The handle http://hdl.handle.net/1887/19939 holds various files of this Leiden University dissertation.

**Author:** Chain, Anne S.Y.
**Title:** Mind the gap: predicting cardiovascular risk during drug development
**Date:** 2012-10-09
Not-In-Trial Simulation I:
Bridging Cardiovascular Risk
From Clinical Trials
To Real Life Conditions

ASY CHAIN (1, 2), JP DIELEMAN (2), C VAN NOORD (3), M DANHOF (1),
MDJM STURKENBOOM (2, 3), D DELLA PASQUA (1, 4)

(1) LEIDEN/AMSTERDAM CENTRE FOR DRUG RESEARCH,
DIVISION OF PHARMACOLOGY, LEIDEN UNIVERSITY, LEIDEN, THE NETHERLANDS
(2) DEPARTMENT OF MEDICAL INFORMATICS AND EPIDEMIOLOGY,
ERSAMUS MEDICAL CENTRE, THE NETHERLANDS
(3) DEPARTMENT OF EPIDEMIOLOGY, ERSAMUS MEDICAL CENTRE,
THE NETHERLANDS
(4) CLINICAL PHARMACOLOGY AND DISCOVERY MEDICINE,
GLAXOSmithKLINE, STOCKLEY PARK, UXBRIDGE, UNITED KINGDOM

British Journal of Clinical Pharmacology - in press
ABSTRACT

Given the assumed risk of proarrhythmias, assessment of QTc-interval prolongation has become a mandatory step in drug development. Currently, however, experimental data are generated from randomised trials in healthy volunteers. The present study was performed to explore discrepancies between drug-induced QTc prolongation in clinical trials and real life conditions. d,l-Sotalol was selected as a paradigm compound to illustrate the potential clinical implications of such differences. The Rotterdam Study cohort was used as the real life reference population. Using clinical trial simulation principles and nonlinear mixed effects modelling, we show that significant differences exist between the drug-induced increase in QTc-interval and observed QTc values. Furthermore, our analysis reveals that the increased prevalence of high QTc values in a real-life population is also due to co-morbidities and concomitant medications, rather than treatment drug alone. These findings substantiate the need to account for these factors when evaluating cardiovascular risk of novel medicinal products.
5.1 INTRODUCTION

In the last two decades, there have been increased concerns around the rising number of proarrhythmia cases due to non-antiarrhythmic drug-induced QTc prolongation to the extent that it has been referred to as a modern “epidemic” [1]. Physiologically, the duration of the QT-interval of the surface electrocardiogram (ECG) represents the ventricular action potential duration. As such, prolonged heart-rate corrected QT- (QTc-) interval may result in early after-depolarisations (EAD), which may induce re-entry, provoke torsade de pointes (TdP) and potentially lead to sudden cardiac death (SCD) [2, 3].

Even though epidemiological evidence regarding the correlation between drug-induced QTc-interval prolongation, risk of fatal arrhythmias and SCD remains under scrutiny [4, 5], QTc prolongation has become the second most common cause for post-market drug withdrawal [6]. In other cases, severe prescribing restrictions have been imposed by regulatory agencies, which impacted on the indication of the drug, its posology, contraindications, special warnings and precautions for use, such as baseline and periodic on-treatment ECGs monitoring. The requirements for information on drug-disease and drug-drug interactions, full description of cardiotoxic adverse effects and their management as well as risk of overdose have also been affected [7]. Not only have the regulatory bodies started to closely monitor the liability for QTc-interval prolongation in the submissions of new chemical entities (NCE), guidelines have also emerged outlining the pre-requisites for the evaluation of drug-induced effects on heart conductivity and QTc-interval during drug development.

The first regulatory guidelines regarding clinical evaluation of the QT/QTc-interval prolongation in the context of new drug development were issued in 1997 by the Committee for Proprietary Medicinal Products (CPMP) of the European Union [8, 9]. More recently, the International Conference on Harmonisation (ICH) Topic E14 guideline was published on the clinical evaluation of QT/QTc-interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs [10]. The ICH guideline introduced the use of the “double-delta” method in a thorough-QT study (TQT) as the state-of-the-art approach for the assessment of QTc-interval prolongation. Furthermore, it recommends a TQT to be completed early in the drug development process to guide further studies and decision making.
From a methodological perspective, the TQT protocol design relies on the use of a positive control as well as supra-therapeutic doses of the investigational drug. The outcome of the analysis is based on the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc-interval, which may not exceed 10 msec for the study to be deemed negative. Whilst the validity as well as the sensitivity of the proposed methodology has been the subject of debate in numerous publications, less attention has been paid to other aspects of the preferred protocol design and interpretation of the findings, which overlook the underlying concentration-QTc effect relationship and consequently supporting evidence of causality [11, 12].

Taking into account concentration-effect relationships, we explore the implications of the preferred protocol design for the assessment of cardiovascular risk under real life conditions. Although it may be understandable and desirable to characterise a drug safety profile in healthy subjects, we show how population selection and inclusion/exclusion criteria lead to a somewhat biased view of drug-induced effects in the target patient population which will receive the treatment after approval. The selected trial population, strict inclusion/exclusion criteria and experimental conditions may make the extrapolation of the findings to a real life population rather cumbersome. In particular, the exclusion of severely ill subgroups, i.e., those who are most susceptible to the potential undesired proarrhythmic effect, is usually not factored in a quantitative manner when evaluating TQT results. In addition, little attention is paid to the role of other factors contributing to QTc-interval prolongation in the target population, as compared to the observed drug effect in a randomised clinical trial involving healthy subjects. The current approach to clinical trials is also too focused on designs aimed at demonstrating efficacy. The number of subjects exposed to the NCE is powered to show benefit rather than to pick up signals from rare but potentially fatal adverse events and no formal procedures exist to mitigate the impact of such differences or support the management of cardiovascular risk in the target population. Finally, many patient subgroups with higher risk factors for TdP are often excluded from the trials. These subgroups include females, elderly subjects, those with predisposed cardiac or non-cardiac diseases associated with diminished repolarisation reserve (and therefore greater susceptibility to QT-interval prolongation), those with pharmacogenetic defects of drug metabolising enzymes or pharmacological targets such as the potassium channels, those susceptible to bradycardia or
electrolyte imbalance, or those receiving drugs with a potential for pharmacokinetic or pharmacodynamic interactions [13, 14].

From a regulatory perspective, questions have also arisen about the efficiency and reliability of pre-approval clinical trials in identifying the clinical risk of torsade de pointes [12, 15]. Given the patient population enrolled, the background noise (arising from spontaneous intra-individual variability in QTc-interval) and the relatively low frequency of clinically significant drug-induced effects, clinical trials may or may not accurately detect the frequency and intensity of QTc-interval prolongation. In fact, it is known that the pro-arrhythmic threshold can vary across compounds with frequency of such events ranging from approximately 1 in 100 (for halofantrine) to 1 in 50000 (for terfenadine) [1].

The evolving concepts in risk management will inevitably lead sponsors, regulatory agencies and other stakeholders to consider how to best evaluate causality and identify the contribution of other factors determining increases in QTc-interval and consequently in cardiovascular risk in the target population. In this investigation we characterise QTc-interval changes following administration of d,l-sotalol (paradigm compound) to healthy subjects in clinical trials and to patients in real life. Our investigation resorts to model-based drug development (MBDD) principles, as the development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data, to improve drug development knowledge management and decision making [16, 17]. In contrast to typical clinical trial simulations [18-20], we make use of simulations to characterise the role of design factors which have been omitted or excluded from a randomised trial, among which those listed under the exclusion criteria or diverging from the clinical conditions relevant for the target population. Thus, we anticipate that our approach will represent a natural extension of ongoing efforts within pharmaceutical industry to improve safety signal detection [21-25].

**5.2 METHODS**

*Real life study population*

The real life population setting was derived from the Rotterdam Study. It is a prospective population-based cohort study, which started with a baseline
visit between 1990 and 1993. All inhabitants of a suburb in Rotterdam, Ommoord, aged 55 years and over were invited to participate. Of the 10 275 subjects invited, 7983 (78%) gave their written informed consent and took part in the baseline examination. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, The Netherlands. Objectives and methods of investigation have been described in detail in other publications [35]. All participants were visited at home for a standardised questionnaire and 7151 were subsequently examined at the research center. A second, third and fourth follow up visit took place, respectively, between 1993 - 1995, 1997 - 1999 and 2002 - 2004. In addition to follow-up examinations, the cohort is continuously monitored for major morbidity and mortality through linkage with general practitioner and municipality records. Drug prescriptions dispensed to participants by automated pharmacies have been routinely stored in the database since 1 January, 1991. For the present study, we included all participants in the Rotterdam Study with at least two consecutive ECG assessments.

All subjects who started treatment with d,l-sotalol during follow-up were included in the this study, with the exception of prevalent users and subjects with left ventricular hypertrophy (LVH), right bundle-branch block (RBBB) and left bundle-branch block (LBBB), who were excluded. The reason for the exclusion of these patients is that LVH, RBBB and LBBB can cause secondary repolarisation changes and atrial fibrillation can cause difficulties in measuring QT-intervals. From the remaining population, “new” d,l-sotalol users were identified as those receiving their first prescription after enrolment into the study. Our analysis included all QTc measurements after the start of d,l-sotalol for all new users.

During the research center visit, non-fasting blood samples were obtained [36]. Body mass index (BMI) was computed as weight divided by height squared. Comorbidities were screened and identified according to standard clinical criteria. Hypertension was defined as systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg and/or use of antihypertensive medications, encompassing grade 2 and grade 3 hypertension compounds according to the World Health Organisation (WHO) criteria [37]. Diabetes mellitus was defined as the use of blood glucose-lowering medication and / or a non-fasting or post-load serum glucose level of 11.1 nmol/L or higher according to the WHO [38]. A history of myocardial infarction was assessed by self-report checked with records from the general
practitioner or cardiologist and/or electrocardiographic evidence. All reported myocardial infarctions were verified against medical records as described in detail previously [39]. Assessment of heart failure at baseline and during follow-up was assessed by reviewing all medical records for the occurrence of at least two signs and symptoms suggestive of heart failure or the use of medication for the indication heart failure and hospital discharge letters. Cases of incident heart failure were obtained by continuously monitoring the participants [40, 41]. The ankle arm index (AAI) was used as potential predictor of cardiovascular diseases and mortality [42].

**Healthy volunteer study population**

A healthy volunteer clinical trial for d,l-sotalol was selected from GlaxoSmithKline’s clinical data repository (study number EXP20001). The primary objective of this study was to assess the role of intrinsic and extrinsic factors on the variability of QTc-interval and was powered to detect a 10 msec increase in QTc according to the ICH E14 double-delta method. The study had a placebo-controlled, three-way crossover design with two placebo periods and one active treatment period. Blood concentrations were taken at -30, 5, 15, 30 and 45 minutes relative to dosing time as well as 1, 2, 4, 8, 10, 18 and 24 hours after dose. The study population comprised of 30 subjects (12 females, 18 males), between the ages of 19 and 47.

Relevant eligibility criteria for inclusion into (items 1-3) / exclusion from (items 4-8) the study for the purposes of our investigation included:

1. Age between 18-55 years, inclusive

2. Non-smoker (subject must have been a non-smoker for at least 3 months prior to screening)

3. Body mass index between 19-30 kg/m², with a weight of 50 – 95 kg, inclusive

4. At screening ECG recording showed abnormal QRST complex morphology, sinus bradycardia (HR<45 bmp, PR > 210 msec) or QTc-interval values above 420 or 440 msec for male and female, respectively.
5. Any medical history which was contra-indicated in the SOTACOR™ product label

6. History of hypertension, asthma, bronchial hyperactivity or peripheral vascular disease, including diabetes.

7. The subject had a history of alcohol or drug abuse

8. The subject was positive for HIV, hepatitis C or hepatitis B surface antigen

**Drug-induced QTc-interval prolongation**

The primary objective of this study was to identify differences in the baseline QTc-interval (i.e. before \(d,l\)-sotalol use) between target patient population and healthy volunteers. The simulation of QTc-intervals was performed in a two-step approach. First, drug concentrations in the target population (i.e., \(d,l\)-sotalol users) were derived using a pharmacokinetic model. QTc-intervals were subsequently obtained using final population pharmacokinetic-pharmacodynamic (PKPD) parameter estimates.

The pharmacokinetics of \(d,l\)-sotalol was described by a two compartment, first-order absorption model with weight as a covariate on clearance using nonlinear mixed effects modelling, as implemented in NONMEM (v5.1, ICON Development Solutions, Ellicott City, MD, USA) [43]. Heart-rate corrected QT-intervals were described by a PKPD model using a Bayesian approach in which physiological (QT and RR) and drug specific (concentration) parameters are parameterised in an independent manner (Equation 1) [44]. A detailed description of model development was described in a previous publication [11].

\[
QT_{c} = QT_{0} \cdot RR^{\alpha} + A \cdot \cos \left( \frac{2\pi}{24} (t - \phi) \right) + \text{slope} \cdot C
\]

*Equation 1*

where, \(QT_{0} \ [\text{msec}]\) is the intercept of the QT-RR relationship. Sex was included as a covariate for this parameter whenever applicable. \(RR \ [\text{sec}]\) is the interval between successive R waves, \(\alpha\) is the individual heart rate
correction factor, $A$ [msec] is the amplitude of circadian rhythm, $t$ is the clock time, $\varphi$ is the phase, slope [msec/concentration] is the linear pharmacodynamic relationship, and $C$ is the predicted concentration of drug at the time of QT-interval measurements.

Drug-induced QTc-intervals in the Rotterdam Study population were then simulated using the PKPD model, taking into account patient characteristics in the real life population. The QTc-interval distribution associated with $d,l$-sotalol exposure in the reference population was simulated assuming full compliance to treatment. Population parameter estimates were used for the simulations (slope = 0.02 msec/ng/ml, intercept ($QT_0$) = 380 msec). Finally, QTc values in the Rotterdam Study population were compared non-parametrically with the observed data.

**ECG measurements**

For the Rotterdam Study cohort, a 10 sec 12-lead ECG, resulting on average of 8-10 heart beats, was recorded with an ACTA electrocardiograph (ESAOTE, Florence, Italy) at a sampling frequency of 500 Hz and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS) to obtain the ECG parameters of interest. The MEANS program has been evaluated extensively and described elsewhere [45, 46]. MEANS determines common onset and offset for all 12 leads together for one representative averaged beat, with the use of template matching techniques, until the end of the T wave. To adjust for heart rate, Bazett’s formula ($QTc = QT / RR^{\frac{1}{2}}$) was used [47]. A total of 1387 digitally stored ECG records were used for this study. On the other hand, ECG measurements in healthy volunteers were recorded in triplicate and read manually from lead II by a blinded cardiographist. The average value from the triplicates was used for data analysis and development of the PKPD model.

**Statistical analysis**

Differences between clinical trials and real-life population:

Observed and expected QTc-intervals were non-parametrically compared visually and statistically, by determining the significance of the differences between the two distributions. Specifically, the Wilcoxon signed-rank test was used to evaluate if the distributions significantly differ from each other with p-value < 0.05.
Covariate effects:

The relative risk (RR) and 95% confidence interval (CI) of the association between "prolonged" QTc, as defined as > 450 ms for males and > 470 msec for females, and concomitant use of medications and presence of comorbidities while on d,l-sotalol prescription were estimated using Cox's proportional hazards analysis [48]. At each ECG measurement, all information concerning medications and comorbidities was updated. For the purpose of this analysis, each measurement from the same subject was treated independently since within-subject variability could not be considered in this analysis.

5.3 RESULTS

After applying the target population selection criteria to the Rotterdam cohort as described in the methods section, 608 subjects were classified as "new" d,l-sotalol users without left ventricular hypertrophy (LVH), right bundle-branch block (RBBB) or left-bundle-branch block (LBBB). The total accumulated follow-up was 4864 years (i.e., an average and standard deviation of 8 ± 1.5 years/subject), during which they all had at least one ECG measurement. At the end, there were a total of 1375 available ECGs, with an average of two per person. Inclusion and exclusion criteria from the phase I d,l-sotalol trials were then applied to this subset to allow further characterisation of the differences between the real life conditions and the clinical trial protocols. Figure 1 reveals that 10.8% of the male population and 3.4% of the female population from the Rotterdam cohort, would have been excluded based on their weight values, which is a covariate used in the clinical pharmacokinetic-pharmacodynamic (PK/PD) model. Similarly, 21.9% male and 14.9% female would not be included due to their baseline QT-interval measurements (Figure 2).

Pharmacokinetic and PKPD model parameters were used to simulate d,l-sotalol concentrations and corresponding QT-intervals and to test if drug effects alone can explain the observed QTc values in observational real life cohort. Drug concentrations were simulated taking into account the individual weights of the elderly population. The simulated QTc-intervals (i.e. the expected QTc) were found to be at variance with the observed values (Figure 3), especially in the male population. Using Wilcoxon T-test, the
results showed that the two distributions significantly differed from each other for both genders with p-values < 0.05. The distribution of QTc values of the d,l-sotalol users in the real life elderly population revealed some dangerously high observed measurements. The model-based predictions for a real life population demonstrated that drug-induced effects alone cannot describe the observed values in the QTc-interval distribution, especially in men.

Figure 1. Weight distribution of males and females in the Rotterdam Study cohort.

Figure 2. Baseline distribution of males and females in the Rotterdam Study cohort.
Not-In-Trial Simulation I

Figure 3. (a) Overlapping distributions showing the discrepancies between observed and simulated results in the male population (left panel) and female population (right panel). The darker colour represents the simulated QTc values and the light colour represents the observed QTc-intervals. The medium shades denote the overlapping areas. (b) QQ-plots comparing the distributions of the QTc-values for male population (left) and female population (right). The deviation from the identity line reflects the residual difference between the observed QTc-intervals and model-predicted dI-sotalol effects under the assumption of comparable pharmacokinetic-pharmacodynamic relationship, as determined in Phase I clinical trials.

The differences between the two populations were evaluated by binary logistic regression, which revealed the contribution of concomitant medications and comorbidities as QTc-prolonging factors. It was found that heart failure, diabetes mellitus, myocardial infarction and hypertension increase the risks of a male having QTc >450 msec and female with QTc >470 msec by 0.4-11.5 fold (Table 1).
Using *d,l*-sotalol alone - < 0.01 4.0 (2.7 - 5.8) < 0.01

Diabetes 4.0 (2.7 - 5.8) < 0.01 6.5 (1.6 - 27.1) < 0.01

Heart Failure 4.4 (3.0 - 6.6) < 0.01 0.8 (0.2 - 3.4) > 0.01

Hypertension 7.4 (4.3 - 12.7) < 0.01 2.4 (1.3 - 4.2) < 0.01

Myocardial Infarction 3.4 (2.3 - 5.127) < 0.01 15.5 (4.9 - 49.3) < 0.01

Table 1. Results of relative risk calculations of the association between “prolonged” QTc and concomitant use of medications and presence of comorbidities while under *d,l*-sotalol prescription. Significance level was set at *p* < 0.05.

5.4 Discussion

In the current investigation we have shown that population selection and inclusion/exclusion criteria applied to clinical protocols in early drug development may lead to significant differences between drug-induced and overall treatment effect size in the target population. Thus far, the evidence of pro-arrhythmia associated with QTc prolongation in real life patients has been primarily linked to drug-induced effects. On the other hand, the signal detected during a TQT study has been deemed sensitive enough to reflect the increase in cardiovascular risk associated with torsadogenic or arrhythmogenic effects of a drug in the target patient population.

Thanks to the use of a model-based approach it was possible to make inferences about drug exposure in patients and evaluate in an integrated manner, how different covariates and sources of variability affect the observed QTc values in real life patients. Our findings suggest that the distribution of observed QTc values in the real life cohort cannot be explained by the effects of *d,l*-sotalol alone. Other causal factors are present, which significantly affect the observed QTc values. In fact, previous publications showed that heart failure, hypertension, diabetes and myocardial infarction increase the risk of QTc prolongation [26-29]. The binary logistic regressions performed on our data revealed that diabetes, heart failure, hypertension and myocardial infarction are indeed risk factors for QTc prolongation in this population. In addition to comorbidities, we
have also identified statistically significant effects of co-medication, both of which contribute to upper tail of the distribution of observed QTc values.

The concepts outlined in the current investigation also show how both clinical trial and epidemiological data can be used in an integrated manner for the purpose of signal detection and improved risk management. Our findings appear to confirm the points highlighted by Black on “the false conflict between those who advocate randomised trials in all situations and those who believe observational data provide sufficient evidence needs to be replaced with mutual recognition of the complementary roles of the two approaches.” [30] Others have also advocated the synergistic potential for using both kinds of data to aid decision making [31-34]. In the design of this study, we apply a parametric approach in which simulations play a central role. As a matter of fact, this is the first time that simulations based on nonlinear hierarchical models are used to characterise the implications of exclusion criteria on overall treatment safety profile.

By applying PKPD modelling concepts to epidemiological data, we have also shown that the concentration-effect relationship achieved from a healthy volunteer trial cannot adequately describe nor predict what is actually happening in real life. The results from the present study suggest that new methodology is required to assess the impact of QTc prolongation in real life population for future compounds. By extension, the relevance of a TQT study, as mandated in the ICH E14 guideline, becomes questionable. Our findings clearly challenge the validity of TQT trials as the state-of-the-art approach for determining the risk of pro-arrhythmia or TdP. Indirectly, our analysis also reveals the shortcomings of the double-delta method currently suggested for the TQT studies. The use of time-matched differences between active and placebo arms does not allow the assessment of potential QTc prolongation in real life situations; as such calculations have no predictive value, nor can be parameterised for the purposes of non-random effects in clinical trial simulations. Another advantage associated with the use of a PKPD model is that even if the pharmacokinetics has been evaluated at supra-therapeutic levels, drug exposure can be extrapolated to reflect drug concentrations observed after therapeutic doses, so that accurate inferences can be made of the corresponding effect on QT-interval. We also anticipate the importance of our approach to assess the characteristics of high-risk population subgroups by introducing such patients into simulation scenarios.
Despite the potential impact of a tool for "not-in-trial" simulations, the proposed approach in this investigation has some limitations. First, it should be noted that the population estimated parameters rather than the individual estimated parameters were used in the PKPD simulations. This reduces the overall inter-individual variability that exists within a population. In addition, an assumption was made that all the subjects in the Rotterdam cohort were fully compliant with medication consumption so that the same plasma concentration range is reached as those in the clinical trial. QT measurements in the Rotterdam Study cohort were taken during the d,l-sotalol prescription. It was therefore assumed that the timing of the QT measurement as well as the differences in measurement equipment contribute to increased random variation without introducing significant bias. Fully automated machine read measurements were used in the Rotterdam cohort, whilst QT-intervals were manually measured by a cardiographist in the clinical trial.

In summary, integration of clinical trial and epidemiological data reveals a flaw in the assumption that findings about drug effects in a clinical trial may be generalisable to the real life population. The assessment of concentration-effect relationships was pivotal for estimating the contribution of drug-induced increase in QTc-intervals. Furthermore, the use of a hierarchical nonlinear mixed effects modelling enabled other causal factors to be incorporated into the evaluation of the overall treatment effect. Our findings show that accurate evaluation of safety requires understanding of treatment response of subjects who are "not-in-trial".
REFERENCES


