that inhibit or are substrates of the CYP3A4 enzyme, the patient is at risk for severe QTc-prolongation and subsequent risk of QT related malignant arrhythmia.[25] Twenty-five years ago, Oberg *et al.*, reported an impressive increase from baseline QTc of 432 ± 39 ms, to 483 ± 62 ms during erythromycin therapy.[26] Overall, 19 (39%) of 49 patients in their study had a moderate to severe delay in ventricular repolarization (QTc ≥ 500 ms). The dosages of erythromycin were much higher than those in our study, and ranged from 18-83 mg kg^{-1} day^{-1}. In our study, the erythromycin dosages ranged from 2-4 mg kg^{-1} day^{-1}.

Fiets *et al*. also studied 51 ICU patients treated with erythromycin as a prokinetic (dose: 200 mg b.i.d. IV).[19] In this study continuous ECG recording was not used, but standard 12-lead ECGs were recorded directly before, and 15 min after the first infusion of erythromycin, as well as 15 min after the third infusion. The QTc-interval increased significantly from 430 ms at baseline to 439 ms (p = 0.03) after 15 min and 444 ms (p = 0.01) after 24 hours. No QTc related arrhythmias were observed. Possibly the difference in outcome with our study, where we did not find changes in the QTc-interval, is caused by the fact that the erythromycin dose used by Fiets *et al*. (200 mg b.i.d.) was twice as high as the dose in our study (100 mg b.i.d.).

Our population included patients with traumatic brain injury and (aneurysmatic) subarachnoid haemorrhage (SAH). SAH often causes a prolongation of the QTc-interval during the acute phase.[27,28] However, we analysed the SAH patients separately and did not a significant difference in QTc-prolongation between SAH patients and other patients.

A diurnal pattern in heart rate and QTc-interval has been reported, related to autonomic regulation of ventricular repolarization, but a circadian rhythm was not observed in our patient population. Most likely this is due to the fact that we studied an intensive care population in whom the day/night activity cycle can be disturbed. Also, the heart rate was constant for all patients during the 26 hour time interval.

One of the hypothesis at the start of the study was that after a drug dose the degree of QTc-interval prolongation would be related to the plasma concentration, either directly or with some delay. This might be important for timing of ECGs to check if, and to what degree, QTc-interval prolongation has occurred following one or more doses of the drug. Our study cannot provide recommendations as to timing of ECGs after initiation for one or more QTc-prolonging drugs, as our study lacks ECG recordings with substantial changes in the QTc-interval over a dose interval.

An important strength of our study is the continuous recording of ECGs in patients admitted to the ICU. There are numerous QT correction formulae to compare measurements at different time points and at different heart rates. Vandenberk *et al*. suggested that the correction formulae of Fridericia and Framingham have the best rate correction and are significantly associated with 30 day and 1-year mortality. However, Robyns *et al*. showed that individualized corrected QTc-intervals derived from continuous ECG recordings are superior to conventional QTc-intervals measured from a standard 12-lead ECG when using linear regression with QT-RR plots used in this study.[29]

Furthermore the timing of administration of the intravenously administered ciprofloxacin and erythromycin was carefully recorded. Although this type of monitoring would have allowed

the detection of even subtle or temporary changes in the QTc-interval, such changes were not found in our study. This brings us to the most important weakness of the study, i.e. the lack of a positive control. At the start of the study it was our hypothesis that we would find a positive signal of QTc-prolongation following the IV administration of these drugs. Ideally we would have wanted to see QTc-interval changes, albeit temporarily, following administration of a well-known QTc-prolonging drug. Although it was expected that the erythromycin treated patients would show at least some degree of QTc-prolongation after infusion of this drug we did not find any effect.

To conclude, intravenous ciprofloxacin and low-dose erythromycin do not have a significant effect on the QTc-interval over a 24-hour time interval in ICU patients. Hence, we advise no routine ECG monitoring when ciprofloxacin 400 mg t.i.d. and low-dose erythromycin 100 mg b.i.d. are used in ICU patients who have no electrolyte abnormalities and no other QTc-prolonging drugs.

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CHAPTER 4

THE RISK OF QTC-INTERVAL PROLONGATION IN BREAST CANCER PATIENTS TREATED WITH TAMOXIFEN IN COMBINATION WITH SEROTONIN REUPTAKE INHIBITORS

Koen G.A.M. Hussaarts
Florine A. Berger
Lisette Binkhorst
Esther Oomen-de Hoop
Roelof W.F. van Leeuwen
Robbert J. van Alphen
Danielle Mathijssen-van Stein
Natasja M.S. de Groot
Ron H.J. Mathijssen
Teun van Gelder

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ABSTRACT

Purpose: Antidepressants like the serotonin reuptake inhibitors (SRIs) are often used concomitantly with tamoxifen (e.g. for treatment of depression). This may lead to an additional prolongation of the QTc-interval, with an increased risk of cardiac side effects. Therefore we investigated whether there is a drug-drug interaction between tamoxifen and SRIs resulting in a prolonged QTc-interval**.**

Methods: Electrocardiograms (ECGs) of 100 patients were collected at steady state tamoxifen treatment, with or without concomitant SRI co-medication. QTc-interval was manually measured and calculated using the Fridericia formula. Primary outcome was difference in QTc-interval between tamoxifen monotherapy and tamoxifen concomitantly with an SRI.

Results: The mean QTc-interval was 12.4 ms longer when tamoxifen was given concomitantly with an SRI (95% CI 1.8 – 23.1 ms; $p = 0.023$). Prolongation of the QTc-interval was particularly pronounced for paroxetine (17.2 ms; 95% CI 1.4 – 3 3.0 ms; $p = 0.040$), escitalopram (12.5 ms; 95% CI 4.4 – 20.6 ms; $p < 0.010$) and citalopram (20.7 ms; 95% CI 0.7 – 40.7 ms; $p = 0.047$), where other agents like venlafaxine did not seem to prolong the QTc-interval. None of the patients had a QTc-interval of > 500 ms.

Conclusion: Concomitant use of tamoxifen and SRIs resulted in a significantly higher mean QTc-interval, which was especially the case for paroxetine, escitalopram and citalopram. When concomitant administration with an SRI is warranted venlafaxine is preferred.

INTRODUCTION

One of the most common causes of cessation of therapeutic use of drugs which have already been marketed is prolongation of the QT-interval, which is defined as a QT-interval > 470 ms in females and > 450 ms in males according to European Society of Cardiology (ESC) guidelines.[1, 2] QT-interval or the heart-rate corrected QT (QTc) interval prolongation is associated with higher risk of polymorphic ventricular tachycardia or Torsade des Pointes (TdP), which may ultimately lead to sudden cardiac death (SCD).[1, 3] The QTc-interval represents the duration between the onset of ventricular depolarization and the completion of repolarization of the myocardium. Several risk factors are associated with an increased risk for QTc-interval prolongation (e.g. hypopotassemia, renal impairment, use of diuretics and other QTc-prolonging drugs and unmodifiable risk factors such as age > 65 years and female gender).[1, 4-6] Furthermore, it has become evident that several classes of anti-cancer drugs are associated with QT prolongation and, therefore, this offers a great challenge in the treatment of cancer patients.[7-9]

The suggested mechanism of drug induced QTc-interval prolongation is inhibition or reduced expression of the Human ether-a-go-go related (hERG) gene that encodes a potassium channel that regulates repolarizing currents (I_{kr}) in the cardiomyocytes or inhibition of late sodium currents.[1, 10] Inhibition of these I_{kr} results in a delay in the ventricular repolarization causing prolongation of the QT-interval (Figure 1).

Some drugs are known I_{kr} inhibitors, but failed to demonstrate a clinical significant QTc-interval prolongation at dosages used in routine clinical practice (e.g. fexofenadine), although some of these drugs still give an increased risk of experiencing TdP.[1] Therefore, the risk of experiencing TdP is not fully linear with the extent of QTc-interval prolongation. Combining QTc-prolonging drugs (drug-drug interaction) may also increase the risk of SCD.[1, 8] The combination of two known QTc-prolonging drugs may result in a cumulative or synergistic prolongation of the QTc-interval and thus increased risk for TdP.[11, 12]

The risk of drug induced QTc-interval prolongation is determined according to Adverse Drug Event Causality Analysis into QTc-prolonging drugs with a '*known*', '*possible*' or '*conditional*' risk for TdP.[13, 14] A drug is categorized as a drug with a *known risk of TdP* if there is substantial positive evidence of prolongation of the QTc-interval and an association with TdP. The risk is scored as '*possible*' if there is substantial evidence which supports the conclusion that drugs can prolong the QTc-interval, but there is insufficient evidence that these drugs are associated with TdP. Finally, the risk is scored as '*conditional*' if there is substantial evidence of QT-interval prolongation with an association with TdP development but only under certain conditions (e.g. overdosing) or because the drug has shown ability to create one or more conditions that facilitate induction of TdP (e.g. by inhibiting metabolism of QTc-proloning drugs). Drugs with a '*known*' risk for QTc-interval prolongation are escitalopram and citalopram. Venlafaxine, imipramine, nortriptyline and tamoxifen are classified as '*possible*' and paroxetine, amitriptyline, sertraline, fluoxetine and fluvoxamine are classified as '*conditional*' according to CredibleMeds®.

One of the anti-cancer drugs, which is a known I_{kr} inhibitor, is the selective ER modulator (SERM) tamoxifen.[8, 15, 16] Since decades, tamoxifen is used in the treatment of breast cancer, where

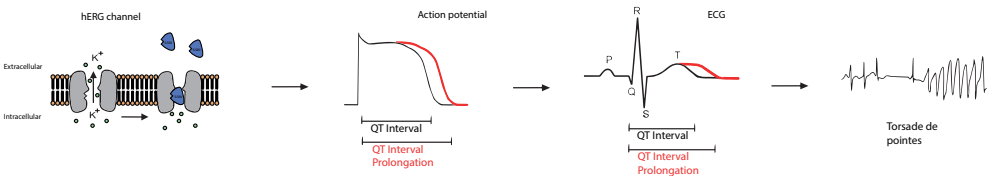

Figure 1. Mechanism of QTc-interval prolongation. Serotonin reuptake inhibitors (SRIs) inhibit the hERG channel and therefore the Ikr (repolarizing potassium (K^+) current) in the cardiomyocyte. This results in a delay of the ventricular repolarization time and therefore in a prolongation of the QTc-interval. Prolongation of the QTc-interval may result in cardiac arrhythmias such as TdP.

it provides suppression of ER-dependent proliferation of breast cancer cells and therefore reduces the risk of disease recurrence and mortality. However, tamoxifen may also lead to I_{kr} inhibition in cardiac tissue and ultimately to prolongation of the QTc-interval.[15] After absorption tamoxifen is converted into several pharmacologically active metabolites of which endoxifen is the most potent. The cytochrome P450 enzymes CYP2D6 and CYP3A4 play a dominant role in the biotransformation of tamoxifen.[17] It has been shown that the use of CYP2D6 or CYP3A4 inhibitors or inducers may lead to a significant alteration in tamoxifen and endoxifen exposure.[18-20] One of the classes of drugs that is known for its ability to inhibit CYP2D6 are the serotonin reuptake inhibitors (SRIs) like the selective serotonin reuptake inhibitors (SSRI) and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine.[21] These drugs are frequently used (by breast cancer patients) for the treatment of depression, anxiety disorders or (tamoxifen-related) hot flashes.[22] The most potent CYP2D6-inhibiting SRIs are paroxetine and fluoxetine.[21] When co-administration of an SRI is necessary with tamoxifen therapy, patients are often treated with weak CYP2D6-inhibiting SRIs like citalopram or escitalopram to minimize the risk of changes in endoxifen plasma concentrations.[19, 20] However, SRIs such as citalopram and escitalopram are also known to cause prolongation of the QTc-interval.[23]

Since both tamoxifen and SRIs may prolong the QTc-interval, the combined use of these drugs may result in an enhanced risk of prolongation of the QTc-interval and therefore ventricular arrhythmias, especially in breast cancer patients since they have often more additional risk factors (e.g. female gender, often older age). At present it is unknown if the effect of combined treatment on the QTc-interval is additive or synergistic. Hence, the objective of this study was to determine whether there is a clinically relevant drug-drug interaction between tamoxifen and SRIs resulting in a prolonged QTc-interval.

MATERIALS AND METHODS

Study design

This observational study was performed between February 2012 and October 2018. Electrocardiogams (ECGs) were collected in the Erasmus University Medical Center in Rotterdam, the Franciscus Vlietland & Gasthuis in Schiedam and the Elisabeth-TweeSteden hospital in Tilburg, the Netherlands. This study has focused on the QTc-interval during treatment with tamoxifen monotherapy compared to treatment with tamoxifen and SRIs (i.e. SSRIs, SNRIs and tricyclic

antidepressants). The study was approved by the local ethics committee of the Erasmus Medical Center in Rotterdam (MEC-2012-109).

Study population

We included a total of 100 adult patients with breast cancer for whom treatment with tamoxifen was indicated. Fifty patients also used an SSRI, venlafaxine or a tricyclic antidepressant, which also inhibits serotonin reuptake and may increase the risk for QTc-interval prolongation (e.g. amitriptyline). ECGs were taken at any time interval following drug intake. Patients were on tamoxifen treatment for at least 4 weeks. Patients were included either retrospectively or prospectively. Patients should not have received chemotherapy or radiotherapy within 4 weeks prior to the ECG-recording. If patients were included prospectively, written informed consent was obtained. If the ECG of patients showed a left or right bundle branch block (LBBB/RBBB), atrial fibrillation or other ECG abnormalities due to cardiac pathology, ischaemia or bigeminy, they were excluded from further analysis owing to interference of these factors with the QTc-interval. ECGs showing a QRS complex of > 120 ms, RR intervals > 1800 ms (defined as the time between two consecutive R waves) or < 500 ms or ECGs with a QTc-interval > 700 ms or < 300 ms were also excluded, since the QTc-interval could not be reliably measured. In addition, patients who used other strong inhibitors/inducers of CYP2D6 and/or CYP3A4 (according to the Flockhart table) were excluded from the analysis.[21] Medication with a *known risk of TdP* according to the CredibleMeds® list of QTc-prolonging drugs, except for tamoxifen and SRIs, was prohibited and considered as exclusion criterion.[13]

Outcome measures and data collection

The primary outcome measure of this study was the difference in QTc-interval duration between tamoxifen monotherapy and tamoxifen therapy with concomitant use of SRIs. Secondary outcomes were the difference in the prevalence of QTc-interval prolongation between the two groups and the identification of risk factors for QTc-interval prolongation. QTc-interval prolongation was defined as a QTc-time of > 470 ms in females and > 450 ms in males, based on the ESC guidelines.[2] Twelve-lead ECGs were recorded and QT-intervals were measured manually by the same researcher for all patients, preferably from lead II, from the onset of the QRS complex to the end of the T-wave, according to the tangent method, and were corrected for heart rate using the Fridericia formula (QTcF).[24] The Fridericia formula is formulated as the QT-interval divided by the RR-interval to the power 0.33 ().[25] For each patient data on characteristics such as age, sex, medical history, tumor localization, previous anti-cancer treatment, laboratory analysis (i.e. liver function [AST, ALT, bilirubin], renal function [creatinin, glomerular filtration rate (eGFR)] , electrolytes [sodium, potassium, calcium, magnesium]) and medication was obtained from electronic patient records (HIX, Chipsoft b.v., Amsterdam, the Netherlands). ECGs were obtained during tamoxifen or tamoxifen concomitant with an SRI therapy, when steady state therapy for both therapies was reached (determined as at least four weeks of use for tamoxifen and one week for SRIs). A baseline ECG was determined as an ECG before start of tamoxifen or SRI therapy.

Statistical analysis

QTc-intervals were compared between patients receiving tamoxifen monotherapy and patients receiving tamoxifen with concomitant SRI therapy. To detect a difference of 15 ms, assuming a standard deviation for QTc-interval time of 26 ms, in mean QTc-interval between both groups with 80% power, a total of one hundred patients was required. Therefore, a total of fifty evaluable patients using tamoxifen monotherapy and fifty evaluable patients using tamoxifen concomitant with an SRI were included in the study. A p-value ≤ 0.05 was considered statistically significant. Data was analyzed using Statistical Package for the Social Sciences (SPSS, IBM SPSS statistics version 24.0, USA). A t-test for independent samples was used to compare the mean QTc-interval between the treatment groups. Furthermore, difference between treatment groups in mean age was also determined using a t-test. For the other patient characteristics the chi-square test was used. Moreover for age, renal function, sodium, potassium, calcium and magnesium a Pearson correlation coefficient was estimated to determine the correlation with the QTc-interval. Correlation for other parameters as tumor localization and previous therapy (e.g. anthracyclines, trastuzumab and radiotherapy) was estimated using a Spearman correlation coefficient. For the secondary outcome the QTc-interval was dichotomized as either prolonged if > 470 ms for females or not prolonged if otherwise, according to the ESC guidelines.[2] Difference in proportion of QT-interval prolongation between groups was determined using the Fisher's exact test. Univariate logistic regression analysis was performed to determine associated risk factors. If there were any significant risk factors they were put into a multivariate analysis.

RESULTS

Participants

A total of 111 breast cancer patients were initially included in this study. Eleven patients were excluded due to a variety of ECG abnormalities at baseline resulting in a total of 100 evaluable patients. Fifty patients were treated with tamoxifen in combination with an SRI (further referred to as index group) and 50 patients were treated with tamoxifen without an SRI (further referred to as control group). All patients were female. The median age of patients in the control group (60; interquartile range (IQR) 50 – 66 years) was significantly higher than the median age of patients in the index group (50; IQR 45 – 59 years; p = 0.01). There were no other statistically significant differences between the two groups and none of the patients experienced cardiac arrhythmias. The most frequently used SRIs in the index group were venlafaxine (30%) and paroxetine (20%). A more detailed overview of the patient characteristics is presented in Table 1.

Primary outcome measures

Mean QTc-interval was 407.5 ± 22.1 ms in the control group and 419.9 ± 24.1 ms in the index group. This resulted in a significant difference in mean QTc-interval of 12.4 ms (95% CI 1.8 – 23.1 ms; p = 0.02) (Table 2). Heart rate was not significantly different between the control group and the index group.

Table 1. Patient characteristics

Characteristic	Index group, n = 50	Control group, n = 50	*p*-value
Age, median (IQR)	50 (45-59)	60 (50-66)	0.01*
< 65 years	41 (82)	37 (74)	
≥ 65 years	9 (18)	13 (26)	
Female, n (%)	50 (100)	50 (100)	NA
Race, n (%)			0.28
Caucasian	45 (90)	45 (90)	
Arabic	4 (8)	1 (2)	
African	1 (2)	1 (2)	
Latino	-	3 (6)	
Number of drugs, n (range)	2 (0-6)	2 (0-4)	0.93
Tamoxifen dose, n (%)			0.20
20 mg	45 (90)	49 (98)	
40 mg	5 (10)	1 (2)	
Type of antidepressant, n (%)			NA
Venlafaxine	15 (30)		
Paroxetine	10 (20)		
Escitalopram	5 (10)		
Citalopram	5 (10)		
Amitriptyline	5 (10)		
Sertraline	4 (8)		
Fluoxetine	3 (6)		
Other	3 (6)		
Renal dysfunction, n (%)	1 (2)	3 (6)	0.30
Electrolyte disturbances, n (%)			
Hyponatremia	2 (4)	0 (0)	0.50
Hypopotassemia	0 (0)	0 (0)	-
Hypocalcemia	3 (6)	2 (4)	1.00
Hypomagnesemia	1 (2)	2 (4)	1.00
Hepatic dysfunction, n (%)	1 (2)	1 (2)	1.00
Antidiabetic use, n (%)	4 (8)	3 (6)	1.00
Loopdiuretic use, n (%)	0 (0)	1 (2)	1.00

IQR (interquartile range), NA (not applicable). Other type of antidepressant were fluvoxamine (n=1), imipramine (n=1) and nortriptyline (n=1).

*p-value < 0.05

Renal dysfunction was defined as estimated Glomerular Filtration Rate (eGFR) < 60 ml/min/1,73m^2, Hyponatremia was defined as a sodium value < 136 mmol L^{-1}, Hypopotassemia was defined as a potassium value < 3.5 mmol L^{-1}, hypocalcemia was defined as a calcium value < 2.2mmol L^{-1}, hypomagnesemia was defined as a magnesium value < 0.7mmol L^{-1} and hepatic dysfunction was defined as increased bilirubin (> 16 umol L^{-1}), increased alanine aminotransferase (ALAT) (> 40 U L^{-1}) or increased aspartate transaminase (ASAT) (> 35 U L^{-1}).

Missing values: Hepatic function (n = 33), hyponatremia (n = 31), hypopotassemia (n = 27), hypocalcemia (n = 60), hypomagnesemia (n = 66) and renal dysfunction (n = 28).

Drugs with a 'known' risk for QTc-interval prolongation are escitalopram and citalopram. Venlafaxine, imipramine and nortriptyline are classified as 'possible' and paroxetine, amitriptyline, sertraline, fluoxetine and fluvoxamine are classified as conditional according to CredibleMeds®

Table 2. QTc times and difference in QTc-interval between treatment groups.

	QTc (Fridericia) time (ms), mean ± SD	QTc-prolongation, n (%)	QTc difference (ms), mean (95% CI)	*p*-value	Heart rate (bpm), mean ± SD
Tamoxifen monotherapy	407.5 ± 22.1	1 (2%)			70 ± 13.6
Tamoxifen with SRI	419.9 ± 24.1	0 (0%)[#]	+ 12.4 (1.8 – 23.1)	0.023[*]	69 ± 10.9
Venlafaxine	408.8 ± 21.5		+ 1.3 (-11.4 – 14.0)	0.840	
Paroxetine	424.7 ± 29.2		+ 17.2 (1.4 – 33.0)	0.040[*]	
Escitalopram	420.0 ± 6.0		+ 12.5 (4.4 – 20.6)	0.007[*]	
Citalopram	428.2 ± 16.6		+ 20.7 (0.7 – 40.7)	0.047[*]	
Amitriptyline	428.8 ± 32.5		+ 21.3 (-0.1 – 42.5)	0.054	
Sertraline	424.3 ± 24.1		+ 17.0 (-5.6 – 39.6)	0.147	
Fluoxetine	414.7 ± 25.6		+ 7.2 (-18.7 – 33.1)	0.590	

BPM (beats per minute), CI (confidential interval), SD (standard deviation), SRI (serotonin reuptake inhibitor)
[*] *p*-value < 0.05. For the analysis of the differences an independent samples t-test was used.
[#] Difference in number of patients with QTc-prolongation was not significant (p = 1.0)

Secondary outcome measures

Analysis with the Fridericia formula resulted in 1 patient with a prolonged QTc-interval, which was in the control group. This resulted in a prevalence of 2% in the control group and a prevalence of 0% in the index group, which was a non-significant difference ($p = 1.00$). None of the patients had a QTc-interval of > 500 ms. SRI subgroup analysis showed a significant difference in mean QTc-interval time for paroxetine (17.2 ms; 95% CI 1.4 – 33.0 ms; $p = 0.04$), escitalopram (12.5 ms; 95% CI 4.4 – 20.6 ms; $p < 0.01$) and citalopram (20.7 ms; 95% CI 0.7 – 40.7 ms; $p = 0.047$) compared to the control group in contrast to the other SRIs, which did not show a significant difference in QTc-interval (Table 2).

For the known risk factors for QTc-interval prolongation, only SSRI use (Spearman r = 0.25; $p = 0.01$), age (Pearson r = 0.24; $p = 0.02$), plasma potassium levels (Pearson r = -0.28, $p = 0.02$), renal dysfunction (Pearson r = -0.24; $p = 0.04$) and the use of >1 concomitant drugs used (Spearman r = 0.23, $p = 0.02$) showed significant correlation with QTc-interval duration. There were no other factors which showed a significant correlation with QTc-interval in general (Table 3). Furthermore possible risk factors as tumor localization (left *versus* right) and (pre)treatment with anthracyclines, radiotherapy or trastuzumab did not show statistically significant correlation with QTc-interval in general. Univariate analysis did not reveal any significant risk factors and therefore a multivariate analysis was not performed. The odds ratios for the individual risk factors could not be measured reliably, since the prevalence of QTc-prolongation was low.

DISCUSSION

To our knowledge, this is the first study that investigated the additional risk of developing QTc-prolongation in patients using tamoxifen in combination with an SRI. This study showed a significant

Table 3. Risk factors for QTc-interval prolongation

Patients	QTc-interval prolongation, n = 1	Correlation coefficient (*p*-value)
Age		0.24 (0.02)*
≥ 65 years, n	1	0.18 (0.07)
Race, n		0.07 (0.47)
Caucasian	0	
Arab	0	
African	0	
Latino	1	
Use of > 1 concomitant drug, n	1	0.23 (0.02)*
SRI use, n	0	0.25 (0.01)*
Type of SRI, n		0.27 (0.06)
Venlafaxine	0	
Paroxetine	0	
Escitalopram	0	
Citalopram	0	
Amitriptyline	0	
Sertraline	0	
Fluoxetine	0	
Other	1	
Renal dysfunction, n	1	-0.24 (0.04)*
Electrolyte disturbances, n		
Hyponatremia	0	-0.19 (0.12)
Hypopotassemia	0	-0.28 (0.02)*
Hypocalcemia	0	-0.14 (0.39)
Hypomagnesemia	0	0.29 (0.09)
Hepatic dysfunction, n	0	0.20 (0.10)
Antidiabetics, n	1	-0.12 (0.24)
Loop diuretics, n	0	-0.10 (0.32)

Number of patients which show QTc-interval prolongation (QTc > 470ms), when using the Fridericia formula.
*p-value < 0.05

difference in the mean QTc-interval between patients treated with tamoxifen monotherapy and patients treated with tamoxifen therapy concomitantly with an SRI, suggesting an additional QTc-prolonging effect if tamoxifen is combined with an SRI. Furthermore, in this study 1% of the patients had a prolonged QTc-interval (> 470 ms). This prevalence is in line with other clinical findings and a recent investigation in cancer patients treated with conventional or targeted anti-cancer therapy.[26, 27]

In this study, ECGs were retrospectively or prospectively collected during tamoxifen steady-state monotherapy or tamoxifen therapy combined with an SRI. One of the main limitations of this study was the absence of a baseline measurement in most of the patients. Therefore, a 'change from baseline' analysis could not be performed. There was a significant difference in mean QTc-interval time between the tamoxifen monotherapy and tamoxifen with SRI treated patients, which is most

likely related to the additive effect of the SRI. As mentioned earlier tamoxifen is an assumed QTc-interval prolonging agent, especially in higher doses.[8, 16] Furthermore there is substantial evidence regarding QTc-interval prolongation by SRIs, showing an average increase in QTc-interval of 10 – 20 ms. QTc-interval prolonging effects seem most prominent in nortriptyline and citalopram with increases of more than 30 ms.[28, 29] Therefore an additive effect of SRIs seems possible on top of the QTc-interval prolonging effects of tamoxifen. However, to determine whether the use of an SRI in combination with tamoxifen is a significant/clinically relevant factor influencing the QTc-interval, more research is needed in patients having both a baseline ECG during tamoxifen use and at least a second ECG where tamoxifen is used in combination with an SRI.

Interestingly, a subgroup analysis of the different SRIs showed a significant increase of the QTc-interval for citalopram, escitalopram and paroxetine, which is in line with the classification on the CredibleMeds® list. In this list, citalopram and also escitalopram has been clearly associated with QTc-interval prolongation. On this list paroxetine is classified as a drug which gives a *conditional risk of TdP*. Several additional factors like antidiabetic drug use, renal dysfunction and multiple drug use may have contributed to QTc-interval prolongation in some of these patients. Furthermore, patients in the control group were significantly older than in the index group. The QTc-interval increases with age, and therefore in elderly patients, the criteria for QTc-interval prolongation will be met more frequently in the index group. We do acknowledge that due to limited sample size in the subgroup our study was underpowered to make definitive conclusions regarding individual drugs.

Although QTc-interval prolongation is carefully investigated during early drug development, its actual influence on overall survival remains unclear. It is clear that QTc-interval prolongation can lead to ventricular tachyarrhythmias (e.g. TdP) and SCD.[1, 3] A recent systematic review from Arunachalam *et al*. showed that ventricular tachyarrhythmias were observed in 2.6% of patients using QTc-interval prolonging drugs, however TdP (0.33%) and SCD (0.03%) were relatively rare.[27] Since the absolute risk of cardiac events is small, physicians always need to weigh the benefits of cessation of a QTc-interval prolonging drug to the disadvantage of discontinuation of a potentially useful drug. If a QTc-interval prolonging drug can be replaced by a non QTc-interval prolonging agent, this should always be considered.

The interaction investigated in this study may be explained at a pharmacodynamic or pharmacokinetic level. Both tamoxifen and SRIs inhibit the I_{kr} and therefore, both may prolong the QTc-interval. Inhibition of CYP2D6 by SRIs results in lower endoxifen plasma levels (especially for strong CYP2D6 inhibitors like paroxetine) and possible more I_{kr} inhibition, because of the higher tamoxifen plasma levels. However preclinical evidence suggests similar I_{kr}-inhibition by both tamoxifen and its metabolites, making this a less likely explanation.[20, 30-32] SRIs like fluoxetine and paroxetine are well known strong CYP2D6 inhibitors, which could alter endoxifen concentrations and deprive patients from optimal oncologic therapy. Escitalopram, citalopram and venlafaxine are weak CYP2D6 inhibitors and therefore are considered safe when administered concomitantly with tamoxifen.[20] However, since escitalopram and citalopram are also *'known'* QTc-interval prolonging drugs, the combination with tamoxifen is not desirable and venlafaxine may be a better alternative

since it seems to prolong the QTc-interval in only a minor extent, as was shown in this study (Table 2). However more research is needed to verify this point.

In conclusion, this study is the first clinical study that investigated the additional risk of QTc-interval prolongation in patients using an SRI concomitantly with tamoxifen. There was a significantly longer mean QTc-interval in the patients who used an SRI, which tended to be most prominent in patients receiving citalopram, escitalopram or paroxetine. The other SRIs, like venlafaxine and fluvoxamine, were not clearly associated with QTc-interval prolonging effects. Based on our data we recommend avoiding citalopram, escitalopram and paroxetine in tamoxifen treated women, and use the others SRIs that do not have this QTc-prolonging effect (e.g. venlafaxine and fluvoxamine) to minimize the possible risk of TdP and cardiac arrhythmias. As the degree of QTc-interval prolongation was limited, and none of the patients in this study reached a QTc-interval of > 500 ms, routinely checking ECGs in patients on combined tamoxifen + SRI treatment does not seem necessary. For patients who have multiple other risk factors for QTc-interval prolongation and are using paroxetine, escitalopram and citalopram checking the QTc-interval duration may increase patient safety.

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CHAPTER 5

THE RISK OF QTC-INTERVAL PROLONGATION IN COVID-19 PATIENTS TREATED WITH CHLOROQUINE

Fleur S. Sinkeler
Florine A. Berger
Harm Jan Muntinga
Marc M. P. M. Jansen

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ABSTRACT

Background: Chloroquine, a quinolone antimalarial drug, is known to potentially inhibit pH-dependent viral replication of the SARS-CoV-2 infection. Therefore, chloroquine is considered as a treatment option for coronavirus disease 2019 (COVID-19). Chloroquine is known for prolonging the QTc-interval, but limited data are available on the extent of this QTc-prolonging effect.

Objective: To assess the QTc-prolonging potential of chloroquine in COVID-19 patients and to evaluate whether this prolongation increases with the cumulative dose of chloroquine and is associated with the peak plasma concentration of chloroquine. Furthermore, the number of patients who prematurely discontinued treatment or had an adjustment in dose due to QTc-interval prolongation was established.

Methods: A retrospective, observational study was performed in patients aged over 18 years, hospitalised for a suspected or proven infection with COVID-19, and therefore treated with chloroquine, with a baseline electrocardiogram (ECG) performed prior to the start of treatment and at least one ECG after starting the treatment.

Results: In total, 397 patients were included. The mean increase in QTc-interval throughout the treatment with chloroquine was 33 ms. Nineteen out of 344 patients unnecessarily had their treatment prematurely discontinued or adjusted due to a prolonged QTc-interval based on the computerised interpretation of the ECG.

Conclusion: Chloroquine treatment in COVID-19 patients gradually increased the QTc-interval. Due to a significant number of overestimated QTc-intervals by computer analysis, it is advisable to measure the QTc-interval manually before adjusting the dose or withdrawing this potentially beneficial medication.

INTRODUCTION

Chloroquine, a quinolone antimalarial drug, is known to inhibit pH-dependent viral replication in vitro for severe acute respiratory syndrome coronavirus (SARS-CoV-1) and several other viruses.[1, 2] Chloroquine can also inhibit the viral replication of SARS-CoV-2 as the necessary concentration (EC_{50}) can be reached with a cumulative dose of 3300 mg.[3, 4] Chloroquine has been considered as a treatment option in the Dutch guidelines since the beginning of the coronavirus disease 2019 (COVID-19) outbreak in the Netherlands.[5]

A common side effect of chloroquine is prolongation of the QTc-interval. It is on the CredibleMeds® list of drugs associated with a *known risk of torsades de pointes (TdP)*.[6] Limited data on the extent of this QT-prolonging effect are available from trials where chloroquine was used as an antimalarial drug [7, 8]. Furthermore, the dosages used in these trials for malaria were lower and the duration was shorter than in the therapy for COVID-19. Recently, a study with 95 patients treated with chloroquine for COVID-19 was published.[9] This study found a mean increase in the QTc-interval of 35 ms, which is remarkably longer than the previously described prolongations of 6 and 16 ms.[7, 8]

In order to further evaluate the QTc-prolongation potential of chloroquine, we conducted a retrospective observational study. The main aim of this study was to assess the QTc-prolongation potential of chloroquine in COVID-19 patients.

METHODS

This retrospective, observational cohort study was conducted at two teaching hospitals in the Netherlands (Elisabeth-TweeSteden Hospital (ETH) in Tilburg and Meander Medical Centre (MMC) in Amersfoort) from 10 March until 22 April 2020. All patients aged over 18 years, hospitalised for a suspected or proven infection with COVID-19, and therefore treated with chloroquine, with a baseline electrocardiogram (ECG) performed prior to the start of treatment and at least one ECG after starting the treatment with chloroquine were included. Due to the retrospective nature of this study, the medical ethical committee of Brabant waived the requirement for individual informed consent.

The main outcome measure was the difference in QTc time (ΔQTc) between the QTc-interval of the baseline ECG (ECG-0) and the first ECG taken after the start of the chloroquine treatment (ECG-1). Secondary outcome measures were the ΔQTc between the QTc-interval of ECG-0 and the last available ECG during chloroquine treatment (ECG-L), and whether the timing of the ECG during the second dosing interval of chloroquine had a relevant effect on the ΔQTc found as the primary outcome measure. We studied the association of several known risk factors associated with an increase of the QTc-interval. For patients from the ETH population, where chloroquine treatment was stopped because of a prolonged QTc-interval (> 500 ms, or an increase > 60 ms from baseline), the QTc-interval was manually recalculated by a cardiologist to verify the justification for stopping chloroquine treatment.

All patients admitted to the hospital with a suspected or proven infection with COVID-19 were treated with chloroquine according to the Dutch guidelines.[5] The dosing regimen for chloroquine

consisted of a loading dose of 600 mg followed by 300 mg twice daily, starting 12 h after the loading dose. The duration of the total regimen was 5 days, reaching a cumulative dose of chloroquine of 3300 mg. The exact administration date and time for all the chloroquine administrations were extracted from the electronic patient record.

The following patient characteristics were obtained from the medical record: sex, age, weight and body mass index, renal function at the start of chloroquine treatment, electrolyte levels prior to and during treatment (potassium, magnesium and calcium) and duration of chloroquine treatment. Comorbidity at the start of the treatment was classified by the Charlson Comorbidity Index. Relevant concurrent use of other potentially QTc-prolonging co-medication, defined as medication with a *known risk of TdP* according to the CredibleMeds® list, was defined as at least one administration 24 h prior to or 48 h after the first dose of chloroquine.[6] The same was done for lopinavir-ritonavir since it is known to significantly increase chloroquine plasma concentration and it was initially mentioned as a potential treatment option for COVID-19 in the first version of the Dutch guidelines and was therefore used in combination with chloroquine.[10]

A baseline ECG, including heart rate, PR interval, corrected QT-interval and QRS duration, was performed prior to initiation of the therapy with chloroquine. The computerised values were used for interpretation using the Marquette 12SL ECG analysis programme (GE Healthcare, Chicago, IL, USA).

The baseline ECG had to be conducted within 1 month before the start of chloroquine therapy. During the COVID-19 pandemic, the first ECG after the start was preferably recorded 24 – 72 h after the initiation of the treatment. For this study, all the available ECGs recorded during the treatment period with chloroquine were extracted from the hospital information system Epic Systems Corporation (Madison, WI, USA) at the ETH, and from Easycare (Healthcare B.V., Deventer, The Netherlands) at the MMC. Available ECGs were allocated to the dosing interval in which they were recorded. Furthermore, the obtained calcium, potassium and magnesium levels within 12 h prior to or after recording of an ECG were linked to that ECG.

For patients in the ETH population who prematurely discontinued treatment or had a dose adjustment, and had a QTc-interval above 500 ms and/or an increase of more than 60 ms from baseline, as measured on ECG during the latest dosing interval, the medical records were searched for the reason for premature discontinuation or adjustment in therapy. All ECGs from patients with an adjusted dose or discontinuation of therapy with a QTc-interval > 500 ms and/or an increase in QTc-interval > 60 ms were manually recalculated by a cardiologist using the method described by Postema and Wilde.[11]

Data were analysed using Statistical Package for the Social Sciences (SPSS, IBM SPSS statistics version 24.0, USA). Descriptive statistics were used to describe baseline characteristics. A linear regression analysis was performed to explore whether the timing of the ECG during the second dosing interval of chloroquine had a relevant effect on the ΔQTc found as the primary outcome measure. An independent t-test was used to determine whether there was a statistically significant difference in QTc-prolongation for sex, renal function or potential QTc-prolonging co-medication. Potential QTc-prolonging co-medication was dichotomised as either use or no use of potential QTc-prolonging co-medication. Renal function was dichotomised as either a renal function above or

under 60 ml min^{-1} per 1.73 m^2. Simple linear regression analysis was used to predict QTc-prolongation from age, baseline electrolyte levels or electrolyte levels around the first ECG after the start. Factors were considered statistically significant if $p < 0.05$. Factors that were associated with a probability of $p < 0.05$ in the univariate analysis were entered into multivariate models to adjust for confounding.

RESULTS

A total of 397 patients were included; 344 patients at the ETH and 53 patients at the MMC. These patients had a baseline ECG before starting treatment and at least one ECG during treatment. Baseline characteristics are displayed in Table 1.

Treatment with chloroquine resulted in a mean QTc-prolongation [± standard deviation (SD)] of 20 ± 39 ms between ECG-0 and ECG-1. Using computerised interpretation, the mean QTc-interval before treatment was 448 ± 34 ms, whereas the mean QTc-interval of ECG-1 was 468 ± 38 ms. This difference was statistically significant with $p < 0.05$. The corresponding QRS intervals were 98 ± 20 ms, 100 ± 22 ms and 101 ± 21 ms for ECG-0, ECG-1 and ECG-L respectively. Figure 1 shows the median, quartiles and mean QTc-interval for ECG-0 and ECG-1.

To evaluate the relationship between the QTc-interval and the cumulative dose of chloroquine, ΔQTc between ECG-0 and ECG-L was evaluated. Intervals were defined as the time between two administrations of chloroquine, where interval 1 was the time between the loading dose of 600 mg and the following dose of 300 mg. In most patients, only a baseline ECG and one ECG after start were measured. However, 155 patients had more ECGs recorded during the treatment. In these patients, the mean dosing interval in which the first ECG after the start was recorded was 2 and the mean interval in which the latest ECG was recorded was 6. From these 155 patients, ΔQTc was calculated for

Table 1. Baseline patient characteristics

Patient characteristics	Total, n = 397
Age (years), mean ± SD	67.8 ± 12.5
Male, n (%)	262 (66%)
BMI (kg/m^2), mean ± SD	28.5 ± 5.6
eGFR < 60 ($ml/min/1.73m^2$), n (%)	116 (42%)
Use of potential QTc-prolonging co-medication, n (%)	106 (27%)
Concurrent use of antiarrhythmic drugs, n (%)	10 (3%)
Co-morbidities, n (%)	
Myocardial infarction	38 (10%)
Congestive heart failure	32 (8%)
Electrolytes prior to starting treatment, mean ± SD	
Potassium ($mmol\ L^{-1}$)	4.2 ± 0.5
Calcium ($mmol\ L^{-1}$)	2.2 ± 0.2
Magnesium ($mmol\ L^{-1}$)	0.8 ± 0.1

BMI (body mass index), SD (standard deviation), eGFR (estimated glomerular filtration rate using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula)

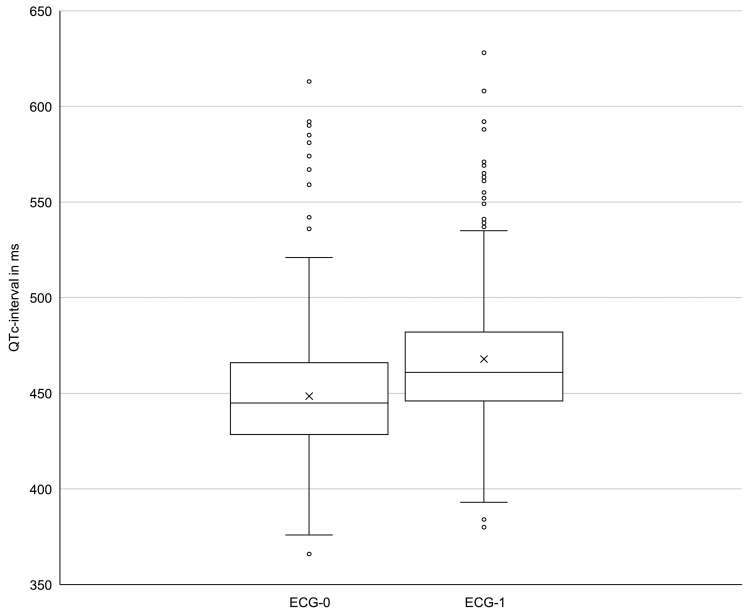

Figure 1. Median QTc-interval with interquartile range for the baseline electrocardiogram (ECG-0) and the first ECG after the start of treatment (ECG-1), based on 397 patients. The mean QTc-interval is displayed as X.

ECG-0 and ECG-L. Figure 2 displays the median, quartiles and mean QTc-interval for ECG-0, ECG-1 and ECG-L. For the 155 patients, the mean QTc-prolongation between ECG-0 and ECG-1 was 20 ± 43 ms. The mean QTc-prolongation between ECG-0 and ECG-L was 33 ± 53 ms. The differences in QTc-interval for ECG-0, ECG-1 and ECG-L were all statistically significant with a *p*-value of < 0.05. In addition, linear regression analysis demonstrated a significant correlation between the increase in QTc-interval and duration of treatment.

To evaluate whether the risk for QTc-prolongation increased as a function of the plasma drug concentration (C_{max}) during a dosing interval, QTc-intervals measured at different time-points during interval 2 (between the second and third administration) were determined for the 179 patients who had an ECG performed in chloroquine dosing interval 2. Figure 3 displays the time after the second administration of chloroquine and the difference between the baseline QTc and the QTc in dosing interval 2.

Sex and renal function were not significantly correlated with the ΔQTc between ECG-0 and ECG-1. Baseline electrolyte levels and those measured around ECG-1 or age were not associated with the ΔQTc between ECG-0 and ECG-1. Only the use of potential QTc-prolonging co-medication had a statistically significant effect on QTc-prolongation (24 ± 47 ms) between ECG-0 and ECG-1, compared to no use of QTc-prolonging co-medication (18 ± 36 ms; $p = 0.004$). However, this was not considered clinically relevant. Univariate analysis revealed only potential QTc-prolonging co-medication to be a risk factor and therefore a multivariate analysis was not performed.

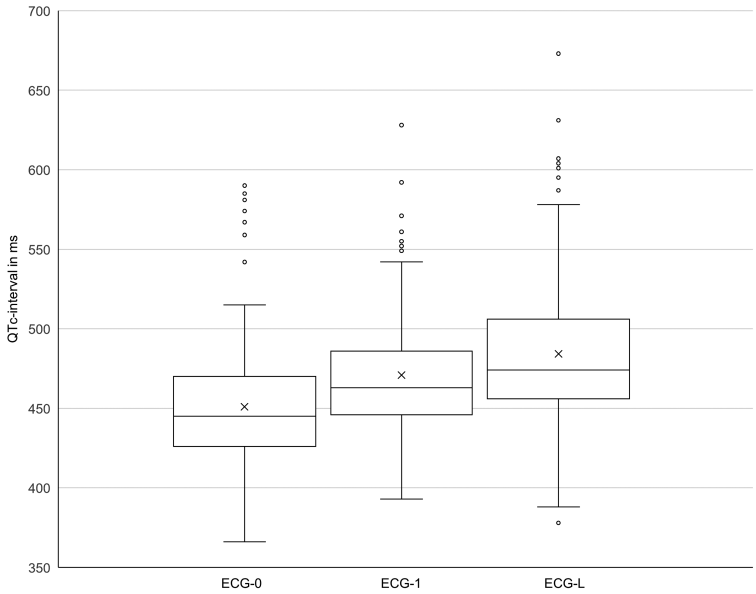

Figure 2. Median QTc-interval with interquartile range for the baseline electrocardiogram (ECG-0), the first ECG after the start of treatment (ECG-1) and the last available ECG during chloroquine treatment (ECG-L), based on 155 patients. The mean QTc-interval is displayed as X.

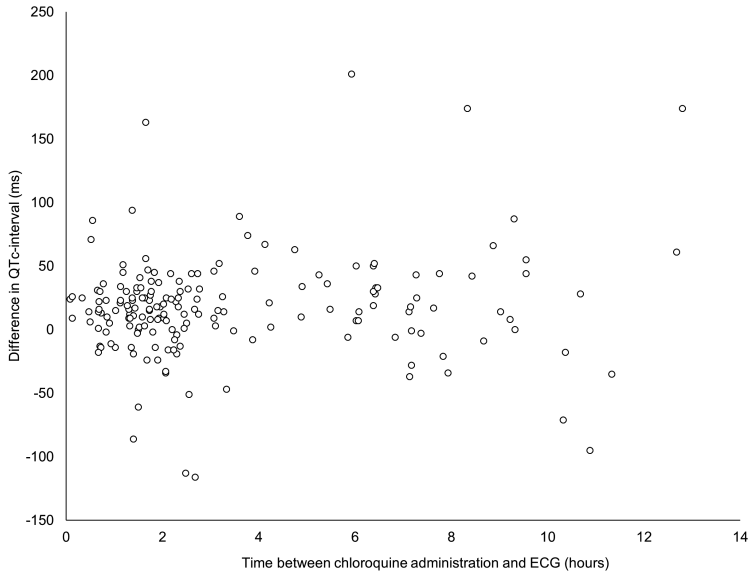

Figure 3. Difference between QTc from the baseline electrocardiogram (ECG-0) and the QTc measured in dosing interval 2 (between second and third administration) plotted against the time between the administration of the second dose of chloroquine and measurement of the ECG.

Seventeen out of 397 patients had a baseline QTc-interval exceeding 500 ms using computerised interpretation. After consulting a cardiologist, treatment with chloroquine was started in all patients. During treatment with chloroquine, 63 patients had a QTc-interval exceeding 500 ms and/or had an increase in QTc > 60 ms. Non-sustained ventricular tachycardia was observed in one patient, who had a manually calculated baseline QTc-interval of 481 ms. After the third dose, the manually calculated QTc-interval of this patient had increased to 540 ms.

Only the group of patients admitted to the ETH was used to identify the number of patients with premature discontinuation or with an adjustment in therapy due to QTc-prolongation. Of the 344 patients, 50 patients (14.5%) had prematurely discontinued or had a dose adjustment of chloroquine. In 27 of these 50 patients (54%), chloroquine was discontinued and three patients had a dose reduction to 150 mg twice daily due to QTc-prolongation. These clinical decisions seem to have been based on the computerised interpretation of the ECG. The ECGs of these 30 patients were manually recalculated by an independent cardiologist. Chloroquine treatment resulted in a mean prolongation of 75 ms for the computerised interpretation and 43 ms for the manually calculated QTc-interval. The manual interpretation disclosed that only 11 patients indeed had a QTc-interval of at least 500 ms and/or an increase in QTc of more than 60 ms.

DISCUSSION

Our study shows that treatment with chloroquine in COVID-19 patients significantly prolongs the QTc-interval with a mean QTc-prolongation of 33 ms throughout the treatment. QTc-prolongation, defined as a QTc-interval above 500 ms or an increase of more than 60 ms from baseline, was seen in a considerable number of patients (16%), even resulting in ventricular tachycardia in one patient.

The QTc-interval seemed to increase continuously after initiation of therapy. This could possibly be explained by the apparent half-life of 1.6 days.[12] Due to this half-life, the plasma concentration will further increase during the 5 days of treatment and steady state would only be reached 7 days after starting therapy. This is supported by the concentration-time profile of chloroquine, where the cumulative dose of chloroquine is highest at the end of the treatment period.[12] Thus, QTc-prolongation and the associated risk of TdP will continue to increase up until the end of the 5-day treatment period.

A study in healthy volunteers showed the QTc-prolongation to be greatest 4 h after the second dose of chloroquine.[7] However, this was not demonstrated in our study. On the contrary, the QTc-prolongation was similar throughout the second dosing interval. Therefore, the timing of an ECG recording within the dosing interval seems irrelevant for chloroquine.

Furthermore, this study demonstrates that 19 patients unnecessarily had their treatment prematurely discontinued or had their dose adjusted due to a prolonged QTc-interval based on the computerised interpretation of the ECG. In our study, electronically measured QTc values might differ from the manually performed measurement due to differences in standard lead selection, U-wave recognition, U wave inclusion or exclusion, and definition of T-wave ending.[11, 13] Another study found only a minor difference between the computerised and manual interpretation of the QTc-interval.[9] However, the reliability of the computerised measurement of

the QTc-interval has been found to be questionable and manual measurement of the QTc-interval is recommended.[11, 13, 14] Based on the present study, it is recommended that a cardiologist is consulted before clinical decisions are made based on the computerised interpretation.

A limitation of this study is the retrospective nature, although our large sample size included various ECGs captured at different time-points during the treatment with chloroquine. A possible bias may have been introduced by not manually recalculating all QTc-intervals. However, computerised interpretation is commonly used in clinical practice; thus our study is a good representation of the normal clinical setting.

CONCLUSION

Chloroquine treatment in COVID-19 patients gradually increased the QTc-interval during the treatment period, most likely due to the pharmacokinetic profile of chloroquine. Due to a significant number of overestimated QTc-intervals by computer analysis, it is advisable to measure the QTc-interval manually before adjusting the dose or withdrawing this potentially beneficial medication.

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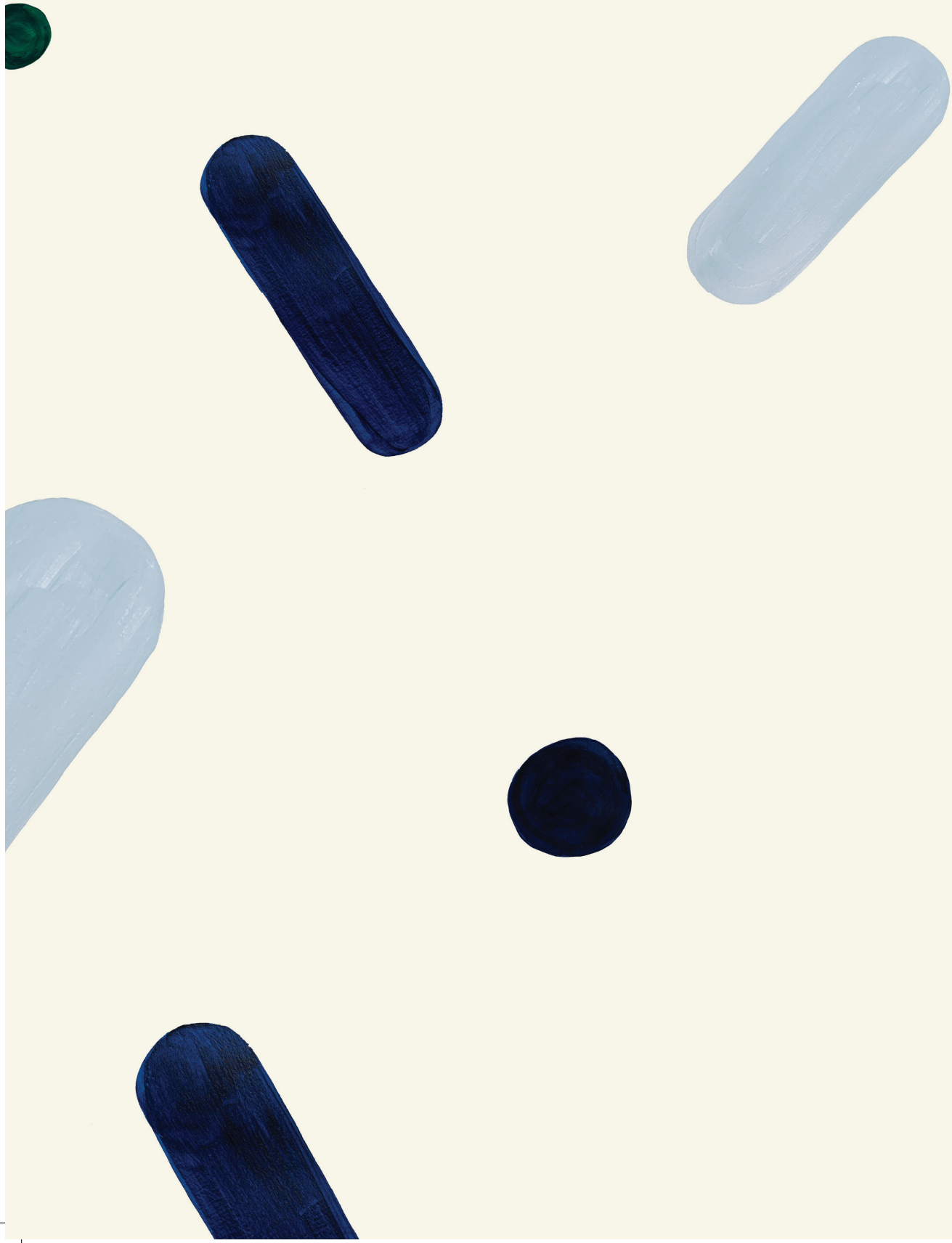
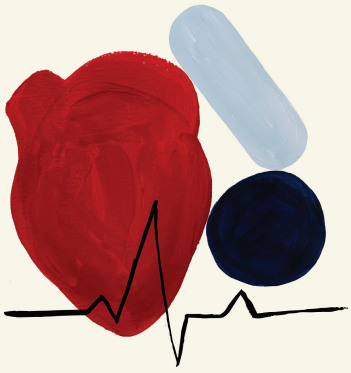


PART II

PREDICTION MODELS



CHAPTER 6

DEVELOPMENT OF A RISK MODEL FOR PREDICTING QTC-INTERVAL PROLONGATION IN PATIENTS USING QTC-PROLONGING DRUGS

Anita N. Bindraban
José Rolvink
Florine A. Berger
Patricia M. L. A. van den Bemt
Aaf F. M. Kuijper
Ruud T. M. van der Hoeven
Aukje K. Mantel-Teeuwisse
Matthijs L. Becker

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ABSTRACT

Background: Numerous drugs prolong the QTc-interval on the ECG and potentially increase the risk of cardiac arrhythmia. This risk is clinically relevant in patients with additional risk factors.

Objective: The objective was to develop and validate a risk model to predict QTc-interval prolongation of eligible ECGs.

Setting: Spaarne Gasthuis (Haarlem/Hoofddorp, The Netherlands).

Method: A dataset was created from ECGs recorded in patients using one or more QTc-prolonging drugs, in the period January 2013 and October 2016. In the development set, independent risk factors for QTc-interval prolongation were determined using binary logistic regression. Risk scores were assigned based on the beta coefficient. In the risk-score validation set, the area under the ROC-curve, sensitivity and specificity were calculated.

Main outcome measure: QTc-interval prolongation, defined as a QTc-interval > 500 ms.

Results: In the development set 12,949 ECGs were included and in the risk-score validation set 6391 ECGs. The proportion of ECGs with a prolonged QTc-interval in patients with no risk factors in the risk-score validation set was 2.7%, while in patients with a high risk score the proportion was 26.1%. The area under the ROC curve was 0.71 (95% CI 0.68 – 0.73). The sensitivity and specificity were 0.81 and 0.48, respectively.

Conclusion: A risk model was developed and validated for the prediction of QTc-interval prolongation. This risk model can be implemented in a clinical decision support system, supporting the management of the risks involved with QTc-interval prolonging drugs.

INTRODUCTION

Numerous drugs prolong the QTc-interval on the ECG.[1, 2] A prolonged QTc-interval is a risk factor for Torsade de Pointes (TdP), a potentially life-threatening arrhythmia.[3] A QT-interval corrected for the heart rate (QTc) is considered as prolonged if it exceeds 450 ms in men or 470 ms in women.[4] Arrhythmias are often associated with QTc-intervals exceeding 500 ms.[2, 4] QTc-prolonging drugs should be avoided if the use will likely result in QTc-intervals above this threshold. Nowadays over 100 drugs are associated with QTc-interval prolongation, and these drugs are enumerated on the list of QTc-prolonging drugs, established by CredibleMeds® (Arizona Center for Education and Research on Therapeutics).[5] Among them are drugs that are frequently used in daily practice and prescribed for non-cardiac indications.

There is much debate about the management of the risks associated with drug induced QTc-prolongation and whether these drugs can be prescribed safely to patients. In addition to drug use, various other risk factors are associated with QTc-prolongation, such as hypokalaemia, older age and female gender.[6, 7] The risk of drug induced QTc-prolongation can frequently be circumvented by selecting an alternative drug that is not associated with QTc-prolongation. Since QTc-prolonging drug use itself will rarely result in QTc-intervals exceeding 500 ms, other risk factors must be present. Therefore, in patients with a low baseline risk of QTc-prolongation, the additional risk of QTc-prolonging drugs is most likely negligible and the use acceptable in clinical practice.[8] However, in patients with a high baseline risk of QTc-prolongation, QTc-prolonging drugs should be either avoided or the QTc-interval should be monitored closely.[9] If QTc-prolongation is seen, the QTc-prolonging drug should be reconsidered or risk factors, such as hypokalaemia, should be intervened upon. Many healthcare information systems generate medication surveillance alerts if two or more QTc-prolonging drugs are prescribed. In patients with no other risk factors for QTc-prolongation, these alerts might be less clinically relevant and it could be considered to suppress these alerts. In patients with a high risk of QTc-prolongation, the use of even one QTc-prolonging drug may be undesirable.

Tisdale *et al*.[10] developed a risk model to predict QTc-prolongation in patients admitted to cardiac critical care units, independent of the use of QTc-prolonging drugs. It is questionable whether this model is also applicable to inpatients at non-cardiac departments and outpatients. Therefore, a risk model was developed in the present study to predict QTc-prolongation in inpatients and outpatients of a general teaching hospital and included only patients using QTc-prolonging drugs. Moreover, in the study by Tisdale *et al*. data were collected from both computerized and paper medical records, while in the present study the aim was to develop a model that does retrieve data automatically from healthcare information systems without manual review. Implementation of the risk model developed by Tisdale *et al*. at the cardiac critical care units resulted in a significant reduction of prescriptions for non-cardiac QTc-prolonging drugs and a significant reduction of patients with a QTc-interval prolongation (QTc > 500 ms).[11] Similarly, a clinical decision support system warning physicians prescribing QTc-prolonging drugs in patients who had an ECG with a QTc-interval > 500 ms in the past, resulted in a higher proportion of physicians to take action.[12] These results emphasize the importance of a clinical decision support system to avoid QTc-interval prolongation.

Aim of the study

This study aimed to develop and validate a risk model to predict QTc-interval prolongation of eligible ECGs for patients using one or more QTc-prolonging drugs. The risk factors included in this risk model are variables that are easily identifiable in a healthcare information systems, making this risk model suitable for use in a clinical decision support system. This risk model will alert healthcare providers in case multiple risk factors are present that may result in a QTc-interval above the threshold of 500 ms.

Ethics approval

No approval of a Medical Ethical Committee was needed according to the Dutch Medical Research Involving Human Subjects Act, because this was a descriptive study. All patient data were processed anonymously, according to privacy legislation.

METHOD

Study design

The design of this study is a retrospective data collection and content analysis. This study was performed at the Spaarne Gasthuis hospital with locations in Haarlem and Hoofddorp, the Netherlands.

Patients and electrocardiograms

An analysis of ECGs recorded between January 2013 and October 2016 was performed in patients who had one or more prescriptions for QTc-prolonging drugs with a *known risk of TdP* according to the CredibleMeds® list (October 2016) at the time of ECG recording.[6] Prescriptions for QTc-prolonging drugs with an 'as needed' frequency were excluded. ECGs of both inpatients and outpatients were included. ECGs were excluded if patients were younger than 18 years of age at the moment the ECG was recorded, had a QRS complex above 120 ms or if they had a QTc-interval of less than 300 ms or more than 600 ms. ECGs with a deviant QTc-interval were excluded, because most likely these are the result of incorrect interpretations of the ECG instead of strongly shortened or prolonged QTc-intervals. If multiple ECGs were recorded within a time period of 4 h, only the last ECG was included.

Data collection

Data were extracted from the hospital information system Epic (Madison, WI, USA), using SAP Crystal Reports (Walldorf, Germany). For all ECGs, the RR, QRS and QTc-interval were extracted and the patients gender and age at the time of the ECG recording. Subsequently, three data extractions were made, first all ECGs and the relevant medication orders at the time of the ECG, second all ECGs with the relevant laboratory values and third all ECGs with the relevant ECG information from the past. Data were processed using Statistical Package for the Social Sciences (SPSS, IBM SPSS statistics version 24.0, USA). ECGs were standard 12-lead resting ECGs with automated analysis by

the MUSE Cardiology Information System. The heart rate (RR), QT and QRS interval were calculated by the MUSE system and saved in the hospital information system Epic.

Study variables

The outcome measurement was a prolonged QTc-interval, defined as a QTc-interval above 500 ms. The Bazett's formula [), where HR is heart rate (beats/min)] was used to correct the QTc-interval for heart rate.[13] This correction is done, because at higher heart rates the QT-interval is shorter. After correction with the Bazett's formula, the QTc-intervals are independent of the heart rate. For each ECG, the following variables were analyzed as possible risk factors for QTc-prolongation at the time of the ECG recording to be included in the risk model: gender, age > 70 years, prescriptions for antidiabetic drugs, antiarrhythmics, acetylsalicylic acid, loop diuretics, thyroid hormones, beta-blockers and non-dihydropyridine calcium antagonists (verapamil/diltiazem), the number of prescriptions of QTc-prolonging drugs, the result of the last laboratory value in the last 7 days before the moment of ECG recording for potassium (≤ 2.9, 3.0 – 3.5 mmol L^{-1} or > 5.0 *versus* 3.5 – 5.0 mmol L^{-1}), calcium (≤ 2.14 mmol L^{-1} or > 2.55 *versus* 2.15 – 2.55 mmol L^{-1}), magnesium (≤ 0.69 mmol L^{-1} or > 1.00 *versus* 0.70 – 1.00 mmol L^{-1}), ALAT (≥ 100 *versus* < 100 U L^{-1}) and eGFR (≤ 60 *versus* > 60 ml min^{-1}) calculated with the MDRD formula, and the maximum QTc-time measured in the last 365 days before the moment of ECG recording. If laboratory values were missing, these values were categorized as the reference value, which is the normal value used by the laboratory of the hospital. Similarly, if no ECG was performed in the 365 days before the ECG, the maximum QTc-time was categorized as not prolonged.

Statistical analysis

Data were entered into Statistical Package for the Social Sciences (SPSS, IBM SPSS statistics version 24.0, USA) and analysed using descriptive statistics and logistic regression. The significance level (α) was determined at 0.05. Of all ECGs included in the study a random sample of two-third of all ECGs was analysed as a development set and the remainder one-third of ECGs was analysed as a risk-score validation set. In the development set, the association between the variable and the QTc-interval was assessed and cut-off values were determined for continuous variables. These cut-off values were used to dichotomize or categorize these variables for analysis. Binary logistic regression was performed for the associations between the risk factors and QTc-interval prolongation, using a backwards conditional stepwise method in the development set. If the variables were significant ($p < 0.05$) they were considered as an independent risk factor. Risk scores were assigned to the risk factors based on their beta coefficient, by dividing the beta coefficient through 0.2 and rounding it to the nearest number. We have chosen to develop a risk model with whole numbers instead of a complex formula, because a risk model with whole numbers is much easier to use in clinical practice and easier to interpret. The value of 0.2 was chosen to have enough discrimination between the effect size of various risk factors. The total risk scores were calculated for each ECG. In the risk-score validation set, sensitivity [true positive/(true positive + false negative)], specificity [true negative/(true negative + false positive)], positive predictive value [true positive/(true

positive + false positive)], Youden's J statistic [sensitivity + specificity-1], negative predictive value [true negative/(true negative + false negative)] and accuracy [true positive + true negative/all] were calculated for the prediction of QTc-interval prolongation using various cut-off values for the risk score. A ROC-curve was made by plotting the sensitivity versus one minus specificity for each cut-off point and the area under the curve was calculated. This study developed both a model in which all variables were analysed and a simplified model in which calcium and magnesium levels and past QTc values were excluded, because these values are not available in all settings.

RESULTS

In the study period, 19,340 ECGs were included that met the inclusion criteria, recorded in 6,927 patients (Table 1). The average age of the patients per ECG was 71.7 years and 52.0% was male. Two or more QTc-prolonging drugs were used in 8.8% of all ECGs. The QTc-interval was prolonged in 1,343 ECGs (6.9%). The ECGs were divided in a development set of 12,949 ECGs, recorded in 5,685 patients, and a risk-score validation set of 6,391 ECGs, recorded in 3,721 patients.

The following risk factors with the accompanying risk score were included in the risk model with binary logistic regression; hypokalaemia ≤ 2.9 mmol L^{-1} (7), the longest QTc-interval in the last 365 days above 500 ms (7), the longest QTc-interval in the last 365 days between 480 and 500 ms (3), hypokalaemia between 3.0 and 3.4 mmol L^{-1} (3), hypocalcemia ≤ 2.14 mmol L^{-1} (3), use of loop diuretics (3), eGFR below 60 ml min^{-1} (2), use of antiarrhythmics (1) and age above 70 years (1). The beta coefficients are given in Table 2.

The maximum risk score, if all risk factors would be present, is 24. In the analyses for the simplified model, calcium and magnesium levels and past QTc results were excluded. The following risk factors with the accompanying risk score were included in the simplified risk model with binary logistic regression: hypokalaemia ≤ 2.9 mmol L^{-1} (8), hypokalaemia between 3.0 and 3.4 mmol L^{-1} (4), use of loop diuretics (4), eGFR below 60 mL min^{-1} (2), use of antiarrhythmics (2), age above 70 years (1) and the use of beta-blockers (1). In this model, the use of beta blockers was a statistically significant additional risk factor. In the simplified model the maximum risk score is 18.

The quality of the predictability of the risk model was analyzed in the risk-score validation set. The mean risk score was 4.0. The proportion of ECGs with a prolonged QTc-interval in patients with a risk score of zero was 2.7%, while in patients with a risk score of 13 or higher the proportion of ECGs with a prolonged QTc-interval was 26.1% (Figure 1). The area under the ROC curve was 0.71 (95% CI 0.68 – 0.73) (Figure 2). The Youden's J statistic was at maximum with a cut-off value of ≥ 5. At this cut-off value the sensitivity was 0.63 and the specificity was 0.69. In Table 3 the performance per cut-off value is given.

In the simplified model, the mean risk score was 3.5 and the proportion of ECGs with a prolonged QTc-interval varied from 4.5% in patients with a risk score of zero to 19.1% in patients with a risk score of 11 or higher (Figure 1). The area under the ROC curve was 0.62 (95% CI 0.60 – 0.65) (Figure 2, Table 3). The Youden's J statistic was at maximum with a cut-off value of ≥ 5. At this cut-off value the sensitivity was 0.48 and the specificity was 0.73.

Table 1. Baseline characteristics of ECG

Characteristics	Development cohort n = 12,949	Validation cohort n = 6,391
Number of patients	5,685	3,721
Number of ECGs per patient; mean ± SD	2.3 ± 2.4	1.7 ± 1.3
Gender (male)	6,732 (52.0%)	3,322 (52.0%)
Age (years); mean ± SD	71.7 ± 12.4	71.6 ± 12.6
QTc-interval (ms); mean ± SD	447 ± 35	448 ± 36
QTc-interval > 500 ms	880 (6.8%)	463 (7.2%)
Number of QTc-prolonging drugs		
1	11,786 (91.0%)	5,853 (91.6%)
2	1,105 (8.5%)	504 (7.9%)
≥3	58 (0.4%)	34 (0.5%)
Use of antiarrhythmics	4,120 (31.8%)	1,997 (31.2%)
Use of beta-blockers	7,643 (59.0%)	3,825 (59.8%)
Use of loop diuretics	2,981 (23.0%)	1,499 (23.5%)
eGFR < 60 ml min^{-1}	2,942 (22.7%)	1,484 (23.2%)
Serum potassium level 3.0 – 3.4 mmol L^{-1}	614 (4.7%)	298 (4.7%)
Serum potassium level ≤ 2.9 mmol L^{-1}	142 (1.1%)	64 (1.0%)
Serum calcium level ≤ 2.14 mmol L^{-1}	655 (5.1%)	271 (4.2%)

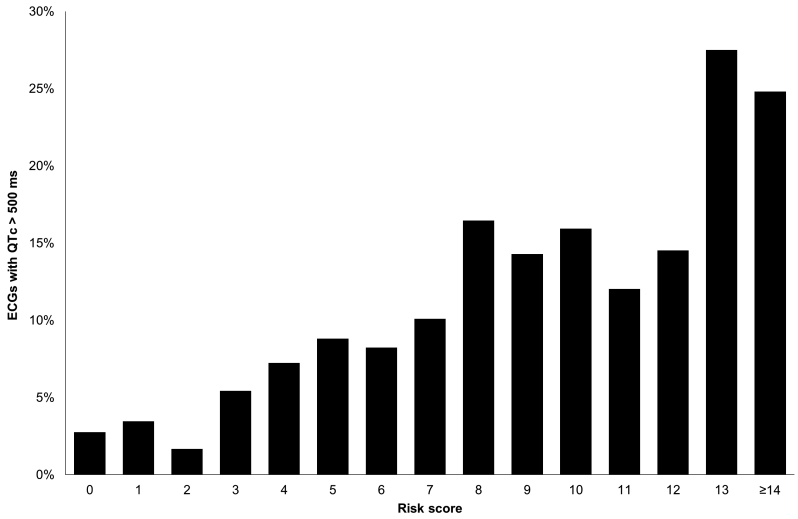
ECG (electrocardiogram), eGFR (estimated glomerular filtration rate), SD (standard deviation)

DISCUSSION

A risk model was developed to predict QTc-prolongation in patients using one or more QTc-prolonging drugs, defined as a QTc- interval of more than 500 ms. The variables that were analysed are automatically available in healthcare information systems. Therefore, this risk model can be implemented in a clinical decision support system, to improve the management of the risks associated with QTc-prolonging drugs. The variables included have been described in the literature as risk factors for QTc-prolongation[3, 6, 10, 14-17], and were therefore analysed. The maximum QTc-interval measured in the last 365 days was selected, because these patients have proven to be at risk for QTc-interval prolongation. A threshold of 500 ms was chosen, because QTc-intervals above this threshold are clinically relevant and have an increased risk of arrhythmias.[2, 4] Many healthcare information systems do not document diagnoses in such a way that they are assessable for clinical decision support systems. Therefore, drug use associated with the diagnosis was included in the risk model. For example, antidiabetic drug use was included as a proxy for the diagnosis diabetes mellitus. In this study, also a model excluding the variables calcium level, magnesium level and maximum QTc-interval measured in the past 365 days was developed, because these variables are not always available, for example in the setting of general practitioners and community pharmacies.

This simplified model may therefore be of value in such settings. In the risk-score validation set, the area under the ROC curve was 0.71. A perfect model that will predict all QTc-prolongations correctly will have an area under the ROC curve of one. There are several reasons why prediction of QTc-prolongation is substantially below one. First, even in patients with a high risk score, the risk of

a)



b)

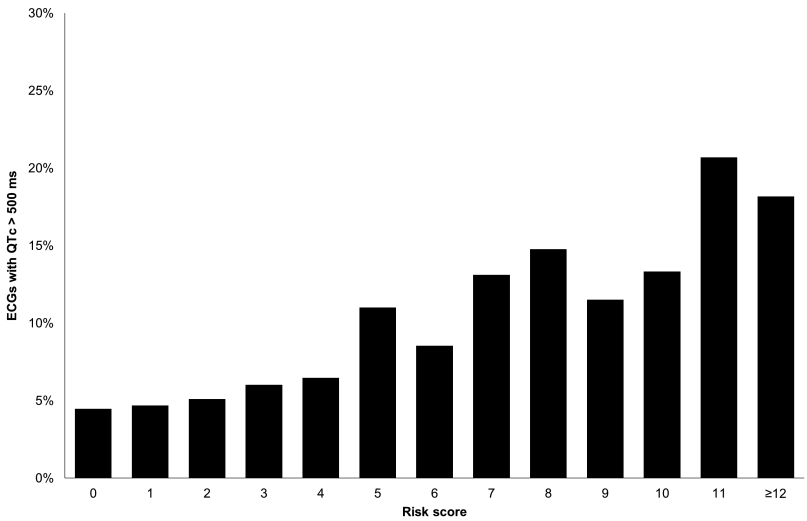


Figure 1. Risk scores and percentages of patients with QTc-interval prolongation based on complete **(a)** and simplified **(b)** models.

QTc-prolongation is rather low and the majority of ECGs in these patients do not have a prolonged QTc-interval. Second, there is variation over time in the QTc-interval independent of risk factors. This intra-individual variation will hamper prediction models. It is the authors' opinion that this model can predict QTc-prolongation to a clinically relevant degree. The proportion of ECGs with a prolonged QTc-interval showed a gradual increase from 2.7% in patients with a risk score of zero to 26.1% in patients with a risk score of 13 or higher. The area under the ROC curve for the simplified

Table 2. Complete and simplified risk models based on the binary logistic regression

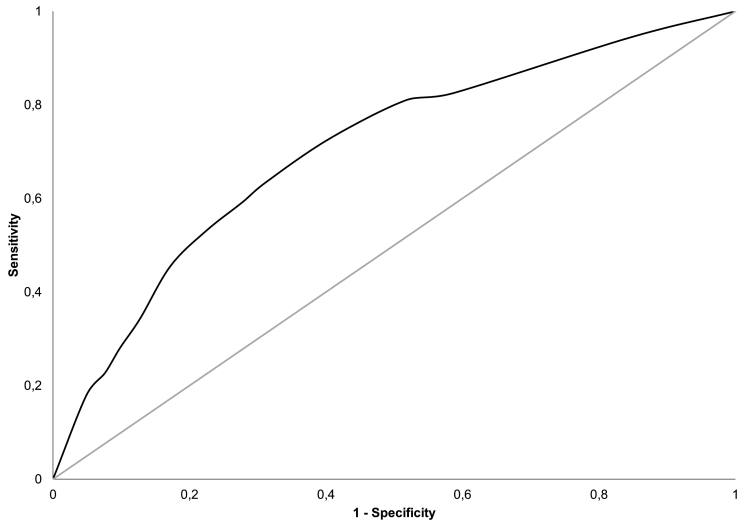
	Complete model [a,b]			Simplified model [a,b]		
Independent risk factor	**Beta coefficient**	**P value**	**Risk score**	**Beta coefficient**	**P value**	**Risk score**
Use of beta-blockers	No independent risk factor			0.191	0.010	1
Age > 70 years	0.206	0.009	1	0.191	0.014	1
Use of antiarrhythmics	0.265	0.001	1	0.493	< 0.001	2
eGFR < 60 ml min^{-1}	0.326	< 0.001	2	0.439	< 0.001	2
Use of loop diuretics	0.503	< 0.001	3	0.713	< 0.001	4
Serum Calcium ≤ 2.14 mmol L^{-1}	0.503	< 0.001	3	Not included in analysis		
Serum Potassium 3.0-3.4 mmol L^{-1}	0.627	< 0.001	3	0.736	< 0.001	4
Maximal QTc 481-500 ms [c]	0.638	< 0.001	3	Not included in analysis		
Maximal QTc > 500 ms [c]	1.321	< 0.001	7	Not included in analysis		
Serum Potassium ≤ 2.9 mmol L^{-1}	1.335	< 0.001	7	1.536	< 0.001	8
Maximum risk score			24			18

[a] Nagelkerke R2; complete model: 0.11; simplified model: 0.057

[b] The logistic equation is for the complete model is: $1/(1 + \exp(-(0.206\ (age > 70) + 0.265\ (use\ antiarrhythmics) + 0.326\ (eGFR < 60) + 0.503\ (use\ loop\ diuretics) + 0.503\ (Ca^{2+} \leq 2.14) + 0.627\ (3.0 \leq K^{+} \leq 3.4) + 0.638\ (481 \leq past\ QTc \leq 500) + 1.321\ (past\ QTc > 500) + 1.335(K^{+} \leq 2.9) - 3.613)))$. And for the simplified model: $1/(1 + \exp(-(0.191(use\ \beta\ blockers) + 0.191(age > 70) + 0.493\ (use\ antiarrhythmics)) + 0.439(eGFR < 60) + 0.713\ (use\ loop\ diuretics) + 0.736\ (3.0 \leq K^{+} \leq 3.4) + 1.536\ (K^{+} \leq 2.9) - 3.442))$

[c] The maximum QTc-time measured in the last 365 days before the moment of ECG recording

a)



b)

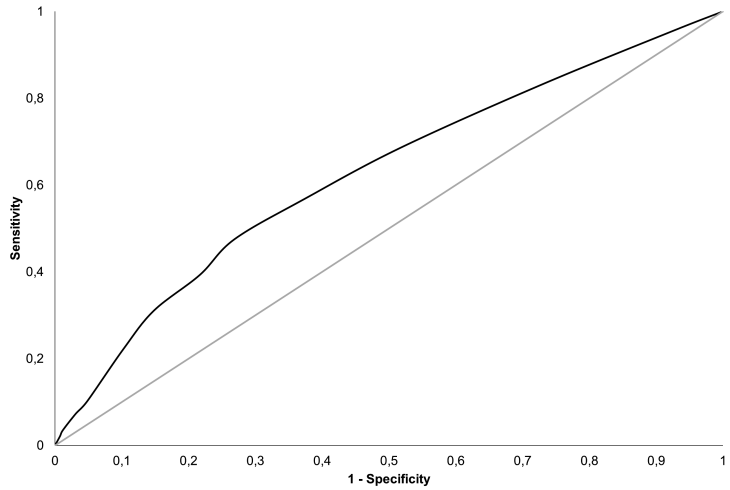


Figure 2. Receiver operating characteristic (ROC) curves of complete **(a)** and simplified **(b)** models

model, excluding magnesium and calcium levels and the maximum QTc-interval in the past 365 days, was 0.62. This model predicted the presence of QTc-interval prolongation to a lesser extent than the full model. Nevertheless, the proportion of ECGs with a prolonged QTc-interval increased from 4.5% in patients with a risk score of zero to 19.1% in patients with a risk score of 11 or higher. In both models, the performance was best and the specificity plus sensitivity highest, if a cut-off value of ≥ 5 was used.

The management of drug induced QTc-prolongation includes a balance between the small risk of TdP and sudden cardiac death, and the risk of withholding first-line therapies and switching to

Table 3. Risk screening accuracy based on complete **(a)** and simplified **(b)** models.

Cut-off value	Sensitivity	Specificity	Youden's J statistic	PPV	NPV	Accuracy
a. Complete model						
≥ 1	0.94	0.15	0.10	0.08	0.97	0.21
≥ 2	0.83	0.41	0.24	0.10	0.97	0.44
≥ 3	0.81	0.48	0.29	0.11	0.97	0.51
≥ 4	0.73	0.59	0.32	0.12	0.97	0.60
≥ 5	0.63	0.69	0.32	0.14	0.96	0.68
≥ 6	0.59	0.72	0.31	0.14	0.96	0.71
≥ 7	0.53	0.78	0.31	0.16	0.95	0.76
≥ 8	0.46	0.83	0.28	0.17	0.95	0.80
b. Simplified model						
≥ 1	0.95	0.08	0.03	0.07	0.96	0.14
≥ 2	0.83	0.27	0.10	0.08	0.95	0.31
≥ 3	0.68	0.48	0.17	0.09	0.95	0.50
≥ 4	0.57	0.63	0.19	0.11	0.95	0.62
≥ 5	0.48	0.73	0.21	0.12	0.95	0.71
≥ 6	0.39	0.78	0.18	0.12	0.94	0.75
≥ 7	0.31	0.85	0.16	0.14	0.94	0.81
≥ 8	0.22	0.90	0.12	0.14	0.94	0.85

PPV (positive predictive value), NPV (negative predictive value)

non QTc-prolonging alternatives. In patients with no risk factors for QTc-prolongation, the risk of drug induced TdP will be minor and withholding these therapies will result in a higher risk of adverse outcomes.[8, 9] Moreover, more frequent recording of ECGs due to the QTc-prolonging effect will be of no added value. To identify these patients, the healthcare provider has to evaluate the risk factors in the medical file of the patient. With a clinical decision support system, this process can be automated which reduces this time-consuming manual evaluation. Many healthcare information systems do alert the healthcare provider for drug–drug interactions between two or more QTc-prolonging drugs. In patients with a low risk for QTc-prolongation, the clinical relevancy of these alerts can be questioned. Presenting too many alerts to a healthcare provider holds the risk that all generated alerts are overridden including the relevant ones, so called alert fatigue.[18, 19] Implementing a clinical decision support system in the medication surveillance can reduce the number of alerts for patients with a low risk of QTc-prolongation. Before implementation of this risk model in medication surveillance, a cut-off value should be set. In patients with a risk score under this cut-off value, filtering of the alert could be considered. A cut-off value of three or above will result in correct identification of patients with a prolonged QTc-interval in 81% of cases (sensitivity), and in patients without a prolonged QTc-interval in 48% of cases (specificity). A higher cut-off value will result in an increase in patients with a prolonged QTc-interval who are not identified by the risk model (lower sensitivity) and an increase in patients with a prolonged QTc-interval who are identified by the risk model (higher specificity) and vice versa. In the limited model, a cut-off value of two or above will result in a sensitivity of 83% and a specificity of 27%. Further studies must reveal whether

implementation of this risk model does result in better medication surveillance and whether this is cost-effective.

In this study, a risk model was developed for patients who were treated in a general teaching hospital using at least one QTc-prolonging drug. Tisdale *et al*. developed a risk model to predict QTc-prolongation in patients admitted to cardiac critical care units.[10] notwithstanding the differences in methodology, there are similarities between the risk models. In both models, older age, use of loop diuretics and hypokalaemia are risk factors. Differences between the models can be explained by the differences in study population and variables studied. In the study by Haugaa *et al*., a risk model was composed that could predict mortality in patients with an electrocardiographically isolated QTc-interval of 500 ms or greater.[20]

This study has some potential strengths and limitations. A set of ECGs in routine clinical practice in a general teaching hospital was used. Since both in and outpatients in all departments were included, the results can be extrapolated to many health care settings, treating patients with similar risks as in this population. However, ECGs will be especially recorded if heart rhythm disturbances are expected, and therefore patients with a prolonged QTc-interval will be over represented in this study. The variables incorporated in this model can be extracted automatically from healthcare systems, making implementation in a clinical decision support system without manual review of the patient files possible. A limitation is that the ECGs were not reviewed manually. In the literature, there is discussion whether manual or automatic assessment of the ECG interval is better.[21] The QT-interval was adjusted using the Bazett's formula. This formula was used, because this is the one most frequently used in clinical practice. Recent studies, however, have shown that other formula's, such as the Fridericia and Framingham formula may perform better.[22]

If multiple ECGs were recorded in the same patient, all ECGs were included. We choose to include multiple ECGs per patient, because patients in whom multiple ECGs are recorded are the patients with the highest number of risk factors. Excluding ECGs in these patients would result in a set of ECGs not representative for all ECGs recorded in the hospital. The potential disadvantage is that the actual confidence intervals are wider than the calculated confidence intervals. Not all laboratory values were available in the patients. Missing values were analysed as being within the normal range, because if deviant values were suspected, these laboratory assessments would have been ordered. However, some deviant values might have been missed, resulting in a too low risk score. Calcium levels are corrected for the albumin levels in clinical practice. In patients with hypoalbuminemia, a too low calcium level may actually be within normal and the albumin adjusted calcium levels may have a stronger correlation with QTc-prolongation. However, such a correction formula would be difficult to implement in an automated clinical decision support system, and therefore calcium levels were analysed without correction. In a sensitivity analysis, we adjusted the calcium level for the albumin level in the risk model, if the albumin level was measured within the 48 h before the calcium level. This model did not have a higher area under the ROC curve in the risk-score validation set.

CONCLUSION

A risk model was developed and validated a for the prediction of QTc-interval prolongation in patients using one or more QTc-prolonging drug. This risk model is implementable in a clinical decision support system, evaluating automatically the information from the healthcare information systems. Implementation may result in a reduction of the number of alerts in patients with a low risk of QTc-prolongation and improve patient safety by reducing alert fatigue.

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CHAPTER 7

DEVELOPMENT AND VALIDATION OF A TOOL TO ASSESS THE RISK OF QT DRUG-DRUG INTERACTIONS IN CLINICAL PRACTICE

Florine A. Berger
Heleen van der Sijs
Matthijs L. Becker
Teun van Gelder
Patricia M. L. A. van den Bemt

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ABSTRACT

Background: The exact risk of developing QTc-prolongation when using a combination of QTc-prolonging drugs is still unknown, making it difficult to interpret these QT drug-drug interactions (QT-DDIs). A tool to identify high-risk patients is needed to support healthcare providers in handling automatically generated alerts in clinical practice. The main aim of this study was to develop and validate a tool to assess the risk of QT-DDIs in clinical practice.

Methods: A model was developed based on risk factors associated with QTc-prolongation determined in a prospective study on QT-DDIs in a university medical center in the Netherlands. The main outcome measure was QTc-prolongation defined as a QTc-interval > 450 ms for males and > 470 ms for females. Risk points were assigned to risk factors based on their odds ratios. Additional risk factors were added based on a literature review. The ability of the model to predict QTc-prolongation was validated in an independent dataset obtained from a general teaching hospital against QTc-prolongation as measured by an ECG as the gold standard. Sensitivities, specificities, false omission rates, accuracy and Youden's index were calculated.

Results: The model included age, gender, cardiac comorbidities, hypertension, diabetes mellitus, renal function, potassium levels, loop diuretics, and QTc-prolonging drugs as risk factors. Application of the model to the independent dataset resulted in an area under the ROC-curve of 0.54 (95% CI 0.51 – 0.56) when QTc-prolongation was defined as > 450/470 ms, and 0.59 (0.54 – 0.63) when QTc-prolongation was defined as > 500 ms. A cut-off value of 6 led to a sensitivity of 76.6 and 83.9% and a specificity of 28.5 and 27.5% respectively.

Conclusion: A clinical decision support tool with fair performance characteristics was developed. Optimization of this tool may aid in assessing the risk associated with QT-DDIs.

BACKGROUND

QTc-prolongation is known as a risk factor for developing ventricular arrhythmias such as Torsade de Pointes (TdP), which may eventually lead to sudden cardiac death. Therefore, a prolonged heart-rate corrected QT(c) interval is used as electrocardiogram (ECG) marker for an increased risk of TdP; and thus a prolonged QTc-interval should be avoided in patient care as a part of risk minimization.[1-3]

QTc-prolongation is defined as a QTc-interval > 450 ms in males and > 470 ms in females according to the European Medicine Agency guidelines.[4, 5] However, arrhythmias are frequently associated with QTc-intervals exceeding 500 ms.[6-8] A prolonged QTc-interval often represents a delayed ventricular repolarization. Roden *et al*. introduced a theory where some physiological mechanisms create a buffer to maintain normal ventricular repolarization, the so-called repolarization reserve. Several risk factors and genetic predisposition can reduce this repolarization reserve causing abnormalities in the ventricular repolarization [9, 10]. Consequently, multiple risk factors are frequently present in case reports describing patients who developed serious QTc-prolongation or TdP.[11, 12]

Several drugs are also responsible for developing QTc-prolongation known as drug induced QTc-prolongation. Currently, over 190 drugs are associated with QTc-prolongation according to the CredibleMeds® QT drug lists of the Arizona Center for Education and Research on Therapeutics (AzCERT). AzCERT categorizes QTc-prolonging drugs into three categories representing the level of certainty on the risk of TdP. More than 50 drugs are categorized as drugs with a *known risk of TdP*.[13] Many of these drugs such as antibiotics and antidepressants are widely used in clinical practice. QTc-prolonging drugs are not further classified with respect to the extent of QTc-prolongation. Also, the exact risk of developing QTc-prolongation when using a combination of QTc-prolonging drugs is unknown. For healthcare professionals, such as physicians and pharmacists, it is difficult to decide whether or not it is safe to proceed treating a patient with combinations of two or more QTc-prolonging drugs, and in whom additional checks of ECGs after treatment initiation are needed.

Other risk factors include hypokalaemia, hypomagnesemia, heart diseases (i.e. ischemic heart diseases, heart failure, and arrhythmia such as atrial fibrillation), and renal impairment. Also, demographic risk factors such as an older age, female sex and genetic predisposition are associated with QTc-prolongation.[2, 12, 14-16] However, the impact of these risk factors on the extent of QTc-prolongation is largely unknown, which makes it challenging to identify patients at risk for QTc-prolongation.

In the Netherlands, QT-DDI alerts are generated by the Computerized Physician Order Entry (CPOE) systems when two or more QTc-prolonging drugs with a *known risk of TdP* are combined. QT-DDI alerts are generated according to the so-called 'G-Standard', a Dutch drug database which supports the different processes in healthcare, such as prescription, dispensing, ordering, reimbursement, and decision support.[17] The current guidelines incorporated in the 'G-Standard' regarding QT-DDIs suggest to substitute or remove one of the interacting agents or perform routine ECG monitoring. As a result, first-line treatments are frequently not adhered to when one of the interacting agents is substituted, especially in primary care where ECG monitoring is often not feasible. In tertiary care, low adherence to guidelines result in many overridden DDI alerts by physicians[18]; and ECG monitoring is rarely performed when QT-DDI alerts are

overridden.[19, 20] With the increasing number of QTc-prolonging drugs, QT-DDI alerts will reduce the physician responsiveness to this particular type of alert, also known as alert fatigue. The use of a smart algorithm which generates specific alerts will reduce alert fatigue in clinical practice.

METHODS

The aim, design and setting

The aim of this study was to develop and validate a clinical decision support tool to assess the risk of QT-DDIs in clinical practice. A prospective, observational study design was chosen to identify potential risk factors of QTc-prolongation in patients using two or more QTc-prolonging drugs with a *known risk of TdP* as part of their usual care. This study was performed in the Erasmus University Medical Center Rotterdam, the Netherlands. An external validation was performed on retrospective data obtained from the Spaarne Gasthuis, a general teaching hospital with locations in Haarlem and Hoofddorp, the Netherlands.

Identification of potential risk factors and data collection

In the prospective study, patients (≥ 18 years) admitted to the Erasmus University Medical Center from September 2015 to March 2016 using two or more QTc-prolonging drugs with a *known risk of TdP*[13] were included. A standard twelve-lead resting ECG (paper speed 25 mm s^{-1}, amplitude 10 mm mV^{-1} and sampling rate 250 Hz) was recorded using the Mortara® ELI-350 ECG device (Milwaukee, Wisconsin, USA) at the estimated time of peak concentration (T_{max}) of the lastly added drug, or at the longest Tmax in case both drugs were started at the same time. Exclusion criteria included ECGs with a QTc-interval > 700 ms or < 300 ms, or with a ventricular rate (VR) > 180 beats per minute (bpm) or < 40 bpm as such ECGs do not allow reliable measurements of QTc-intervals; however, these ECGs were not present in our cohort. Patients with a congenital long QT syndrome, an implantable cardioverter-defibrillator (ICD) or a pacemaker were excluded. Also, patients with a left or right bundle branch block (LBBB/RBBB), atrial fibrillation or other ECG abnormalities due to cerebral pathology, ischemia or bigeminy were excluded as these comorbidities interfere with the QTc-interval.

The following data were prospectively collected from the electronic patient health record (Elpado, Rotterdam, the Netherlands): general patient characteristics including comorbidities and the medical condition at time of the ECG recording as well as the dose of the interacting drugs. The serum sodium (mmol L^{-1}), potassium (mmol L^{-1}), magnesium (mmol L^{-1}), and calcium (mmol L^{-1}) levels were collected within 5 days before or after the ECG recording, collecting the measurement closest to the ECG recording. Calcium levels were corrected for albumin levels.[21] The estimated glomerular filtration rate (eGFR, mL min^{-1}) using the Modification of Diet in Renal Disease (MDRD) formula, creatinine (μmol L^{-1}), aspartate transaminase (ASAT, U L^{-1}), alanine aminotransferase (ALAT, U L^{-1}), and bilirubin (μmol L^{-1}) were also obtained within 5 days before or after the ECG recording. Concomitant medication data were collected from the CPOE system Medicator (Computer Sciences Corporation (CSC) Healthcare Group, Leiden, the Netherlands) within 8 h prior to the ECG recording.[22] The QT-intervals were manually measured, preferably from lead II, from the onset of

the QRS-complex to the end of the T-wave using the tangent method. The QT-interval was adjusted for heart rate using the Bazett () and Fridericia () formula.[23,24]

Statistical analysis

Data were analyzed using Statistical Package for Social Science (SPSS, IBM SPSS Statistics version 21.0, Armonk, NY, United States). The QTc-interval was dichotomized as either prolonged or not prolonged (QTc > 450 ms for males and QTc > 470 ms for females).[8] Univariate logistic regression analysis was performed to determine potential risk factors, due to small sample size no multivariate logistic regression analysis was performed. Effect sizes were presented as odds ratios (OR) with their corresponding 95% confidence intervals (95% CI). A risk score of 1 to 3 points was assigned to potential risk factors based on their log odds ratios: ≤ 0.44 = 1 point; 0.45 – 0.94 = 2 points; ≥ 0.95 = 3 points.

Literature review on risk factors

A small dataset will not identify all potential risk factors and a model can benefit from the information of previous studies. Therefore, a literature review was performed.[25, 26] Additional risk factors from this review were incorporated into the model when they are easily obtainable in tertiary and primary care. Large cohort studies were retrieved from the database Medline. Study population, cases of QTc-prolongation, formula to correct for heart rate, cut-off values of QTc-prolongation and the statistically significant risk factors associated with QTc-prolongation were evaluated. The level of evidence was determined based on the level of significance in the studies evaluated. Also, reviews on drug induced QTc-prolongation were included to select relevant risk factors.[2, 6, 12] A risk score of 1 or 2 points was assigned to the additional risk factors based on the level of evidence.

External validation

The validity of the model was assessed in an independent dataset from a general teaching hospital to evaluate model performance and clinical usefulness. All ECGs that were recorded in routine clinical practice of ambulatory and hospitalized patients using two or more QTc-prolonging drugs between January 21st, 2013 and October 10th, 2016 were extracted from the hospital information system EPIC (Madison, WI, USA) using SAP Crystal Reports (Walldorf, Germany). All ECGs were standard twelve-lead resting ECGs with automatically calculated heart rates (RR), QT-intervals and QRS-complexes by the MUSE Cardiology Information System. Firstly, for ECGs with QRS-complexes > 120 ms, the QT-intervals were corrected using the following equation: . The QT-intervals were then corrected for heart rate using the Bazett and Fridericia formula.[24] A prolonged QTc-interval was defined as QTc > 450 ms for males and > 470 ms for females identical to the development cohort. Because arrhythmias are often associated with a QTc > 500 ms, we performed a post-hoc analysis in which QTc-prolongation was defined as QTc > 500 ms.[6, 7] ECGs with a QTc-interval > 700 ms or < 300 ms, or a VR > 180 bpm or < 40 bpm were excluded. Each patient was only included once using the first ECG available. Of these patients, data on risk factors included in the risk model were extracted such as age, sex, serum potassium (mmol L^{-1}), eGFR based on the MDRD (mL min^{-1}), cardiac comorbidities

(based on Anatomical Therapeutic Chemical Classification (ATC) C01), hypertension (based on ATC C02, C03, C07 – C09), diabetes mellitus (based on ATC A10) concomitant medication such as loop diuretics (based on ATC C03CA) and the use of QTc-prolonging drugs at time of ECG recording.[27]

The QTc-intervals > 450 ms in males and > 470 ms in females, and as post-hoc analysis QTc-intervals > 500 ms as measured by the ECG were taken as outcome measures, to which the performance of the model was compared. The model's potential clinical usefulness was assessed by its ability to distinguish patients with and without QTc-prolongation. The discriminative ability was quantified with receiver operating characteristics (ROC)-analyses, also known as concordance statistic (C-statistic). Cut-off points for the model were selected by maximizing the difference between sensitivity and 1 minus specificity. The primary focus was maximizing the sensitivity to identify low-risk patients, while keeping specificity at an acceptable level. Therefore, a cut-off value with a sensitivity of > 75% in order to increase the specificity as much as possible is accepted. Specificity, sensitivity, accuracy, the false omission rate and the Youden's index were calculated as these are the most relevant parameters for assessing clinical usability. Data are presented as mean with their standard deviation (SD) and median with their interquartile range (IQR).

RESULTS

Study population

In total, 107 patients were included in the development dataset, and 1579 patients were included in the validation dataset. The flowchart of inclusion is shown in Figure 1 and the patients characteristics in Table 1. The median age of the validation cohort was significantly higher than the median age of the development cohort (77 to respectively 56 years old).

Identification of risk factors

Of the 107 patients (43% female, median (IQR) age 56 (23) years) included, twenty-seven (25.2%) showed a prolonged QTc-interval on the ECG during treatment with two or more QTc-prolonging drugs. In none of these patients the QTc-interval was prolonged to more than 500 ms. The results of the univariate logistic regression analyses using the Bazett formula are presented in Table 2. A history of arrhythmia (OR 3.52; 95% CI 1.03 – 12.07) and hypertension (OR 3.44; 95% CI 1.36 – 8.86) were significantly associated with QTc-prolongation. The use of loop diuretics (OR 3.65; 95% CI 1.18 – 11.25) was also identified as a potential risk factor for QTc-prolongation when using the Fridericia formula. Risk score points were assigned to the potential risk factors based on their odds ratios (Table 3).

Review from literature on additional risk factors

The literature review included reviews and cohort studies with 8,453 patients in total.[2, 15, 28-33] Of the 8,453 patients, 1,772 patients (21%) showed QTc-prolongation assuming the studies were sufficiently powered to determine potential risk factors.[15, 28-31] In most studies[15, 29, 30], hypokalaemia was highly associated with QTc-prolongation with a significance level of $p < 0.01$. Due to the level of significance and the number of studies, severe hypokalaemia (≤ 2.5 mmol L^{-1}) was allocated 2 points

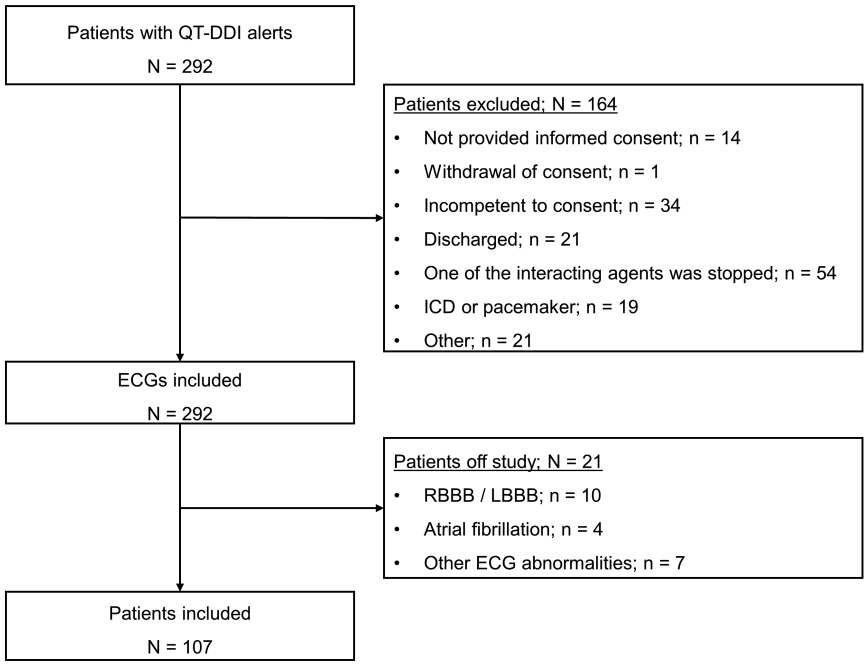

Figure 1. Flowchart of patient inclusion of the development cohort. DDI (drug-drug interactions), RBBB/LBBB (right or left bundle branch block)

Table 1. Patient characteristics of the development and validation cohort

Patient characteristics	Development cohort n = 107	Validation cohort n = 1,579	*p*-value
Age (years), median (IQR)	56.0 (23.0)	77.0 (17.0)	< 0.001[a]
≤ 50, n (%)	38 (35.5)	94 (6.0)	< 0.001[b]
51 – 75, n (%)	60 (56.1)	646 (40.9)	
≥ 76, n (%)	9 (8.4)	839 (53.1)	
Female, n (%)	46 (43.0)	731 (46.3)	0.507[b]
Comorbidities, n (%)			
Cardiac comorbidities	17 (15.9)	664 (42.1)	< 0.001[b]
Hypertension	30 (28.0)	1064 (67.4)	< 0.001[b]
Diabetes Mellitus	13 (12.1)	357 (22.6)	0.011[b]
eGFR (MDRD) (≤ 50ml min^{-1}), n (%)	9 (8.4)	439 (27.8)	< 0.001[b]
Hypokalaemia (< 3.5mmol L^{-1}), n (%)	5 (4.7)	158 (10.0)	0.023[b]
> 2 QTc-prolonging drugs c, n (%)	7 (6.5)	101 (6.4)	0.953[b]
Loop diuretics, n (%)	23 (21.5)	400 (25.3)	0.376[b]

eGFR (estimated glomerular filtration rate), IQR (interquartile range)

[a] Independent t test

[b] Chi-square test

[c] QTc-prolonging drugs with a *known risk of TdP*[13]

Missing values: Development cohort: eGFR (n = 2), K^+ (n = 1); Validation cohort: eGFR (n = 311), K^+ (n = 266)

Table 2. The association of several risk factors with QTc-prolongation in the development cohort (Bazett formula)

Potential determinant	QTc- prolongation n = 27	No QTc-prolongation n = 80	OR	95% CI
Age (in years) median; IQR	58.0; 14.0	54.5; 23.0	1.02	0.99 – 1.05
≤ 25, n (%)	1 (3.7)	4 (5.0)	*Ref.*	*Ref.*
26 – 50, n (%)	5 (18.5)	28 (35.0)	0.71	0.07 – 7.79
51 – 75, n (%)	17 (63.0)	43 (53.8)	1.58	0.17 – 15.19
≥ 76, n (%)	4 (14.8)	5 (6.3)	3.20	0.25 -41.21
Female gender, n (%)	4 (14.8)	42 (52.5)	0.16	0.05 – 0.50*
Caucasian race, n (%)	26 (96.3)	74 (92.5)	2.11	0.24 – 18.35
BMI (kg $m^{2\,-1}$) [a], mean ± SD	25.7 ± 4.3	27.3 ± 5.3	0.93	0.85 – 1.03
Clinical departments, n (%)				
Medical Units	14 (51.9)	69 (86.3)	*Ref.*	*Ref.*
Surgical Units	9 (33.3)	8 (10.0)	5.55	1.82 – 16.86*
Cardiac Units	4 (14.8)	3 (3.8)	6.57	1.32 – 32.66*
Comorbidities				
Myocardial infarction	1 (3.7)	1 (1.3)	3.04	0.18 – 50.32
Heart failure	1 (3.7)	3 (3.8)	0.99	0.10 – 9.91
Arrhythmia	6 (22.2)	6 (7.5)	3.52	1.03 – 12.07*
Hypertension	12 (48.1)	17 (21.3)	3.44	1.36 – 8.68*
Diabetes Mellitus	5 (18.5)	8 (10.0)	2.05	0.61 – 6.89
COPD/Asthma	1 (3.7)	11 (13.8)	0.24	0.03 – 1.96
Hematological malignancies	12 (44.4)	55 (68.8)	0.36	0.15 – 0.89*
Hepatic dysfunction [b], n (%)				
Increased ASAT (> 170 / 150 U L^{-1})	-	3 (3.8)	-	-
Increased ALAT (> 220 / 160 U L^{-1})	-	1 (1.3)	-	-
Increased bilirubin (> 16 µmol L^{-1})	2 (7.4)	16 (20.0)	0.33	0.07 – 1.55
eGFR ≤ 50ml min^{-1} (MDRD) [c], n (%)	3 (11.1)	6 (7.5)	1.50	0.35 – 6.47
Electrolyte disturbances [d], n (%)				
Hyponatremia (< 136 mmol L^{-1})	2 (7.4)	19 (23.8)	0.25	0.06 – 1.17
Hypokalaemia (< 3.5 mmol L^{-1})	2 (7.4)	3 (3.8)	2.03	0.32 – 12.83
Hypocalcemia (< 2.2 mmol L^{-1})	7 (25.9)	17 (21.3)	1.29	0.39 – 4.22
Hypomagnesemia (< 0.7 mmol L^{-1})	4 (14.8)	10 (12.5)	1.33	0.34 – 5.29
Concomitant medication, median; IQR	8.0; 4.0	8.0; 4.0	1.02	0.86 – 1.20
Loop diuretics, n (%)	8 (29.6)	15 (18.8)	1.83	0.67 – 4.95
QTc-prolonging drugs [e], n (%)				
0	4 (14.8)	11 (13.8)	*Ref.*	*Ref.*
1	6 (22.2)	28 (35.0)	0.59	0.14 – 2.50
≥2	17 (63.0)	41 (51.3)	1.14	0.32 – 4.09

Ref. (reference value), eGFR (estimated glomular filtration rate), IQR (interquartile range), BMI (body mass index), SD (standard deviation), OR (odds ratio), 95% CI (95% confidence interval)

* Statistically significant

[a] Missing values: BMI: no QTc (n = 1)

[b] Missing values: ASAT/ASAT: QTc (n = 5), no QTc (n = 7); Bili: QTc (n = 4), no QTc (n = 9)

[c] Missing values: eGFR: no QTc (n = 2)

[d] Missing values: Na^{+}/K^{+}: no QTc (n = 1); Ca^{2+}: QTc (n = 12), no QTc (n = 38); Mg^{2+}: QTc (n = 14), no QTc (n = 40)

[e] Other than the QTc-prolonging drugs with a *known risk of TdP*[13]

Table 3. Risk scores assigned to potential risk factors based on their Log OR

	Bazett formula			Fridericia formula		
Predictors	**Log OR**	**Score**	**OR (95% CI)**	**Log OR**	**Score**	**OR (95% CI)**
Age (in years)						
≤25	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*
26 – 50	-0.15	0	0.71 (0.07 – 7.79)	-	-	-
51 - 75	0.20	1	1.58 (0.17 – 15.19)	-	-	-
≥76	0.51	2	3.20 (0.25 – 41.21)	-	-	-
Arrhythmia	0.55	2	3.52 (1.03 – 12.07)	-	-	-
Hypertension	0.54	2	3.44 (1.36 – 8.68)	0.77	2	5.92 (1.92 – 28.27)
Loop diuretics	-	-	-	0.56	2	3.65 (1.18 – 11.24)

Ref. (reference value), OR (odds ratio), 95% CI (95% confidence interval)

and moderate hypokalaemia (2.6–3.4 mmol L^{-1}) was allocated 1 point in the model. Female sex was associated with QTc-prolongation in three studies [15, 30, 31] with a significance level of $p < 0.05$, so 1 point was assigned to female sex [2, 32]. The comorbidities renal failure and diabetes mellitus showed limited evidence in the studies with significance levels of $p < 0.05$.[30, 32] For QTc-prolonging drugs eliminated primarily by renal excretion, an impaired renal function can cause accumulation and toxicity of the QTc-prolonging drugs. Hemodialysis patients are also at increased risk for QTc-prolongation due to electrolyte abnormalities.[34] In addition, long-term glycemic variabilities in patients with diabetes mellitus, can induce QTc-prolongation; both comorbidities were therefore assigned 1 point in the model.[35, 36] The use of QTc-prolonging drugs with a *known risk of TdP* was highly associated with QTc-prolongation in several studies ($p < 0.01$).[2, 11, 15, 29, 30] As the model focused on patients using two or more QTc-prolonging drugs with a *known risk of TdP*, QTc-prolonging drugs with a *known risk of TdP* were incorporated in the model with 1 point. The QTc-prolonging drugs with a *possible* and *conditional risk of TdP* were not found to be associated with QTc-prolongation in multiple cohort studies, and were therefore not taken into account. The final clinical risk model, is presented in Table 4.

External validation

In total, 6,361 ECGs of patients using two or more QTc-prolonging drugs were extracted from the hospital information system EPIC (Madison, WI, USA). The ECGs included in the validation dataset belonged to 2,514 unique patients. Because perioperative patients and patients admitted to the intensive care unit (ICU) were not included in the development cohort, we excluded QT-DDI alerts in the validation cohort with propofol as these alerts concerned perioperative and ICU patients. Also, 2 ECGs were excluded because the heart rates were > 180 bpm.

Eventually, the validation cohort consisted of 3,891 ECGs of 1,579 unique patients. The mean QTc-interval of the first ECG available was 453.7 ms. In total, 655 (41.5%) ECGs showed a prolonged QTc-interval defined as > 450/470 ms (m/f). The mean ± SD risk score of patients with a QTc-

interval > 450/470 ms (m/f) was 7.4 ± 2.5; the mean ± SD risk score of patients with a normal QTc-interval was 7.2 ± 2.5.

The area under the ROC-curve (AUROC) was 0.54 (95% CI 0.51 – 0.56) as shown in Figure 2. The performance characteristics of the model are presented in Table 5. The selected optimal cut-off value was 6; 26.3% of all patients scored < 6 points. This cut-off value led to a sensitivity of 76.6% and a specificity of 28.5% to predict patients with a QTc-interval > 450/470 ms (m/f). Figures 3 and 4 show the distribution of the risk scores in the external validation.

Post hoc analysis

In total, 155 ECGs (9.8%) showed a QTc-interval exceeding 500 ms. The mean ± SD risk score of patients with a QTc-interval > 500 ms was 7.9 ± 2.5; the mean ± SD risk score of patients with a normal QTc-interval was 7.2 ± 2.5. The area under the ROC-curve (AUROC) was 0.59 (95% CI 0.54 – 0.63)

Table 4. The risk model

Risk factors	Score
Age (in years)	
51 – 75	1
≥ 76	2
Female gender	1
Comorbidities	
Cardiac comorbidities	2
Hypertension	2
Diabetes Mellitus I and II	1
eGFR ≤ 50 mL min^{-1} (MDRD)	1
Potassium levels	
≤ 2.5 mmol L^{-1}	2
2.6 – 3.4 mmol L^{-1}	1
Loop diuretics	2
QTc-prolonging drugs with a *known risk of TdP* [a]	1

[a] Classified according to the CredibleMeds® QT drug lists[13]

Table 5. Performance characteristics of the risk model in the external validation when using different cut-off values

Performance characteristics	Cut-off-value ≥ 5		Cut-off value ≥ 6		Cut-off value ≥ 7	
	> 450/470 ms	> 500 ms	> 450/470 ms	> 500 ms	> 450/470 ms	> 500 ms
Sensitivity (%)	86.3	91.0	76.6	83.9	63.8	69.0
Specificity (%)	16.3	15.9	28.5	27.5	40.4	39.5
False Omission Rate (%)	37.3	5.8	36.8	6.0	38.9	7.9
Accuracy (%)	0.45	0.23	0.48	0.33	0.50	0.42
Youden's index (%)	2.6	6.9	5.1	11.3	4.2	8.5

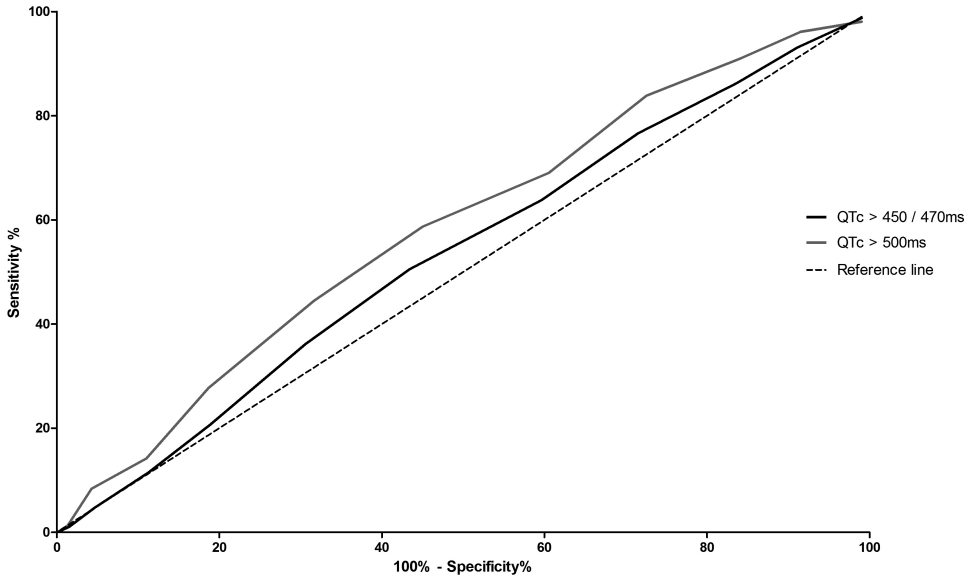

Figure 2. ROC-curves (> 450/470 ms and > 500 ms) of the risk model in the external validation

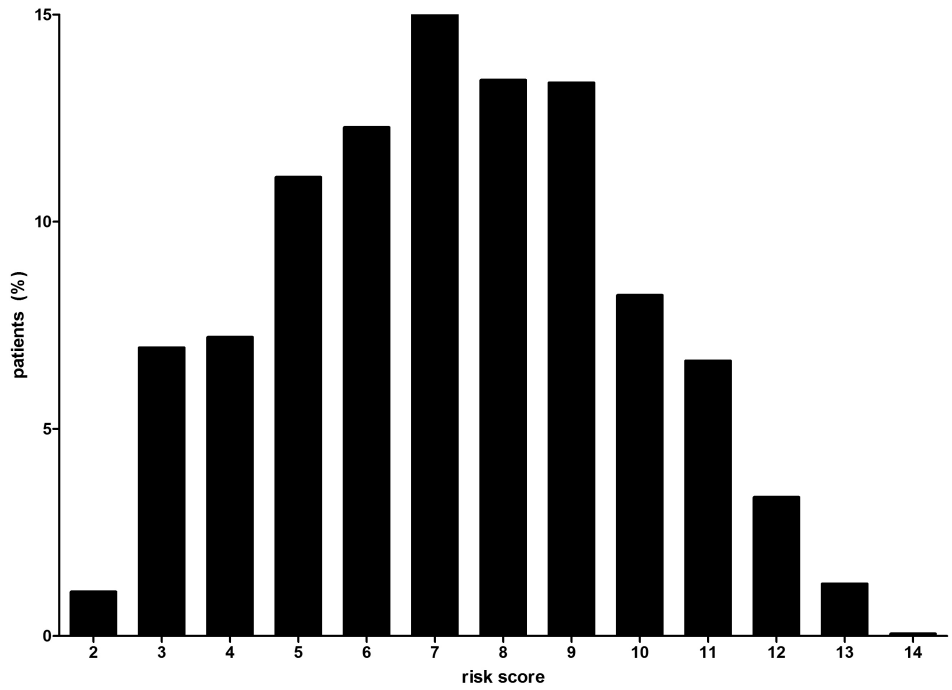

Figure 3. Distribution of the risk scores in the external validation cohort

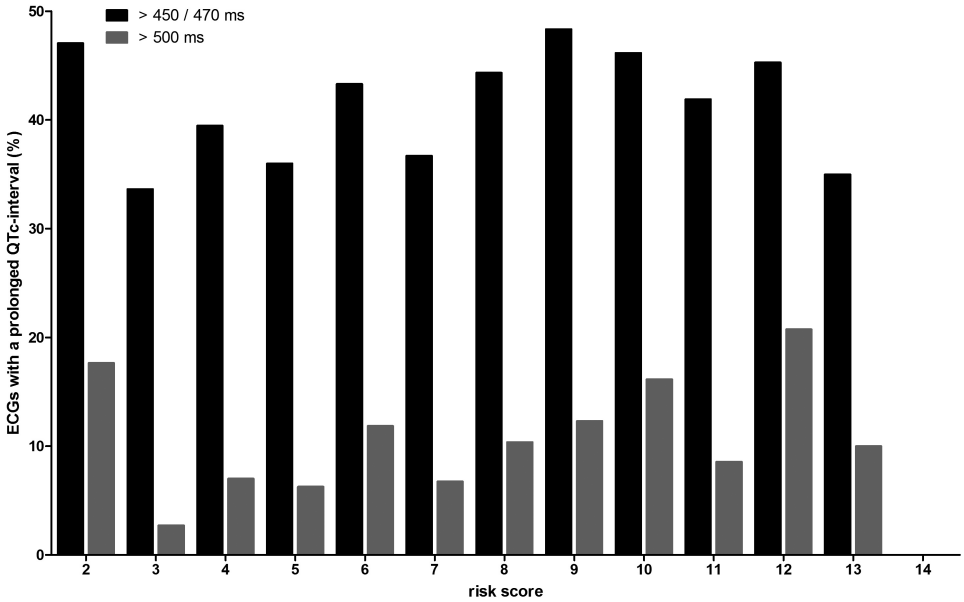

Figure 4. Proportion of ECGs with QTc-prolongation (>450/470 ms and >500 ms) versus risk scores in the external validation

as shown in Figure 2. The cut-off value of 6 led to a sensitivity of 83.9% and a specificity of 27.5% to predict patients with a QTc-interval >500 ms. Figures 3 and 4 show the distribution of the risk scores in the external validation when QTc-prolongation was defined as >500 ms.

DISCUSSION

We have developed a tool which enables the identification of patients with an increased risk of QTc-prolongation when using two or more QTc-prolonging drugs with a *known risk of TdP*. We chose to develop a tool based on seven predictors, that could easily be implemented in everyday practice. The model was externally validated using an independent dataset of a general teaching hospital, showing the robustness of the model. Implementing such a model in clinical practice might enhance the identification of high-risk patients which will support healthcare providers in selecting patients in whom the risk of QTc-prolongation is such that therapy adjustment and/or additional ECG monitoring is required. At the same time such a model might also identify patients at low risk for developing cardiac arrhythmia, and in whom there is no need for monitoring ECGs after drug initiation, but further improvement of the tool is needed. However, it should be noted that the tool is not designed to fully replace healthcare providers in handling QT drug-drug interactions.

The model, developed in a university medical center, showed insufficient discrimination abilities (AUROC <0.60) when applied to a dataset from a general teaching hospital. In the development cohort, we used a cut-off value of 450 ms in men and 470 ms in women for a prolonged QTc-interval using the Bazett formula. The Bazett formula often overestimates the QTc-interval in patients with

sinus tachycardia [37]. In the development cohort, 91.6% of the patients had heart rates within the range of 60–100 bpm. Arrhythmias are often associated with QTc-intervals exceeding 500 ms.[1, 8, 38] Therefore, we performed a post hoc analysis to compare both reference values. The AUROC curve was 0.54 (95% CI 0.51 – 0.56) for QTc > 450/470 ms, but increased when QTc-prolongation was defined as QTc > 500 ms (0.59; 95% CI 0.54 – 0.63). We were aiming for high sensitivities to generate low numbers of false negatives, in order to not miss patients at high risk for TdP. The model was more sensitive in identifying QTc-intervals exceeding 500 ms. The optimized cut-off value of 6 resulted in a sensitivity of 76.6% for the prediction of QTc > 450/470 ms and 83.9% for the prediction of QTc > 500 ms. However, the low specificity (27.5%) means that the model incorrectly labels patients at risk for QTc-prolongation. Nevertheless, we focused on optimizing sensitivity in order to prevent missing patients at risk for QTc-prolongation by accepting sub-optimal specificity values. As the current guidelines generate alerts in all patients, the guidelines lead to a specificity of zero, so even a specificity of 27.5% is an improvement. A perfect prediction model is not feasible because there is a wide variability in the QTc-interval independent of risk factors. And also, the incidence of QTc-intervals above 500 ms is relatively low.[8, 19, 39] Nevertheless, the sensitivity and specificity value of 83.9 and 27.5% should be optimized before broad implementation in clinical practice can be recommended.

Ideally, the model should be developed and validated with TdP as primary outcome. As linear correlation is lacking, it is questionable whether a prolonged QTc-interval is an adequate marker for predicting the risk of TdP.[40] Unfortunately, it is nearly impossible to identify cases of TdP, because ECGs are frequently not available to ensure TdP actually occurred. Furthermore, even in high risk populations the incidence of TdP is extremely low, so exceptionally large patient populations are needed to study TdP as primary endpoint. So a prolonged QTc-interval is still the most validated and frequently used surrogate marker in clinical practice.[2, 41]

Several studies have already introduced risk models for predicting QTc-prolongation/TdP. Haugaa *et al*. developed the 'pro-QTc' risk score, however, the primary endpoint in their study was mortality which is a different endpoint than the primary endpoint used in this study.[38] Tisdale *et al*. developed a risk score via a similar approach, but included only patients admitted to cardiac care units.[15] Consequently, generalizability to a general population may be limited. Vandael *et al*. recently developed an optimized RISQ-PATH score to detect high-risk patients for developing QTc-prolongation.[42] However, when this model was applied to patients using two or more QTc-prolonging drugs, the sensitivity of the model was 94.5%, but the specificity of the model was even lower than our model (22.1%). Moreover, the RISQ-PATH score of Vandael *et al*. consists of too many predictors which are frequently not available and, therefore, this tool cannot be used in clinical practice. In addition, this tool needs to be implemented in the clinical decision support system before it is applicable in primary care, which does not seem feasible with the current electronic patient health records. We aimed to develop a risk score to detect high-risk patients when using two or more QTc-prolonging drugs which is easily applicable in both primary and hospital care.

A major strength of this study is that we externally validated the risk model in an independent dataset from a general teaching hospital. External validations are able to determine the generalizability of predicting models in different settings.[43]

Several limitations of our study need to be addressed. First, the study was limited by a single-center design for model development; however, patients were admitted to all general nursing departments representing a general hospital population. Second, the sample size was relatively small which increased the risk of model overfitting; a common problem in models derived from small datasets. By validating the model in a large external dataset and by adding predictors based on a review of literature, the risk of overfitting was minimized.[25, 26] In the validation cohort, there might have been selection bias as the prevalence of QTc-prolongation (41.5%) was quite high compared to the overall prevalence found in the literature review (21%). We retrospectively collected these data, so presumably, ECGs were mainly recorded in high-risk patients. Our model does not take into account the QTc-interval at baseline. Given that the risk on QTc-prolongation increases when a high baseline QTc-interval is present, we chose to exclude this potential predictor because baseline ECGs are frequently not available in clinical practice. Also, the small dataset precluded the inclusion of too many predictors in the model. Third, the tool does not take into account the variety of QT-DDIs as our aim was to develop an easily obtainable model that can be used in different healthcare settings. Because of the different pharmacological pathways of the QTc-prolonging drugs via inhibition of the hERG channels or Cytochrome P450 enzymes, stratification of QT-DDIs is extremely complex and larger studies need to be conducted for each QT-DDI separately.[44, 45]

The performance characteristics of the model were not perfect. Also after performing a post-hoc analysis, the discrimination ability of the model remained limited. This can be explained by the discrepancies between the development and validation cohort. First, the validation dataset included patients from all departments including ICU patients, whereas the development dataset only included patients from medical wards. Unfortunately, we could not exclude these patients in the validation dataset, because it was unknown to which department patients had been admitted. Therefore, we decided to exclude patients using propofol in order to exclude perioperative and ICU patients as much as possible. Also, patients with ICDs or ECG abnormalities were not excluded in the validation cohort because these data could not be extracted. Therefore, we excluded ECGs with deviant heart rates and QTc-intervals. We did correct the QT-interval for wide QRS-complexes to limit ECG exclusions. Second, the QTc-intervals of the development cohort were manually measured, while the QTc-intervals of the validation cohort were automatically calculated by the MUSE Cardiology Information System. But most importantly, the retrospective design of the external validation where only patients in whom an ECG was recorded during use of the QTc-prolonging drugs were included, may have led to selection bias. ECGs are more likely to be recorded in vulnerable patients. According to the high prevalence of comorbidities in the validation cohort, this was probably the case. But even in high risk populations, QTc-prolongation is not always present resulting in false positives. Also, ECGs are more likely to be recorded in patients with underlying cardiac diseases or with suspected QTc-prolongation even if they only have a few risk factors, resulting in false negatives. Our preliminary results must therefore be confirmed in large studies where this selections bias is not present. The usability of the tool must be evaluated in a clinical setting. For future perspectives, this tool must be further studied to assess its effect when it is integrated in an electronic decision support system before implementation can be recommended. A clinical decision support system is extensively used by pharmacists, as it is part of their job to read

DDI alerts. Ideally, the system will automatically calculate a risk score for the individual patient and only generate alerts in high-risk patients resulting in more specific alerts. Such a study should be performed in large patient groups with clinically relevant endpoints.

CONCLUSION

To conclude, we developed and validated a tool to predict patients at risk for QTc-prolongation when using two or more QTc-prolonging drugs. The model is able to predict patients at risk for QTc-prolongation (>500 ms) with a sensitivity of 83.9% and specificity of 27.5% at an optimized cut-off value of 6. This tool might contribute to support the risk management of QT-DDIs in clinical practice, but further testing of the tool is needed in study cohorts without any selection bias. Eventually, a clinical decision support tool will support healthcare providers in selecting patients in whom monitoring ECGs or switching therapy can be withheld, without compromising patient safety.

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CHAPTER 8

COMPARISON OF TWO ALGORITHMS TO SUPPORT MEDICATION SURVEILLANCE FOR DRUG-DRUG INTERACTIONS BETWEEN QTC-PROLONGING DRUGS

Florine A. Berger
Heleen van der Sijs
Teun van Gelder
Aaf F.M. Kuijper
Patricia M.L.A. van den Bemt
Matthijs L. Becker

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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 4,987 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 ≥ 3 and ≥ 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 ≥ 2 QTc-prolonging drugs. Implementation of digital algorithms in clinical decision support systems could support the risk management of QT-DDIs.

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 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 S1). 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 QTc-prolonging drugs are prescribed. Secondary aim was to explore the distribution of risk scores in the study cohort.

MATERIALS AND METHODS

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

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

(a) Bindraban *et al.*

(b) Berger *et al.*

[†]QTc-prolonging drugs with a known risk of TdP [12]

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.

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.

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 S1) 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 QTc-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: $\mathrm{QTadjusted} = \mathrm{QT} - (\mathrm{QRS} - 120)$. The heart rate corrected QT-intervals were then calculated using the Bazett formula ($\mathrm{QTcB} = \mathrm{QT}/\sqrt{\mathrm{RR}}$).[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.

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.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS, IBM SPSS statistics version 24.0, USA) 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.

RESULTS

Study cohort

Of the 16,285 QT-DDI alerts, we excluded 199 QT-DDI alerts of patients younger than 18 years old; 1,604 QT-DDI alerts, because one of the QTc-prolonging drugs was temporarily stopped; 2,657 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 ≤ 2 min after identical QT-DDI alerts in the same patient. In total, 10,870 QT-DDI alerts were included that met the inclusion criteria, and these were generated in 4,987 individual patients. The median patient

age was 70 years (interquartile range, IQR: 24 years), and 52.0% were female (Table 2, Table S2). For 2,846 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 1,796 unique ECGs were recorded within 7 days after a QT-DDI alert (Figure 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.

Main outcomes

The performance characteristics per cut-off value and ROC curves of both algorithms are shown in Figure 2 or Table S3.

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

Table 2. Characteristics of the QT-DDI alerts

QT-DDI 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 (%)	9,990 (91.9)
Clinical departments	6,117 (61.2)
Peri-operative departments	2,770 (27.7)
Intensive Care Units	1,103 (11.0)
Top 5 QT-DDIs, n (%)	
droperidol – ondansetron	1,663 (15.3)
ciprofloxacin – ondansetron	1,361 (12.5)
haloperidol – ondansetron	1,142 (10.5)
propofol – ondansetron	1,001 (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 (%)	2,846 (26.2)
No. QT-DDI alerts with ECG within 365 days prior to QT-DDI alert, n (%)	6,586 (60.6)
eGFR (ml min^{-1}; CKD-EPI), mean ± SD	69.6 ± 28.8
Renal dysfunction (≤ 60 ml $min\ L^{-1}$), n (%)	2,036 (18.7)
Potassium serum level (mmol L^{-1}) mean ± SD	4.10 ± 0.56
Hypokalaemia (< 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)

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 = 5,215; potassium, n = 5,327; calcium; n = 8,631

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

Characteristics	n = 1,796	SD	unit
Number of patients	1,301		
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

ECG (electrocardiogram), QT-DDI (QT drug-drug interaction), SD (standard deviation), HR (heart rate)

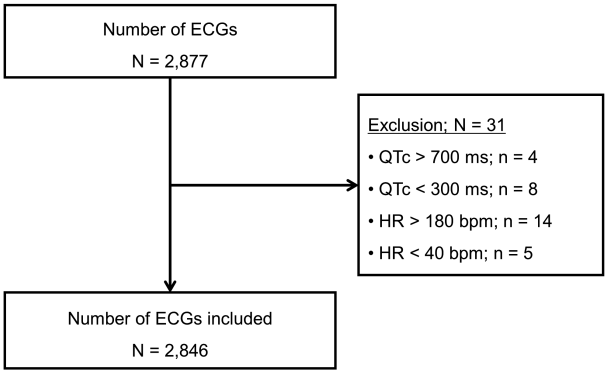

Figure 1. Flowchart of inclusions of ECGs. Abbreviations: ECG, electrocardiogram; bpm, beats per minute; HR, heart rate

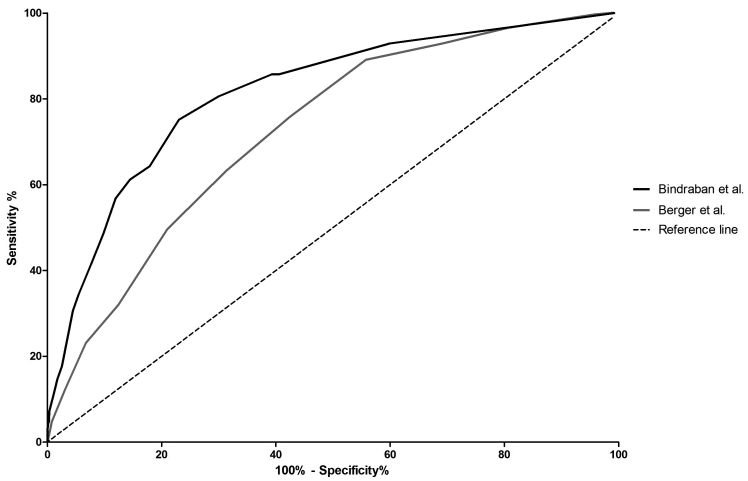

Figure 2. ROC curves of the algorithms. Youden's index Bindraban et al. 0.521 and Berger et al. 0.334

a cut-off value of ≥ 5 (0.521; Bindraban *et al.*) and ≥ 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 ≥ 3 and ≥ 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 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 Figure 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 Figure 4, QTc-intervals > 500 ms are plotted against the risk scores of the algorithms.

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

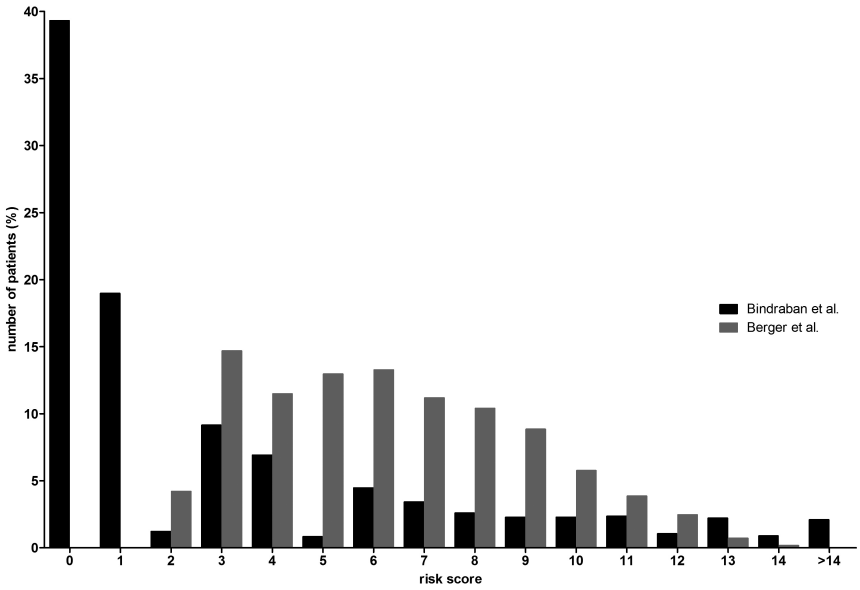

Figure 3. Distribution of the risk scores using two different algorithms.

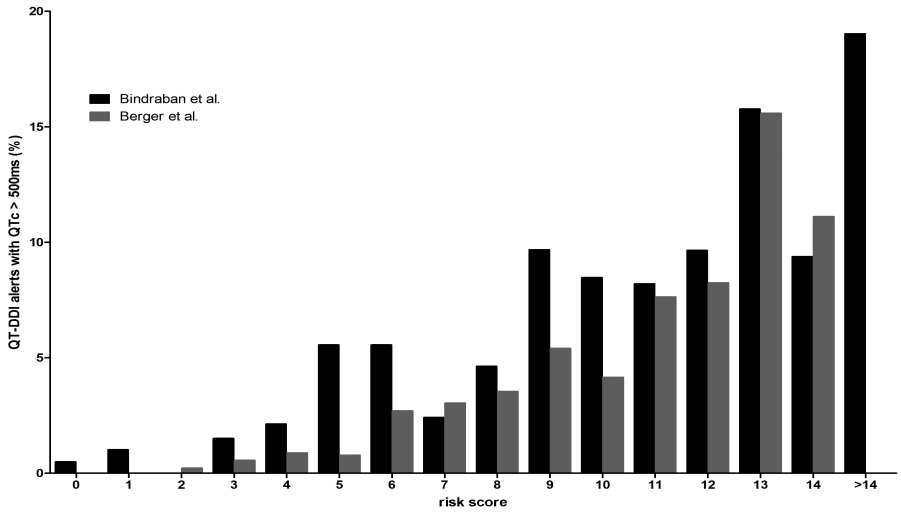

Figure 4. Risk score versus proportion of QT-DDI alerts with QTc > 500ms.

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 QTc-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 S2). 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.* 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.* 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.* 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.* 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.* 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*. 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 *versus* 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 prospectively 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.

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SUPPLEMENTARY DATA

Table S1. QT-DDI alerts are generated based the information in the 'G-standard' 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 S2. Characteristics of QT-DDI alerts stratified by recorded ECGs.

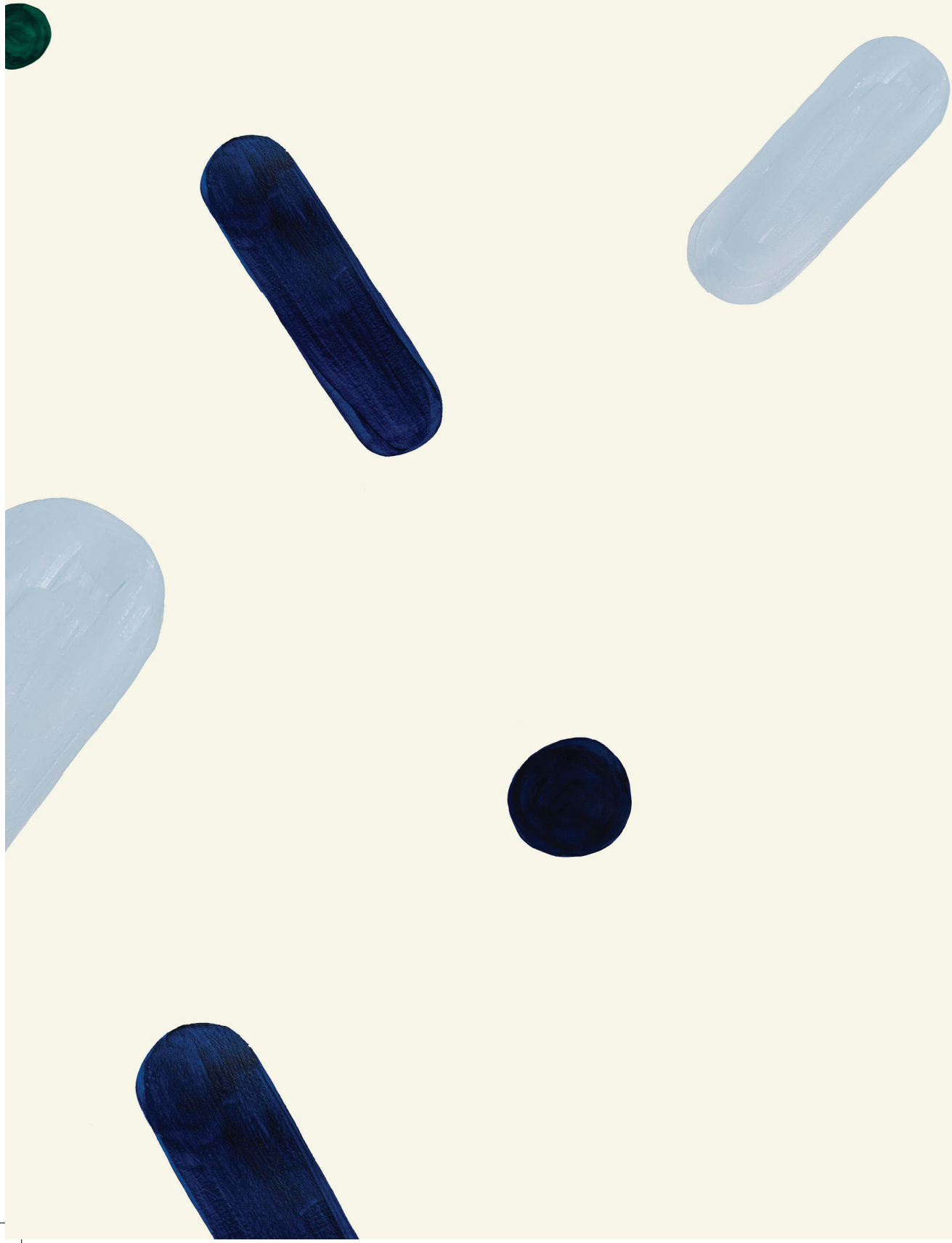
QT-DDI characteristics	ECGs recorded n = 2,877	No ECGs recorded n = 7,933
Age (years), median (IQR)	77 (68-85)	67 (52-78)
≤ 50, n (%)	153 (5,3)	1,828 (22.9)
51 – 75, n (%)	1,102 (38,3)	3,637 (45,5)
≥ 76, n (%)	1,623 (56,4)	2,528 (31,6)
Female, n (%)	1,292 (44.9)	4,357 (54.5)
Outpatients, n (%)	133 (4.6)	747 (9.3)
Inpatients, n (%)	2,744 (94.7)	7,214 (90.3)
Clinical departments	1,865 (68.0)	4,252 (58.7)
Peri-operative departments	327 (11.9)	2,443 (33,7)
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)	1,223 (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 (%)	2,464 (85.6)	4,122 (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)	1,039 (13.0)
Potassium serum level (mmol L^{-1}) mean ± SD	4.12 ± 0.60	4.10 ± 0.53
Hypokalaemia (< 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)

CKD-EPI (chronic kidney disease epidemiology collaboration), ECG (electrocardiogram), eGFR (estimated glomular filtration rate), IQR (interquartile range), No. (number), QT-DDI (QT drug-drug interaction), SD (standard deviation)
Missing values: CKD-EPI, n = 591 (ECG) / 4,624 (no ECG); potassium, n = 613 (ECG) / 4,714 (no ECG); calcium; n = 2,945 (ECG) / 6,686 (no ECG)

Table S3. Performance characteristics of Bindraban *et al.* and Berger *et al.*

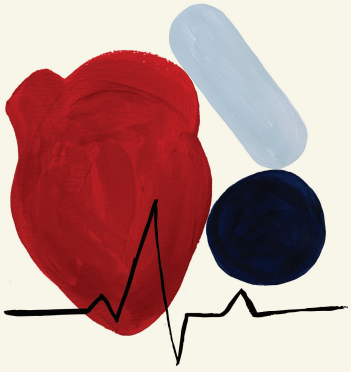
Cut-off value	Sensitivity	Specificity	Youden's index	NPV	PPV	Accuracy
Bindraban *et al.*						
≥ 1	92.9	40.2	0.331	99.5	4.1	0.42
≥ 2	85.7	59.5	0.452	99.3	5.6	0.60
≥ 3	85.7	60.8	0.465	99.4	5.7	0.61
≥ 4	80.6	70.0	0.506	99.2	7.0	0.70
≥ 5	75.2	77.0	0.521	99.1	8.3	0.77
≥ 6	73.5	77.8	0.512	99.1	8.4	0.78
Berger *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

NPV (negative predictive value), PPV (positive predictive value)



PART III

MANAGEMENT OF QTC-PROLONGING DRUG-DRUG INTERACTIONS



CHAPTER 9

THE USE OF A CLINICAL DECISION SUPPORT TOOL TO ASSESS THE RISK OF QT DRUG-DRUG INTERACTIONS IN COMMUNITY PHARMACIES

Florine A. Berger
Heleen van der Sijs
Teun van Gelder
Patricia M.L.A. van den Bemt

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ABSTRACT

Introduction: The handling of drug-drug interactions regarding QTc-prolongation (QT-DDIs) is not well defined. A clinical decision support (CDS) tool will support risk management of QT-DDIs. Therefore, we studied the effect of a CDS tool on the proportion of QT-DDIs for which an intervention was considered by pharmacists.

Methods: An intervention study was performed using a pre- and post-design in 20 community pharmacies in the Netherlands. All QT-DDIs that occurred during a before- and after-period of three months were included. The impact of the use of a CDS tool to support the handling of QT-DDIs was studied. For each QT-DDI, handling of the QT-DDI and patient characteristics were extracted from the pharmacy information system. Primary outcome was the proportion of QT-DDIs with an intervention. Secondary outcomes were the type of interventions and the time associated with handling QT-DDIs. Logistic regression analysis was used to analyze the primary outcome.

Results: Two hundred and forty-four QT-DDIs pre-CDS tool and 157 QT-DDIs post-CDS tool were included. Pharmacists intervened in 43.0% and 35.7% of the QT-DDIs pre- and post-CDS tool respectively (OR 0.74; 95% CI 0.49 – 1.11). Substitution of interacting agents was the most frequent intervention. Pharmacists spent 20.8 ± 3.5 minutes (mean ± SD) on handling QT-DDIs pre-CDS tool, which was reduced to 14.9 ± 2.4 minutes (mean ± SD) post-CDS tool. Of these, 4.5 ± 0.7 minutes (mean ± SD) were spent on the CDS tool.

Conclusion: The clinical decision support tool might be a first step into developing a tool to manage QT-DDIs via a structured approach. Improvement of the tool is needed in order to increase its diagnostic value and reduce redundant QT-DDI alerts.

INTRODUCTION

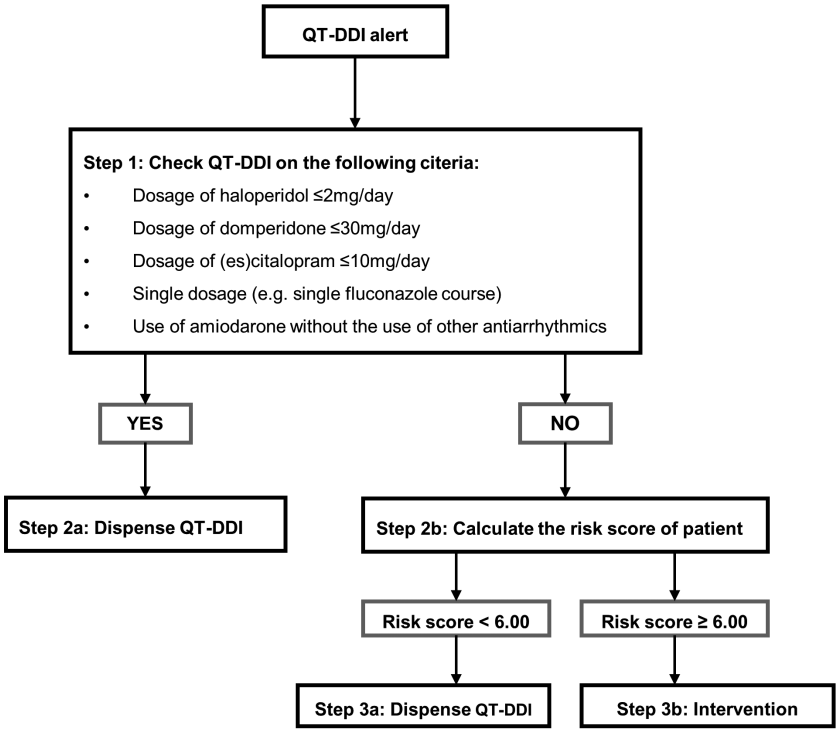
Drug-drug interactions (DDIs) regarding QTc-prolongation are common in daily practice due to the high number of drugs known for prolonging the QTc-interval. Currently, over 50 drugs are associated with causing Torsade de Points (TdP) by prolonging the QTc-interval, according to the CredibleMeds® QT-drug lists of the Arizona Center for Education and Research on Therapeutics (AzCERT).[1] This number has been increasing over the years as new drugs are added to the QT-drug list due to monthly reviews of AzCERT. [2] QTc-prolongation is used as a surrogate marker for the risk of TdP, a ventricular tachycardia which may ultimately lead to ventricular fibrillation or sudden cardiac death.[3-5] Although QTc-prolongation is not the perfect marker for arrhythmia risk as many other risk factors play a role in developing TdP, it has become the primary safety parameter among health care professionals, because it is still the most validated marker for the proarrhythmic potency of drugs.[5-7]

Although a QTc-prolonging drug in itself will rarely induce clinically relevant QTc-prolongation (> 500 ms), a combination of QTc-prolonging drugs in patients with multiple risk factors can result in QTc-intervals above 500 ms.[8, 9]

The Dutch drug database 'G-standard', which contains information for clinical decision support, describes the current guidelines for risk management of drug safety alerts. In the Netherlands, clinical decision support (CDS) systems in primary and secondary care generate QT-DDI alerts when two QTc-prolonging drugs with a *known risk of TdP* are combined. More than 40% of the processed drug prescriptions lead to drug safety alerts. [10] However, the specificity of the alerts generated by CDS systems is very low, resulting in a low number of interventions. At the moment, there is a complete lack of discrimination when handling these QT-DDIs. Many of the generated QT-DDI alerts do not require an intervention. With the increasing number of QTc-prolonging drugs, alert fatigue could be imposed on physicians. Low specificity alerts contribute to noncompliance with current guidelines.[11-15] To decrease the alert burden, more advanced clinical rules including clinical parameters such as patient characteristics and laboratory values are used to improve the specificity of the alerts and decrease the alert rate.[16-20]

In the case of QT-DDI alerts, an advanced clinical rule should be able to discriminate low- and high-risk patients for developing QTc-prolongation. QT-DDI alerts are redundant in patients with no other risk factors for QTc-prolongation. In high-risk patients, QTc-prolonging drugs should be either substituted or routine ECG monitoring is required. This clinical rule should be developed irrespective of the QTc-prolonging drugs involved in the QT-DDIs, due to insufficient data on the absolute effect on QTc-prolongation of these drugs. A risk profile of each individual patient will improve accuracy of QT-DDI alerts and support the risk management of QT-DDIs.[8]

Therefore, a CDS prediction tool was developed to assess the risk of QT-DDIs for developing QTc-prolongation (Figure 1).[21, 22] The main aim of this study was to determine the effect of such a CDS tool on the interventions made by pharmacists in primary care. We also explored the usability of the CDS tool in clinical practice.



Risk factors	Score
1. Age (in years)	
51 – 75	1
≥ 76	2
2. Female gender	1
3. Comorbidities	
Cardiovascular comorbidity	2
Hypertension	2
Diabetes Mellitus (I and II)	1
4. Renal function, eGFR (MDRD)	
≤50 mL min^{-1}	1
Missing value	1
5. Potassium serum level	
≤2,5 mmol L^{-1}	2
2.6 – 3.4 mmol L^{-1}	1
Missing value	1
6. Loop diuretics	2
7. QTc-prolonging drugs[1]	1 per drug

Figure 1. Clinical Decision Support tool to assess the risk of QT-DDIs.
[1] QTc-prolonging drugs with *a known risk of TdP*[7]

METHODS

Development of a prediction model

This CDS prediction model was developed by performing a prospective observational study in 107 patients using two or more QTc-prolonging drugs with a *known risk of TdP*[1] to identify risk factors for QTc-prolongation[21]. A standard twelve-lead resting ECG was recorded at the estimated time of peak concentration (T_{max}) of the lastly added drug, or at the longest T_{max} in case both drugs were started at the same time. Risk factors were identified using logistic regression analyses and risk points were assigned based on the odds ratios. Additional risk factors were incorporated into the model based on a literature review on risk factors for QTc-prolongation. The CDS tool was validated in an external dataset (n = 8,453) resulting in an area under the receiver operating characteristic-curve of 0.59 (95% CI 0.54 – 0.63) when QTc-prolongation was defined as > 500 ms due to many false positive results. The selected optimal cut-off value was 6; 26.3% of all patients scored < 6 points. A sensitivity of 83.9% and a specificity of 27.5% was accomplished with a cut-off value of 6. The discriminative ability of the tool is not perfect, so optimization of the tool is required.[22] On the other hand, there is currently a complete lack of discrimination when handling these QT-DDIs. There should be a balance between the number of alerts generated by the CDS systems and its effect on patient care. Although not perfect, this tool is still able to reduce the number of redundant QT-DDI alerts.

Study design

An intervention study was performed using a pre- and post-design in 20 community pharmacies in the Netherlands. We implemented the use of the CDS tool (consisting a paper-based flowchart) to study the impact on the handling of QT-DDIs.

All QT-DDIs that occurred during a pre- and post-CDS tool period of three months were included. The QTc-prolonging drugs involved in the QT-DDIs are listed at the CredibleMeds® QT-drug list with a *known risk of TdP* (Table S1). Only pharmacies using the pharmacy information system Pharmacom® (by TSS Pharma Partners) in the region of Rotterdam (Rijnmond) were included to ensure conformity in data capture and data extraction. The medical ethics review board of the Erasmus University Medical Center approved the protocol and waived the requirement for obtaining informed consent (MEC-2015-513). The study was conducted according to the principles of the Declaration of Helsinki.

Study population

All QT-DDIs including QTc-prolonging drugs with a *known risk of TdP* that occurred in the community pharmacies during a study period of 3 months before and 3 months after implementation of the CDS tool were included. QT-DDIs of patients younger than 18 years old were excluded.

Outcome measures

The primary outcome measure of this study was the proportion of QT-DDIs in which pharmacists intervened. An intervention was defined as a consultation with prescribers to discuss the clinical relevance of the QT-DDI, and proposal for further actions to be taken (hereafter referred to as

intervention). Secondary outcome measures were the types of interventions made by pharmacists. The interventions for the QT-DDIs were subsequently categorized in (I) dispensing both drugs on account of the prescriber, (II) ECG monitoring, (III) substitution of one of the interacting agents, (IV) dose adjustments or (V) (temporarily) stopping one of the interacting agents. We have also studied the difference between first-time prescriptions and repeat-prescriptions on the handling and types of interventions. Another secondary outcome measure was the time spent on handling QT-DDIs. Finally, the CDS tool was evaluated by pharmacists on usability in clinical practice.

Data collection

For all QT-DDIs, the following variables were collected: the management of the QT-DDI including interventions, the interacting drugs and the dosages of interacting drugs.

For all patients: age, gender, comorbidities (registered as drug-disease interactions) were collected. Concomitant drug use was retrieved from the medication history up to one year prior to the QT-DDI alert. The following laboratory values were collected, if registered in Pharmacom®: renal function, liver function parameters and electrolyte serum levels. Patient data were handled confidentially and were extracted anonymously according to the Dutch Personal Data Protection Act (Wbp). All patients with QT-DDI alerts were captured in an electronic clinical data management system (OpenClinica, LLC, Waltham, United States).

Clinical Decision Support Tool

The CDS tool was implemented in the participating community pharmacies after a 3 month baseline analysis as a tool to support the electronic handling of QT-DDI alerts. The CDS tool consisted of a paper-based flowchart identifying patients that were at increased risk for developing QTc-prolongation as is shown in Figure 1. The criteria of step 1 of the flowchart were based on a literature review and an expert panel with two cardiologists with expertise in electrophysiology and publications in the field. [23-30] Before implementation, the pharmacists were trained in using the CDS tool. The CDS tool was expected to be used for all QT-DDI alerts during the post-implementation period. When patients scored ≥ 6 using the tool, an intervention by pharmacists was recommended. The risk scores and types of interventions were documented using a paper form.

Usability Clinical Decision Support Tool

After a period of 3 months, the tool was evaluated by the pharmacists on usability in clinical practice using the System Usability Scale (SUS) of Brooke.[31, 32] The SUS is based on 3 usability measures suggested by the International Organization for Standardization (ISO)-9241-11: effectiveness, efficiency and satisfaction. The SUS consists of a 10-item questionnaire covering subjective items of usability using a 5-point Likert scale with a degree from total disagreement (1) to total agreement (5). For evaluation of the CDS tool, 10 items were formulated so that they were compatible for the CDS tool (Table S2). Items 1, 3, 6, 7 and 9 were positively formulated and items 2, 4, 5, 8 and 10 were negatively formulated. The SUS score was calculated, firstly, by recalculating the score of each item (1 – 5) to a range from 0 – 4 using the following formula; for the positively formulated items:

scale position minus 1, and for the negatively formulated items: 5 minus scale position. Secondly, the sum of these scores was multiplied by 2.5 to obtain the overall SUS score.[31] Total SUS scores range from 0 – 100, if SUS scores are < 60 the system is considered to be unacceptable, 60 – 70 is acceptable, 70 – 80 is good, 80 – 90 is very good and > 90 is excellent.[32, 33]

Statistical analysis

Based on information provided by the Stevens Institute for Research (SIR) in Leiden, the Netherlands, Dutch community pharmacies on average dispense QTc-prolonging drugs 140 times a year with a QT-DDI (interaction code 6297). That results in 0.5 QT-DDIs per day per pharmacy in which the DDI-causing drug is dispensed. A QT-DDI does not always result in dispensing, so we estimate that 1 QT-DDI per day per pharmacy will be handled. So, in 3 months (pre and post measurement) approximately 45 QT-DDIs per pharmacy were expected to be monitored, which would result in a total number of 900 QT-DDIs in 20 community pharmacies. With an alpha of 0.05 and a power of 80%, a difference in proportion of QT-DDIs with intervention of 60% (pre) *versus* 66% (post) can be established using logistic regression, estimating that in 60% of the QT-DDIs an intervention is carried out.

The primary outcome was determined by dividing the number of QT-DDIs with an intervention by the total number of QT-DDIs. Univariate logistic regression analysis was used to analyse the primary outcome between the measurements before and after implementation of the CDS tool. If a variation in interaction characteristics occurred between the before- and after-period, the primary outcome was adjusted using multivariate logistic regression analysis. Odds ratios (OR) and their 95% confidence intervals (95% CI) were reported. Secondary outcome measures were analyzed using descriptive statistics.

RESULTS

Study population

The baseline characteristics of the participating community pharmacies are presented in Table 1. The after-period included 16 community pharmacies because four pharmacists, and therefore four pharmacies discontinued their participation because of construction work of the pharmacy and shortages in personnel. A total of 928 QT-DDI alerts were generated during the pre- and post-CDS tool phase, of which 401 QT-DDIs were included for analysis. In the before-period, 244 QT-DDIs belonging to 233 patients were included for analysis. Six QT-DDIs were excluded because they occurred in patients < 18 years old (Figure 2). In the after-period, a total of 157 QT-DDIs of 149 patients were included, as shown in Figure 3. Only 23 patients were included in both the before- and after-period; in 17 patients the QT-DDIs were identical.

The baseline patient characteristics of patients in the before- and after-period are shown in Table 2. The two groups did not significantly differ in patient characteristics. The median (interquartile range) age of the total cohort was 65 (28) years and most QT-DDI alerts belonged to female patients (64.1%). From only a limited numbers of patients the renal function parameters (10.2%) and potassium levels (0.8%) could be extracted from Pharmacom®. In clinical practice, pharmacy

Table 1. Baseline characteristics of the participating community pharmacies

Pharmacy characteristics	Cohort, n = 20
FTE pharmacists, mean ± SD	1.7 ± 0.9
FTE pharmacy assistants, mean ± SD	7.0 ± 3.3
HKZ certificates, n (%)	
None	-
Chain certificate	7 (35)
Own certificate	13 (65)
Collaboration with other community pharmacies, n (%)	
None	8 (40)
< 5	4 (20)
5 – 25	3 (15)
> 25	5 (25)
GPs responsible for > 80% of prescriptions, n (%)	
1 – 3	5 (25)
4 – 6	10 (50)
7 – 9	3 (15)
≥ 10	2 (10)
Shared patient records with GP, n (%)	14 (70)
Community Health Centre, n (%)	12 (60)
Use of EPR in Pharmacom®, n (%)	18 (90)
% of renal function parameters available, mean ± SD	71.7 ± 20.9
% of potassium serum levels available, mean ± SD	58.1 ± 31.9
% of shared contra-indications with GP, mean ± SD	77.2 ± 19.7

FTE (fulltime-equivalent), SD (standard deviation), HKZ (Harmonization quality assessment in Health Sector), GP (general practitioner), EPR (electronic patient record)

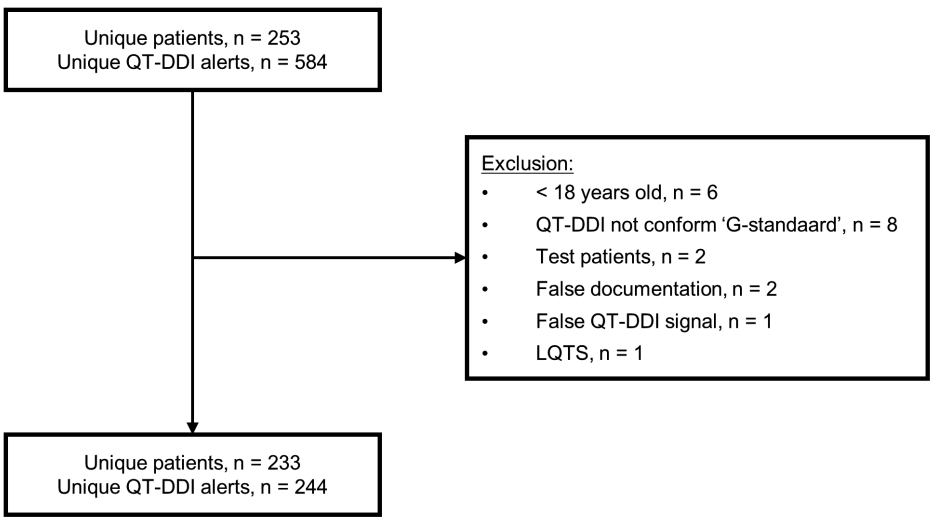


Figure 2. Flowchart of QT-DDI inclusions in before-period. LQTS (long QT syndrome), QT-DDI (QTc-prolonging drug-drug interactions).

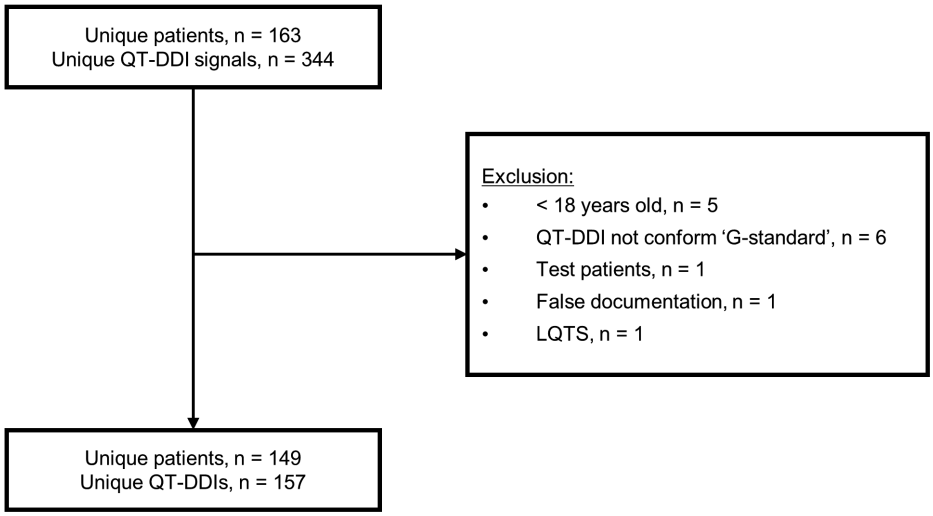


Figure 3. Flowchart of QT-DDI inclusions in after-period. LQTS (long QT syndrome), QT-DDI (QTc-prolonging drug-drug interactions).

information systems are frequently linked to the information system of the general practitioners (GPs). Unfortunately, it was not possible to retrieve these variables from the GP information system due to privacy legislation. There was no significant difference in the proportion of first-time prescriptions in the QT-DDIs in the before-period (62.5%) compared to the after-period (73.9%, p = 0.08). In both periods, the QT-DDI that occurred most frequently was (es)citalopram – haloperidol (10.8% and 10.7%, respectively). The top-10 QT-DDIs and QTc-prolonging drugs are presented in Table 3. When drug groups were classified, the most common QT-DDI was a QTc-prolonging drug combined with an antiarrhythmic agent class III (34.0%) in the before-period and a QTc-prolonging drug combined with a QTc-prolonging antibiotic (32.5%) in the after-period. The mean ± SD number of QT-DDIs per pharmacy was 12.2 ± 7.6 in the before-period and 9.8 ± 5.1 in the after-period.

Outcome measures

There was no significant difference in the proportion of QT-DDIs for which an intervention was made after implementing the CDS tool; 43.0% before and 35.7% after implementation (OR 0.74; 95% CI 0.49 – 1.11; p = 0.14). A sensitivity analysis, performed by excluding 23 patients who were included in both the pre- and post-period, had no effect on the significance of the primary outcome (OR 0.78; 95% CI 0.50 – 1.21; p = 0.27).

An interacting agent was substituted in 41.0% of the interventions in the before-period and in 46.4% in the after-period. In 37.7% of the QT-DDIs with intervention, the QTc-prolonging drugs were dispensed in the before-period, and in 26.8% of the QT-DDIs in the after-period. Almost 12% of all alerts were incorrect QT-alerts because one of the interacting agents was already stopped or the combination was not given simultaneously. In 5.2% of the QT-DDIs, pharmacists did not properly

Table 2. Baseline characteristics of study population

Patient characteristics	before-period n = 233	after-period n = 149	p-value
Age (years), median; IQR	66.0; 26.0	63.0; 31.0	0.86 [a]
≤50, n (%)	60 (25.8)	41 (27.5)	0.72 [b]
51 – 75 , n (%)	113 (48.5)	66 (44.3)	
≥76, n (%)	60 (25.8)	42 (28.2)	
Female gender, n (%)	154 (66.1)	91 (61.1)	0.32 [b]
BMI, median; IQR	31.9 *(n = 1)*	24.5 *(n = 1)*	-
Comorbidities, n (%)			
Myocardial infarction	25 (10.7)	17 (11.4)	0.84 [b]
Heart failure	13 (5.6)	2 (1.3)	0.06 [c]
Arrhythmia	14 (6.0)	3 (2.0)	0.08 [c]
Hypertension	68 (29.2)	43 (28.9)	0.95 [b]
Diabetes Mellitus	39 (16.7)	29 (19.5)	0.50 [b]
COPD/Asthma	42 (18.0)	23 (15.4)	0.51 [b]
CVA/TIA	5 (2.1)	8 (5.4)	0.09 [b]
Renal dysfunction	16 (6.9)	12 (8.1)	0.66 [b]
Liver dysfunction	9 (3.9)	4 (2.7)	0.77 [c]
Others	111 (47.6)	74 (49.7)	0.70 [b]
Renal dysfunction with renal function, n (%)			
eGFR (MDRD) ≤ 50 mL min^{-1}	11 (4.7) *(n = 20)*	10 (6.7) *(n = 19)*	0.97 [b]
Electrolyte disturbances, n (%)			
Hyponatremia (Na^+ < 136 mmol L^{-1})	- *(n = 1)*	- *(n = 2)*	-
Hypokalemia (K^+ < 3.5 mmol L^{-1})	- *(n = 1)*	- *(n = 2)*	-

BMI (Body Mass Index), COPD (Chronic Obstructive Pulmonary Disease), CVA (Cerebrovascular Accident), eGFR (estimated Glomerular Filtration Rate), IQR (Interquartile Range), MDRD (Modification of Diet in Renal Disease), TIA (Transient Ischemic Attack)

[a] Independent t test

[b] Chi-square test

[c] Fisher's Exact test

document their actions. The variety of interventions performed by pharmacists are presented in Table 4.

After implementation, 157 QT-DDI alerts were handled electronically. However, pharmacists completed the paper forms in only 30.6% of the QT-DDI alerts. Of these, thirty QT-DDIs (63.5%) could be dispensed without intervention according to the flowchart of the CDS tool. Pharmacists dispensed the QT-DDI with no intervention, and therefore adhered to the flowchart in 19 cases (63.3%). In the remaining cases (n = 11), prescribers were consulted. Note that six (54.5%) of these cases included amiodarone, of which five (83.3%) had a risk score ≥ 6; in these cases, an intervention was performed. Of the 18 QT-DDIs where the flowchart advised to score patients using the risk model, four patients scored < 6; these QT-DDIs were dispensed without intervention. In all patients with a risk score ≥ 6, prescribers were consulted and in 92.8% an intervention was performed. Taken all QT-DDIs into account, the overall compliance of the CDS tool by pharmacists was 75%.

Table 3. Top 10 QT-DDIs

QT-DDIs	before-period n = 244 (%)	after-period n = 157 (%)
1. haloperidol – (es)citalopram	26 (10.7)	17 (10.8)
2. amiodarone – ciprofloxacin	13 (5.3)	7 (4.5)
3. azithromycin – (es)citalopram	12 (4.9)	13 (8.3)
4. (es)citalopram – fluconazole	11 (4.5)	5 (3.2)
5. azithromycin – domperidone	10 (4.1)	2 (1.3)
6. sotalol – ciprofloxacin	10 (4.1)	5 (3.2)
7. haloperidol – ciprofloxacin	9 (3.7)	7 (4.5)
8. sotalol – flecainide	8 (3.3)	6 (3.8)
9. sotalol – (es)citalopram	7 (2.9)	-
10. azithromycin – fluconazole	6 (2.4)	10 (6.4)
Missing values	*1*	*2*

Table 4. Type of intervention

Interventions	before-period, n = 244 (%)	after-period n = 157 (%)	p-value
Dispensed on account of prescriber	30 (12.3)	12 (7.6)	
Substitution of one of the interacting agents	43 (17.6)	26 (16.6)	
(Temporarily) stopping one of the interacting agents	23 (9.4)	15 (9.6)	
Dose adjustments	4 (1.6)	3 (1.9)	
ECG monitoring	5 (2.0)	-	
Total	105 (43.0)	56 (35.7)	0.14

When we focus on the criteria of step 1 of the flowchart, the proportion of interventions when QT-DDIs included amiodarone did not differ between both periods (48.1% *versus* 47.6%; $p = 0.97$). The proportion of interventions decreased in QT-DDIs including (es)citalopram ≤ 10 mg (42.3% *versus* 17.3%; $p = 0.07$), domperidone ≤ 30 mg (45.9% *versus* 9.1%; $p = 0.03$) and haloperidol ≤ 2 mg (35.7% *versus* 20.6%; $p = 0.15$). Only in the case of domperidone, the proportion of interventions decreased significantly between the before- and after-period. The difference in types of interventions for QT-DDIs including first-time prescriptions or repeat-prescriptions are shown in Table 5.

Time spent by pharmacists

In the before-period, nine pharmacists documented the time spent on the management of QT-DDIs in 56 QT-DDIs. On average, pharmacists spent 21 minutes on the management of QT-DDIs, as shown in Table 6. Consultation with the prescriber was the most time-consuming and took 10 minutes on average. In five cases the handling of QT-DDIs encompassed more than 1 day, because

Table 5. Intervention rate of alerts divided into first-time (FP) and repeat (RP) prescriptions.

	Before-period		After-period	
	Intervention (%)	**No intervention (%)**	**Intervention (%)**	**No intervention (%)**
FP	87 (57.2)	65 (42.8)	47 (41.2)	67 (58.8)
RP	18 (19.6)	74 (80.4)	9 (20.9)	34 (79.1)
P-value [a]	< 0.001		0.018	

[a] Chi square test

Table 6. Time for handling QT-DDIs in community pharmacies *before* implementation of CDS tool

Time-management QT-DDIs	**FP, n = 38**		**RP, n = 12**		**Discharge, n = 5**	
	n (%)	**minutes (mean ± SD)**	**n (%)**	**minutes (mean ± SD)**	**n (%)**	**minutes (mean ± SD)**
Literature	19 (50.0)	2.6 ± 4.4	3 (25,0)	0.9 ± 1.7	4 (80.0)	10.4 ± 11.9
Consult prescriber	26 (68.4)	12.3 ± 26.8	2 (16,7)	1.0 ± 2.4	3 (60.0)	11.0 ± 16.7
Consult PA	18 (47.4)	1.8 ± 2.5	6 (50,0)	2.8 ± 3.5	3 (60.0)	2.6 ± 4.2
Documentation in PIS	32 (84.2)	2.6 ± 3.7	7 (58,3)	2.8 ± 3.8	5 (100.0)	5.8 ± 4,.1
Consult patient	23 (60.5)	2.5 ± 3.2	3 (25,0)	2.8 ± 8.6	2 (40.0)	3.2 ± 6.6
Other	6 (15.8)	0.8 ± 2.1	2 (16,7)	0.2 ± 0.4	-	-
Total, mean ± SD		*22.6 ± 28.8*		*10.8 ± 11.1*		*33.0 ± 34.2*

PA (Pharmacy assistant), PIS (Pharmacy Information System)

the pharmacists could not reach the prescriber. Nevertheless, these days were not counted in the overall time as this does not represent the time pharmacists actually spent on QT-DDIs.

After implementation, time management was documented in 48 QT-DDIs (Table 7). Pharmacists selected a variety of QT-DDIs. Based on these QT-DDI, Pharmacists spent on average 15 minutes on the management of QT-DDIs, approximately 6 minutes less than in the before-period. Time spent on consultation with the prescriber was reduced to 4 minutes. Of these 15 minutes, nearly 5 minutes were spent on completing the CDS flowchart.

Usability CDS prediction tool

The mean ± SD SUS score of the CDS tool was 74.1 ± 19.1 (14 pharmacists). The highest (maximum of 4) mean score per question was 3.5 and was scored on question 1 regarding satisfaction; pharmacists would like to use the CDS tool in clinical practice. The lowest (minimum of 0) mean score per question was scored on question 4 regarding reliability; pharmacists expected to need the support of different literature sources, besides the tool, to safely manage QT-DDIs. Three pharmacists ranked the CDS tool < 60 and considered the tool as "*unacceptable*", mainly because the tool was time-consuming in their opinion. The overall suggestion of most pharmacists was to eventually integrate the clinical decision support tool into the pharmacy information system.

Table 7. Time for handling QT-DDIs in community pharmacies *after* implementation of CDS tool

Time-management QT-DDIs	FP, n = 40		RP, n = 4		Discharge, n = 1	
	n (%)	minutes (mean ± SD)	n (%)	minutes (mean ± SD)	n (%)	minutes (mean ± SD)
Literature	-	-	-	-	-	-
Consult prescriber	23 (57.5)	4.5 ± 6.1	-	-	-	-
Consult PA	17 (42.5)	1.3 ± 2.3	2 (50.0)	0.7 ± 0.6	1	4.0
Documentation in PIS	36 (90.0)	2.0 ± 2.0	3 (75.0)	3.0 ± 2.0	1	2.0
Consult patient	17 (42.5)	1.8 ± 3.4	1 (25.0)	0.3 ± 0.6	1	10.0
Other	8 (20.0)	1.7 ± 4.1	1 (25.0)	0.7 ± 1.2	1	3.0
Clinical rule	37 (92.5)	4.4 ± 4.5	3 (25.0)	7.0 ± 6.9	1	1.0
Total, mean ± SD		*15.0 ± 16.3*		*11.7 ± 7.6*		*20.0*

PA (Pharmacy assistant), PIS (Pharmacy Information System)

DISCUSSION

To our knowledge, this was the first study on a CDS tool to support the handling of QT-DDIs in community pharmacies. Our study has shown that the implementation of an advanced CDS tool did, not significantly, reduce the proportion of QT-DDIs for which an intervention was made (43.0% – 35.7%; $p = 0.14$). However, pharmacists seemed to spend less time on the management of QT-DDIs when the CDS tool was used (6 minutes per QT-DDI). Overall, the pharmacists were satisfied using the tool to support the management of QT-DDIs in clinical practice.

At first, we hypothesized that an advanced CDS tool would result in more interventions, but more than 70% of the QT-DDI alerts did not require an intervention according to the CDS tool and could be considered as irrelevant. Several other studies show that specification of alert triggers by advanced clinical decision rules could decrease the alert rate up to 90%.[34-37] In total, 75% of QT-DDIs were handled with the CDS tool. Pharmacists did not comply with the flowchart of the CDS tool when the QT-DDIs included amiodarone, because they did not feel comfortable dispensing QT-DDIs with amiodarone. Therefore, if the tool is implemented in clinical practice, education on the risks of QTc-prolongation and TdP can be useful to achieve more compliance by pharmacists.

Repeat prescriptions for chronic medication are common in primary care. However, many QT-DDI are only relevant at the start of therapy, and are, therefore, more likely to be followed by an intervention.[11] In our study, 50% of the first-time prescription QT-DDIs were followed by an intervention and 21% of the repeat-prescription QT-DDIs were followed by an intervention, as is shown in Table 7. The CDS tool enables reassessment of repeat-prescription QT-DDIs when the condition of a patient might change during chronic treatment where a patient might become a high-risk patient.

Van der Sijs *et al*. showed that QT-DDI overriding rarely (33%) results in ECG recording in a hospital setting. [38] Expectedly, our study showed that in primary care this percentage is even lower (1.7%), as ECG recording is not feasible in community pharmacies. The CDS tool does not specify management

recommendations when an intervention is required, as an individualized risk assessment depending on the patient's situation by a health care professional is still important to determine the type of intervention. The combination of QTc-prolonging drugs may result in potential fatal TdP, which rarely occurs. Consensus exists that measuring the QTc-interval on the ECG is the best option to predict which patients are at risk, and the QTc is a proxy for the patient outcome. However, making ECGs for all patients filling their prescriptions in community pharmacies is not feasible and not necessary, because the QTc-prolongation risk may vary considerably among patients and QT-DDIs do not always require intervention.

A strength of this study was the pre- and post-design of the study which enables us to study the current handling of QT-DDIs. Also, the 20 community pharmacies included in this study represent the general Dutch community pharmacies according to the Dutch Foundation for Pharmaceutical Statistics (SFK) Facts & Figures of 2015.

This study also has some potential limitations. First, the tool was paper-based and was not integrated into the electronic CDS system of the community pharmacies. Consequently, the documentation of the QT-DDIs was limited because work processes in community pharmacies are fully digitalized. Only 48 forms were completed *versus* the 157 unique QT-DDIs generated by the CDS system in the after-period. We do realize that due to these limited completed forms our study was underpowered to make definitive conclusions regarding the tool. We hypothesize that the non-significant decrease in interventions in this study, might turn into a significant decrease in interventions when performed in a larger dataset. Thereby, it should be noticed that the discriminative ability of the tool was poor, and missed errors may have occurred.

Second, apart from the criteria incorporated in step 1 of the flowchart, the tool does not stratify the various QT-DDIs. Although the QTc-prolonging drugs have different pharmacological pathways for inducing QTc-prolongation, it is relatively unknown whether combining QTc-prolonging drugs with different pharmacological pathways has an additive or synergistic effect on the extent of QTc-prolongation.[39, 40] Therefore, in this study we assumed the synergistic effect of the QTc-prolonging drugs to be similar. Also, the number of laboratory values retrieved from the pharmacy information systems was low. In reality, this number of available laboratory values is higher because pharmacy information systems are frequently linked to information systems of GPs. In 58.1% of the included pharmacies, the pharmacy information system was linked to the GP information system as shown in Table 1. Additionally, a potassium level of < 2.5 mmol L^{-1} scores two points according to the risk model, however, it is unlikely that an outpatient would have a value this low and any measurement this low would likely have been managed in an inpatient setting. Although the aim of the present study was to evaluate how such a tool would perform in a primary care setting, the tool was also developed for use in hospitals, and in such a setting a low potassium level may occur.

In total, four pharmacies dropped out of the study due to construction work of the pharmacy and shortages of personnel. These could potentially lead to biased results, but as these pharmacists dropped-out before the implementation of the tool, this is probably not the case.

For future perspectives, this clinical decision support tool deserves further investigation to assess its effect when it is integrated in the pharmacy information system. Such a study should be performed in large patient groups with clinically relevant endpoints such as QTc-prolongation

before implementation in clinical practice can be recommended. Ideally, the system will then automatically calculate a risk score for the individual patient and only generate alerts if the risk score is > 6, resulting in more specific alerts.

In conclusion, these results suggest that the clinical decision support tool might be an effective tool to manage QT-DDIs via a structured approach, through which a more specific advice can be given to prescribers. Also, if the condition of patients were to change during chronic treatment, the CDS tool can easily identify these potential harmful changes. Pharmacists are satisfied to use the tool and it has proven to be feasible in clinical practice. However, optimization of the tool is required before implementation in clinical practice.

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SUPPLEMENTARY DATA

Table S1. QTc-prolonging drugs with a *known risk of TdP*

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 S2. Questionnaire evaluation clinical rule

System Usability Scale (SUS)*						
		Totally disagree				**Totally agree**
1	I think that I would like to use this clinical rule frequently.	1	2	3	4	5
2	I found the clinical rule unnecessarily complex.	1	2	3	4	5
3	I thought the clinical rule was easy to use.	1	2	3	4	5
4	I think that I would need the support of different literature sources, besides the clinical rule, to handle QT-interactions.	1	2	3	4	5
5	I quickly make mistakes with the calculation and method of the clinical rule.	1	2	3	4	5
6	I found the consecutive steps of the clinical rule logical.	1	2	3	4	5
7	I would imagine that most people would learn to use this clinical rule very quickly.	1	2	3	4	5
8	I found the clinical rule difficult to use.	1	2	3	4	5
9	I felt very confident using the clinical rule.	1	2	3	4	5
10	I needed to learn a lot of things before I could get going with the clinical rule.	1	2	3	4	5
11	What would you suggest to optimize the usability of this clinical rule?					

CHAPTER 10

MEDIA ATTENTION REGARDING SUDDEN CARDIAC DEATH ASSOCIATED WITH DOMPERIDONE USE DOES NOT AFFECT IN HOSPITAL ECG RECORDING

Florine A. Berger
Selma Saâïd
Teun van Gelder
Bruno H. C. Stricker
Matthijs L. Becker
Patricia M. L. A. van den Bemt

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ABSTRACT

Purpose: In March 2013, regulatory warnings concerning the potential risks of domperidone caused considerable media attention in the Netherlands. The aim of the study was to assess the effect of regulatory warnings and the resulting media hype on the frequency of electrocardiogram (ECG) monitoring of inpatients using domperidone. We also studied the effect on the frequency of prescribing domperidone by physicians.

Methods: A 2-centre, observational, retrospective cohort study was performed. Inpatients using domperidone in two hospitals in the Netherlands during a period of 384 days before and after the media hype were included. The main outcomes were (1) the proportion of domperidone users with ECGs before and/or during domperidone treatment, (2) the proportion of patients with an ECG before and during treatment, and (3) the proportion of patients with an ECG during treatment. Secondary outcome was the proportion of domperidone prescriptions comparing the before- and after-period.

Results: 428 patients were included. The main outcomes (respectively (1) relative risk (RR) 1.02; 95% confidence interval (CI) 0.85 – 1.21; (2) RR 1.06; 95% CI 0.60 – 1.85 and (3) RR 1.27; 95% CI 0.80 – 2.01) were not different. After stratifying for hospital, no significant differences were found. A statistically significant decrease (RR 0.40; 95% CI 0.35 – 0.45) in numbers of prescriptions was found for the university medical centre only.

Conclusion: No effect of the media hype was found on the intensity of ECG monitoring in domperidone users. In the university medical centre, domperidone prescriptions were reduced.

INTRODUCTION

Domperidone is widely used for treatment of nausea and vomiting, dyspepsia associated with delayed gastric emptying, gastro-oesophageal reflux and oesophagitis.[1-3] The concern about the cardiovascular safety of domperidone flared up in the mid-1980s when the intravenous formulation of domperidone was withdrawn from the market after serious cardiac events.[4-7] Since then, information has piled up about the possible association between oral domperidone use and cardiotoxicity.[8-14] In March 2013, a reassessment of domperidone was requested by the Belgian authorities named the Federal Agency for Medicines and Health Products (FAMHP). This reassessment was performed by the Pharmacovigilance Risk Assessment Committee (PRAC), a committee at the European Medicines Agency (EMA) that is responsible for assessing and monitoring safety issues for human medicines.[15] This caused considerable media attention in the Netherlands, in which the drug was claimed to be responsible for up to 10 cases of sudden cardiac death (SCD).[16] Domperidone is known to block human ether-a-gogo-related gene (hERG) channels. By blocking these channels, the repolarization will be delayed which is reflected in a longer QTc-interval on the ECG, a risk factor for Torsade de Pointes (TdP).

Previous studies show that media attention and regulatory changes influence the prescribing behaviour of physicians. A 2002 Cochrane review identified fifteen mass media health interventions and five studies of media coverage; all but one was associated with a change in health service use.[15] Media hypes regarding potential risks of drugs frequently result in a decrease in drug use and prescriptions among patients.[16-21] The majority of these studies focus on the effect on drug use and drug prescriptions; so far as we are aware, the effect of media attention on monitoring drug safety has never been extensively studied.

In daily practice ECGs are not routinely recorded before and/or after prescription of domperidone. Physicians are not always aware of the risks of QTc-time prolonging drugs, including domperidone.[22] However, awareness may have increased after the media hype of March 2013, resulting in an increased frequency of ECG monitoring. Furthermore, the publicity on domperidone may have resulted in a reduced willingness to prescribe domperidone. Therefore, a study was designed that aimed primarily to compare the proportion of domperidone users with ECG monitoring in a period before and after the media attention. Secondary objective was to compare the proportion of domperidone prescriptions in relation to all anti-emetic prescriptions in both periods.

METHODS

Study design

A 2-centre, observational, retrospective study of two cohorts of patients on treatment with domperidone was performed. The first cohort included patients whose domperidone treatment was initiated between February 23rd, 2012 and March 12th, 2013; further referred to as "before-period". This period represents the ECG monitoring of patients using domperidone before the media hype at March 13th, 2013. The second cohort included patients whose domperidone treatment was initiated between March 14th, 2013 and April 1st, 2014; further referred to as "after-period". This period represents the ECG monitoring of patients using domperidone after the media hype.

In this two centre study, patients were included in both a university medical centre (Erasmus University Medical Centre (EMC) in Rotterdam, the Netherlands) and in a teaching hospital setting (Spaarne Hospital (SH) in Hoofddorp, the Netherlands). In the EMC, the electronic prescribing system Medicator (Computer Sciences Corporation (CSC) Healthcare Group in Leiden, the Netherlands) is used, which documents all prescriptions in the hospital. Regrettably, this system does not register the actual administrations of medication to patients. Therefore, this study will only take into account the prescriptions of domperidone regarding the EMC. The SH, on the contrary, uses the electronic system named Epic (Epic Systems in Verona, Wisconsin, the United States), which also documents the actual administrations in addition to drug prescriptions. Therefore, with regard to the SH, this study will take into account all administrations of domperidone.

Ethical approval for collecting retrospective data as part of the QT-DOM study was obtained from the medical ethics committee of the Erasmus University Medical Centre (MEC-2015-022).

Source population

In the EMC all domperidone prescriptions during the study period (February 1st, 2012 to April 1st, 2014) were extracted, whereas in the SH all administered domperidone dosages were extracted. Extraction was performed by selection of ATC-code A03FA03 which covers all domperidone formulations available in the Netherlands. After the first extraction, the study period was shortened to February 23rd, 2012 to April 1st, 2014 to create two equal study periods of 384 days. The study population for this study comprised of unique patients who were on treatment with domperidone in both hospitals during the previously mentioned dates. Only hospitalized patients whose domperidone was initiated for the first time during both periods were included. Patients were excluded if the initiation date of domperidone was not in the appropriate study period or when domperidone treatment was already used at home. We randomly selected a proportion of patients of all eligible patients, that could be fully screened within a time frame of five months due to limited manpower available for this non-funded study and that minimally complied with the calculated sample size.

Outcome measures

The first primary outcome measure was (1) the proportion of patients with one or more ECGs before and/or during domperidone treatment in the before- and after-period. ECGs recorded before initiation of domperidone treatment (with a maximum of 90 days) or during treatment were included for the assessment of the primary outcome as a reflection of any kind of domperidone monitoring. Also, (2) the proportion of patients with an ECG before and during domperidone treatment as a reflection of "ideal" monitoring and (3) the proportion of patients with an ECG during domperidone treatment in the before- and after-period were studied as primary outcome measures (Figure 1).

Secondary outcome measures were (1) the number of prescriptions of domperidone as a proportion of the number of all anti-emetic drug prescriptions (alizapride, aprepitant, droperidol, domperidone, granisetron and metoclopramide) in the EMC and (2) the number of administrations

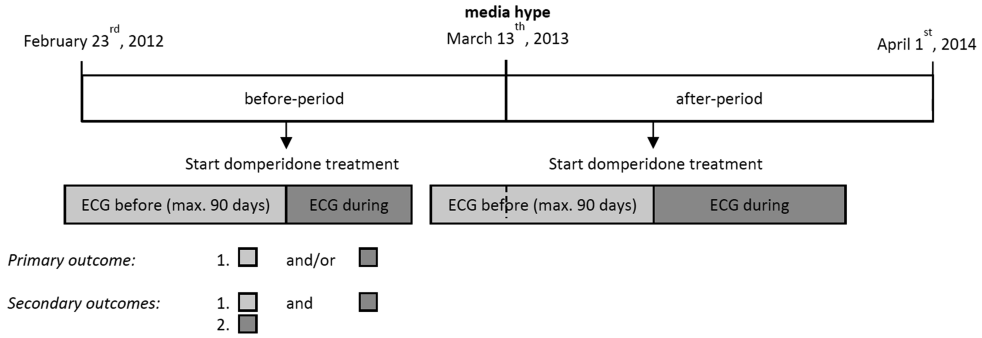

Figure 1. Timeline of study design. ECG (electrocardiogram)

of domperidone as a proportion of the number of administrations of all anti-emetic drugs (aprepitant, domperidone, droperidol, fosaprepitant, granisetron, metoclopramide and ondansetron) in the SH in the before- and after-period.

Exploratory outcomes were the number of domperidone prescriptions in the Netherlands in defined daily dose (DDD), the number of dispensings and the number of domperidone users, obtained from 2009 to 2014 from the Drugs and Medical devices Information Project (GIP) databank.[25]

Data collection

The following data were obtained from the electronic patient records: daily dose of domperidone, plasma sodium and potassium levels, plasma creatinine level, estimated glomerular filtration rate (eGFR), weight, height, cardiac morbidities in present or past, total amount of concomitant medication, other QTc-time prolonging drugs according to the Arizona Centre for Education and Research on Therapeutics (AZCERT) QT drug list by risk group *known risk of TdP*[23], CYP3A4 inhibiting drugs[24] and clinical department of admission. Laboratory results within a maximum of 5 days before or after initiation of domperidone were taken into account.

Twelve-lead ECGs were selected if recorded maximally 90 days prior to the initiation date of domperidone. Although ECG recordings made within 90 days prior to domperidone use will not be related to the initiation of domperidone (and thus will not be influenced by the media attention), this conservative approach was chosen as it is unlikely for physicians to record a new ECG at start of domperidone treatment when such a recent recording is already present. To adjust for the difference in general ECGs recorded in the EMC between the two study periods, the total number of ECGs recorded in the EMC during the study periods was requested from the Business Intelligence Centre (BIC) of the EMC.

Due to the limitations in the electronic hospital system in the SH, no data of the total number of ECGs, nor data of height, weight, cardiac morbidities, total amount of concomitant medication and clinical department of admission were obtainable from this centre.

Statistical analysis

For this retrospective study a sample size calculation was performed. It was estimated that an ECG recording was obtained in 50% of the patients before March 13th, 2013 and in 70% of the patients after March 13th, 2013. With an alpha of 0.05 and a power of 80%, 103 patients were needed in each cohort to find a significant relative risk. Therefore, a total of 206 patients had to be included for this study.

Data were analysed using Statistical Package for the Social Sciences (SPSS, IBM SPSS statistics version 21.0, USA). Analyses were done for both hospitals combined and for each hospital individually. The independent t-test was used to compare continuous variables, assuming equal or unequal variances between the two cohorts, and Chi-Square test or Fisher's Exact test, as appropriate, was used for categorical variables. Comparisons for non-normally distributed continuous parameters were performed using the non-parametric Mann Whitney U test. P values were calculated for each variable. A *p*-value of 0.05 was used to define statistical significance for all calculations. Relative risks (RR) are presented as mean with 95% confidence intervals (CI).

To analyse if domperidone use changed nationally, a graph over the last 5 years was made but no formal statistical testing was used.

RESULTS

Study population

In total, 1,432 medication orders of domperidone were identified in the EMC during the 24 months study period. Of 718 unique patients, 472 medication orders were randomly selected and screened for eligibility. 223 patients were excluded due to an initiation date outside the study period and 6 patients were excluded due to lack of patient information. In 1 patient, domperidone treatment was never started. In total, 241 patients in the EMC met the inclusion criteria. More patients (n = 135) were treated before the media hype, than after the media hype (n = 106).

In total, 384 admissions were screened for eligibility in the SH. These admissions consisted of 276 unique patients of whom 33 patients were excluded because of the inappropriate initiation date of domperidone; in 56 patients domperidone treatment was already used at home. A total of 187 patients were included in the SH of whom 118 in the before-period and 69 in the after-period (Figure 2).

A summary of baseline characteristics is presented in Table 1. The baseline characteristics are presented for both hospitals combined. The median age of the study population was 60 years and 54% of the patients were female. Approximately 80% of the study population was 18 years or older and the median daily dose of domperidone was 30 milligrams (mg) in both cohorts.

There were no significant differences between the two groups in the before- and after-period when the cohorts of the hospitals were combined.

Primary outcomes

The frequency of ECG monitoring in patients on treatment with domperidone before and after the media attention is summarized in Table 2. There was no difference in the proportion of patients

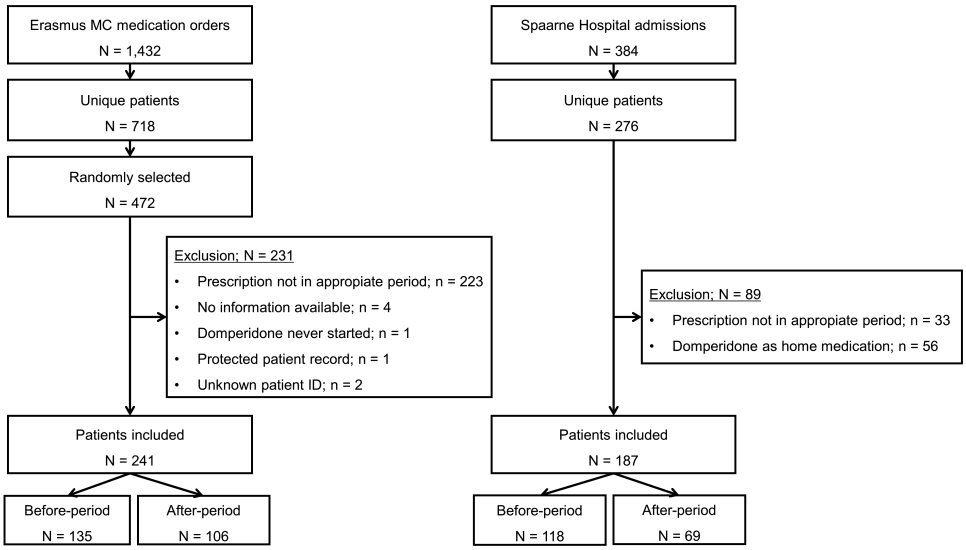

Figure 2. Flow chart of included patients of the Erasmus MC (left) and the Spaarne Hospital (right)

in whom an ECG was made within 90 days before initiation of domperidone treatment and/or during domperidone treatment (RR 1.02; 95% CI 0.85 – 1.21) when comparing the before and after media hype time periods. Also after stratification for hospital, no differences in primary outcome were found between the before- and after-period (EMC: RR 1.12; 95% CI 0.88 – 1.43; SH: RR 0.92; 95% CI 0.71 – 1.19). The monitoring of patients by recording an ECG before and during treatment was not significantly increased after the media hype (RR 1.06; 95% CI 0.60 – 1.85). In both hospitals in only 26 (10.3%) patients an ECG was monitored both before and during domperidone treatment in the time period before the media hype and this percentage did not increase (10.9%) in the time period after the media hype.

The recordings of ECGs during treatment increased from 13.0% to 16.6% after the media hype. However, this increase was not statistically significant (RR 1.27; 95% CI 0.80 – 2.01). After stratification for hospital, again no differences in secondary outcomes were found between the before- and after-period (EMC: respectively RR 1.56 (95% CI 0.67 – 3.62); RR 1.46 (95% CI 0.74 – 2.85) and SH: RR 0.81 (95% CI 0.37 – 1.77); RR 1.17 (95% CI 0.62 – 2.22).

The total number of ECGs recorded in the EMC in the before-period was 56,362 compared to 58,015 ECGs in the after-period. This increase of 3% in ECG recordings will not explain the fact that no differences in ECG monitoring was found in the primary outcome measures.

Secondary outcomes

The changes in prescribing behaviour of physicians for each hospital are summarized in Table 3. In the period before the media hype the proportion of the number of domperidone prescriptions as proportion of all anti-emetic prescriptions in the EMC was 6.5%. After the media attention this

proportion was decreased to 2.6%. This is a significant decrease in medication orders of 60% (RR 0.40; 95% CI 0.35 – 0.45). In the SH, no difference was found in prescribing domperidone after the media attention (1.1% *versus* 1.2%; RR 1.11; 95% CI 0.92 – 1.32).

Table 1. Baseline characteristics for both hospitals combined.

Demographics	**before-period n = 253**	**after-period n = 175**	***p* value**
Female, n (%)	137 (54.2%)	95 (54.3%)	0.98 [b]
Age (years), median (IQR)	60.0 (43)	60.0 (32)	0.89 [a]
Adult,[c] n (%)	204 (80.6%)	144 (82.3%)	0.67 [b]
Daily dose, [d] mg, median (IQR)	30.0 (40)	30.0 (30)	0.59 [a]
Sodium (mmol L^{-1}), mean ± SD	138.6 ± 4.7	138.9 ± 4.2	0.51 [a]
Potassium (mmol L^{-1}), mean ± SD	4.2 ± 0.7	4.2 + 0.6	0.72 [a]
Creatinin (µmol L^{-1}), median (IQR)	68.5 (45)	65.0 (35)	0.22 [a]
eGFR (ml min^{-1}), median (IQR)	90.0 (38)	90.0 (18)	0.09 [a]
BMI[§] (kg/m^2), mean ± SD	21.9 ± 6.2	21.4 ± 5.0	0.52 [a]
Cardiac comorbidities,[e] n (%)	31 (23.0%)	21 (19.8%)	0.56 [b]
Comedication,[e] n (%)			0.82 [b]
0-4 other drugs	46 (34.1%)	32 (30.2%)	
5-9 other drugs	45 (33.3%)	46 (43.4%)	
≥10 other drugs	44 (32.6%)	28 (26.4%)	
Other QT-prolonging drugs, n (%)			0.42 [b]
0	194 (76.7%)	137 (78.3%)	
1	45 (17.8%)	33 (18.9%)	
≥2	14 (5.5%)	5 (2.9%)	
CYP3A4-inhibiting drugs, n (%)			0.18 [b]
0	218 (86.2%)	144 (82.3%)	
1	30 (11.9%)	30 (17.1%)	
≥2	5 (2.0%)	1 (0.6%)	
Clinical department,[e] n (%)			0.25 [b]
Paediatrics	47 (34.8%)	27 (25.5%)	
Internal medicine	28 (20.7%)	18 (17.0%)	
Neurology	25 (18.5%)	21 (19.8%)	
Surgery	12 (8.9%)	14 (13.2%)	
Oncology	21 (15.6%)	20 (18.9%)	
Other	2 (1.5%)	6 (5.7%)	

BMI (body mass index), eGFR (estimated glomerular filtration rate), IQR (interquartile range), SD (standard deviation)
Missing Values: Na^+ (n = 47), K^+ (n = 46), Creatinin (n = 47) eGFR (n = 116), BMI (n = 209)
[a] Independent *t*-test
[b] Chi-square test
[c] ≥ 18 years
[d] 'If necessary' is not taken into account because of unknown daily dose (n = 89)
[e] Only EMC data

Exploratory outcomes

Figure 3 shows the quantities of defined daily dose (DDD), dispensing's and numbers of users of domperidone (ATC-code A03FA03) over the last 5 years. The figure shows an increase of quantities of defined daily dose (DDD), dispensings and users from 2009 to 2011. In 2012-2013 the quantities of DDD, dispensings and users declined probably due to the media attention and restrictions regarding domperidone. However, the dispensings and users of domperidone were increasing in 2014, whereas the quantities of DDD are still declining.

Table 2. Primary outcomes (%) in both hospitals combined.

Outcome measures	before-period n = 253	after-period n = 175	RR (95% CI)
≥1 ECG	138 (54.5%)	97 (55.4%)	1.02 (0.85 – 1.21)
≥1 ECG before AND ≥ 1 ECG during	26 (10.3%)	19 (10.9%)	1.06 (0.60 – 1.85)
≥1 ECG during	33 (13.0%)	29 (16.6%)	1.27 (0.80 – 2.01)

CI (confidence interval), ECG (electrocardiogram), RR (relative risk)

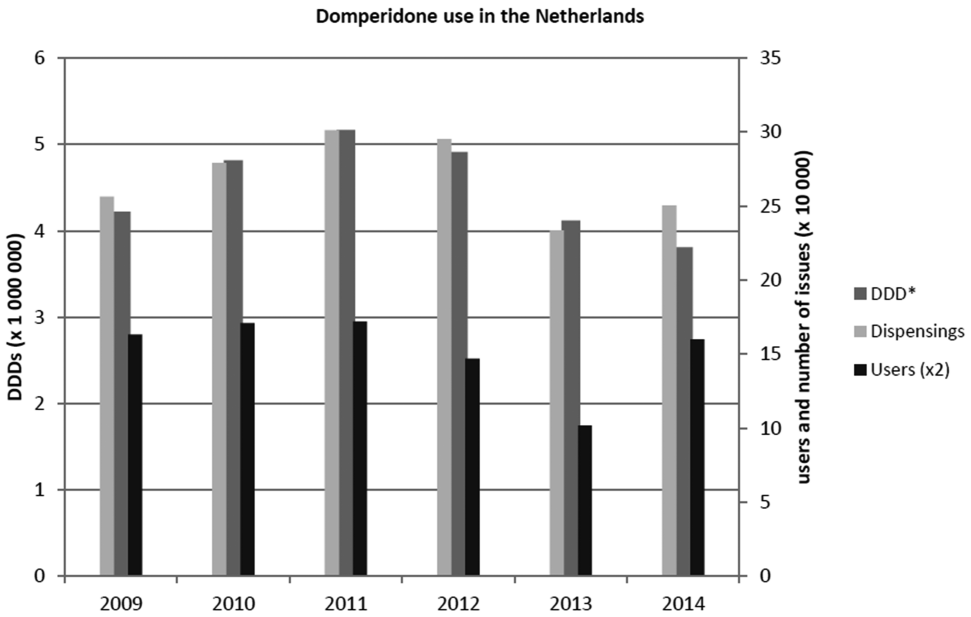

Figure 3. Domperidone use over time in terms of quantity of *defined daily dose (DDD), amount of dispensings and users.[25]

Table 3. Change in prescribing behaviour of physicians (%) in Erasmus MC and Spaarne Hospital.

	Erasmus MC			Spaarne Hospital		
	before-period n = 16,203	**after-period n = 13,313**	**RR (95% CI)**	**before-period n = 24,362**	**after-period n = 16,324**	**RR (95% CI)**
Prescriptions	1,050 (6.5%)	344 (2.6%)	0.40 (0.35 – 0.45)	-	-	-
Administrations	-	-	-	274 (1.1%)	203 (1.2%)	1.11 (0.92 – 1.32)

CI (confidence interval), RR (relative risk)

DISCUSSION

To our knowledge, this is the first study exploring the association between media attention regarding the potential risks of domperidone use in March 2013 and the practice of ECG monitoring by physicians. In our study no statistically significant association was found between the media attention and ECG monitoring practice in domperidone patients in both an academic and a general hospital setting. However, in the university medical centre a decrease of 60% in domperidone prescriptions was found after the media hype; in the teaching hospital no effect was found. Nevertheless, it should not be forgotten that before the media hype, domperidone prescriptions formed a very small proportion of all anti-emetic administrations in the teaching hospital (1.1%), where this was 6.5% in the university medical centre. Therefore, further reduction in domperidone prescriptions was not feasible in the teaching hospital. Other unknown differences between both hospitals may possibly account for these results as well.

Previous studies have shown that media attention on drugs could result in changes in the prescribing behaviour of physicians and drug use among patients. In 1995, the use of third generation contraceptives fell dramatically because of the warning by the Committee on Safety of Medicines on the risk of thromboembolism associated with these contraceptives.[17] Also, in the Netherlands a change in prescribing of hormone replacement therapy occurred due to the publication of the Million Women Study.[18] Ruiter *et al*. suggest with their study on dispensing patterns of rosiglitazone and pioglitazone that prescribers may react to safety communications such as 'Direct Healthcare Professional Communications' (DHPCs) or EMA press releases.[19] However, this study focused mainly on the effect of the media hype concerning the safety of domperidone. The regulatory restrictions on the use of domperidone were endorsed in April 2014 by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh).[28]

Figure 3 shows a decrease in dispensings and users of domperidone of respectively 61,710 and 22,509 from 2012 to 2013. However, the media attention might have influenced the prescription behaviour of domperidone only for a short time, as we see a decrease in 2013 only. In a study on the influence of media and educational interventions on calcium-channel blockers on first-line prescribing of antihypertensive drugs, Maclure *et al*. support this finding by stating that changes in prescribing practices occur gradually with the accumulation of small impacts from educational interventions and lay media attention.[20] A recent study by Matthews *et al*. showed that increased rates of cessation after media coverage were no longer observed after six months in post hoc analyses.[21]

Despite the concerns on domperidone safety, the ECG monitoring of domperidone was surprisingly poor in these two hospitals. In our study, approximately 10% of the patients were monitored before and during domperidone treatment.

In our study we defined a baseline ECG as any ECG recorded within 90 days prior to the initiation date of domperidone. In the vast majority of the cases these ECG recordings had not been made because of the upcoming start of domperidone treatment, but for other reasons. We did count these ECGs, as physicians are not likely to record a new baseline ECG before domperidone

treatment whenever such a recent ECG is already present. The frequency of ECG monitoring during treatment was a secondary objective and the study was not powered for this endpoint. Table 2 shows that after the media hype the frequency of ECG monitoring after domperidone increased from 12.7% to 16.6%. This difference was not statistically significant, however. In a much larger study this 3.9% difference might be statistically significant, but still clinically irrelevant.

According to literature, little is known about the effect of media attention on monitoring drug safety. This study showed a different impact of the media attention on physicians' patient monitoring and prescribing in the different hospital settings.

CONCLUSION

To summarize, no significant difference was found in the practice of ECG monitoring prior to or following initiation of domperidone treatment, comparing time periods before and after regulatory warnings and vast media attention for the potential risks of this drug. Despite the concerns that were raised with respect to the safety of domperidone, ECG monitoring is only done in a minority of the patients. We did find a substantial decrease (60%) in domperidone prescriptions in the university medical centre, after the media hype.

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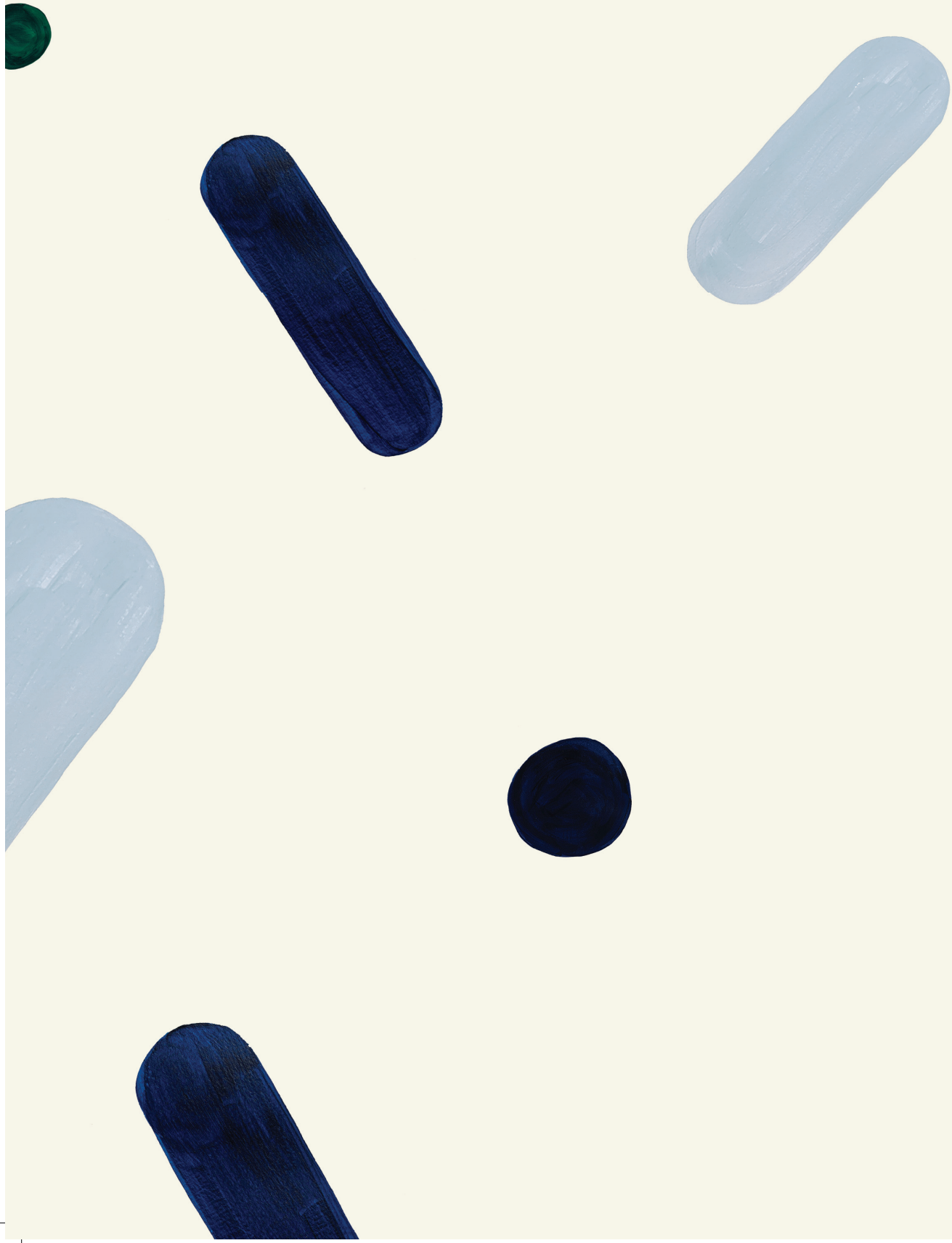
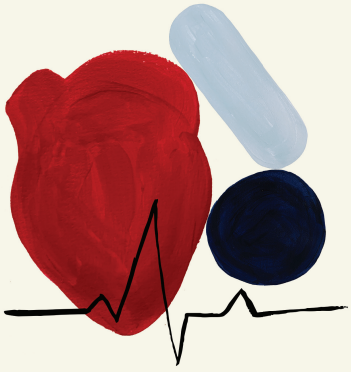


PART IV

GENERAL DISCUSSION, SUMMARY AND APPENDICES



11 CHAPTER

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Currently, more than 200 drugs are known to prolong the QT or heart-rate corrected QT (QTc) interval. Among these, frequently used drugs such as antibiotics and psychotropic drugs are present.[1] QTc-interval prolongation is a risk factor for the development of life-threatening ventricular arrhythmia such as Torsades de Pointes (TdP), which may ultimately lead to sudden cardiac death. When QTc-intervals exceed 500 milliseconds (ms) or increase by more than 60 ms from baseline, the risk of ventricular arrhythmias is very high.[2] And each 10 ms increase in the QTc-interval causes an approximate 5–7% increase in the risk of developing TdP.[3, 4] 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.[5-8] 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 without further diagnostic procedures such as checking ECG before and/or after initiation of drug treatment.[9, 10] The aim of this thesis was to provide guidance on safe prescription practices by gaining more insight into the prevalence and associated risk factors of QTc-prolongation in patients using QTc-prolonging drugs. We performed several studies to contribute to a better understanding of the complex association between QTc-prolonging drugs and their pro-arrhythmic effects. First, we studied the effect of various QTc-prolonging drugs on the QTc-interval in different populations. Subsequently, we developed and evaluated two prediction models in order to identify patients at increased risk for QTc-prolongation. Finally, we investigated the effect of a prediction model on the number of interventions made by pharmacists in community pharmacies, and studied the impact of media attention on the prescribing behavior of clinicians in the specific case of domperidone.

In this final chapter our main findings are discussed and put into a broader perspective. For an adequate interpretation of our findings, we will first discuss a number of uncertainties in the association of drug induced QTc-prolongation with incidence of TdP.

No clarity in rarity

The occurrence of TdP in a general population is extremely rare.[8, 11] Many patients with a prolonged QTc-interval will never experience TdP and vice versa. Data on the incidence of drug induced TdP are limited, and estimating the exact incidence remains challenging, mainly because TdP is often transient, not recognized or not registered on the ECG.[12] Our knowledge on the incidence and risk factors of QTc-prolongation is predominantly based on clinical studies during drug development (known as thorough QT studies), on large epidemiological cohort studies and post-marketing surveillance.[9, 13, 14] Despite the considerable attention that is paid to drug induced TdP over the past years, the absolute number of drug induced TdP cases is remarkably low.[15] According to pharmacovigilance data, the annual reporting rates of drug induced LQTS/TdP per million persons vary between 0.08 and 1.2.[16-18] However, when active surveillance programs are introduced, these incidences appear to be significantly higher.[12, 16] For specific drugs, the incidence is even harder to estimate due to the variation in relative risk and the number of prescriptions for that specific drug. Therefore, the question arises whether we should focus so much on such a rare and

incomprehensible side effect. For example, ciprofloxacin is most known for its QTc-prolonging effect (which seems negligible) resulting in ECG monitoring or withdrawal of ciprofloxacin therapy, but we rarely withhold ciprofloxacin therapy because of its other severe side effects such as tendinitis. In addition, in the studies we report in **Chapter 2** and **3** we did not find clinically important QTc-interval prolongation in patients treated with ciprofloxacin. Withholding first-line therapies, or implementing intensive ECG monitoring might do more harm, on economical or patient grounds, than the very low risk of ventricular arrhythmias. For example, Poncet *et al*. found a number of psychiatric patients needed to screen (ECG) to avoid one TdP of 1,128.[19] Whether or not to maintain strict safety measures remains an extremely difficult and ethical discussion.

QTc-prolongation is an independent risk factor of TdP and is commonly used as a surrogate marker of the risk of developing ventricular arrhythmias. However, a linear correlation is lacking, so it is questionable whether a prolonged QTc-interval may be used as such.[20] The perfect endpoint for future research remains open for discussion. Regrettably, TdP as primary endpoint seems unfeasible; exceptionally large patient populations are needed due to the rarity of the event, even in high risk populations. All-cause mortality or sudden cardiac death (SCD) are non-specific endpoints which are subject to confounding. Patients at risk of drug induced TdP are often older and suffer from underlying cardiac diseases. Given that TdP is not feasible as an endpoint and QTc is (although not linearly) associated with TdP, the best outcome for safety studies is still QTc-time.[21, 22] Therefore, we decided to perform our studies with a focus on QTc-prolongation as primary endpoint. In Part I, we investigated the QTc-prolonging effect of several QTc-prolonging drugs in hospitalized and ICU patients, none of the patients included in the studies developed TdP.

Unravelling the mechanisms

The second issue we have to address, is the knowledge gap in the underlying mechanism of inducing QTc-prolongation and TdP. The exact mechanism and factors attributing to this phenomenon still need to be unravelled. The suggested mechanism of drug induced QTc-interval prolongation is inhibition or reduced expression of the human ether-a-go-go related (hERG) gene that encodes a potassium channel that regulates repolarizing currents (Ikr) in the cardiac myocytes.[23] Inhibition of these Ikr results in a delay in the ventricular repolarization causing prolongation of the QT-interval. The QTc-prolonging potential might be explained by the different mechanisms of inhibition of, or affinity to the hERG channels. However, literature is contradicting regarding the central role of hERG channels.[24, 25] More than 20 currents, subdivided into depolarizing and repolarizing currents, are involved in the action potential generation of cardiac myocytes, and these currents and channels might also play a role in prolonging the QTc-interval.[9, 25] The exact role and mechanisms of other risk factors such as electrolyte disturbances, cardiovascular diseases, genetic predisposition, comorbidities, increasing age and female gender also remain an interesting point of discussion.[5-7, 21, 26-30] Women have a 2-fold higher risk to develop QTc-prolongation, probably due to an effect of oestrogens on prolonging the QTc-interval. Additionally, females have a higher baseline QTc-interval.[8, 11, 31] In cardiovascular diseases, several factors such as downregulation of potassium channels, remodelling of the heart or conduction disorders might contribute to pro-arrhythmic effects. The mechanisms of other comorbidities (e.g. hypertension, diabetes mellitus) contributing

to QTc-prolongation remain partly unknown.[32, 33] Renal insufficiency affects the pharmacokinetics of QTc-prolonging drugs enhancing the QTc-prolonging effect and diuretics may indirectly affect the repolarization by causing electrolyte disturbances or because of the underlying disease heart failure. However, several studies identified diuretics as independent risk factor of QTc-prolongation. [21, 34] Finally, literature remains inconclusive on the synergistic effect of multiple QTc-prolonging drugs. Meid et al and Heemskerk *et al*. did not find an additive effect on the QTc-interval when more than two QTc-prolonging were used.[7, 35] In **Chapter 4**, we found increasing age (Pearson r = 0.24; *p* = 0.02), low potassium levels (Pearson r = -0.28, p = 0.02), renal dysfunction (Pearson r = -0.24; *p* = 0.04) and the use of > 1 concomitant QTc-prolonging drugs (Spearman r = 0.23, *p* = 0.02) to be associated with QTc-prolongation. Heemskerk *et al*. showed that increasing numbers of risk factors for QTc-prolongation had an increasing effect on the QTc-interval. [7] This finding was in line with several other studies that stated that multiple risk factors contribute to the development of drug induced QTc-prolongation and TdP.[11, 36] These findings confirm the theory of Roden *et al*. regarding the repolarization reserve: this theory describes that a physiological cardiac repolarization reserve is genetically determined for every person and compensates for factors decreasing repolarization currents during the action potential. The more factors reducing this repolarization reserve, the higher the risk of QTc-prolongation and TdP.[37] In **Chapter 6** and **7**, the majority of these risk factors were included in the algorithms which showed moderate discriminative abilities to identify high risk patients for developing QTc-prolongation. This might be explained by an incorrect scoring of the potential risk factors. Large-scale studies are needed to further elucidate the exact role of the different factors involved in developing QTc-prolongation or TdP.

Definition of heart-rate adjusted QT-prolongation

Unfortunately, there is still no worldwide consensus on the cut-off values and formulas to determine QTc-prolongation. In the past, a QTc-interval exceeding 440ms was regarded as borderline QTc-prolongation. Nowadays, a QTc-interval above 450 ms in males and above 470 ms in females is generally considered to be prolonged according to the European Medicine Agency (EMA) guidelines.[38, 39] The American Heart Association (AHA) considers QTc-intervals to be prolonged when they exceed 470 ms in males and 480 ms in females.[40] In children, the number of studies on QTc-interval prolongation remains limited. A QTc-interval > 500 ms or increase of 60 ms from baseline is widely considered to be the cut-off point at which the risk of TdP is very high and intervention is needed.[21, 22] The measurement of the QTc-interval is also an interesting point of discussion. Unfortunately, computer-derived measurements used in clinical practice, contain many errors, particularly in patients with complex and noisy T-waves and U-waves. [22] Therefore, the QTc-interval should preferably be measured manually. However, Viskin *et al*. found that less than 50% of the cardiologists and less than 40% of non-cardiologists calculated the QTc-interval correctly.[41] Another disadvantage of the lack of agreement among experts about standardizing approaches measuring QTc-intervals manually is the intra- and inter-observer variability and errors that may occur. [41, 42]

Also, it should be noticed that the magnitude of the change in QTc that needs to be measured to define a QTc-prolonging effect is rather small compared to the relatively high baseline. And this is further complicated by the intra- and interpatient variability of the QTc-interval which is determined by a diurnal pattern or changes in heart rate.[43] In **Chapter 3**, this substantial variability of the QTc-interval in a heterogeneous ICU population during a 24-hour period was clearly shown due to the multiple QTc data points every 30 seconds. Finally, a limiting factor for interpreting the QTc-formula is the lack of consensus on the different correction formulae to calculate the heart-rate correct QT-interval. The most frequently used formulae are the Bazett and Fridericia formula. The Bazett formula is known for overestimating the QTc-interval at higher heart rates and underestimating the QTc-interval at lower heart rates, but is widely used in literature. The Fridericia formula is known to give a better prediction at higher heart rates.[44] Therefore, we used these two formulae in the first part of our thesis to explore the QTc-prolonging effect of several drugs. In **Chapter 5 – 8**, we used computer-derived QT-intervals and adjusted them for heart-rate using the Bazett formula, because manual interpretation could not be achieved due to the large number of ECGs. In all studies, we excluded heart rates above 180 beats per minute (bpm) and below 40 bpm to minimize over- or under correction of the QTc-interval. Nevertheless, these findings should be interpreted with caution.

In the future, it would be beneficial if the authorities standardized a QTc-formula that is widely used in future research and clinical practice. Also, optimization of the ECG devices to correctly measure the QTc-interval is required, especially for large-scale epidemiological studies. In clinical practice, the automatically calculated QTc-interval reported on the ECG is widely used by clinicians, and therefore, it is necessary that literature is based on similar values. It is important that ECG devices report correct QTc-intervals.

QTc-prolonging potential of drugs

Finally, we need to deliberate on the fourth and final issue which we have tried to answer in this thesis. The extent of the QTc-prolonging effect is unknown for the majority of the QTc-prolonging drugs. Nevertheless, it can be stated that there is an association between a prolonged QTc-interval and ventricular arrhythmias.[45-47] This association is also found in several large epidemiological studies. Straus *et al*. found a 3-fold higher risk of SCD for non-cardiac drugs.[45] Also, Chou *et al*. focus on the risk of ventricular arrhythmias and cardiovascular death among patients using macrolides and fluoroquinolones.[46] They found significant increases in the risks of ventricular arrhythmia and cardiovascular death for the use of azithromycin (4.32; 95% CI 2.95 – 6.33) and moxifloxacin (3.30; 95% CI 2.07 – 5.25). Clarithromycin or ciprofloxacin were not associated with adverse cardiac outcomes.

In **Chapter 2**, we found a low prevalence of QTc-prolongation (4.7%) and an increase of the QTc-interval of 10.7 ms (95% CI 7.2 – 14.1 ms) during ciprofloxacin – fluconazole therapy. However, this increase is considered to be negligible in relation to the daily QTc-variability. No risk factors were associated with QTc-prolongation during this treatment. Given the low prevalence and limited increase of the QTc-interval, routine ECG monitoring in haematological patients using ciprofloxacin and fluconazole is in our view no longer necessary. In this study, the majority of the patients took

ciprofloxacin orally. The risk of QTc-prolongation is often greater in association with intravenous administration, presumably as a result of higher (peak) plasma drug concentrations and greater cardiovascular exposure.[48, 32] Therefore, in **Chapter 3**, we studied the effect of intravenous ciprofloxacin during a 24-hour dose interval in ICU patients. At the start of this study our hypothesis was that the continuous recording of the QTc-interval in these patients might allow for the detection of changes in the QTc-interval immediately following intravenous administration of ciprofloxacin. This study however showed no evident effect on the QTc-interval over time when compared to a control group. Other studies confirmed this finding and this brings us to the conclusion that ciprofloxacin monotherapy lacks a clinically relevant QTc-prolonging effect. For this frequently prescribed drug the implication is that in daily practice the safety measures associated with QTc-interval prolongation are likely to be superfluous. Introduction on the CredibleMeds® QT drug list in 2016, resulted in a Dutch teaching hospital in 4.2 QT drug-drug interaction (QT-DDI) alerts with ciprofloxacin per day, which was an increase of 22.3% for the total number of QT-DDI alerts. The number of ECG recording before and after the QT-DDI increased by 8.7%.[49] Therefore, the clinical relevance of the CredibleMeds® QT drug lists should be questioned. The Arizona Center for Education and Research on Therapeutics (AzCERT) has developed a process to place drugs in risk categories for their clinical ability to cause TdP and QTc-prolongation. AzCERT collects its data from different sources including the FDA adverse event reporting system (FEARS), the WHO adverse events database, case reports and reports in medical literature.[14] However, the evaluation of causality is often difficult and evidence is frequently incomplete due to the low number of cases and the high number of drug users. Still, there is a growing number of drugs that have been added to the lists since 1999 when it was established. AzCERT should focus more on the QTc-prolonging potential of the drugs. In recent years, the lists have been revised approximately every 30–45 days, but surprisingly no drugs have been removed from the lists.[14] The rising number of drugs on the list will result in more and more alerts, and from previous research we know that this overload of non-specific alerts leads to alert fatigue [50, 51] By switching off alerts, and limit the alerts to only those that are clinically relevant, patient safety will improve.

In **Chapter 3**, we also studied the effect of low-dose erythromycin during a 24-hour dose interval in ICU patients. Erythromycin in doses of 1000 mg 4 times daily is known to have a significant effect on the QTc-interval, especially when it is administered intravenously or co-administered with other QTc-prolonging drugs that inhibit or are substrates for CYP3A4 enzymes.[52] Twenty-five years ago, Oberg *et al.*, reported an increase from baseline QTc of 432 ± 39 ms, to 483 ± 62 ms during erythromycin therapy. [48] This increase was marked as impressive, however, the increase was less than 60 ms, and the mean QTc-interval during erythromycin therapy was < 500 ms. In ICU patients, low-dose erythromycin is often used as a prokinetic drug. Fiets *et al*. found a QTc increase of 9 ms (p = 0.03) after 15 min and 14 ms (p = 0.01) after 24 hours.[53] No QTc related arrhythmias were observed. Possibly the difference in outcome with our study, where we did not find changes in the QTc-interval, is caused by the fact that the erythromycin dose used by Fiets *et al*. (200 mg b.i.d.) was twice as high as the dose in our study (100 mg b.i.d.). Based on our data we conclude that proactive ECG monitoring in patients treated with low-dose erythromycin (100 mg b.i.d.) is not necessary. These

findings should be incorporated into a clinical rule, where no alert will be generated if ciprofloxacin or low-dose erythromycin is prescribed. Moreover, these patients are already monitored in the ICU.

Also, the effect of psychotropic drugs on the QTc-interval is well-known by clinicians and has increasingly gained attention in clinical practice. Among these, some antidepressants have been shown to prolong the QTc-interval. A meta-analysis by Beach *et al.* showed that SSRIs were associated with a limited increase in QTc-interval compared to placebo (6.10 ms; 95% CI 3.47 - 8.73; $p < 0.001$) and citalopram was associated with significantly larger QTc-prolongation than sertraline, paroxetine, and fluvoxamine.[54] In **Chapter 4**, we studied the potential drug-drug interaction between tamoxifen and SRIs resulting in a prolonged QTc-interval. ECGs of 100 patients were collected at steady state tamoxifen treatment, with or without concomitant SRI co-medication. The mean QTc-interval was 12.4 ms longer when tamoxifen was given concomitantly with an SRI (95% CI 1.8 – 23.1 ms; $p = 0.023$). None of the patients had a QTc-interval of > 500 ms. Prolongation of the QTc-interval was particularly pronounced for escitalopram (12.5 ms; 95% CI 4.4 – 20.6 ms; $p < 0.01$) and citalopram (20.7 ms; 95% CI 0.7 – 40.7 ms; $p = 0.047$), where other agents like venlafaxine did not seem to prolong the QTc-interval. Therefore, when concomitant administration with an SRI is warranted in high-risk patients, venlafaxine is preferred, although the risk for other SRIs is relatively small. In 2011, the FDA released several drug safety communications regarding the cardiotoxicity of (es) citalopram use. It stated that both citalopram and escitalopram cause QTc-interval prolongation in a dose-dependent manner, and doses should not exceed 40 mg/day in adults and 20 mg/day in patients > 65 years old.[55] The impact of drug safety communication regarding (es)citalopram was investigated by Schachtele *et al.* and they found that physicians adhered to the dose restrictions, but (es)citalopram was still often prescribed in combination with other QTc-prolonging drugs.[56]

In March 2013, regulatory warnings concerning the potential risks of domperidone caused considerable media attention in the Netherlands.[57] In **Chapter 10**, the effect of regulatory warnings and the resulting media hype on the frequency of electrocardiogram (ECG) monitoring of inpatients using domperidone and the effect on the frequency of prescribing domperidone by physicians was studied. No effect of the media hype was found on the intensity of ECG monitoring in domperidone users. However, in one of the university medical centres we did find that the number of domperidone prescriptions was reduced.

Another drug that gained increasingly attention in the media during the COVID-19 pandemic, was the antimalarial drug chloroquine. In the early stages of the pandemic, chloroquine was recommended as a treatment option in the Dutch guidelines, but was also known for its QTc-prolonging effect.[58] In **Chapter 5**, we studied the QTc-prolonging potential of chloroquine in COVID-19 patients and evaluated whether this prolongation was associated with a higher cumulative dose or with the peak plasma concentration of chloroquine. We found that chloroquine treatment in COVID-19 patients gradually increased the QTc-interval with 33 ms from baseline. Another important finding was that a significant number of overestimated QTc-intervals by computer analysis caused prematurely discontinuation or dose adjustments of chloroquine. Therefore, it is advisable to measure the QTc-interval manually before adjusting the dose or withdrawing first-line treatments.

Challenges of clinical decision support systems

To decrease the alert burden, more advanced algorithms including clinical parameters such as patient characteristics and laboratory values are needed to improve the specificity of the alerts and decrease the alert rate. In **Chapter 6** and **7**, we have developed two algorithms to optimize the risk management of patients using two or more QTc-prolonging drugs. In **Chapter 8**, we compared both algorithms in an external dataset. Besides acceptable sensitivities, the specificity of both algorithms remained low and an adequate positive predictive value (PPV) is lacking. This low specificity and PPV is also found in other algorithms developed by several research groups.[2, 6, 59-61] This might be explained by the high interpatient variability of the QTc-interval. Also, the algorithms do not take into account the variety of QT-DDIs in combination with various dosages, and because of the different pharmacological pathways of the QTc-prolonging drugs via inhibition of the hERG channels or Cytochrome P450 enzymes, stratification of QT-DDIs is extremely complex and larger studies need to be conducted for each QT-DDI separately. Also, the algorithms lack information on the genetic predisposition of patients, which is extremely difficult to incorporate in an algorithm. Overfitting is a key problem in many prediction models. This is either because the number of events is small, or because many potential predictors are studied. Steyenberg *et al*. described seven steps to reliably develop a prediction model, these steps should be taken into account in future research.[62]

In **Chapter 9**, we implemented a paper-based tool developed in **Chapter 7** into primary care. Unfortunately, we did not find a significant effect on the proportion of advices given to prescribers. To successfully implement an algorithm in a hospital setting or primary care, the algorithm should be incorporated in an electronic Clinical Decision Support System (CDSS) and only generate QT-DDI alerts in high-risk patients. This remains challenging, because all covariates should be documented into the system. Especially in primary care, this is still not the case. But also in a hospital setting this continues to be problematic, for example, comorbidities are often entered as free text and not in a data format enabling extraction into a clinical rule.

Additionally, the algorithm should be successfully integrated into the clinical workflow. Implementation of such a tool often introduces new steps and each step must be evaluated. Thereby, CDSSs are frequently subject to updates, and new insights of QTc-prolonging drugs can be gained, so the algorithm should be maintained continuously. Such an algorithm is only sufficient, if it shows a significant decrease in QT-DDI alerts by suppressing irrelevant alerts and giving clear guidance what to do and why. Nowadays, QT-DDI alerts are frequently overridden[50], so before and during the implementation of the algorithm healthcare professionals should be carefully trained how to deal with these new alerts; thereupon these alert will not be misinterpreted. Adding extra information on level of seriousness could possibly prevent a high override rate. Also, experiences should be evaluated to fine-tune the workflow of the algorithm when necessary.

FUTURE PERSPECTIVES

This thesis has contributed to knowledge on different levels with regard to the risk management of QTc drug-drug interactions. The management of drug induced QTc-prolongation involves balancing between the extremely small risk of TdP and sudden cardiac death, and the risk of

withholding first-line therapies and switching to non QTc-prolonging alternatives. In the studies presented in this thesis, we only found a small increase of the QTc-interval, which can be considered as not clinically relevant, even though these drugs are listed on the QT-drug lists, These findings suggest that routine ECG-monitoring or withholding first-line therapies is not necessary in patients with little to no risk factors. This means that we need to abandon the zero-risk policy for all types of QTc-prolonging drugs and only adopt the zero-risk policy for high-risk patients and high-risk drugs to mitigate the risk on TdP as much as possible. A 'comply or explain' approach, as mentioned in the legal significance of professional standards for pharmaceutical care of The Royal Dutch Pharmacy Association (KNMP) could be adopted for the lower risk patients and drugs.[63]

The question arises what the consequences are if this approach leads to complications, or worse, fatalities. The argument could potentially be made that the explanation for not applying ECG-monitoring or withholding therapy in a given case is insufficient or based on a wrong assessment of the case at hand, which may lead to legal liabilities for the healthcare professionals. This problem might explain why the zero-risk policy is still being followed: a zero risk policy regarding QTc-prolonging drugs is also a zero-risk policy for the healthcare provider. However, the zero-risk policy is not always followed in healthcare, many guidelines and treatments accept a certain degree of risk, which makes it quite unusual that the extremely small risk of developing TdP due to drug induced QTc-prolongation is so widely acknowledged as potential risk. To overcome this problem, it would help if the so-called 'G-standard', a Dutch drug database which supports the different processes in healthcare, such as prescription, dispensing, ordering, reimbursement, and decision support, would substantiate in what situation it is allowed to not withhold first-line therapy or monitor patients intensively.[64]

The findings of this thesis provide guidance in making adequate risk assessments, however, there are still several steps to overcome in the future.

* Further understanding the mechanisms of QTc-prolongation

Further understanding of the link between QTc-prolongation and TdP is needed. This requires more fundamental research, but also clinical and epidemiological insight to better define the conditions and covariates. When focusing on the exposure-effect relation of specific QTc-prolonging drugs, population pharmacokinetic-pharmacodynamics (PK/PD) modelling may contribute to understanding the effect of important covariates. PK/PD models are statistical techniques based on parameter distributions to predict the effect and efficacy of drug dosing over time.[65] Also, the intra- and interpatient variability can be characterized using these models. Several study groups are already exploring this field of research.[66]

* Uniformity of QTc-interval cut-off values and measurements

The lack of standardization and variability in study designs results in limitations in interpretation and potentially biased findings. Preferably, the QTc-interval is measured from lead II from the beginning of the onset of the QRS complex to the end of the T-wave. Due to errors in computerized QTc-time, the QTc-interval should be measured manually. However, the measurement of the QTc-interval is

challenging and should be taught carefully to clinicians. Postema *et al.* showed a successful method to teach unexperienced clinicians to measure a correct QT-interval.[67] On the other hand, in large clinical and epidemiological trials manually measurements of QTc-interval remains challenging. As mentioned before, the ECG devices should be further developed in order to measure adequate QT-intervals in the near future. Also, it is extremely important that the various formulas for calculating the QTc-interval are prospectively validated and compared to each other to find out which formula has the best correlation with clinical outcomes. This formula should then be incorporated in the ECG devices, so a correctly measured QTc-interval is accessible for each health care professional.

* Optimization and implementation of clinical decision support tools

The next important gap to overcome concerns knowledge translation: after unravelling all the aforementioned issues, the development of a clinical decision support tool is highly recommended. The development of two algorithms in **Chapter 6** and **7** was a step towards optimizing the risk management of QTc-drug drug interactions. Given its diagnostic characteristics, the algorithms need further optimization. Preferably, the optimized tool should be implemented into the electronic decision support system; the clinicians would only receive QTc-prolonging drug-drug interactions alerts in high-risk patients. In the mean-time, particularly high-risk situations should be defined based on clinical variables. This requires knowledge of the drug's characteristics, including PK/PD parameters such as route of elimination and drug interactions, knowledge on factors that are contributing to the development of TdP, and an adequate interpretation of the QTc-interval in which pharmacists could fulfil an important role as drug-expert.

In conclusion, it remains challenging with the relative paucity of information to provide guiding information that can help clinicians and patients make informed decisions about drugs that can prolong the QT-interval. However, our findings show a limited risk of drug induced QTc-prolongation and these are the first steps towards a better balance between risks and risk management measures. Currently, we issue far too many alerts for QTc-prolonging drug-drug interactions, resulting in a high workload on the one hand, whilst on the other hand creating alert fatigue. As a result, important warnings are at risk to be overlooked in the pile of irrelevant alerts. By using an algorithm to filter out alerts for patients with a very low risk of QTc-prolongation, we are left with a selection that needs true attention. In that way, we move from a zero tolerance QTc-prolongation handling, to an intelligent balancing of risks. This thesis has placed the first steps towards such balanced risk management.

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12 CHAPTER

SUMMARY
NEDERLANDSE SAMENVATTING

SUMMARY

Many frequently used drugs, such as antibiotics and psychotropic drugs, are known to prolong the QT or heart-rate corrected QT (QTc) interval. Currently, more than 200 drugs are listed on the QT drug list of the Arizona Center for Education and Research on Therapeutics (AzCERT). QTc-interval prolongation is a serious risk factor for the development of life-threatening arrhythmia such as Torsades de Pointes (TdP). TdP is a rare ventricular arrhythmia which may ultimately lead to sudden cardiac death. When QTc-intervals exceed 500 ms or increase by more than 60 ms from baseline, the risk of ventricular arrhythmias increases. Other risk factors such as electrolyte disturbances, cardiovascular diseases, genetic predisposition, increasing age and female gender have a substantial role in developing QTc-prolongation and TdP as well. 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 drugs is tolerated in clinical practice. In all other patients, QTc-prolonging drugs should be avoided or carefully monitored. The Dutch database for medication surveillance used in healthcare information systems 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. These QTc-prolonging drug-drug interaction (QT-DDI) alerts are generated by the support system based on the prescribed drugs, without taking into account other risk factors for developing QTc-prolongation or TdP. The implication is that these non-specific alerts are also shown in patients who do not have (many) additional risk factors for QTc-prolongation, potentially leading to alert fatigue. The aim of this thesis was to provide guidance on safe prescription practices by gaining more insight into the prevalence and associated risk factors of QTc-prolongation in patients using QTc-prolonging drugs, and to explore some risk minimalisation strategies. In **Chapter 1**, the knowledge gaps and challenges regarding drug induced QTc-prolongation are introduced.

Part I – QTc-prolongation in clinical practice

Part I reports on the prevalence and associated risk factors of QTc-prolongation of various QTc-prolonging drugs in heterogeneous patient populations. **Chapter 2** describes the prevalence of QTc-prolongation in 170 patients using ciprofloxacin and fluconazole combination therapy. Ciprofloxacin and fluconazole combination therapy is frequently used as prophylaxis for infections in patients with haematological malignancies. The prevalence of QTc-prolongation in this population was 4.7% and no risk factors were found to be associated with QTc-prolongation. The overall increase of the QTc-interval was 10.7 ms (95% CI 7.2 – 14.1 ms). Given the low prevalence and minimal increase in QTc-prolongation, the routine ECG monitoring which is currently advocated in patients on this combination therapy should be reconsidered. The study in **Chapter 3** examined the dynamics of the QTc-interval during a 24-hour dose interval of intravenous ciprofloxacin or low-dose erythromycin in ICU patients. Continuous ECG data were collected from 2 hours before to 24 hours after the first administration and were compared to control groups. QTc-analyses were performed using high-end Holter software with 30 seconds time slots resulting in more than 50,0000 QTc data points per patient group. Surprisingly, we found no evident effect of ciprofloxacin or erythromycin administration on the QTc-interval. The findings in **Chapter 2** and **3** suggest that ciprofloxacin and low dose erythromycin have a negligible effect on the QTc-interval.

In **Chapter 4**, we conducted a study to investigate the QTc-prolonging effect of serotonin re-uptake inhibitors (SRI) in 50 breast cancer patients treated with tamoxifen compared to 50 breast cancer patients with tamoxifen monotherapy. This retrospective study showed that the mean QTc-interval was 12.4 ms (95% CI 1.8 – 23.1 ms) longer when tamoxifen was given concomitantly with an SRI. Prolongation of the QTc-interval was particularly pronounced for paroxetine (17.2 ms; 95% CI 1.4 – 33.0 ms) and citalopram (20.7 ms; 95% CI 0.7 – 40.7 ms). When tamoxifen was combined with venlafaxine, no effect on the QTc-interval was seen, so venlafaxine is the preferred drug in patients treated with tamoxifen.

At the beginning of the outbreak of the COVID-19 virus in the Netherlands, chloroquine, a quinolone antimalarial drug, was incorporated as first-line treatment in the Dutch guidelines. A common side effect of chloroquine is prolongation of the QTc-interval. Therefore, in **Chapter 5**, we retrospectively studied the QTc-prolonging effect of chloroquine in 397 patients with COVID-19. We found a mean increase of the QTc-interval of 33 ms from baseline after initiation of chloroquine. Consequently, routine ECG monitoring during treatment with this drug in COVID-19 patients can be supported. This study also demonstrated that 19 patients unnecessarily had their treatment prematurely discontinued or had their dose adjusted due to a prolonged QTc-interval based on the computerised misinterpretation of the ECG. Due to a significant number of overestimated QTc-intervals by computer analysis, it is advisable to measure the QTc-interval manually before adjusting the dose or withdrawing this drug, which was considered to be potentially beneficial at the beginning of the COVID pandemic. More recently, however, The Dutch Working Party on Antibiotic Policy (Dutch acronym is SWAB) has removed this drug from the current (November 2020) treatment guidelines for COVID-19.

Part II – Prediction models

Part II of the thesis focused on the development of smart signalling tools to support the risk management of QT-DDIs by reducing redundant QTc-prolonging drug-drug interactions alerts. Previous studies have shown that the development of risk models to predict patients at risk of QTc-prolongation and/or TdP is quite challenging. **Chapter 6** described a risk model that was successfully developed in a large retrospective dataset in a general teaching hospital (sensitivity 81%, specificity 48%). The variables that were analysed, such as age, gender, loop diuretics, potassium and calcium levels, antiarrhythmic drugs and baseline QTc-intervals, are routinely collected in healthcare information systems. Therefore, this risk model can be implemented in a clinical decision support system, to improve the management of the risks associated with QTc-prolonging drugs. In **Chapter 7**, a clinical prediction model was developed based on risk factors associated with QTc-prolongation obtained in a prospective study on QT-DDIs in a university medical centre. This risk model included the following predictors: age, gender, cardiac comorbidities, hypertension, diabetes mellitus, renal function, potassium levels, co-treatment with loop diuretics, and QTc-prolonging drugs. The model had a sensitivity of 83.9%, but due to the low specificity (27.5%), the prediction model needs further optimization before implementation in clinical practice is possible. The performance characteristics of both algorithms were compared in **Chapter 8**, where both algorithms were validated in an external dataset. For this goal a dataset was created from

QT-DDI alerts generated for in- and outpatients at a general teaching hospital between November 2016 and March 2018. Both algorithms showed good discriminative performance (sensitivities of 85.7% and 89.1%, and specificities of 60.8% and 44.3%), and were able to identify patients at risk for QTc-prolongation when using ≥ 2 QTc-prolonging drugs.

Part III – Risk management of QTc-prolonging drug-drug interactions

In **Part III**, we studied two approaches to risk management of drug induced QTc-prolongation. In **Chapter 9**, we describe the effect of a clinical prediction model on the handling of QT drug-drug interactions in primary care before and after the use of a paper-based prediction model in 20 community pharmacies. This study showed no differences in types of interventions by pharmacists before and after the use of the clinical prediction tool. However, they spent less time on handling the QT-DDI and were overall satisfied to use the model. This might be a first step into developing a tool to manage QT-DDIs via a structured approach, but the tool still needs improvement in order to increase its diagnostic value and implementation in an electronic decision support system is required.

Risk communication through media attention, might be a potential tool to affect prescriber's behaviour in managing the potential risks of drug induced QTc-prolongation. According to literature, little is known about the effect of media attention on monitoring drug safety. Therefore, in **Chapter 10,** the effect of media attention regarding sudden cardiac death associated with domperidone was studied. This study showed a different impact of the media attention on physicians' patient monitoring and prescribing in the different hospital settings. We found no effect on the frequency of ECG monitoring, but a significant decrease in domperidone prescriptions was seen in a university medical centre.

Finally, in **Chapter 11**, we discussed our main findings and put them into a larger perspective. Also, recommendations for clinical practice and future research were made.

NEDERLANDSE SAMENVATTING

Torsades de Pointes (TdP) is een levensbedreigende ritmestoornis van het hart die kan leiden tot plotseling overlijden. Ritmestoornissen van het hart zijn zichtbaar te maken via het opnemen van een zogenaamd elektrocardiogram (ECG). Het karakteristieke beeld wordt gekenmerkt door diverse toppen en dalen, aangeduid met letters van het alfabet (Q, P, R, S, T). De tijd tussen die toppen zegt iets over bepaalde hartafwijkingen. Verlenging van het QT-interval op het ECG is een belangrijke risicofactor voor het ontstaan van TdP. Als het QTc-interval (het voor hartfrequentie gecorrigeerde QT-interval) groter is dan 500 ms of toeneemt met 60 ms, neemt het risico op TdP significant toe.

Het "*Arizona Center for Education and Research on Therapeutics*"(AzCERT) publiceert een lijst met QTc-verlengende geneesmiddelen, de zogenaamde AzCERT lijst. Hierop staan meer dan 200 geneesmiddelen vermeld die het QTc-interval verlengen, waaronder veel voorkomende geneesmiddelen zoals antibiotica en psycho-actieve geneesmiddelen. Andere risicofactoren voor QTc-verlenging en TdP zijn afwijkende waarden van elektrolyten in het bloed (zoals kalium), hart- en vaatziekten, erfelijke aanleg, leeftijd en het vrouwelijk geslacht. QTc-verlengende geneesmiddelen worden veel gebruikt. Bij patiënten met weinig tot geen risicofactoren is dat geen probleem, omdat het risico op hartritmestoornissen hoogstwaarschijnlijk verwaarloosbaar is. Bij hoog-risico patiënten worden combinaties van QTc-verlengende geneesmiddelen vermeden of worden regelmatig ECGs gemaakt om het QTc-interval zorgvuldig te monitoren. De Nederlandse elektronische voorschrijf- en apotheeksystemen genereren een signaal wanneer twee of meer QTc-verlengende geneesmiddelen worden voorgeschreven of verstrekt. Deze signalen voor QTc-verlenging (QT-DDI) houden geen rekening met andere risicofactoren voor QTc-verlenging. Dit leidt tot onnodig veel irrelevante signalen bij patiënten die weinig tot geen risicofactoren hebben. Het gevolg is dat artsen en apothekers moe worden van alle signalen. Hierdoor zien ze de wel relevante signalen over het hoofd.

Het doel van dit proefschrift was handvatten te geven voor veilig en effectief gebruik van QTc-verlengende middelen. Geprobeerd is meer inzicht te krijgen in hoe vaak QTc-verlenging voorkomt bij verschillende patiëntgroepen die QTc-verlengende geneesmiddelen gebruiken. Ook is gekeken naar risicofactoren voor QTc-verlenging bij die patiënten. Daarnaast was het doel om enkele strategieën te bekijken, die bedoeld zijn om de risico's in te perken. In **hoofdstuk 1** worden eerst de uitdagingen rondom geneesmiddel-geïnduceerde QTc-verlenging en de bijbehorende onderzoeksvragen uiteengezet.

Deel I – QTc-verlenging in de klinische praktijk

In **deel I** worden onderzoeken beschreven die kijken naar hoe vaak QTc-verlenging voorkomt in verschillen groepen patiënten. Ook kijken de onderzoeken naar risicofactoren hiervoor. **Hoofdstuk 2** beschrijft hoe vaak QTc-verlenging voorkomt bij 170 patiënten die gelijktijdig ciprofloxacine en fluconazol gebruiken. Deze antimicrobiële middelen worden vaak in combinatie gebruikt om infecties bij patiënten met bloedkanker te voorkomen. QTc-verlenging bleek bij 4,7% van deze patiënten op te treden. Er werden geen risicofactoren gevonden voor QTc-verlenging.

Het QTc-interval was gedurende de therapie toegenomen met 10,7 ms. Doordat QTc-verlenging weinig voorkwam en ook niet groot was, lijkt het routinematig afnemen van ECGs bij deze combinatie niet zinvol. Het onderzoek in **hoofdstuk 3** beschrijft het verloop van het QTc-interval gedurende 24 uur bij IC-patiënten die intraveneus werden behandeld met ciprofloxacine of laag gedoseerd erytromycine . Erytromycine is in hoge dosering een antimicrobieel middel, maar wordt in lage dosering gebruikt om de maaglediging te versnellen. Continue ECG metingen van 2 uur voor tot 24 uur na de eerste toediening van deze geneesmiddelen werden vergeleken met controlegroepen. Verrassend genoeg vonden we geen significant effect van ciprofloxacine of laag gedoseerd erytromycine op het QTc-interval gedurende de eerste 24-uur. De bevindingen in zowel **hoofdstuk 2**, als **hoofdstuk 3** suggereren dat ciprofloxacine en laag gedoseerd erytromycine een verwaarloosbaar effect hebben op het QTc-interval. Intensieve ECG-monitoring lijkt dus niet nodig.

In **hoofdstuk 4** beschrijven we het QTc-verlengende effect van serotonineheropnameremmers (SRI) bij 50 borstkankerpatiënten die behandeld werden met tamoxifen. Dit hebben we vergeleken met 50 borstkankerpatiënten die tamoxifen monotherapie kregen. Dit retrospectieve onderzoek toonde aan dat het gemiddelde QTc-interval 12,4 ms langer was wanneer tamoxifen gelijktijdig met een SRI werd gegeven. Dit was met name het geval bij het gebruik van paroxetine (17,2 ms) en citalopram (20,7 ms). In beide gevallen bleef de toename onder de 60 ms. Wanneer tamoxifen werd gecombineerd met venlafaxine, werd geen significant effect op het QTc-interval gezien. Venlafaxine zou dus de voorkeur kunnen hebben bij hoog-risico patiënten die met tamoxifen worden behandeld. Het risico bij de andere middelen is echter ook beperkt.

Aan het begin van de uitbraak van het Sars-CoV-2 virus in Nederland werd chloroquine, een antimalariamiddel, als behandeling opgenomen in de Nederlandse richtlijnen. Chloroquine is ook opgenomen in de AzCERT-lijst als QTc-verlengend geneesmiddel met een bewezen risico op TdP. Daarom hebben we in **hoofdstuk 5** het QTc-verlengende effect van chloroquine bij 397 patiënten met de ziekte COVID-19 onderzocht. We vonden een gemiddelde toename van het QTc-interval van 33 ms na start van chloroquine. Deze toename onderstreept het belang van ECG-monitoring bij COVID-19 patiënten gedurende chloroquine gebruik. Het QTc-interval werd zowel door ECG-software als handmatig gemeten en berekend. Bij 19 patiënten werd op basis van het automatisch weergegeven QTc-interval chloroquine in dosis verlaagd of gestaakt, terwijl handmatige berekening geen QTc-verlenging aantoonde. Om onterecht staken of verlagen van de dosis chloroquine te voorkomen, wordt aanbevolen om het QTc-interval handmatig te meten. Inmiddels is chloroquine echter verwijderd uit de behandelingsrichtlijnen voor COVID-19, vanwege gebrek aan effectiviteit.

Deel II – Predictie modellen

Deel II van het proefschrift richt zich op de ontwikkeling van modellen die het risico op QTc-verlenging kunnen voorspellen. **Hoofdstuk 6** beschrijft de ontwikkeling van zo'n voorspellend model met behulp van gegevens vastgelegd in medische dossiers in een perifeer opleidingsziekenhuis. Niet alleen leeftijd, geslacht, kalium- en calciumspiegels en het gebruik van bepaalde diuretica ("plaspillen") en anti-aritmica waren beschikbaar in het elektronisch patiëntendossier in dit ziekenhuis, maar ook het QTc-interval. In **hoofdstuk 7** is een predictie model ontwikkeld op

basis van een onderzoek naar QTc-verlengende geneesmiddelinteracties in een universitair medisch centrum. Het risicomodel bevatte de volgende voorspellers: leeftijd, geslacht, hart- en vataandoeningen, hoge bloeddruk, diabetes mellitus, nierfunctie, kaliumspiegels, gelijktijdig gebruik van bepaalde diuretica en QTc-verlengende geneesmiddelen. Het model had helaas nog veel vals-positieve signalen en moet dus nog verder verbeterd worden. De prestaties van beide voorspellende modellen werden vergeleken in **hoofdstuk 8**, door gebruik van een gegevens uit een perifeer opleidingsziekenhuis. De gegevens bestonden onder andere uit QTc-verlengende interactiesignalen die in een periode tussen november 2016 en maart 2018 zijn gegenereerd. Beide modellen waren gevoelig voor QTc-verlenging, maar gaven toch veel vals-positieve signalen. De gevoeligheid betekent gelukkig dat er weinig hoog-risico patiënten gemist worden.

Deel III - Risicomanagement van QTc-verlengende geneesmiddelinteracties

In **deel III** worden twee benaderingen voor risicomanagement van geneesmiddel-geïnduceerde QTc-verlenging gepresenteerd. **Hoofdstuk 9** beschrijft het effect van het voorspellende model uit **hoofdstuk 7**, op de afhandeling van QT-verlengende geneesmiddelinteracties in 20 openbare apotheken. Voor en na gebruik van het model, waarbij op papier een score werd berekend, was er geen verschil in de wijze van afhandelen van de interacties. Echter, de apothekers besteedden wel minder tijd aan de afhandeling van QTc-verlengende geneesmiddelinteracties en waren over het algemeen zeer tevreden over het gebruik van het model, waarbij wel de wens naar voren kwam om het model uiteindelijk te implementeren in het elektronische apotheek informatie systeem. Dit onderzoek is de eerste stap naar een gestructureerde aanpak om QTc-verlengende geneesmiddelinteracties af te handelen. Echter, het model moet verder worden verbeterd om nog beter risicopatiënten te kunnen ontdekken.

Risico communicatie via media-aandacht kan een manier zijn om het gedrag van de voorschrijver te beïnvloeden. In de literatuur is er nog weinig bekend over het effect van media-aandacht op het monitoren van de veiligheid van geneesmiddelen. Daarom is in **hoofdstuk 10** het effect van media-aandacht voor het optreden van ernstige hartritmestoornissen bij domperidon bestudeerd. Domperidon is een middel tegen misselijkheid, dat QTc-verlenging geeft en daardoor de kans op hartritmestoornissen verhoogt. Dit onderzoek toonde een verschillend effect van de media-aandacht aan op het monitoren van patiënten en het voorschrijfgedrag van artsen in twee verschillende ziekenhuizen. We vonden geen effect op de hoeveelheid afgenomen ECGs in beide ziekenhuis. In een universitair medisch centrum werd wel een significante afname van het aantal voorschriften van domperidon waargenomen.

Tot slot bespreken we in **hoofdstuk 11** onze belangrijkste bevindingen en plaatsen deze in een breder perspectief. Ook worden aanbevelingen gedaan voor de klinische praktijk en toekomstig onderzoek. Met dit proefschrift hebben we een eerste stap gezet naar de optimalisatie van risicomanagement rondom geneesmiddel-geïnduceerde QTc-verlenging in de klinische praktijk. Momenteel worden er te veel QTc-verlengende geneesmiddelinteractie signalen gegenereerd.

Dit leidt tot signaalmoeheid, waardoor relevante signalen worden ondergesneeuwd in de grote hoeveelheid niet-relevante signalen. Met behulp van een algoritme kunnen we deze irrelevante signalen wegfilteren. De signalen die dan overblijven, zullen de aandacht krijgen die ze verdienen. Op deze manier draagt dit proefschrift bij aan een betere balans in het risicomanagement van QTc-verlenging door geneesmiddelen.

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APPENDICES

AUTHORS & AFFILIATIONS

LIST OF PUBLICATIONS

PHD PORTFOLIO

DANKWOORD

ABOUT THE AUTHOR

AUTHORS & AFFILIATIONS

Affilitations during the conductance of the research

Robbert J. van Alphen

Department of Internal Medicine, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands

Matthijs L. Becker

Pharmacy Foundation of Haarlem Hospitals, Haarlem, the Netherlands

Patricia M. L. A. van den Bemt

Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, the Netherlands

Anita N. Bindraban

Pharmacy Foundation of Haarlem Hospitals, Haarlem, the Netherlands

Lisette Binkhorst

Department of Hospital Pharmacy, HAGA Hospital, the Hague, the Netherlands

Annoek E. C. Broers

Department of Haematology, Erasmus University Medical Centre, Rotterdam, the Netherlands

Jeroen J. H. Bunge

Department of Intensive Care, Erasmus University Medical Centre, Rotterdam, the Netherlands

Teun van Gelder

Department of Clinical Pharmacy & Toxicology, Leiden University Medical Centre, Leiden, the Netherlands

Natasja M. S. de Groot

Department of Cardiology, Erasmus University Medical Centre, Rotterdam, the Netherlands

Ruud T. M. van der Hoeven

Pharmacy Foundation of Haarlem Hospitals, Haarlem, the Netherlands

Nicole G. M. Hunfeld

Department of Hospital Pharmacy & Intensive Care, Erasmus University Medical Centre, Rotterdam, the Netherlands

&

Koen G.A.M. Hussaarts

Department of Medical Oncology, Erasmus University Medical Centre, Rotterdam, the Netherlands

Marc M.P.M. Jansen

Department of Clinical Pharmacy, Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands

Aaf F.M. Kuijper

Department of Cardiology, Spaarne Gasthuis, Hoofddorp, the Netherlands

Roeloef W.F. van Leeuwen

Department of Hospital Pharmacy, Erasmus University Medical Centre, Rotterdam, the Netherlands

Aukje K. Mantel-Teeuwisse

Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht, The Netherlands.

Danielle Mathijssen-van Stein

Department of Internal Medicine, Franciscus Vlietland & Gasthuis, Schiedam, the Netherlands

Ron H.J. Matthijssen

Department of Medical Oncology, Erasmus University Medical Centre, Rotterdam, the Netherlands

Nico Monadian

Erasmus University Rotterdam, Rotterdam, The Netherlands

Harm Jan Muntinga

Department of Cardiology, Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands

Esther Oomen-de Hoop

Department of Medical Oncology, Erasmus University Medical Centre, Rotterdam, the Netherlands

Jose Rolvink

Pharmacy Foundation of Haarlem Hospitals, Haarlem, the Netherlands

Selma Saaid

Department of Hospital Pharmacy, Franciscus Vlietland & Gasthuis, Schiedam, the Netherlands

Bart Santbergen

Department of Haematology, Erasmus University Medical Centre, Rotterdam, the Netherlands

Fleur S. Sinkeler

Department of Clinical Pharmacy, Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands

Bruno H.C. Stricker

Department of Epidemiology, Erasmus University Medical Centre, Rotterdam, the Netherlands

Heleen van der Sijs

Department of Hospital Pharmacy, Erasmus University Medical Centre, Rotterdam, the Netherlands

Willem van Weteringen

Department of Paediatric Surgery, Erasmus University Medical Centre – Sophia Children's Hospital, Rotterdam, the Netherlands

&

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PhD Portfolio

Name PhD student: F.A. Berger	**PhD period:**	**15/07/2015 - 01/12/2020**
Erasmus MC Department: Hospital Pharmacy	**Promotores:**	**Prof. dr. T. van Gelder**
Research school: MolMed		**Prof. dr. P.M.L.A. van den Bemt**
	Supervisor:	**Dr. I.H. van der Sijs**

1. PhD training	**Year**	**Workload (ECTS)**
Courses		
Open Clinica	2015	0.3
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2016	1.0
CPO course ('Patient Orientated Research')	2016	0.3
Basic introduction course on SPSS	2016	1.0
Systematic literature search in Pubmed and Endnote	2017	0.5
Biomedical English Writing and Communication	2017	3.0
Research Integrity	2017	0.3
Seminars and workshops		
E-Xpert ECG Introduction Electrocardiography	2016	0.2
PhD day Erasmus MC	2016	0.3
NIH Principles of Pediatric Clinical Pharmacology	2017	1.0
CHDR First in Human Clinical Trials	2018	0.3
(Inter)national conferences		
ESC congress, Rome, Italy	2016	1.0
Clinical Pharmacology Research day, Rotterdam (oral)	2016	0.8
PRISMA symposium KNMP, Amersfoort (oral)	2016	0.8
FIGON Dutch Medicines Days, Ede (oral)	2016	0.8
NVZA Ziekenhuisfarmaciedagen, Amersfoort (oral)	2016	0.8
ICPE congress, Montreal, Canada (poster 2x)	2017	0.3
PRISMA symposium KNMP, Amersfoort (oral 2x)	2017	0.8
TOPICS in IC, Lunteren (oral)	2017	0.8
Symposium 'Tijd voor Kwaliteit' NVKFB, Rotterdam	2017	0.3
NVKFB scientific meeting, Utrecht (poster)	2018	0.3
ICPE congress, Prague, Czech Republic (poster)	2018	0.3
NVZA Ziekenhuisfarmaciedagen, Arnhem, 2018 (oral 2x)	2018	0.8
Zeeuwse studiedagen, Catzand (oral)	2019	0.8
GGG Congress, Amsterdam	2018	0.3
Other		
Department of Hospital Pharmacy journal club	2015-2019	1.0
Clinical Pharmacology meetings	2015-2019	2.0
2. Teaching		
Lecturing		
Teaching pharmacology to medical students	2015-2019	3.0
Supervising Masters theses		
L. Noordhof (6 months research master)	2015	2.0
N. Monadian (6 months research master)	2016	2.0

PhD Portfolio (continued)

	Year	Workload (ECTS)
A.N. Kütükçüoglu (6 months research master)	2017	2.0
Other		
Deel Basis Kwalificatie Onderwijs (BKO)	2016	1.2
3. Additional activities		
Fellowship Clinical Pharmacology	2017 – 2019	3.0
Promeras Board Member – Treasurer	2017 – 2019	3.0
Member of Promovendi Netwerk Nederland (PNN)	2018 – 2019	1.0
Member of the Task Force QT-interactions, KNMP	2017 – 2020	1.0
Editor of 4CP abstracts	2018 – 2020	1.0
Organising committee ToxEd symposium, Rotterdam	2017	0.5
Organising committee Lessons Learned symposium, Rotterdam	2018	0.3

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ABOUT THE AUTHOR

Florine Anne Berger was born on September 7th, 1989 in Rotterdam, the Netherlands. In 2003, she moved with her family to Haren (Groningen), the Netherlands. After graduation from secondary school at the Preadinius Gymnasium in Groningen in 2007, she moved to Australia for one year to obtain her Cambridge Exam and travel the continent. In 2008 she started her Pharmacy studies at the Rijksuniversiteit Groningen, the Netherlands. She obtained her bachelors' degree in 2012 and her masters' degree in 2015. During her masters' studies, she spent six months in London, UK to conduct research at the Royal Free Hospital and University College of London Institute for Liver and Digestive Health under the enthusiastic supervision of prof. dr. Massimo Pinzani and dr. Krista Rombouts. Also, she performed a 6-weeks project in Ghana and followed an internship of 8 weeks at the Sint Elisabeth Hospital in Willemstad, Curacao. Her opportunities to be an employee around the globe inspired her to view the world from a broader perspective.

Florine started her professional career at the Department of Hospital Pharmacy of the Erasmus University Medical Center Rotterdam, where she performed the research presented in this thesis under supervision of prof. dr. Teun van Gelder and prof. dr. Patricia M.L.A. van den Bemt. During her research period she she completed her fellowship clinical pharmacology in 2019. Also, she was a board member of Promeras (representing body of all PhD students at the Erasmus MC).

In February 2019 Florine started her specialist training in hospital pharmacy at the Meander Medical Centre in Amersfoort and Tergooi Hospitals in Hilversum and Blaricum under supervision of dr. Elsbeth Nagtegaal and dr. Paul D. van der Linden.

Florine lives together with Max Bierkens in Amsterdam, the Netherlands.