Chapter 7
Pharmacometrics in Cardiovascular Safety

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7.1 Introduction

Approximately one third of all drug discontinuation from preclinical discovery to postapproval stage is caused by drug safety (Kola and Landis 2004; Laverty et al. 2011). Within this category, cardiovascular (CV) safety is a major cause of attrition (Redfern et al. 2010), with drug-induced prolongation of cardiac repolarization and proarrhythmic liabilities being the main reasons for labeling restrictions and drug withdrawals (Darpö 2007; Gwathmey et al. 2009; Redfern et al. 2010). Table 7.1 shows an impact of CV adverse effect throughout the pharmaceutical drug development life cycle. In the case of late-stage adverse events, it can lead to termination of the program, labeling restrictions, prescribing restrictions, requirements for postmarketing studies and in a worst-case scenario, to drug discontinuation or withdrawal. It is therefore not surprising that the assessment of CV liabilities, especially drug-induced prolongation of cardiac repolarization and QT interval have become a primary focus of both pharmaceutical industry and regulatory agencies. These issues were addressed by International Conference on Harmonisation (ICH), which released S7B and E14 documents that address methods of preclinical and clinical assessment of cardiac repolarization (Anon 2005a, b). Table 7.2 shows a list of these

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Table 7.1 Relative contributions and frequency of different toxicities by organ function during preclinical and clinical drug development as well as postapproval stage. (Adapted from Redfern et al. 2010)

Phase	"Nonclinical"	Phase I	Phase I–III	Phase III/ marketing	Postmarketing
Impact	Causes of attrition	Serious ADRs	Causes of attrition	ADRs on label	Withdrawal from sale
Source	Car (2006)	Sibille et al. (1998)	Olson et al. (2000)	BioPrint® (2006)	Stevens and Baker (2009)
Number of drugs assessed	88 (stopped)	23	82 (stopped)	1138	47
Cardiovascular	27%	9%	21%	36%	45%
Hepatotoxicity	8%	7%	21%	13%	32%
Haematology/ BM	7%	2%	4%	16%	9%

preclinical and clinical models, which are currently used in evaluation of CV safety during pharmaceutical drug development.

Since CV liabilities, especially drug-induced delayed repolarization and QT interval prolongation, became a great concern for both pharmaceutical industry and regulatory agencies, it also became increasingly important to assess these liabilities early in the drug development process. Ideally, these liabilities should be assessed before the new chemical entity (NCE) is tested in humans for the first time, however, it is also beneficial at other stages of clinical drug development, for example, before the drug is tested in patients or before it is tested in larger population. The main purpose of the assessment in preclinical stages is to select the right compound, i.e., the one that can be safely administered to humans. In the clinical stages, it is important to have the correct quantitative understanding via the right clinical study design to understand the right dose and schedule that are safe to patients. To this end, pharmacometric (model-based) tools have become increasingly beneficial in achieving this goal; they allow making predictions under new circumstances, for example during new dosing regimen or in the alternative patient population, and also allow extrapolating across different systems, for example from in vitro or in vivo to clinical. This is particularly important along the value chain in pharmaceutical industry as it helps to select and progress the best compounds. In addition, it is also beneficial for the regulatory submissions, where pharmacometric tools can be used to describe the observed data and predict risk for a particular compound. Opportunities to use pharmacometric models in various stages of drug life cycle are provided in Table 7.2.

In this chapter, we will review how pharmacometrics can be used to assess the risk of CV liabilities with the main focus on QT interval. We will explain how mathematical models can be used to gain understanding of the drug-induced CV effects using either descriptive or mechanism-based modeling, where underlying mechanisms of action are taken into account, as well as how they can be used for extrapolation and prediction of real-life population and to inform clinical trials.

Table 7.2 Summary of techniques and models used in evaluation as well as opportunities for pharmacometric modeling in cardiovascular safety during pharmaceutical drug development

Technique	Summary	Reference	Opportunities for pharmacometric analysis
QSAR	Quantitative structure–activity relationship (QSAR) models relate physicochemical properties of a compound to its ability to block hERG	(Gavaghan et al. 2007; Inanobe et al. 2008; Clark and Wiseman 2009)	Predictive models of hERG blockage based on fragment descriptors
hERG assay	Measurement of inhibition of the potassium current through hERG; usually few ascending concentrations of NCE and major metabolites are tested to determine a concentration–effect relationship; preparations are made using human cells expressing hERG channel	(Brown 2004; Pollard et al. 2010)	In silico APD models; mechanism-based modeling of QT prolongation, e.g., using operational model of agonism
Other cardiac ion channel assays	Measurement of inhibition of ion channels other than hERG, such as: hNav1.5, hCav1.2, hKv4.3/hKChIP2.2, hKv7.1/hminK, and hKv11.1	For example: Harmer et al. (2008)	In silico APD models; mechanism-based modeling of QT and other CVS parameters, e.g., blood pressure
Purkinje fibers assay	Drug-induced changes in repolarization of action potentials are measured using isolated Purkinje fibers; species used in preparations include dog, rabbit, and guinea pig	(Terrar et al. 2007)	Reverse modeling for predicting ion channel pharmacology
Lagendorff heart model	APD, conduction, triangulation, reverse-use dependency, and instability are measured using isolated, perfused animal heart; species used in preparations include rabbit and guinea pig	(Szilágyi et al. 2004; Valentin et al. 2004; Wu et al. 2004; Suter 2006)	
Ventricular wedge	CVS measurements are taken in the arterially perfused isolated left ventricular wedge preparation; species used in preparations include rabbit and dog	(Chen et al. 2006; Benson et al. 2008)	"Virtual ventricular wedge"
Anaesthetized animal model	ECG measurements and cardiac contractility are measured, while animals are kept under anesthesia (usually to prevent unwanted events such as seizures); it is possible to relate the observed CV effects to the drug concentration using PK/PD modeling; species used in studies include dog and guinea pig	(Ollerstam et al. 2007b; Heath et al. 2011)	PK/PD modeling of CVS parameters such as QT, HR, BP and others for: (1) analysis of preclinical data, (2) optimal preclinical study design, (3) predicting clinical liabilities, and (4) clinical study design

Table 7.2 (continued)

Technique	Summary	Reference	Opportunities for pharmacometric analysis
Conscious animal model	ECG measurement, heart rate, and blood pressure are measured in conscious animals that are free to move; it is possible to relate the observed CV effects to the drug concentration using PK/PD modeling; species used in studies include dog, monkey, and minipig	(Ando et al. 2005; Ollerstam et al. 2006, 2007a, b; Markert et al. 2009; Watson et al. 2011)	
First time in human (FTIH)	ECG measurement, heart rate and blood pressure are measured, usually in healthy males; it is a placebo-controlled trial, with strict inclusion/exclusion criteria (with exclusion of females, elderly and volunteers with underlying CV diseases or those taking additional medications that may interact with the tested drug), where escalating doses of drug are tested	(Patat 2000; Buoen et al. 2005)	Nonlinear mixed-effects PK/PD modeling; Bayesian modeling for (1) analysis of clinical data, (2) clinical trial simulations, (3) "not-in-trial" simulation
Thorough QT study (TQT)	Clinical trial introduced in 2005 by ICH to assess QT prolongation risk; it requires positive control treatment arm (using moxifloxacin) and manually read ECG; QT prolongation risk is assessed using "double-delta" method with a threshold of 10 ms	(Anon 2005b)	
Pharmacovigilance	Postmarketing safety data monitoring, including adverse event reporting	FDA Adverse Event Reporting System (FAERS, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm), VigiBase from Uppsala Monitoring Centre (http://whoumc2010.phosdev.se/), (Dumouchel 1999; Clark and Wiseman 2009)	Bayesian data mining; significance analysis using relative reporting ratio

The first section of this chapter provides a summary of CV end points, which are collected during preclinical and clinical studies. The following section is dedicated to the modeling of QT interval and contains a description of modeling and simulation approaches as well as examples of their application in both preclinical and clinical stages of drug life cycle. This will include (1) early discovery phase, where in silico methods are implemented, (2) in vivo studies, where modeling can be beneficial, for example, in optimizing study design as well as (3) in clinical trials, and (4) in large patient populations. The remaining sections of this chapter are dedicated to CV parameters other than QT interval—namely heart rate (HR) and blood pressure (BP), and the application of pharmacometric tools in their assessment.

The work presented here is focused on CV safety; however, there are also numerous examples of the use of pharmacometrics in CV diseases. In this case, changes in CV parameters are treated as a desired effect, rather than unwanted events that need to be avoided, as it is treated here. For more information on the pharmacometrics in CV diseases, we refer readers to the book chapter by Mould et al. (2011).

7.2 CV Parameters

There are various undesired CV effects that can be induced by drugs. These include signs such as palpitations, hypo and hypertension, arrhythmias, stroke or sudden cardiac death, and can range between relatively minor to potentially fatal events. To assess the risk of these effects, it is important to monitor biomarkers that can provide useful information about changes within the CV system. In this chapter, we provide a list of CV biomarkers that are commonly measured during the in vitro, in vivo, and clinical tests as listed in Table 7.2.

7.2.1 QT Interval

QT interval is an index of ventricular cell action potential durations (APD; Fig. 7.1a) in the heart's sinus rhythm (Shah 2002). On the electrocardiogram (ECG), it is defined as a distance between two distinct waves—Q (onset of ventricular excitation) and T (end of repolarization), as can be seen in Fig. 7.1b, and it is usually expressed in milliseconds (ms). Prolongation of QT interval represents a delay in ventricular repolarization and it can lead to a potentially fatal arrhythmia Torsades de Pointes (TdP; Fig. 7.1c; Moss 1999). QT prolongation has been used as a surrogate biomarker of TdP and it is currently mandatory to assess NCE's liability to prolong QT interval in preclinical models (Anon 2005a). TdP is rare; however, it can degenerate into ventricular fibrillation and can cause sudden cardiac death. Risk of drug-induced TdP is one of the major reasons for

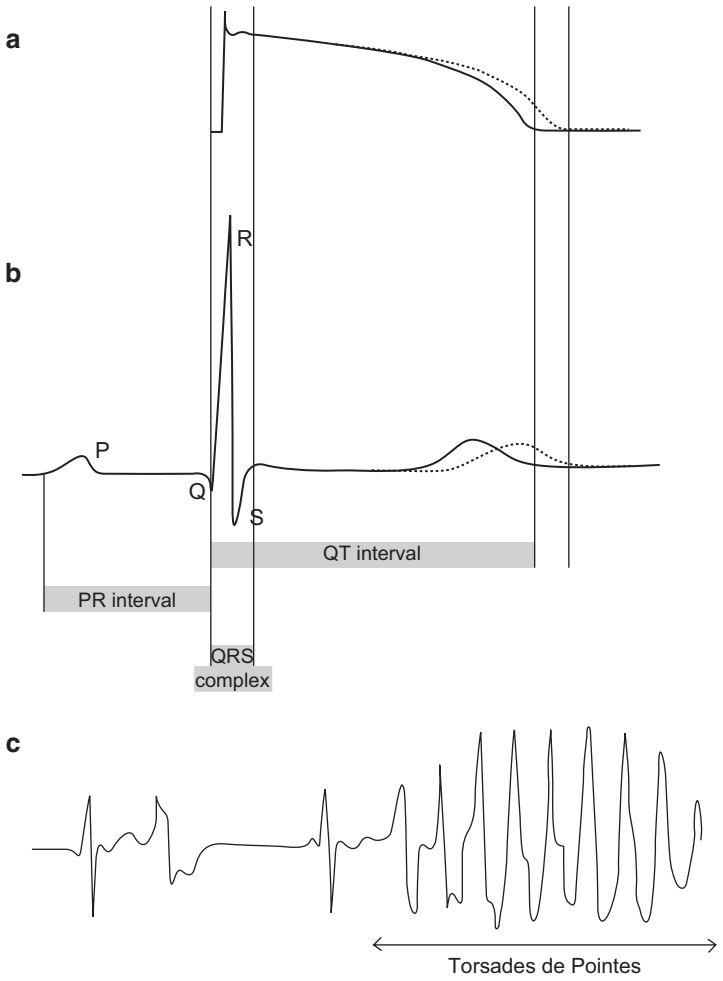

Fig. 7.1 **a** Schematic representation of action potential (*solid line*) and its changes due to hERG inhibition (*dotted line*). **b** ECG with distinct waves (*P*, *Q*, *R*, *S*, *T*), with normal (*solid line*) and prolonged (*dotted line*) QT interval. **c** Electrocardiogram of Torsades de Pointes

drug discontinuation and withdrawals and therefore, a primary concern for the pharmaceutical industry.

Normal QT interval in healthy humans is defined as ≤430 ms for men and ≤450 ms for women. However, it is known that QT interval may be affected by many factors other than drug concentrations, for example, changes in HR, circadian rhythm, potassium levels, glycemia, food intake, and age (Molnar et al. 1996; Nagy et al. 1997; Piotrovsky 2005; Christensen et al. 2010; Chain et al. 2012). It is therefore important to take this into account in order to accurately assess the QT prolongation risk. QT interval is routinely corrected for changes in the HR using standard methods such as Bazzet's (1920), Fridericia's (1920), Van de Water's et al. (1989)

formulae, or individual correction factors (Ollerstam et al. 2007a). Also, circadian rhythm effects can be adjusted for, for example, by including oscillatory component which describes circadian variation in the modeling of drug-induced QT changes (Piotrovsky 2005; Chain et al. 2011).

7.2.2 Heart Rate

HR can be measured from a pulse rate or directly from ECG, as an inverse of a distance between two consecutive R waves. Normal range for resting HR is between 60 and 100 beats per min (defined by the American Heart Association, www.heart.org) and it depends on various factors such as age, body weight, and level of fitness. Rapid increases in HR, for example, induced by drugs can lead to ventricular tachycardia and potentially cause sudden cardiac death; therefore, it is an important parameter measured during safety assessment. Decrease in HR, bradycardia, is also a common clinical problem, although its relevance is poorly understood (Ovsyshcher and Barold 2004).

7.2.3 Blood Pressure

Along with the HR, BP is the main vital sign measurement taken during clinical trials. It is usually measured on the upper arm in humans and expressed as systolic over diastolic pressure, with normal range being less than 120 mmHg for systolic pressure and less than 80 mmHg for diastolic pressure (defined by the American Heart Association, www.heart.org). Increased BP (hypertension) has been associated with an increased risk of age-specific death from a stroke, ischemic heart disease, and other vascular diseases (Prospective Studies Collaboration 2002). Low BP (hypotension) is less dangerous; a common form of hypotension is orthostatic (postural) hypotension, which occurs during sudden changes of position and is often associated with various medications. Although the symptoms are usually limited to dizziness, orthostatic hypotension can lead to falls and injuries, which can be especially hazardous in elderly patients (Tonkin and Wing 1992; Verhaeverbeke and Mets 1997; Shibao et al. 2007).

7.2.4 QRS Complex

Similar to QT, QRS complex can be measured directly from ECG (see Fig. 7.1b) and it includes ventricular activation, depolarization, and contraction (John and Fleisher 2006). Normal duration of QRS complex is usually less than 120 ms (John and Fleisher 2006). Prolongation of QRS interval has been associated with inhibition of Na^+ channel (hNav1.5), which is responsible for the depolarization of cardiomyocytes. Inhibition of this cardiac channel results in a decrease in the rate of

depolarization and consequently slows the velocity of excitation conduction. Although QRS prolongation is not currently addressed in the ICH guidelines, pharmaceutical industry is recognizing its importance and there is an increasing need to better understand drug-induced effects on Na^+ channel (Gintant et al. 2011; Harmer et al. 2011; Erdemli et al. 2012). QRS prolongation is thought to be associated with proarrhythmic risk, especially in patients with underlying cardiac diseases (Kashani and Barold 2005; Adesanya et al. 2008; Sumner et al. 2009). The risk in healthy humans however, is still not fully understood (Seger 2006).

7.2.5 PR Interval

PR interval can be measured on the ECG as the interval between the beginning of the P wave and the beginning of the QRS complex (see Fig. 7.1b) and it represents atrial activity. Normal values range between 120 and 200 ms and prolongation of the interval of more than 200 ms is known as first-degree atrioventricular block (John and Fleisher 2006). It has been suggested that prolongation of PR interval can be linked to an increased risk of atrial fibrillation (Cheng et al. 2009). PR interval prolongation can be caused by inhibition of Na^+ or Ca^{2+} channels (Nav1.5 and hCav1.2, respectively).

7.2.6 Beat-to-Beat Variability

Beat-to-beat variability of the QT interval is a measure of repolarization instability. It has been shown that beat-to-beat variability predicts the risk of TdP well and it was suggested that it can be potentially used as a complementary marker of proarrhythmic risk (Hondeghem et al. 2001; Hinterseer et al. 2008; Jacobson et al. 2011; Varkevisser et al. 2012). New approaches have been developed to assess this temporal variability, for example tangent method (Dota et al. 2002), template matching (Berger et al. 1997), and delta T50 method (Abrahamsson et al. 2011).

7.2.7 Cardiac Contractility

Cardiac contractility represents the capacity of the muscular tissue of the heart to contract (see for example, Mason et al. 1971). Cardiac contractility modifications can lead to clinical signs such as hypo or hypertension, orthostatic deficit or palpitations, which have been reported in 43 % of phase I studies (Moors et al. 2007; Lainee 2009). Currently, there are no defined guidelines for the assessment of cardiac contractility; however, the importance of screening for the potential contractility issues has been recognized by pharmaceutical industry and recently its assessment became a standard within preclinical development (Moors et al. 2007; Norton et al. 2009; Cooper et al. 2011; Bazan et al. 2012).

7.3 Modeling of QT Interval

7.3.1 PK/PD models

QT effects in clinical trials can be quantified in relation to the unbound plasma concentration of the drug through the use of pharmacokinetic and pharmacodynamic (PK/PD) modeling (see for example, Derendorf and Meibohm 1999; Gabrielsson and Weiner 2000; van der Graaf and Gabrielsson 2009). In this approach, QT response is related to the concentration of the drug by describing concentration–QT relationship. Common PD models used to describe QT response include linear (Eq. 7.1), log–linear (Eq. 7.2), simple and sigmoid E_{max} (Eq. 7.3):

$$E = \mathrm{SL} \times C \tag{7.1}$$

$$E = m \times \ln(C + C_0) \tag{7.2}$$

$$E = \frac{E_{max} \times C^{\gamma}}{EC_{50} + C^{\gamma}} \tag{7.3}$$

where E is the effect, C is the concentration of drug, SL is a slope of a linear concentration–effect relationship, m is the slope of the linear segment of the concentration–effect curve, E_{max} is the maximum effect, EC_{50} is the concentration at which the effect is half of E_{max}, and γ is Hill exponent, which in a simple E_{max} model is equal to 1. It is also possible to use alternative parameterization of the E_{max} models (see for example, Gabrielsson and Weiner 2000; Piotrovsky 2005; Groth 2008).

The QT interval can be affected by factors such as changes in HR, circadian rhythm, gender, or age. Therefore, in order to accurately evaluate the effect of the drug, these factors need to be taken into account. An example of a comprehensive PK/PD model, which implements drug effect as well as changes in HR and circadian rhythm is shown in Eq. (7.4) below (Piotrovsky 2005):

$$QT_c = QT_0 \times RR^{\alpha} \times (1 + \mathrm{CIRC} + E) \tag{7.4}$$

where E is a drug-induced effect and can be replaced by any PD models shown in Eqs. (7.1–7.3), QT_0 is a QT baseline parameter, which may differ between males and females, RR^{α} is a correction term for RR change, and CIRC represents the circadian rhythm, which can be described in terms of multiple cosine functions with different periods. An example of circadian rhythm function, which consists of three cosine functions with periods of 24, 12, and 6 h is shown in Eq. (7.5) below (Piotrovsky 2005):

$$CIRC = A_1 \cos\left(\frac{2\pi(t-\phi_1)}{24}\right) + A_2 \cos\left(\frac{2\pi(t-\phi_2)}{12}\right) + A_3 \cos\left(\frac{2\pi(t-\phi_3)}{6}\right) \tag{7.5}$$

where A_x correspond to individual amplitudes and ϕ_x represent phases of the circadian variation component. Similar implementation was also presented recently by Chain et al. and is shown in Eq. (7.6; Chain et al. 2011):

$$QT_c = QT_0 \times RR^{\alpha} + A \times \cos\left(\frac{2\pi}{24}(t - \phi)\right) + E \tag{7.6}$$

where QT_0 is the intercept of the QT–RR relationship and α is the correction factor for HR.

Drug-induced QT response can be instantaneous, i.e., in a situation where a maximum QT effect is observed at the time of maximum drug concentration. In such cases, QT effect can be directly linked to the drug exposure. However, often a time delay between plasma concentration and effect (hysteresis) is observed. It is then necessary to account for this time delay, which can be done by applying effect compartment or indirect response models (Holford and Sheiner 1981; Dayneka et al. 1993; Jusko and Ko 1994; Gabrielsson and Weiner 2000).

In recent years, population PK/PD models have become increasingly popular in the assessment of concentration–effect relationship in CV safety. The advantage of using population models is the ability to estimate the between-subject variability (BSV) i.e., in order to understand how PK and PD parameters may vary across subjects. Additionally, it is also possible to characterize "unexplained" variability in the population, which is the remaining variability, still observed after all other sources have been taken into account. This may include, for example, variability due to the measurement error. In addition to the estimation of various sources of variability, population models also allow to relate covariates such as gender, body weight, renal function, to PK/PD parameters. The approach that is commonly used in population modeling is the nonlinear mixed effect method, which is valuable especially if only sparse data are available. In this method, the population parameters are estimated as well as Bayesian estimates of individual subject parameters. One of the limitations in this method can be lack of identifiability of some parameters, especially if complex models are applied with very sparse data that may not always cover sufficient dynamic range. As a result, it may not be possible to estimate parameters with confidence or alternatively, the analysis may result in parameters that are physically implausible. Detailed information about population modeling and nonlinear mixed effect methods can be found in Sheiner and Beal (1980, 1982), Karlsson et al. (1995), Yano et al. (2001), Tornøe et al. (2004), and Pillai et al. (2005).

Interestingly, the use of Bayesian hierarchical models has been rather limited in the field of PK/PD modeling of QT effects. These methods are computationally intensive and run times may take much longer when compared to the maximum likelihood methods. However, since the introduction of the Markov chain Monte Carlo techniques, they have gained popularity thanks to their many advantages. One of them is the fact that there is no requirement for linearity or normality in the data and so inference is based directly on the desired model. Additionally, the posterior distribution, which is obtained in the form of a random sample, fully reflects all acknowledged sources of uncertainty. In the Bayesian approach, the uncertainty about

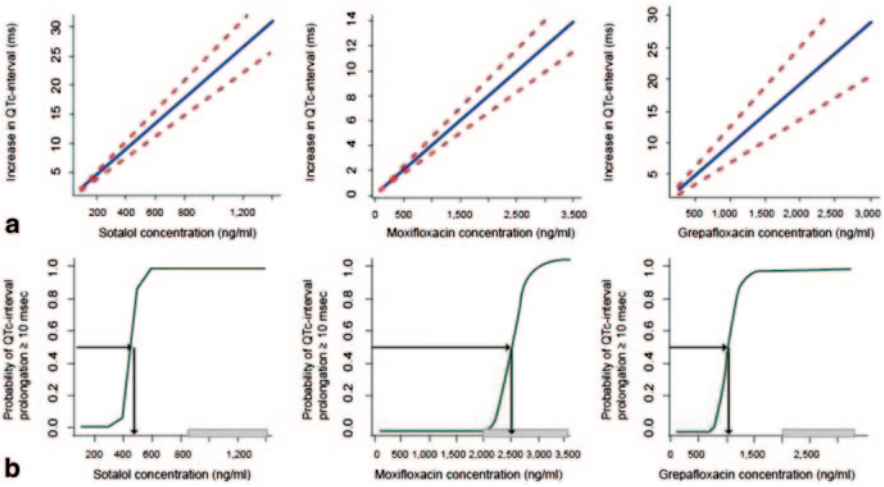

Fig. 7.2 **a** Concentration–QT effect relationships for three QT prolongers: sotalol, moxifloxacin, and grepafloxacin and **b** corresponding probability curves for *QT*c prolongation ≥ 10 ms, obtained through Bayesian modeling. (Reprinted with permission from (Chain et al. 2011)

a parameter is expressed in terms of probability and it can be interpreted in a natural and transparent manner. In the case of QT interval, it can be for example, expressed as a probability of 10 ms increase at a given drug concentration. An example of such probability curves produced using Bayesian modeling of QT prolongation can be found in Fig. 7.2. Another advantage is the ability to incorporate prior information into an analysis. For QT modeling, this can be, for example, prior results from an earlier clinical trial or information about QT–RR relationship and circadian variability. In depth review about the Bayesian approach and its use in PK/PD modeling can be found in Lunn et al. (2002).

7.3.2 Preclinical Models for Predicting Human QT Liability

Since QT prolongation is an important concern in drug development, it is beneficial to detect it as early as possible, ideally before the compound is tested in humans. If a compound is associated with QT prolongation and torsadogenic risk, it would be advantageous to exclude it from the pipeline early and avoid further costly development. Also, most importantly, it would be beneficial from a safety point of view, as it would avoid unnecessary exposure of human volunteers to potentially harmful drugs.

Pharmaceutical companies have employed a range of preclinical assays and tests to eliminate torsadogenic risk and to support the selection of the most appropriate candidate for testing in human trials. The main techniques employed during preclinical development are listed in Table 7.2. In the subsequent paragraphs of this

section, we provide a description of various mathematical methods that utilize data provided during these tests and which can be used to predict human QT liability.

7.3.2.1 In Silico Modeling Using In Vitro Data

The mechanism underlying QT prolongation and the occurrence of TdP is complex at cellular tissue and organ level. QT interval is determined by a balance between inward and outward ion currents, and its prolongation is primarily caused by a blockage of the delayed rectifier potassium current (IKr), encoded by human ether-a-go-go-related gene (hERG; Curran et al. 1995). When hERG is blocked, it causes a reduction in repolarizing currents and hence an increase in the time during which membrane voltage remains at elevated levels. This can be seen as an increase in cell's APD, as it is schematically represented in Fig. 7.1a. Subsequently, an increase in APD gives rise to QT prolongation (Fig. 7.1b). However, the occurrence of TdP cannot be explained purely by an inhibition of a single ion channel. Some drugs can block other channels, in addition to hERG, which may affect QT response (Bril et al. 1996; Martin et al. 2004). For example, if drug inhibits both hERG and other channel that carry currents which oppose repolarization (such as fast sodium channel, I_{Na}), it may result in a situation, where a drug is a hERG blocker; however, it does not cause QT prolongation (Schmitt et al. 2008). For this reason, most pharmaceutical companies include other ion channels, in addition to hERG, in their in vitro high-throughput screens (Harmer et al. 2011; Wible et al. 2008; Chen et al. 2009).

Various mathematical models have been developed to gain an understanding of the underlying processes in ion channel kinetics and action potential (AP) properties. These include models developed by: Winslow et al. (1999), Fox et al. (2002), Hund and Rudy (2004), Mahajan et al. (2008), and Grandi et al. (2010). Figure 7.3 shows a schematic representation of one of the models, a mathematical canine ventricular cell model developed by Hund and Rudy (2004). These mathematical models have been adapted by the pharmaceutical industry to simulate drug-induced effect on AP using experimental in vitro data from various ion channels. For example, Bottino et al. demonstrated how IC_{50} values from five ion channels (hERG, $I_{Na,\ sus}$, I_{CaL}, I_{Ks}, I_{to1}, I_{NaCa}) can be used to simulate canine transmural ECG, which was used as an analog for the human ECG (Bottino et al. 2006). More recently, Davies et al. presented an in silico AP (isAP) model, which was able to predict changes in canine myocyte APD using concentration–effect curve data from five ion channels (hNav1.5, hCav1.2, hKv4.3/hKChIP2.2, hKv7.1/hminK, and hKv11.1). Authors showed that they were able to account for physiological inter-dog variability within the model; they also considerably reduced variation within the dataset by using only one source to generate all ion channel data, IonWorks (Schroeder et al. 2003). The developed isAP model was validated using 53 compounds, which included both ion channel inhibitors and simulators, as well as both single and multi-ion channel blockers. Predictions made by isAP were compared to the experimental measurements of APD performed using canine left ventricular midmyocardial myocytes and the model was found to be 81 % predictive (Davies et al. 2012). A similar approach

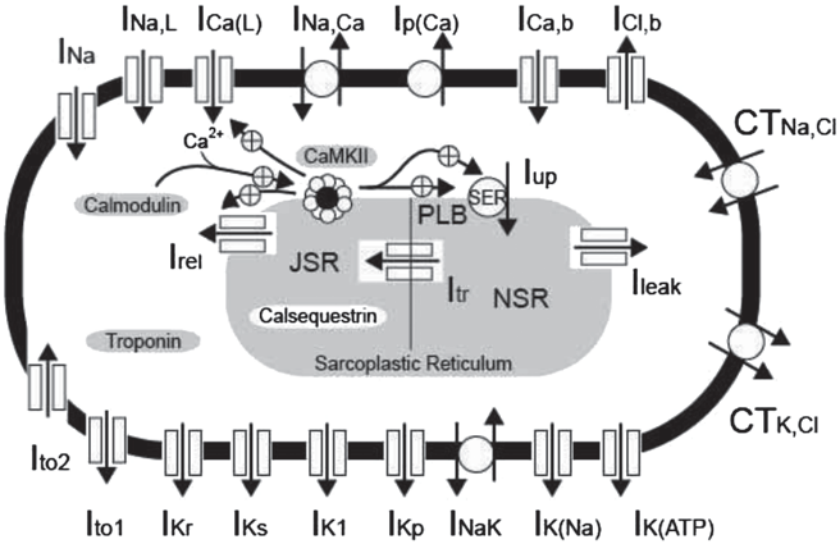

Fig. 7.3 Schematic representation of mathematical canine ventricular cell model developed by Hund and Rudy (2004). *Symbols: CaMKII* Ca^{2+}/calmodulin-dependent protein kinase, *JSR* junctional sarcoplasmic reticulum, *NSR* network sarcoplasmic reticulum, *PLB* phospholamban, CT_{NaCl} Na^{+}–Cl– cotransporter, CT_{KCl} K^{+}–Cl– cotransporter, I_{up} Ca^{2+} uptake from myoplasm to NSR, I_{leak} Ca^{2+} leak from NSR to myoplasm, I_{rel} Ca^{2+} release from JSR to myoplasm, I_x specific ion currents. (Reprinted with permission from Hund and Rudy 2004)

has been also adapted by Mirams et al. (2011). These authors used IC_{50} data from three ion channels: hERG, $I_{Na,}$ and I_{CaL} from 31 drugs to perform in silico modeling of ventricular cells and predict changes in APD. Simulations were performed for rabbit, dog, and human ventricular myocytes using various pacing protocols. The predictive power was then quantified by comparing predictions from the in silico models to the risk of TdP, using risk classification introduced by Redfern et al. (2003). These authors showed that they were able to accurately predict TdP risk for both pure hERG and multi-ion channel blockers, and demonstrated that APD prolongation correlated best with the torsadogenic risk out of all evaluated in silico markers (Mirams et al. 2011).

The examples presented above show that in silico models can be successfully used for compound selection through the assessment of the putative QT liability in early stages of drug discovery, namely during lead identification and optimization, along with the generation of the high-throughput screening of ion channel activity. Mathematical calculations can be performed in a short time, e.g., by using a distributed computing server, and thus such in silico models can be treated as an additional virtual high-throughput screen. It is clear that the use of in silico models can be highly beneficial during drug development: From an ethical point of view, it enables replacement and reduction of animals (thus addressing the 3R concept: replacement, refinement, and reduction, see for example, Fink et al. 2009 or www.nc3rs.org.uk); additionally, it can result in cost and time reduction. They can provide additional

information about cardiac liability and can therefore help select the most appropriate compounds to be taken forward to the preclinical testing. However, when using in silico methods, one should be aware of their underlying assumptions and limitations. For example, predictions are made using in vitro data from cell lines expressing cardiac ion channels, which may not always accurately reflect the native state of ion channels in vivo. Additionally, the accuracy of the in silico models to predict QT risk depends on the complexity of the mathematical model—for example on the number of ion channels used, inclusion of G-protein-coupled receptors (GPCRs), or kinases, all of which may be affected by a compound and as a consequence have an effect on the QT interval. There are also many other "in vivo modulators," i.e., factors that are present in the whole organism but are not accounted for in the in silico model. This may include, for example, hormonal regulation, signals from the nervous system, or underlying CV diseases.

7.3.2.2 Mechanism-Based Modeling Using In Vitro Data

The discovery of a link between QT prolongation and the inhibition of hERG potassium channel resulted in an establishment of an in vitro hERG assay (see Table 7.2). Currently, this screening method is widely used to detect a delayed repolarization risk (Brown 2004; Anon 2005a) and usually few ascending concentrations of NCE are tested to determine a concentration–effect relationship. Safety margins are generally calculated as a 30–40-fold difference between hERG IC_{50} and maximum free plasma concentration reached in in vivo or clinical studies (Redfern et al. 2003; Gintant 2011). Although these calculations are useful, they do not allow to quantitatively assess the extent of QT prolongation. Such assessment, i.e., a quantification of the relationship between in vitro channel inhibition and in vivo/clinical QT outcome is possible using mechanism-based PK/PD approach. In this approach, it is possible to characterize specific processes that take place between the administration of the drug and observed response, such as (1) PKs of a drug, (2) potential delays in target site distribution (hysteresis), (3) receptor binding, and (4) activation as well as (5) transduction.

With mechanism-based models, it is possible to distinguish between drug-specific (such as receptor binding) and system-specific parameters (signal transduction) and consequently to extrapolate from in vitro to in vivo as well as between species (for a review, see Danhof et al. 2005; Ploeger et al. 2009). Even though these models do not include all complexity of the actual physiological and pharmacological processes, they incorporate receptor theory concepts and thus allow predicting effects in vivo based on the parameters derived from in vitro assays.

The mechanism-based approach was used by Jonker et al., where operational model of pharmacologic agonism (Black and Leff 1983) was applied to relate the magnitude of hERG inhibition to the clinical QT response for a selective hERG blocker, dofetilide (Jonker et al. 2005). The authors linked in vitro properties of the drug, i.e., affinity and activity and the unbound plasma concentration to the QT effect by using the following operational model of agonism:

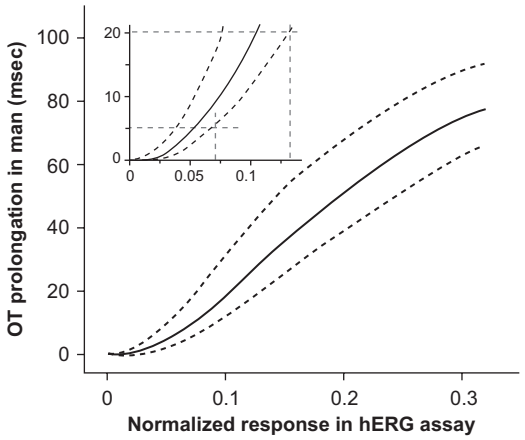

Fig. 7.4 Relationship between inhibition of in vitro hERG ion channel and absolute QT change in humans. *Solid curve* represents the median, while *dashed curves* correspond to the 95% confidence interval. The insert represents a zoomed in section of the graph, which corresponds to the change in QT interval of up to 20 ms. (Reprinted by permission from Macmillan Publishers Ltd: Clinical Pharmacology & Therapeutics (Jonker et al. 2005)

$$QT_{CF} = QT_0 + \frac{QT_m \times (\tau \times C)^n}{(K_I + C)^n + (\tau \times C)^n} \tag{7.7}$$

where QT_0 corresponds to the average QT baseline, QT_m is the maximum QT prolongation, τ is the transducer ratio, K_I is the dofetilide concentration resulting in 50% hERG current inhibition, and n represents a slope factor (Jonker et al. 2005). The dimensionless parameter τ corresponds to the half-maximum response in the hERG assay and it is defined as a ratio of the maximum current inhibition (I_{max}) to the fraction of inhibited hERG channels. The final model included additional parameters, such as system specific development of tolerance with long-term administration and the implementation of an effect compartment to account for hysteresis. The authors applied a population PK/PD approach to perform calculations and therefore were able to estimate the inter- and intraindividual variability. As a result, they were able to describe the relationship between the in vitro inhibition of hERG and the extent of the QT prolongation in human. This relationship can be seen in Fig. 7.4. According to the model, 10% inhibition of hERG corresponds to 20 ms change in QT interval. Similar relationships were reported in a presentation at the Modeling and Simulation (M&S) workshop between European Medicines Agency (EMA) regulators and European Federation of Pharmaceutical Industries and Associations industry (EFPIA; Visser et al. 2013).

Such model is an important step forward in predicting in vivo and clinical QT liabilities using parameters derived from in vitro screens. It provides a potential to quantitatively assess proarrhythmic risk in humans at relevant drug concentrations. However, since the model was developed using a pure hERG blocker, it is important to note that one should be cautious when extrapolating this model to other drugs, specifically ones that may potentially affect multiple ion channels. As it was mentioned in the previous section, and also highlighted by the authors themselves, inhibition or simulation of many channels may affect QT response. Therefore, future models need to be developed, that can relate inhibition of multiple ion channels to the clinical QT response.

7.3.2.3 Descriptive and Semi-mechanistic PK/PD Modeling Using In Vivo Data

QT interval, along with other ECG parameters and vital signs is often measured during in vivo studies using anesthetized and/or conscious animal models (see Table 7.2). Since plasma samples are also taken during the studies, it is possible to apply PK/PD modeling to describe the concentration–effect relationship. This type of analysis in preclinical studies has become increasingly popular in recent years and has been used, for example, to describe drug-induced QT changes in rats, marmosets, dogs, and monkeys (Ohtani et al. 2000; Ollerstam et al. 2006, 2007a, b; Komatsu et al. 2010; Dubois et al. 2011; van der Graaf et al. 2011; Watson et al. 2011; Chain 2012; Parkinson et al. 2013). This section will provide examples of how the application of PK/PD modeling has led to improvements in preclinical study design (Sect. 2.2.3.1) as well as development of methods to predict clinical QT outcomes based on preclinical data (Sect. 2.2.3.2).

Application to Optimal Study Design

As mentioned in Sect. 2.1, many drugs exhibit a temporal difference between plasma concentration and QT response (Le Coz et al. 1995; Hanada et al. 1999; Ohtani et al. 2000; Ollerstam et al. 2006). This situation can occur, for example, when (1) target space is in a separate compartment than plasma, (2) the response is driven by turnover, or (3) there is slow on/off target binding (Danhof et al. 2008; Gabrielsson et al. 2010). The presence of hysteresis can significantly affect the interpretation of study results. For example, if it is ignored, it may lead to incorrect calculations of safety margins and consequently incorrect predictions of safe clinical doses as illustrated by Gabrielsson et al. (2011). It is therefore necessary to account for hysteresis, for example by applying an effect compartment model or indirect response models (see Sect. 2.1). However, these models can be used only when meaningful data are available, i.e., when QT measurements are taken at informative time points after drug administration. Such meaningful data can be obtained using "time series approach," where measurements are taken during both upswing and downswing of the concentration and response time curves. It can then be used to fit a PK/PD model and fully characterize onset, intensity, and duration of response. This type of experimental design is thought to have more statistical power in terms of calculating variability and confidence intervals (Gabrielsson et al. 2010). It also allows for discrimination of system specific properties, such as turnover parameters and drug-specific properties (for example, E_{max}, EC_{50}). An example of optimizing experimental design to obtain informative data was presented by Ollerstam et al., where authors recommended the use of slow, continuous intravenous (IV) infusions followed by a wash out, instead of a rapid, stepwise infusion or a single oral dose (Ollerstam et al. 2006, 2007a). The authors showed that the concentration range produced by such slow infusions was similar to the range obtained after rapid infusions or multiple bolus injections regimen; however, in the former approach the increase in concentration

was more gradual and therefore less likely to exhibit transient fluctuations, which may result in higher variability. As a consequence, the estimation of concentration–QT effect relationship can be more precise. The authors also highlighted the need to collect measurements not only during the infusions but also during the wash-out period as these data may provide useful information in case of a delayed QT effect (Ollerstam et al. 2007a). Another advantage of using slow infusions is a reduction in the unwanted hemodynamic effects. It has been previously shown that the risk of TdP and the presence of hemodynamic effects, such as rapid increase in HR and tachycardia are related to the rate of infusion (Kleinbloesem et al. 1987; van Harten et al. 1988; Carlsson et al. 1993; Detre et al. 2005). These effects have been observed in relation to rapid-rise regiments; therefore, the use of slow infusions that produce gradual concentration increase is more favorable. Additionally, such slow and gradual rise in concentration can also be quickly terminated in cases when serious adverse effects occur.

Once the preclinical study is optimally designed and the meaningful data are collected, the next step is to perform PK/PD analysis in the most appropriate way. In another work published by Ollerstam and colleagues, the authors investigated various approaches in data processing in order to develop the most optimal method. As a result, it was recommended that QT interval should be corrected individually for HR and vehicle effects, and the linear correction was found to be most appropriate for this purpose (Ollerstam et al. 2007a). Additionally, the authors highlighted the need to exclude from the analysis the QT measurements which follow rapid increases in HR. This recommendation is associated with the fact that there is often a time delay between sudden HR changes and changes in QT interval. It was shown that it may take up to few minutes for the QT interval to adapt (Lau et al. 1988; Batchvarov et al. 2002; Malik 2004; Pueyo et al. 2004). Although the QT/RR hysteresis is a known phenomenon, it is often ignored in the analysis of QT data. This can potentially lead to an under- or overestimation of the QT response after drug administration, therefore it is important to take the abrupt HR changes into consideration. This is especially important in preclinical studies where conscious animals are used. During these studies, animals are free to move while the CV measurements are taken which can often lead to sudden changes in HR.

Application to In Vivo: Clinical Predictions

An accurate PK/PD description of drug-induced QT effect in preclinical species is a first step in translational research. It is a basis for extrapolation of preclinical PK/PD models into humans and predicting clinical effects at the intended drug exposures. The next step is to understand and quantify the translational link between two species. The rationale behind this type of translational analysis is to describe and quantify PK/PD relationship in preclinical animal and in human and then compare drug-specific PK/PD parameters between two species. For example, if both animal and human concentration–QT response relationships are described using a linear PD model (see Eq. 7.1), the resulting slope parameters can be directly compared

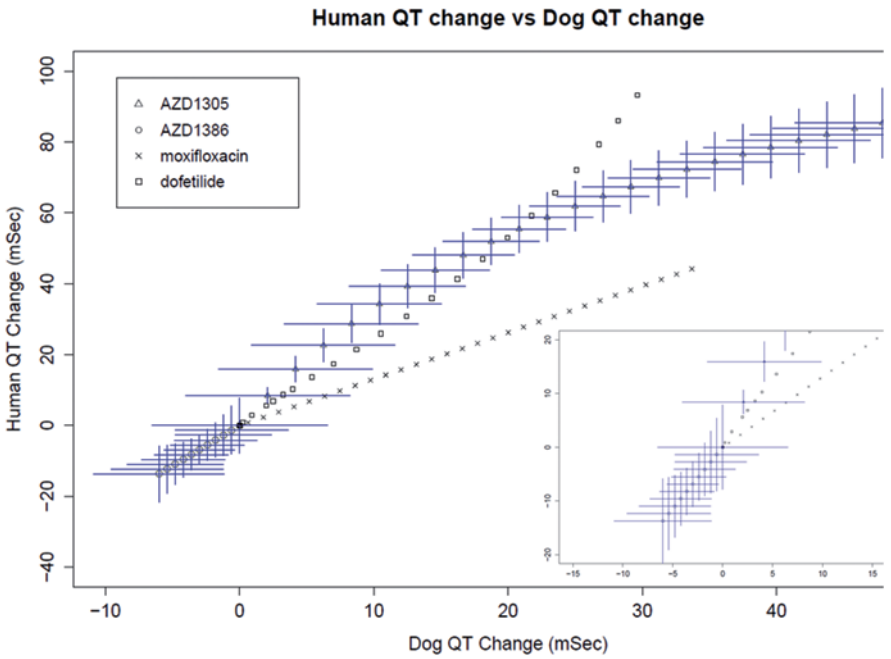

Fig. 7.5 Translational relationship between absolute QT change in dog (*x-axis*) and human (*y-axis*). Data from four compounds are plotted, and each compound is represented by a different symbol. *Lines* correspond to 95% confidence interval. The *insert* represents a zoomed in initial section of the plot. (Reprinted from Parkinson et al. 2013, with permission from Elsevier)

between two species. Similarly, if the E_{max} model is used (see Eq. 7.3), it is then possible to compare the respective EC_{50} values. Consequently, if the drug-specific parameters are consistent across two species, this knowledge can be then used to make clinical predictions for future compounds using preclinical PK/PD parameters.

An example of such translational analysis between conscious dog and human was recently presented by Parkinson et al. using four drugs—two proprietary compounds along with moxifloxacin and dofetilide (Parkinson et al. 2013). The authors used PK/PD modeling to (1) establish a relationship between QT response in dog and man at matching free concentrations of the drug and to (2) investigate whether such a relationship is consistent across all compounds or if it depends on the underlying mechanism(s) of action. The results showed that although there was high variability in the data, the translational relationship was similar for both pure hERG and multi-ion channel blockers at low delta-*QT*c intervals. The developed translational relationship between dog and human can be found in Fig. 7.5 and according to this analysis, a QT_c change of 2.5–8 ms in dog corresponds to a 10-ms change in man (Parkinson et al. 2013). Although this analysis was limited to four compounds and more examples are needed in order to fully understand the translational relationship between two species, it is nevertheless an important step forward in development of quantitative predictive method for the assessment of clinical QT liabilities.

The translation between dogs and humans was also assessed recently by Dubois et al. using moxifloxacin (Dubois et al. 2011) and by Chain et al. using moxifloxacin, sotalol, and cisapride (Chain 2012). In this work, a Bayesian PK/PD approach was used to predict clinical QT effects. Preclinical and clinical outcomes were expressed as a probability of QT prolongation greater than or equal to 10 ms at a given exposure level. Using this method, the authors showed that it was possible to distinguish between drug- and system-specific properties, which can allow direct comparison of drug-specific properties across two species. The results showed that dogs were less sensitive to the QT prolongation than humans, as judged by the slopes of their concentration–effect relationship and the concentration range of QT prolongation probability (Dubois et al. 2011).

Similar translational analyses were performed for other preclinical species. For example, Watson et al. applied PK/PD modeling to describe QT response induced by moxifloxacin in monkeys. The authors used a direct linear relationship between plasma concentration and QT response, described earlier in this chapter in Eq. (7.1), and then compared the slope of developed relationship to the slope values reported for humans in literature. The comparison revealed that although the slope of the concentration–QT response relationship in monkeys was lower than in humans, the parameters from both species were within threefold of mean estimate. Therefore, it was concluded that there is a good agreement between two species. In addition, this work confirmed the conclusion drawn earlier by Jonker et al. (2005) that 10 ms increase in QT_c can be induced by systemic exposures which give rise to less than 10% blockage of the hERG channel in vitro (van der Graaf et al. 2011; Watson et al. 2011).

When performing such translational analyses, it is important to remember that the translational relationship between preclinical animal and human may be different depending on the preclinical species used. For example, monkeys were found to be more sensitive than dogs to QT prolongation caused by moxifloxacin (Dubois et al. 2011). On the other hand, their sensitivity to QT prolongation was very similar to that of marmosets (Komatsu et al. 2010; Watson et al. 2011). Furthermore, the translational relationship between a given preclinical animal and human may also be influenced by a measurement method or other factors such as anesthesia. For example, Ollerstam et al. demonstrated that QT response in dogs may be significantly different depending on the type of dog model used. Specifically, the authors compared concentration–QT responses from three types of dog models, namely conscious, paced, and anesthetized, using four known QT prolongers (dofetilide, moxifloxacin, cisapride, and terfenadine). The analysis demonstrated that anesthetized dogs had much lower sensitivity to QT prolongation than either conscious or paced dogs. The authors suggested that these differences can be attributed to the influence of anesthesia on the metabolic processes in animals and/or a direct effect of anesthetics on the QT interval (Ollerstam et al. 2007b).

The overview presented in this section shows that there is a growing body of evidence that thorough preclinical QT (TpQT) evaluation could provide an effective and efficient quantitative decision framework for derisking of QT liability in man (van der Graaf et al. 2011). A combination of in vitro assays and in vivo studies

together with sophisticated mathematical approaches such as in silico models and PK/PD offer a comprehensive package to assess cardiac liabilities. These methods can help not only in detection and early discontinuation of potentially harmful substances before they are tested in humans but alsocan provide information about more subtle CV effects, which could potentially cause issues later in clinical development.

7.3.3 Clinical QT Modeling

7.3.3.1 QT Modeling in Clinical Studies

Given the potentially fatal consequences of QT_c prolongation, a concentration-dependent adverse drug reaction, regulatory authorities have reacted to this relatively recent "pharmacoepidemic" by denying or delaying the approval of a number of new drugs and placing severe restrictions on the use of many old and some new drugs because of concerns arising from their potential to prolong the QT/QT_c interval. For the implications for public health, scientific efforts have faced a parallel movement driven by health authorities, which have imposed the introduction of supposedly effective measures for the approval of novel compounds (Chain 2012). In 2005, the guidance introduced and mandated the performance of thorough QT (TQT) studies as the basis to systematically evaluate and demonstrate a compound's liability to cause *QT*c prolongation (ICH E14 guideline). In addition to outlining the assessment procedures for evaluating prolonged ventricular repolarization, the ICH E14 document requires the use of a positive control and supratherapeutic doses of the investigational drug to ensure accuracy and sensitivity of the experimental protocol (Anon 2005b). Suggestions are also given regarding the timing of the studies as well as the methodologies and interpretations used in the evaluation of QT measurements.

The primary analysis of a TQT study is not a pharmacometric analysis, but an analysis based on the "double-delta" method, where the time-matched mean *QT*c interval difference between active and placebo treatments, both adjusted for baseline, is taken. The result of the assessment must exclude 10 ms to be deemed safe, i.e., a negative study (Anon 2005b). Requiring that the largest time-matched mean difference between the drug and placebo QT_c interval to be around 5 ms or less implies that the one-sided 95 %-CI should exclude an effect of > 10 ms for every single measurement. This analysis has some issues, which is reviewed in more detail by Boos et al. (2007), Tsong et al. (2008), and Chain (2012). For example, the drug exposure and hence the underlying concentration–effect relationship, which determines the clinical relevance of drug-induced effects are not taken into an account (Rohatagi et al. 2009; Chain et al. 2011). Many authors have previously highlighted the importance of establishing the relationship between drug concentrations and changes in QT_c interval and provided examples that illustrate how this type of assessment has been useful during regulatory review

(Gobburu 2007; Garnett et al. 2008; Zaręba 2007; Bloomfield and Krishna 2008). Such assessment can therefore be a powerful alternative method to the double delta or any time point-based analysis. In particular, nonlinear mixed effects modeling of the concentration–QT relationship, mentioned in the previous section, allows the integration of data across all time points as well as all available treatment groups. Moreover, it relies on individual responses, instead of averaging the QT response at each time point, which enables better understanding of the uncertainty in response as well as the impact of outliers (Bloomfield and Krishna 2008).

Along with modeling and simulation techniques, one additional proposal is to consider the integration of ECG measurements in other mandatory clinical trials to generate additional evidence in support of establishing the CV safety profile of the compound. Given the statistical and scientific issues, the ethical burden and financial consequences of a TQT study, which is currently mandatory, the feasibility of using first time in human (FTIH) studies as the basis for evidence synthesis to investigate the propensity for proarrhythmic effects is a valuable alternative. FTIH studies (see Table 7.2) are a mandatory step in the drug development process. As it was reviewed by Chain (2012), in principle, the doses or dose range evaluated during escalation could enable the evaluation of the concentration–effect curve, providing evidence for drug effects not only at therapeutic level but also at supratherapeutic levels. From a safety and tolerability perspective, PD measures are monitored frequently or continuously throughout the dosing interval in parallel to PK sampling. In addition, the possibility of including a benchmark or positive control arm in a typical FTIH trial is not entirely excluded. The many historical studies with moxifloxacin (Florian et al. 2011) can be used in an integrated manner as benchmark or as priors during data analysis. Finally, in the instance where a TQT study is not feasible due to ethical considerations (see for example, Rock et al. (2009), regulatory authorities often rely heavily on FTIH studies as well as preclinical studies where QT prolongation was assessed. Thus, the limited information available can be enhanced by the incorporation of modeling and simulations results.

7.3.3.2 PK/PD Simulations in Clinical Studies

In Sect. 2.2, we have provided examples of the use of pharmacometric tools in preclinical development, where they can be applied to describe, explain, and predict clinical QT liabilities, improve decisions on compound selection during drug development, and to help design of clinical trials. Model based methods, which have increased in popularity in recent years, have also led to generation of new tools that can be used in clinical drug development. Here, modeling can be used to analyze study results, as it was mentioned in the previous section, but more importantly, it can also be applied to perform extrapolations to new situations. This can be beneficial for regulatory reviews and approvals after late phase clinical studies.

These extrapolations are possible through the computer simulations of clinical trials (CTS). In this approach, the existing knowledge of PK and PD properties of the drug is gathered and then used to simulate various hypothetical scenarios

of clinical trials (for a review, see Aarons et al. 2001; Girard 2005; Holford et al. 2010). This approach provides an opportunity to explore various study designs prior to actual experiments—for example, to investigate scenarios such as various population size with different sets of demographic features (e.g., only females, only patients at a certain age, or with a certain average HR value), various dose range and regimen, sampling scheme, etc. Additionally, it is possible to evaluate the consequences of protocol deviations, e.g., by simulating dropout and treatment compliance. In the case of QT prolongation, CTS can be valuable for a design of the most appropriate dosing regimen that may reduce drug-induced QT prolongation or to select the maximal dose at which the QT prolongation is absent. However, it is important to remember that CTS must be based on an accurate PK/PD model, supported by existing data. If the underlying model is not informative, e.g., in a case when appropriate data were not collected (for example, if there are no data available from females or elderly patients), extrapolating to many hypothetical scenarios will not be possible. The requirement for high-quality data that support CTS is emphasized by a common expression "garbage in, garbage out" and should always be remembered when performing extrapolations.

An example of application of PK/PD simulation in management of QT prolongation was presented by Isbister et al. The authors performed computer simulations using a previously developed PK/PD model, in order to establish guidelines for the management of citalopram overdose, a drug that is known to cause QT prolongation at high exposures (Isbister et al. 2006). As a result, they were able to (1) establish a minimum dose after which decontamination with single-dose activated charcoal was recommended, (2) establish a minimum dose, after which additional cardiac monitoring was needed, as well as (3) determine minimum monitoring time for patients who overdosed the drug. In addition, simulations provided information to develop guidelines for dose adjusting in elderly patients, women, and patients with underlying cardiac diseases. This study illustrated how mathematical simulations can be utilized to help clinicians to decide which patients require treatment after drug overdose, e.g., in the form of decontamination and/or additional cardiac monitoring. Similar approach was also used to establish guidelines for reducing risk of QT prolongation and TdP in methadone users (Florian et al. 2012). Simulations were proven successful in finding maximal dose below which QT interval was not prolonged above a certain threshold. It was also possible to identify factors that may contribute to the methadone-induced QT prolongation, such as gender or use of concomitant medications or substances that can additionally affect hERG channel, such as cocaine (Florian et al. 2012).

Clinical trial simulations can also be valuable in choosing the most optimal method of QT data analysis. This approach has been presented by Bonate et al., where the authors explored the power of various metrics that can be used to analyze QT data, such as maximal QT change from baseline, maximal QT interval or inclusion of QT baseline as a covariate. Simulations using different metrics revealed that area under the QT interval time curve with baseline QT interval as a covariate was the most powerful test to detect drug-induced QT changes (Bonate 2000).

7.3.3.3 Prediction of CV Risk in Patient Population

Despite numerous efforts aimed at improving signal detection of CV events for new medicines (Haverkamp et al. 2000; Netzer et al. 2001; Shah and Hondeghem 2005), none of them have focused on what actually happens after the drug has been approved and released into the general population. Although many postmarketing surveillance trials and spontaneous adverse events reporting have been used to monitor the incidence of supraventricular arrhythmias, TdP, and other safety events (Dekker et al. 1994; de Bruyne et al. 1999; Montanez et al. 2004), there is still an important advantage in knowing what can be expected so that mitigation plans can be made in advance. Furthermore, inclusion and exclusion criteria are imposed on clinical trial protocols to mitigate risk and prevent the most vulnerable patients from exposure to an experimental agent for which the risk to benefit ratio is unknown at the time of the investigation. Subsequently, however, drug prescription is not restricted or contraindicated for those patients who were excluded during the clinical development phase. Implicitly, the current practice imposes the assumption that such inclusion/exclusion criteria do not alter treatment outcome. Inferential methods offer an opportunity to address this issue in a more quantitative and systematic manner.

Many other causal factors are often present, which significantly affect the observed QT_c values in the real-life patient population. In fact, previous publications showed that heart failure, hypertension, diabetes and myocardial infarction all increase the risk of QT_c prolongation (Makkar et al. 1993; Choy et al. 1999; Nowinski et al. 2002; Torp-Pedersen et al. 1999). In addition to comorbidities, concomitant medications can also be a major contributor in prolonging the QT_c intervals. The crucial question from the regulatory perspective is "How efficient and reliable are the pre-approval clinical trials in identifying the clinical risk of TdP, given the patient population enrolled, background noise arising from spontaneous intraindividual variability in QT_c interval and the relatively low frequency of the clinically significant drug-induced effect?" (Bonate and Russell 1999).

Primarily, safety trial designs are highly efficacy oriented. 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 CV risk in the target population. Many subgroups of patients, especially those most at risk of TdP during the uncontrolled clinical use, exposed to the drug in question are usually excluded from these trials. These include: (1) females, (2) the elderly, (3) those with predisposing cardiac or noncardiac diseases associated with diminished repolarization reserve and therefore greater susceptibility to prolongation of the QT interval, (4) those with pharmacogenetic defects of drug metabolizing enzymes or pharmacological targets such as the potassium channels, (5) those susceptible to bradycardia or electrolyte imbalance, or (6) those receiving drugs with a potential for PK or PD interactions (Shah 2004, 2005). Therefore, the scope for detecting drug–drug or drug–disease interactions in clinical trials is very limited.

Given the patient population enrolled, the background noise (arising from spontaneous intraindividual variability in QT_c 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 QT_c interval prolongation. In fact, it is known that the proarrhythmic threshold can vary across compounds with frequency of such events ranging from approximately 1 in 100 (for halofantrine) to 1 in 50,000 (for terfenadine; Shah 2004). 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 QT_c interval and consequently in CV risk in the target population. Thus, there is a need to widen the views on risk management beyond the evolving perspective from clinical pharmacology experts and regulators, i.e., that the liability for QT_c interval prolongation cannot be assessed accurately without an assessment of the concentration–effect relationships (Garnett et al. 2008). The concept of "not-in-trial simulation," in theory, enables quantitative evaluation of the implication of all factors contributing to QT_c interval prolongation in the real-life population, in addition to the observed drug effects investigated during clinical trials.

Model-based drug development (MBDD) principles offer advantages in the development and the application of pharmacostatistical models of drug efficacy and safety from preclinical and clinical data, to improve drug development knowledge management and decision making (Kola and Landis 2004; Food and Drug Administration 2004). It is also possible to utilize the techniques to make inferences about drug exposure in patients and evaluate in an integrated manner, how different covariates and sources of variability affect the observed QT_c values in real-life patients. In contrast to typical clinical trial simulations (Chan and Holford 2001; Gobburu and Marroum 2001), "not-in-trial" simulations allow the integration of PK/PD relationships. It can be applied to characterize the role of design factors, which have been omitted or excluded from a randomized trial. Thus, this novel approach will represent a natural extension of ongoing efforts within the pharmaceutical industry to improve safety signal detection where pharmacological basis is established for the assessment of causality, discriminating drug-induced from other (drug-unrelated) effects (Pater 2005; Lalonde et al. 2007; Pollard et al. 2008; DiMasi et al. 2010; Laverty et al. 2011). Specifically, safety data can be derived from epidemiological or pharmacoepidemiological studies, which are planned and performed after drug approval. It is feasible to consider integrating clinical trial and epidemiological data for the purpose of signal detection and improve risk management. As Black explained, "the false conflict between those who advocate randomized 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" (Black 1996). Others have also advocated the synergistic potential for using both kinds of data to aid decision making (Atkins 2007; Landewe and van der Heijde 2007; Hannan 2008; Yang et al. 2010).

In summary, simulation techniques can play an important role in the integration of clinical trial and epidemiological data for the prediction and interpretation of safety findings. The assessment of estimating the overall increase in QT_c intervals

must take into account different sources and contributors. Information of nondrug induced causal factors can be quantified using epidemiological techniques and incorporated with the drug-induced evaluation for the assessment of the overall effect.

7.4 Pharmacometrics in the Assessment of HR

7.4.1 Preclinical Models for Predicting Human HR Liability

Previous sections of this chapter provided multiple examples of the use of modeling and simulation in the assessment of QT prolongation in both preclinical and clinical drug development. Such extensive work resulted in great improvements in the understanding of the underlying mechanisms of QT prolongation and development of new methods in its assessment as well as in predicting the clinical outcome. Unfortunately, a lot less work has been done on other CV parameters, such as BP or HR (Howgate 2013). As a consequence, we have a limited knowledge on the mechanisms that underlie changes in these parameters and hence limited tools to assess their liability in humans. For example, it was recently highlighted that dog is a poor preclinical model for predicting changes in HR and BP in human, even though it is very valuable in predicting QT prolongation (Ewart et al. 2013).

In fact, only very recently researchers started to apply PK/PD modeling techniques to understand the concordance between preclinical species and man for HR. An example of such work was presented by Langdon et al., where authors used PK/PD modeling to describe drug-induced HR changes in dogs and humans and performed an analysis of the predictive value of the preclinical model (Langdon et al. 2010). The approach used was similar to the semi-mechanistic method described in Sect. 3.3.2—i.e., a direct linear model (Eq. 7.1) was applied along with the implementation of circadian rhythm to account for daily variation in HR. The resulting concentration–HR response profiles were then compared between two species. The analysis revealed that both dogs and humans were equally sensitive to HR changes; additionally, the authors were able to successfully predict human HR response using slope (i.e., drug-specific parameter) of the concentration–effect relationship from the dog (Langdon et al. 2010). Although this work was limited to only one compound, with unknown mechanism that underlie CV changes, it is an important step toward integrating the use of PK/PD modeling in the assessment of HR changes in preclinical species and building a translational model to predict the clinical outcome.

Other examples of the application of PK/PD modeling in the assessment of HR include the development of preclinical turnover model of biorhythms in rats published by Sällström et al. (2005). The complex model described baseline values for HR, BP, and temperature and their characteristic changes during the 24-h period, taking into account the asymmetric patterns and differences between day and night. The final model also included hypothermic response, tolerance development, and

the effects due to animal handling. Such model is of great value as it can help to separate the actual drug effect from biorhythms. This is especially important in preclinical studies, where animal handling (for example, during drug administration or while changing water bottles) can introduce disturbances in CV measurements. An understanding of asymmetric patterns and differences between day and night in biorhythms is also valuable for optimal study design, for example, when planning a dosing regimen or laboratory settings, such as 12:12 light–dark cycle (Sällström et al. 2005).

7.4.2 Application in Clinical Studies

In recent years, some effort has been made in the development of a global model that could describe basic control mechanisms and systems in the CV system, such as baroreceptor loop or systemic and pulmonary circulation. Such model could be used to simulate CV parameters—HR and BP. Complex mathematical models have been developed which includes, for example, work by Kappel and Peer (1993), Francheteau et al. (1993), Hentschel (2008), Choi and Sun (2005), and van de Vooren et al. April (2007). However, a common problem with complex models such as global models of circulatory system described above is structural identifiability of parameters. If the parameters are unidentifiable globally or locally, the model cannot be used to estimate unique parameters in the case when experimental data are available (see for example, Bellman and Åström 1970; Cobelli and DiStefano 1980). In order to apply such complex physiological models in the analysis of real data, models need to be simplified, for example, by using reparameterization techniques. An example was provided by Cheung et al., who reparameterized circulatory system model (Cheung et al. 2012). In this approach, the authors proved that it is possible to reduce number of parameters in the model and uniquely estimate them, without compromising mechanistic interpretation of the model. The parameters in their final, reparameterized model included: (1) PK parameters of the drug, such as clearance and volume of distribution, (2) PD parameters, such as *Emax* and EC_{50}, (3) physiological parameters, such as steady-state values of HR, mean arterial pressure, and total peripheral resistance, (4) parameters representing controls acting on HR, mean arterial pressure, and total peripheral resistance, and (5) time constant parameters. A schematic representation of this model can be found in Fig. 7.6. This example shows that it is possible to use even complex mechanistic models and implement them in practice.

Also, much simpler, semi-mechanistic models can be used in the clinical assessment of HR. A practical example was shown by Chaubaud et al., who used clinical trial simulation approach to assess the best design for phase III trial in patients with angina pectoris (Chabaud et al. 2002). The authors used experimental data to develop a complex PK/PD model, which included the presence of active metabolites, partial competitive agonists, and hysteresis. The final model was then used to simulate a large number of hypothetical trials. HR changes were used as simulated end

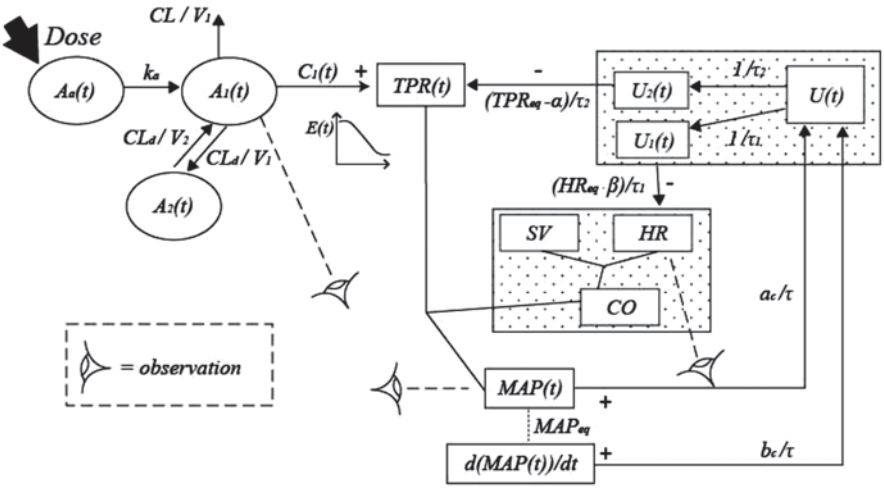

Fig. 7.6 A schematic representation of a circulatory system model. *Aa*, *A1*, *A2*, *HR*, *SV*, *CO*, *TPR* correspond to the depot, central, peripheral, HR, stroke volume, cardiac output, and total peripheral resistance, respectively. *MAP*, *HR*, *SV*, and *CO* represent mean aerial pressure, HR, stroke volume, and cardiac output, respectively. (Reprinted from Cheung et al. (2012), with permission from Elsevier)

point, and were then used to derive a binary clinical outcome—chest pain/attack of angina. The rationale behind this approach was an assumption that reduction in HR in patients with coronary artery disease will result in a decrease of angina pectoris risk. In addition, the model also included simulation of bradycardia as an unwanted adverse effect in the case when HR was below a certain threshold. The results from the simulations provided information about a minimum dose, below which no efficacy would be observed, as well as a maximum dose, above which large number of adverse effects would be present. In addition, it was also possible to recommend the most optimal dosing regimen, i.e., a single dose taken in the morning was found to be more effective when compared to twice-daily treatment. The authors suggested that this could be explained by variations of HR between day and night.

7.5 Pharmacometrics in the Assessment of BP

7.5.1 Preclinical Models for Predicting Human BP Liability

Modeling and simulation of BP is often closely connected with HR. As it was mentioned in the previous section, complex physiological models of circulatory system include BP as one of the simulated parameters. There are, however, examples where BP is the primary focus of the analysis; this is the case when changes

in BP can be linked to the underlying pharmacological mechanism. For example, it is known that the inhibition of calcium channels can produce a reduction of BP, therefore calcium agonists are used in the treatment of hypertension (Goa and Sorkin 1987; Liau 2005; Yasunari et al. 2005). In order to link this known mechanism of action to the clinical response, Shimada and coworkers performed PK/PD analysis of eight calcium channel blockers (CCB; Shimada et al. 1996). The authors successfully applied an effect compartment model to explain long lasting and slow response of several agents; they were also able to relate in vitro findings from calcium channel binding studies to the clinical effect observed in hypertensive patients. They found a significant correlation between in vitro dissociation constant and estimated in vivo EC_{50} values, which can be beneficial for future predictions (Shimada et al. 1996). Another translational study was presented by Snelder et al. (2011)—in this work, a mechanism-based PK/PD approach was used to establish a translational link between preclinical data and clinical response. It was demonstrated that changes in BP, which are regulated by the CV system can be effectively described by a mathematical model. The model included feedback between BP, cardiac output, and total peripheral resistance and was evaluated using marketed drugs with different mechanisms of action. The authors showed that their approach can be successfully used in predicting clinical response and simulation of new conditions (Snelder et al. 2011).

7.5.2 Application in Clinical Studies

In clinical studies, PK/PD modeling methods can be used to assess changes in BP, for example, in order to select the most optimal dosing regimen. Kleinbloesem et al. applied modeling techniques to demonstrate the effects of slow and rapid IV infusions of nifedipine (Kleinbloesem et al. 1987). It was shown that the rate of increase of the drug is related to the observed changes in BP; this phenomenon was also reported by others (for example, Nakaya et al. 1983; van Harten et al. 1988).

The importance of mathematical models for the assessment of BP during clinical development and regulatory submissions was also recently highlighted in a communication published by FDA which presented the impact of pharmacometrics on regulatory decisions (Lee et al. 2011). One example presented in this work included a calcium channel antagonist, which was developed for the management of BP. It was shown that the original clinical trial submitted to the FDA employed an aggressive dosing regimen which resulted in unwanted BP overshoot and its oscillations. After a regulatory enquiry into these undesired effects, a clinical trial simulation was performed, where a PK/PD model developed using experimental data from the actual clinical trial was used to explore alternative, less aggressive dosing regimens. As a result, it was possible to simulate an alternative dosing regimen, where the target BP reduction was achieved without the presence of unwanted side effects (Lee et al. 2011). Thanks to the computer simulation, it was therefore possible to address regulatory concerns without having to perform costly clinical trials.

Another example was provided by Bhattaram et al. in a similar publication from FDA (Bhattaram et al. 2005). In this case, the evaluated drug was reported to cause hypotension as a side effect. Initially the submission was not approved, partly due to the unwanted side effects on BP. Similar to the previous example, clinical trial simulations were performed in order to address the regulatory concerns. An alternative dosing regimen was explored and proved to minimize the risk of hypotension. In this case, the clinical trial simulation was followed by the actual study; however, the results from simulation were directly used to design the clinical study. The results from the study were in close agreement with the simulation and consequently, the drug was approved (Bhattaram et al. 2005).

7.6 Conclusions

This chapter provided multiple examples of the use of pharmacometric methods in the assessment of QT prolongation as well as other CV parameters, namely HR and BP. It is clear that modeling and simulation can be valuable in the assessment of CV safety during preclinical and clinical drug development as they can aid decision making (e.g., selection of compounds, go/no-go decisions), the design of clinical trials and ensure the safety of human volunteers. Additionally, they can also be beneficial in regulatory submissions—for example, the application of clinical trial simulations can result in approval of doses or dosing regimens that have not been directly assessed during the actual clinical trials. PK/PD modeling can also be valuable in providing confirmatory evidence of effectiveness or safety of tested drugs. In fact, FDA has reported recent increase in submissions where pharmacometric tools have been used and has highlighted their significance by noting that such methods were often crucial in the regulatory decision making (Bhattaram et al. 2005; Lee et al. 2011).

7.7 Summary

- CV safety is a major cause of drug attrition, with drug-induced prolongation of cardiac repolarization and proarrhythmic liabilities being the main reasons for labeling restrictions and drug withdrawals.
- The assessment of cardiac liabilities is crucial in the drug development process. It is important to detect potential liabilities early, ideally before drug is tested in humans for the first time to protect safety of human volunteers and to stop unsuccessful compounds early.
- Pharmacometric (model-based) tools can be beneficial in preclinical assessment, for example, through the use of (1) in silico APD models, (2) descriptive and semi-mechanistic PK/PD models of CV parameters (e.g., QT interval, HR, BP), or (3) mechanism-based models of QT prolongation (e.g., operational model of agonism).

- Preclinical models can be used to aid clinical trial design as well as extrapolating across different systems (e.g., from in vitro or in vivo to clinical) and hence predicting clinical outcomes. For example, it has been established that 10 ms change in QT_c in human is associated with drug exposures that give rise to:
  - ~5 % blockage of hERG in vitro assay
  - ~5 ms QT_c change in monkeys
  - ~2.5–8 ms QT_c change in dogs
- Pharmacometric tools can be used in clinical drug development, where they allow making predictions under new circumstances, for example, during new dosing regimen or in the alternative patient population (clinical trial simulations), as well as aid the design of clinical studies, or even predicting QT effects in real-life population (not-in-trial simulation).

References

Aarons L, Karlsson MO, Mentré F, Rombout F, Steimer JL, van Peer A COST B15 Experts (2001) Role of modelling and simulation in Phase I drug development. Eur J Pharm Sci 13:115–122

Abrahamsson C, Dota C, Skallefell B, Carlsson L, Halawani D, Frison L, Berggren A, Edvardsson N, Duker G (2011) DeltaT50—a new method to assess temporal ventricular repolarization variability. J Electrocardiol 44(4):477.e1–477.e9

Adesanya CO, Yousuf KA, Co C, Gaur S, Ahmed S, Pothoulakis A, Suryaprasad A, Gupta S (2008) Is wider worse? QRS duration predicts cardiac mortality in patients with right bundle branch block. Ann Noninvas Electrocardiol 13(2):165–170

Ando KHT, Kanno A, Ikeda H, Imaizumi M, Shimizu N, Sakamoto K, Shin-ichi Kitani S, Yamamoto Y, Hizume S, Nakai K, Kitayama T, Yamamoto K (2005) QT PRODACT: in vivo QT assay with a conscious monkey for assessment of the potential for drug-induced QT interval prolongation. J Pharmacol Sci 99:487–500

Anon (2005a) ICH S7B: the non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002841.pdf. Accessed 1 Feb 2013

Anon (2005b) International conference on harmonisation—ICH E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf. Accessed 1 Feb 2013

Atkins D (2007) Creating and synthesizing evidence with decision makers in mind: integrating evidence from clinical trials and other study designs. Med Care 45(10 Suppl 2):S16–S22

Batchvarov VN, Ghuran A, Smetana P, Hnatkova K, Harries M, Dilaveris P, Camm AJ, Malik M (2002) QT–RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. Am J Physiol Heart Circ Physiol 282(6):H2356–H2363

Bazan C, Barba DT, Hawkins T, Nguyen H, Anderson S, Vazquez-Hidalgo E, Lemus R, Moore J, Mitchell J, Martinez J, Moore D, Larsen J, Paolini P (2012) Contractility assessment in enzymatically isolated cardiomyocytes. Biophys Rev 4:231–243

Bazett HC (1920) The Q–T intervals, Heart 7: 353

Bellman R, Åström KJ (1970) On structural identifiability. Math Biosci 7(3–4):329–339

Benson AP, Aslanidi OV, Zhang H, Holden AV (2008) The canine virtual ventricular wall: a platform for dissecting pharmacological effects on propagation and arrhythmogenesis. Prog Biophys Mol Biol 96(1–3):187–208

Berger RD, Kasper EK, Baughman KL, Marban E, Calkins H, Tomaselli GF (1997) Beat-to-beat QT interval variability: novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. Circulation 96(5):1557–1565

Bhattaram V, Booth B, Ramchandani R, Beasley BN, Wang Y, Tandon V, Duan J, Baweja R, Marroum P, Uppoor R, Rahman N, Sahajwalla C, Powell JR, Mehta M, Gobburu JS (2005) Impact of pharmacometrics on drug approval and labeling decisions: a survey of 42 new drug applications. AAPS J 7(3):E503–E512

Black N (1996) Why we need observational studies to evaluate the effectiveness of health care. BMJ 312:1215–1218

Black JW, Leff P (1983) Operational models of pharmacological agonism. Proc R Soc Lond Ser B Biol Sci 220(1219):141–162

Bloomfield D, Krishna R (2008) Commentary on the clinical relevance of concentration/QTc relationships for new drug candidates. J Clin Pharmacol 48(1):6–8

Bonate P (2000) Rank power of metrics used to assess QTc interval prolongation by clinical trial simulation. J Clin Pharmacol 40(5):468–474

Bonate P, Russell T (1999) Assessment of QTc prolongation for non-cardiac-related drugs from a drug development perspective. J Clin Pharmacol 39(4):349–358

Boos DD, Hoffman D, Kringle R, Zhang J (2007) New confidence bounds for QT studies. Stat Med 26(20):3801–3817

Bottino D, Penland RC, Stamps A, Traebert M, Dumotier B, Georgieva A, Helmlinger G, Lett GS (2006) Preclinical cardiac safety assessment of pharmaceutical compounds using an integrated systems-based computer model of the heart. Prog Biophys Mol Biol 90(1–3):414–443

Bril A, Gout B, Bonhomme M, Landais L, Faivre J-F, Linee P, Poyser RH, Ruffolo Jr RR (1996) Combined potassium and calcium channel blocking activities as a basis for antiarrhythmic efficacy with low proarrhythmic risk: experimental profile of BRL-32872. J Pharmacol Exp Ther 276(2):637–646

Brown AM (2004) Drugs, hERG and sudden death. Cell Calcium 35(6):543–547

Buoen C, Bjerrum OJ, Thomsen MS (2005) How first-time-in-human studies are being performed: a survey of phase I dose-escalation trials in healthy volunteers published between 1995 and 2004. J Clin Pharmacol 45(10):1123–1136

Car BD (2006) Enabling technologies in reducing drug attrition due to safety failures. Am Drug Discov 1:53–56

Carlsson L, Abrahamsson C, Andersson B, Duker G, Schiller-Linhardt G (1993) Proarrhythmic effects of the class III agent almokalant: importance of infusion rate, QT dispersion, and early afterdepolarisations. Cardiovasc Res 27(12):2186–2193

Chabaud S, Girard P, Nony P, Boissel J (2002) Clinical trial simulation using therapeutic effect modeling: application to ivabradine efficacy in patients with angina pectoris. J Pharmacokinet Pharmacodyn 29(4):339–363

Chain ASY (2012) Mind the gap: predicting cardiovascular risk during drug development. Doctoral dissertation, Universiteit Leiden

Chain ASY, Krudys KM, Danhof M, Della Pasqua O (2011) Assessing the probability of drug-induced QTc-interval prolongation during clinical drug development. Clin Pharmacol Ther 90(6):867–875

Chain ASY, Sturkenboom MCJM, Danhof M, Pasqua OED (2012) Establishing in vitro to clinical correlations in the evaluation of cardiovascular safety pharmacology. Drug Discov Today Technol. http://dx.doi.org/10.1016/j.ddtec.2012.07.001. Accessed Oct 2012

Chan PL, Holford NHG (2001) Drug treatment effects on disease progression. Annu Rev Pharmacol Toxicol 41:625–659

Chen X, Cordes JS, Bradley JA, Sun Z, Zhou J (2006) Use of arterially perfused rabbit ventricular wedge in predicting arrhythmogenic potentials of drugs. J Pharmacol Toxicol Meth 54(3):261–272

Chen MX, Helliwell RM, Clare JJ (2009) In vitro profiling against ion channels beyond hERG as an early indicator of cardiac risk. Curr Opin Mol Ther 11:269–281
Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, Benjamin EJ, Ramachandran SV, Thomas JW (2009) Long-term outcomes in individuals with prolonged pr interval or first-degree atrioventricular block. JAMA 301:2571–2577
Cheung SYA, Majid O, Yates JWT, Aarons L (2012) Structural identifiability analysis and reparameterisation (parameter reduction) of a cardiovascular feedback model. Eur J Pharm Sci 46(4):259–271
Choi YH, Sun Y (2005) Modeling and simulation of baroreflex regulation of heart rate in response to respiratory fluctuations in arterial pressure. Key Eng Mater 227–279:28–32
Choy AMJ, Darbar D, Dell'Orto S Roden DM (1999) Exaggerated QT prolongation after cardioversion of atrial fibrillation. J Am Coll Cardiol 34(2):396–401
Christensen TF, Randløv J, Kristensen LE, Eldrup E, Hejlesen OK, Struijk JJ (2010) QT measurement and heart rate correction during hypoglycemia: is there a bias? Cardiol Res Prac 2010:961290
Clark M, Wiseman JS (2009) Fragment-based prediction of the clinical occurrence of long qt syndrome and torsade de pointes. J Chem Inform Model 49:2617–2626
Cobelli C, DiStefano JJ (1980) Parameter and structural identifiability concepts and ambiguities: a critical review and analysis. Am J Physiol Regul Integr Comp Physiol 239(1):7–24
Cooper CM, Skinner M, Antrobus B, Brown S, Lainee P, Valentin J (2011) Echocardiography: a sensitive, clinically translatable biomarker for cardiac contractility. J Pharmacol Toxicol Meth 64(1):29
Curran ME, Splawski I, Timothy KW, Vincen GM, Green ED, Keating MT (1995) A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 80(5):795–803
Danhof M, Alvan G, Dahl S, Kuhlmann J, Paintaud G (2005) Mechanism-based pharmacokinetic-pharmacodynamic modeling: a new classification of biomarkers. Pharm Res 22(9):1432–1437
Danhof M, de Lange ECM, Della Pasqua OE, Ploeger BA, Voskuyl RA (2008) Mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) modeling in translational drug research. Trend Pharmacol Sci 29(4):186–191
Darpö B (2007) Detection and reporting of drug-induced proarrhythmias: room for improvement. Europace 9(Suppl 4):iv23–iv36
Davies MR, Mistry HB, Hussein L, Pollard CE, Valentin J, Swinton J, Abi-Gerges N (2012) An in silico canine cardiac midmyocardial action potential duration model as a tool for early drug safety assessment. Am J Physiol Heart Circ Physiol 302(7):H1466–H1480
Dayneka NL, Garg V, Jusko WJ (1993) Comparison of four basic models of indirect pharmacodynamic responses. J Pharmacokinet Biopharm 21:457–478
de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE (1999) Prolonged QT interval predicts cardiac and all-cause mortality in the elderly: the Rotterdam study. Eur Heart J 20(4):278–284
Dekker JM, Schouten EG, Klootwijk P, Pool J, Kromhout D (1994) Association between QT interval and coronary heart disease in middle-aged and elderly men. The zutphen study. Circulation 90(2):779–785
Derendorf H, Meibohm B (1999) Modeling of pharmacokinetic/pharmacodynamic (PK/PD) relationships: concepts and perspectives. Pharmaceut Res 16:176–185
Detre E, Thomsen MB, Beekman JD, Petersen K, Vos MA (2005) Decreasing the infusion rate reduces the proarrhythmic risk of NS-7: confirming the relevance of short-term variability of repolarisation in predicting drug-induced torsades de pointes. Br J Pharmacol 145(3):397–404
DiMasi JA, Feldman L, Seckler A, Wilson A (2010) Trends in risks associated with new drug development: success rates for investigational drugs. Clin Pharmacol Ther 87(3):272–277
Dota C, Skallefell B, Edvardsson N, Fager G (2002) Computer-based analysis of dynamic qt changes: toward high precision and individual rate correction. Ann Noninvasive Electrocardiol 7(4):289–301

Dubois VFS, Chain A, van de Graaf P, Leishman D, Gallacher D, McMahon N, Danhof M, Pasqua OD (2011) Interspecies comparison of moxifloxacin induced QTc-interval prolongation. Population Approach Group in Europe (PAGE) Meeting. Abstr 2226

Dumouchel W (1999) Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am Stat 53(3):177–190

Erdemli G, Kim AM, Ju H, Springer C, Penland RC, Hoffmann PK (2012) Cardiac safety implications of hNav1.5 blockade and a framework for pre-clinical evaluation. Front Pharmacol 3:1–9

Ewart L, Aylott M, Deurinck M, Engwall M, Gallacher D, Geys H, Jarvis P, Ju H, Leishman D, Leong L, McMahon N, Mead A, Milliken P, Sherington J (2013) The animal model framework and the predictive power of the conscious telemetered dog for cardiovascular events in phase I clinical trials. Manuscript in preparation

Fink M, Noble PJ, Noble D (2009) Mathematical models in cardiac electrophysiology research—implications for the 3Rs, NC3Rs. 19:1–8. www.nc3rs.org.uk

Florian JA, Tornøe CW, Brundage R, Parekh A, Garnett CE (2011) Population pharmacokinetic and concentration–QTc models for moxifloxacin: pooled analysis of 20 thorough QT studies. J Clin Pharmacol 51(8):1152–1162

Florian J, Garnett CE, Nallani SC, Rappaport BA, Throckmorton DC (2012) A modeling and simulation approach to characterize methadone QT prolongation using pooled data from five clinical trials in MMT patients. Clin Pharmacol Ther 91(4):666–672

Food and Drug Administration (2004) Innovation or stagnation: challenge and opportunity on the critical path to new medical products. FDA Report, pp 1–38

Fox JJ, McHarg JL, Gilmour RF (2002) Ionic mechanism of electrical alternans. Am J Physiol Heart Circ Physiol 282(2):H516–H530

Francheteau P, Steimer JL, Merdjan H, Guerret M, Dubray C (1993) A mathematical model for dynamics of cardiovascular drug action: application to intravenous dihydropyridines in healthy volunteers. J Pharmacokinet Biopharmaceut 21:489–510

Fridericia LS (1920) Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. Acta Med Scand 53(1):469–486

Gabrielsson JL, Weiner DL (1999) Methodology for pharmacokinetic/pharmacodynamic data analysis. Pharm Sci Technol Today 2(6):244–252

Gabrielsson J, Weiner D (2000) Pharmacokinetic and pharmacodynamic data analysis: concepts & applications (3rd edn.). Apotekarsocieteten, Swedish Pharmaceutical Society, Sweden

Gabrielsson J, Green AR, van der Graaf PH (2010) Optimising in vivo pharmacology studies—practical PKPD considerations. J Pharmacol Toxicol Meth 61(2):146–156

Gabrielsson J, Fjellstrom O, Ulander J, Rowley M, van der Graaf PH (2011) Pharmacodynamic-pharmacokinetic integration as a guide to medicinal chemistry. Curr Top Med Chem 11:404–418

Garnett CE, Beasley N, Bhattaram VA, Jadhav PR, Madabushi R, Stockbridge N, Tornøe CW, Wang Y, Zhu H, Gobburu JV (2008) Concentration–QT relationships play a key role in the evaluation of proarrhythmic risk during regulatory review. J Clin Pharmacol 48(1):13–18

Gavaghan C, Arnby C, Blomberg N, Strandlund G, Boyer S (2007) Development, interpretation and temporal evaluation of a global QSAR of hERG electrophysiology screening data. J Comput-Aided Mol Des 21(4):189–206

Gintant G (2011) An evaluation of hERG current assay performance: translating preclinical safety studies to clinical QT prolongation. Pharmacol Ther 129(2):109–119

Gintant GA, Gallacher DJ, Pugsley MK (2011) The "overly-sensitive" heart: sodium channel block and QRS interval prolongation. Br J Pharmacol 164(2):254–259

Girard P (2005) Clinical trial simulation: a tool for understanding study failures and preventing them. Basic Clin Pharmacol Toxicol 96(3):228–234

Goa K, Sorkin E (1987) Nitrendipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of hypertension. Drugs 33(2):123–155

Gobburu J (2007) PKPD modeling can be used in lieu of the endpoint definition in ICH E14. Paper presented at: Drug Information Association, Food and Drug Administration, Heart Rhythm

Society Symposium QT Issues in Drug Development: the evolving science, practical issues, and regulatory implications. Washington, DC
Gobburu JV, Marroum PJ (2001) Utilisation of pharmacokinetic–pharmacodynamic modelling and simulation in regulatory decision-making. Clin Pharmacokinet 40:883–892
Grandi E, Pasqualini FS, Bers DM (2010) A novel computational model of the human ventricular action potential and Ca transient. J Mol Cell Cardiol 48(1):112–121
Groth AV (2008) Alternative parameterisations of saturable (Emax) models allowing for nesting of non-saturable models. Population Approach Group in Europe (PAGE) Meeting. Abstr 1371
Gwathmey JK, Tsaioun K, Hajjar RJ (2009) Cardionomics: a new integrative approach for screening cardiotoxicity of drug candidates. Exp Opin Drug Metabol Toxicol 5(6):647–660
Hanada E, Ohtani H, Kotaki H, Sawada Y, Sato H, Iga T (1999) Pharmacodynamic analysis of the electrocardiographic interaction between disopyramide and erythromycin in rats. J Pharma Sci 88(2):234–240
Hannan EL (2008) Randomized clinical trials and observational studies guidelines for assessing respective strengths and limitations. JACC: Cardiovasc Interv 1(3):211–217
Harmer AR, Abi-Gerges N, Easter A, Woods A, Lawrence CL, Small BG, Valentin J, Pollard CE (2008) Optimisation and validation of a medium-throughput electrophysiology-based hNav1.5 assay using IonWorks™. J Pharmacol Toxicol Meth 57(1):30–41
Harmer A, Valentin J, Pollard C (2011) On the relationship between block of the cardiac Na+ channel and drug-induced prolongation of the QRS complex. Br J Pharmacol 164(2):260–273
Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, Escande D, Franz M, Malik M, Moss A, Shah R (2000) The potential for QT prolongation and pro-arrhythmia by non-anti-arrhythmic drugs: clinical and regulatory implications: report on a policy conference of the european society of cardiology. Cardiovasc Res 47(2):219–233
Heath BM, Cui Y, Worton S, Lawton B, Ward G, Ballini E, Doe CPA, Ellis C, Patel BA, McMahon NC (2011) Translation of flecainide- and mexiletine-induced cardiac sodium channel inhibition and ventricular conduction slowing from nonclinical models to clinical. J Pharmacol Toxicol Meth 63(3):258–268
Hentschel S (2008) Modeling and simulation of blood pressure in rats. Master's degree Thesis: Faculty of Mathematics and Natural Sciences. University of Oslo
Hinterseer M, Thomsen MB, Beckmann B, Pfeufer A, Schimpf R, Wichmann H-, Steinbeck G, Vos MA, Kaab S (2008) Beat-to-beat variability of QT intervals is increased in patients with drug-induced long-QT syndrome: a case control pilot study. Eur Heart J 29(2):185–190
Holford NHG, Sheiner LB (1981) Understanding the dose-effect relationship: clinical application of pharmacokinetic–pharmacodynamic models. Clin Pharmacokinet 6:429–453
Holford N, Ma SC, Ploeger BA (2010) Clinical trial simulation: a review. Clin Pharmacol Ther 88(2):166–182
Hondeghem LM, Carlsson L, Duker G (2001) Instability and triangulation of the action potential predict serious proarrhythmia, but action potential duration prolongation is antiarrhythmic. Circulation 103(15):2004–2013
Howgate EM (2013) Cross-species scaling of cardiovascular safety pharmacology using PKPD modelling and simulation. A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Medical and Human Sciences
Hund TJ, Rudy Y (2004) Rate dependence and regulation of action potential and calcium transient in a canine cardiac ventricular cell model. Circulation 110(20):3168–3174
Inanobe A, Kamiya N, Murakami S, Fukunishi Y, Nakamura H, Kurachi Y (2008) In silico prediction of the chemical block of human ether-a-go-go-related gene (hERG) K+ current. J Physiol Sci 58:459–470
Isbister G, Friberg L, Duffull S (2006) Application of pharmacokinetic-pharmacodynamic modelling in management of QT abnormalities after citalopram overdose. Intensive Care Med 32(7):1060–1065
Jacobson I, Carlsson L, Duker G (2011) Beat-by-beat QT interval variability, but not QT prolongation per se, predicts drug-induced torsades de pointes in the anaesthetised methoxamine-sensitized rabbit. J Pharmacol Toxicol Meth 63(1):40–46

John AD, Fleisher LA (2006) Electrocardiography: the ECG. Anesthesiol Clin 24:697–715
Jonker DM, Kenna LA, Leishman D, Wallis R, Milligan PA, Jonsson EN (2005), A pharmacokinetic-pharmacodynamic model for the quantitative prediction of dofetilide clinical QT prolongation from human ether-a-go-go-related gene current inhibition data. Clin Pharmacol Ther 77:572–582
Jusko WJ, Ko HC (1994) Physiologic indirect response models characterize diverse types of pharmacodynamic effects. Clin Pharm Ther 56(4):406–419
Kappel F, Peer RO (1993) A mathematical model for fundamental regulation processes in the cardiovascular system. J Math Biol 31(6):611–631
Karlsson M, Beal S, Sheiner L (1995) Three new residual error models for population PK/PD analyses. J Pharmacokinet Biopharm 23(6):651–672
Kashani A, Barold SS (2005) Significance of QRS complex duration in patients with heart failure. J Am Coll Cardiol 46:2183–2192
Kleinbloesem CH, Brummelen PV, Danhof M, Faber H, Urquhart J, Breimer DD (1987) Rate of increase in the plasma concentration of nifedipine as a major determinant of its hemodynamic effects in humans. Clin Pharm Ther 41(1):26–30
Kola I, Landis J (2004) Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 8:711–716
Komatsu R, Honda M, Holzgrefe HH, Kubo J, Yamada Y, Isobe T, Kimura K, Itoh T, Tamaoki N, Tabo M (2010) Sensitivity of common marmosets to detect drug-induced QT interval prolongation: moxifloxacin case study. J Pharmacol Toxicol Meth 61(3):271–276
Lainee P (2009) Incidence of cardiac contractility issues in safety pharmacology studies: is the core battery sufficient? J Pharmacol Toxicol Meth 60(2):252
Lalonde RL, Kowalski KG, Hutmacher MM, Ewy W, Nichols DJ, Milligan PA, Corrigan BW, Lockwood PA, Marshall SA, Benincosa LJ, Tensfeldt TG, Parivar K, Amantea M, Glue P, Koide H, Miller R (2007) Model-based drug development. Clin Pharmacol Ther 82(1):21–32
Landewe R, van der Heijde D (2007) Primer: challenges in randomized and observational studies. Nat Clin Pract Rheum 3(11):661–666
Langdon G, Davis JD, McFadyen LM, Dewhurst M, Brunton NS, Rawal JK, van der Graaf PH, Benson N (2010) Translational pharmacokinetic?pharmacodynamic modelling; application to cardiovascular safety data for PF-00821385, a novel HIV agent. Br J Clin Pharmacol 69(4):336–345
Lau CP, Freedman AR, Fleming S, Malik M, Camm AJ, Ward DE (1988) Hysteresis of the ventricular paced QT interval in response to abrupt changes in pacing rate. Cardiovasc Res 22(1):67–72
Laverty H, Benson C, Cartwright E, Cross M, Garland C, Hammond T, Holloway C, McMahon N, Milligan J, Park B, Pirmohamed M, Pollard C, Radford J, Roome N, Sager P, Singh S, Suter T, Suter W, Trafford A, Volders P, Wallis R, Weaver R, York M, Valentin J (2011) How can we improve our understanding of cardiovascular safety liabilities to develop safer medicines? Br J Pharmacol 163(4):675–693
Le Coz F, Funck-Brentano C, Morell TM, Ghadanfar MM, Jaillon P (1995) Pharmacokinetic and pharmacodynamic modeling of the effects of oral and intravenous administrations of dofetilide on ventricular repolarization. Clin Pharmacol Ther 57:533–542
Lee JY, Garnett CE, Gobburu JVS, Bhattaram VA, Brar S, Earp JC, Jadhav PR, Krudys K, Lesko LJ, Li F, Liu J, Madabushi R, Marathe A, Mehrotra N, Tornoe C, Wang Y, Zhu H (2011) Impact of pharmacometric analyses on new drug approval and labelling decisions: a review of 198 submissions between 2000 and 2008. Clin Pharmacokinet 50:627–635
Liau C (2005) Barnidipine: a new calcium channel blocker for hypertension treatment. Exp Rev Cardiovasc Ther 3(2):207–213
Lunn DJ, Best N, Thomas A, Wakefield J, Spiegelhalter D (2002) Bayesian analysis of population PK/PD models: general concepts and software. J Pharmacokinet Pharmacodyn 29:271–307
Mahajan A, Shiferaw Y, Sato D, Baher A, Olcese R, Xie L, Yang M, Chen P, Restrepo JG, Karma A, Garfinkel A, Qu Z, Weiss JN (2008) A rabbit ventricular action potential model replicating cardiac dynamics at rapid heart rates. Biophys J 94(2):392–410

Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH (1993) Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA 270(21):2590–2597

Malik M (2004) Errors and misconceptions in ECG measurement used for the detection of drug induced QT interval prolongation. J Electrocardiol 37(Suppl 0):25–33

Markert M, Stubhan M, Mayer K, Trautmann T, Klumpp A, Schuler-Metz A, Schumacher K, Guth B (2009) Validation of the normal, freely moving gottingen minipig for pharmacological safety testing. J Pharmacol Toxicol Meth 60(1):79–87

Martin RL, McDermott JS, Salmen HJ, Palmatier J, Cox BF, Gintant GA (2004) The utility of hERG and repolarization assays in evaluating delayed cardiac repolarization: influence of multi-channel block. J Cardiovasc Pharmacol 43(3):369–379

Mason DT, Braunwald E, Covell JW, Sonnenblick EH, Ross J (1971) Assessment of cardiac contractility: the relation between the rate of pressure rise and ventricular pressure during isovolumic systole. Circulation 44(1):47–58

Mirams GR, Cui Y, Sher A, Fink M, Cooper J, Heath BM, McMahon NC, Gavaghan DJ, Noble D (2011) Simulation of multiple ion channel block provides improved early prediction of compounds' clinical torsadogenic risk. Cardiovasc Res 91(1):53–61

Molnar J, Zhang F, Weiss J, Ehlert FA, Rosenthal JE (1996) Diurnal pattern of QTc interval: how long is prolonged? Possible relation to circadian triggers of cardiovascular events. J Am Coll Cardiol 27(1):76–83

Montanez A, Ruskin JN, Hebert PR, Lamas GA, Hennekens CH (2004) Prolonged qtc interval and risks of total and cardiovascular mortality and sudden death in the general population: a review and qualitative overview of the prospective cohort studies. Arch Intern Med 164(9):943–948

Moors J, Philip K, Harmer A, Lainee P, Valentin JP (2007) Incidence of cardiac contractility issues in safety pharmacology studies: is the core battery sufficient. The Society of Safety Pharmacology annual meeting (abstract)

Moss AJ (1999) The QT interval and torsade de pointes. Drug Safety 21:5–10

Mould D, Frame B, Taylor T (2011) Modeling and simulation in the development of cardiovascular agents. In: Kimko HHC, Peck CC (eds). Springer, New York, pp 199–226

Nagy D, DeMeersman R, Gallagher D, Pietrobelli A, Zion AS, Daly D, Heymsfield SB (1997) QTc interval (cardiac repolarization): lengthening after meals. Obes Res 5:531–537

Nakaya H, Schwartz A, Millard RW (1983) Reflex chronotropic and inotropic effects of calcium channel-blocking agents in conscious dogs. Diltiazem, verapamil, and nifedipine compared. Circ Res 52(3):302–311

Netzer R, Ebneth A, Bischoff U, Pongs O (2001) Screening lead compounds for QT interval prolongation. Drug Discov Today 6(2):78–84

Norton K, Iacono G, Vezina M (2009) Assessment of the pharmacological effects of inotropic drugs on left ventricular pressure and contractility: an evaluation of the QA interval as an indirect indicator of cardiac inotropism. J Pharmacol Toxicol Meth 60(2):193–197

Nowinski K, Gadler F, Jensen-Urstad M, Bergfeldt L (2002) Transient proarrhythmic state following atrioventricular junction radiofrequency ablation: pathophysiologic mechanisms and recommendations for management. Am J Med 113(7):596–602

Ohtani H, Taninaka C, Hanada E, Kotaki H, Sato H, Sawada Y, Iga T (2000) Comparative pharmacodynamic analysis of Q–T interval prolongation induced by the macrolides clarithromycin, roxithromycin, and azithromycin in rats. Antimicrob Agents Chemother 44(10):2630–2637

Ollerstam A, Visser SA, Persson AH, Eklund G, Nilsson LB, Forsberg T, Wiklund SJ, Gabrielsson J, Duker G, Al-Saffar A (2006) Pharmacokinetic-pharmacodynamic modeling of drug-induced effect on the QT interval in conscious telemetered dogs. J Pharmacol Toxicol Meth 53(2):174–183

Ollerstam A, Persson AH, Visser SA, Fredriksson JM, Forsberg T, Nilsson LB, Eklund G, Wiklund SJ, Gabrielsson J, Duker G, Al-Saffar A (2007a) A novel approach to data processing of the QT interval response in the conscious telemetered beagle dog. J Pharmacol Toxicol Meth 55(1)35–48

Ollerstam A, Visser SA, Duker G, Forsberg T, Persson AH, Nilsson LB, Bjorkman JA, Gabrielsson J, Al-Saffar A (2007b) Comparison of the QT interval response during sinus and paced rhythm in conscious and anesthetized beagle dogs. J Pharmacol Toxicol Meth 56(2):131–144

Olson H, Betton G, Robinson D, Thomas K, Monro A, Kolaja G, Lilly P, Sanders J, Sipes G, Bracken W, Dorato M, Van Deun K, Smith P, Berger B, Heller A (2000) concordance of the toxicity of pharmaceuticals in humans and in animals. Regul Toxicol Pharmacol 32(1):56–67

Ovsyshcher IE, Barold SS (2004) Drug induced bradycardia. Pacing Clin Electrophysiol 27(8):1144–1147

Parkinson J, Visser SAG, Jarvis P, Pollard C, Valentin JP, Yates JWT, Ewart L (2013) Translational pharmacokinetic-pharmacodynamic modeling of QTc effects in dog and human. J Pharmacol Toxicol Meth 68:357–366

Patat AA (2000) Designing and interpreting the results of first-time-to-man studies. Dialogues Clin Neurosci 2:203–12

Pater C (2005) Methodological considerations in the design of trials for safety assessment of new drugs and chemical entities. Curr Control Trials Cardiovasc Med 6:1

Pillai G, Mentra F, Steimer J (2005) Non-linear mixed effects modeling: from methodology and software development to driving implementation in drug development science. J Pharmacokinet Pharmacodyn 32(2):161–183

Piotrovsky V (2005) Pharmacokinetic-pharmacodynamic modeling in the data analysis and interpretation of drug-induced QT/QTc prolongation. AAPS 24:609–624

Ploeger BA, van der Graaf PH, Danhof M (2009) Incorporating receptor theory in mechanism-based pharmacokinetic–pharmacodynamic (PK–PD) modeling. Drug Metab Pharmacokinet 1:3–15

Pollard CE, Valentin J, Hammond TG (2008) Strategies to reduce the risk of drug-induced QT interval prolongation: a pharmaceutical company perspective. Br J Pharmacol 154(7):1538–1543

Pollard C, Abi Gerges N, Bridgland-Taylor M, Easter A, Hammond T, Valentin J (2010) An introduction to QT interval prolongation and non-clinical approaches to assessing and reducing risk. Br J Pharmacol 159(1):12–21

Prospective Studies Collaboration (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one milion adults in 61 prospective studies. Lancet 360:1903–1913

Pueyo E, Smetana P, Caminal P, Bayes de Luna A, Malik M, Laguna P (2004) Characterization of QT interval adaptation to RR interval changes and its use as a risk-stratifier of arrhythmic mortality in amiodarone-treated survivors of acute myocardial infarction. IEEE Trans Biomed 51:1511–1520

Redfern WS, Carlsson L, Davis AS, Lynch WG, MacKenzie I, Palethorpe S, Siegl PKS, Strang I, Sullivan AT, Wallis R, Camm AJ, Hammond TG (2003) Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. Cardiovasc Res 58(1):32–45

Redfern WS, Ewart L, Hammond TG, Bialecki R, Kinter L, Lindgren S, Pollard CE, Roberts R, Rolf MG, Valentin JP (2010) Impact and frequency of different toxicities throughout the pharmaceutical life cycle. Toxicol 114:1081

Rock E, Finkle J, Fingert H, Booth B, Garnett C, Grant S, Justice R, Kovacs R, Kowey P, Rodriguez I, Sanhai W, Strnadova C, Targum S, Tsong Y, Uhl K, Stockbridge N (2009) Assessing proarrhythmic potential of drugs when optimal studies are infeasible. Am Heart J 157(5):827–836, 836.e1

Rohatagi S, Carrothers TJ, Kuwabara-Wagg J, Khariton T (2009) Is a thorough QTc study necessary? The role of modeling and simulation in evaluating the qtc prolongation potential of drugs. J Clin Pharmacol 49(11):1284–1296

Sällström B, Visser SG, Forsberg T, Peletier L, Ericson A, Gabrielsson J (2005) A pharmacodynamic turnover model capturing asymmetric circadian baselines of body temperature, heart rate and blood pressure in rats: challenges in terms of tolerance and animal-handling effects. J Pharmacokinet Pharmacodyn 32(5–6):835–859

Schmitt J, Ehrlich JR, Hohnloser SH (2008) New antiarrhythmic drugs for the treatment of atrial fibrillation. Herz Cardiovasc Dis 33:562–567
Schroeder K, Neagle B, Trezise DJ, Worley J (2003) IonWorks™ HT: a new high-throughput electrophysiology measurement platform. J Biomol Screen 8(1):50–64
Seger DL (2006) A critical reconsideration of the clinical effects and treatment recommendations for sodium channel blocking drug cardiotoxicity. Toxicol Rev 25:283–296
Shah RR (2002) The significance of QT interval in drug development. Br J Clin Pharmacol 54(2):188–202
Shah RR (2004) Drug-induced QT interval prolongation: regulatory perspectives and drug development. Ann Med 36:47–52
Shah RR (2005) Drug-induced QT interval prolongation—regulatory guidance and perspectives on hERG channel studies. In: The hERG cardiac potassium channel: structure, function and long QT syndrome. John Wiley & Sons Ltd, Chichester, pp 251–285
Shah RR, Hondeghem LM (2005) Refining detection of drug-induced proarrhythmia: QT interval and TRIaD. Heart Rhythm 2(7):758–772
Sheiner LB, Beal SL (1980) Evaluation of methods for estimating population pharmacokinetic parameters. I. Michaelis–Menten model: routine clinical pharmacokinetic data. J Pharmacokinet Biopharm 8:553–571
Sheiner LB, Beal SL (1982) Bayesian individualization of pharmacokinetics: simple implementation and comparison with non-Bayesian methods. J Pharm Sci 71:1344–1348
Shibao C, Grijalva CG, Raj SR, Biaggioni I, Griffin MR (2007) Orthostatic hypotension-related hospitalizations in the united states. Am J Med 120(11):975–980
Shimada S, Nakajima Y, Yamamoto K, Sawada Y, Iga T (1996) Comparative pharmacodynamics of eight calcium channel blocking agents in Japanese essential hypertensive patients. Biol Pharm Bull 19:430–437
Sibille M, Deigat N, Janin A, Kirkesseli S, Vital Durand D (1998) Adverse events in phase-I studies: a report in 1015 healthy volunteers. Eur J Clin Pharmacol 54(1):13–20
Snelder N, Ploeger B, Danhof M, Stanski D, Rigel D, Webb R, Feldman D, Luttringer O (2011) Quantitative understanding of drug effects on the interrelationship between mean arterial blood pressure, cardiac output and total peripheral resistance, Population Approach Group in Europe (PAGE) Meeting., Abstr 2058
Stevens JL, Baker TK (2009) The future of drug safety testing: expanding the view and narrowing the focus. Drug Discov Today 14(3–4):162–167
Sumner G, Salehian O, Yi Q, Healey J, Mathew J, Al-Merrii K, Al-Nemer K, Mann JFE, Dagenais G, Lonn E (2009) The prognostic significance of bundle branch block in high-risk chronic stable vascular disease patients: a report from the HOPE trial. J Cardiovasc Electrophysiol 20(7):781–787
Suter W (2006) Predictive value of in vitro safety studies. Curr Opin Chem Biol 10(4):362–366
Szilágyi S, Pollesello P, Levijoki J, Kaheinen P, Haikala H, Édes I, Papp Z (2004) The effects of levosimendan and OR-1896 on isolated hearts, myocyte-sized preparations and phosphodiesterase enzymes of the guinea pig. Eur J Pharmacol 486(1):67–74
Terrar D, Wilson C, Graham S, Bryant S, Heath B (2007) Comparison of guinea-pig ventricular myocytes and dog Purkinje fibres for in vitro assessment of drug-induced delayed repolarization. J Pharmacol Toxicol Meth 56(2):171–185
Tonkin A, Wing L (1992) Aging and susceptibility to drug-induced orthostatic hypotension. Clin Pharm Ther 52(3):277–285
Tornøe CW, Agersø H, Jonsson EN, Madsen H, Nielsen HA (2004) Non-linear mixed-effects pharmacokinetic/pharmacodynamic modelling in NLME using differential equations. Comput Meth Prog Biomed 76(1):31–40
Torp-Pedersen C, Møller M, Bloch-Thomsen P, Køber L, Sandøe E, Egstrup K, Agner E, Carlsen J, Videbæk J, Marchant B, Camm AJ (1999) Dofetilide in patients with congestive heart failure and left ventricular dysfunction. N Engl J Med 341(12):857–865
Tsong Y, Shen M, Zhong J, Zhang J (2008) Statistical issues of QT prolongation assessment based on linear concentration modeling. J Biopham Stat 18:564–584

Valentin J, Hoffmann P, De Clerck F, Hammond T, Hondeghem L (2004) Review of the predictive value of the Langendorff heart model (Screenit system) in assessing the proarrhythmic potential of drugs. J Pharmacol Toxicol Meth 49(3):171–181

Van de Vooren H, Gademan MGJ, Swenne CA, TenVoorde BJ, Schalij MJ, van der Wall EE (2007) Baroreflex sensitivity, blood pressure buffering, and resonance: what are the links? Computer simulation of healthy subjects and heart failure patients. J App Physiol 102(4):1348–1356

Van de Water A, Verheyen J, Xhonneux R, Reneman RS (1989) An improved method to correct the Q–T interval of the electrocardiogram for changes in heart rate. J Pharmacol Meth 22:207–217

Van der Graaf P, Gabrielsson J (2009) Pharmacokinetic–pharmacodynamic reasoning in drug discovery and early development. Future Med Chem 1:1371–1374

Van der Graaf PH, Watson KJ, Gorczyca WP, Umland J, Zhang Y, Chen X, Sun SZ, Fermini B, Holbrook M (2011) Towards a thorough preclinical QT (TpQT) study paradigm: pharmacokinetic-pharmacodynamic (PKPD) modelling of qtc effects of moxifloxacin in cynomolgus monkeys. Population Approach Group in Europe (PAGE) Meeting. Abstr IV–36

Van Harten J, van Brummelen P, Zeegers R, Danhof M, Breimer D (1988) The influence of infusion rate on the pharmacokinetics and haemodynamic effects of nisoldipine in man. Br J Clin Pharmacol 25(6):709–717

Varkevisser R, Wijers SC, van der Heyden MAG, Beekman JDM, Meine M, Vos MA (2012) Beat-to-beat variability of repolarization as a new biomarker for proarrhythmia in vivo. Heart Rhythm 9(10):1718–1726

Verhaeverbeke I, Mets T (1997) Drug-induced orthostatic hypotension in the elderly: avoiding its onset. Drug Saf Int J Med Toxicol Drug Exp 17:105–118

Visser SAG, Manolis E, Danhof M, Kerbusch T (2013) Modeling and simulation in early development. CPT Pharmacomet Sys Pharmacol. Accepted

Watson KJ, Gorczyca WP, Umland J, Zhang Y, Chen X, Sun SZ, Fermini B, Holbrook M, van der Graaf PH (2011) Pharmacokinetic–pharmacodynamic modelling of the effect of Moxifloxacin on QTc prolongation in telemetered cynomolgus monkeys. J Pharmacol Toxicol Meth 63(3):304–313

Wible BA, Kuryshev YA, Smith SS, Liu Z, Brown AM (2008) An ion channel library for drug discovery and safety screening on automated platforms. Assay Drug Dev Technol 6:765–780

Winslow RL, Rice J, Jafri S, Marbán E, O'Rourke B (1999) Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, II: model studies. Circ Res 84(5):571–586

Wu L, Shryock JC, Song Y, Li Y, Antzelevitch C, Belardinelli L 2004 Antiarrhythmic effects of ranolazine in a guinea pig in vitro model of long-QT syndrome. J Pharmacol Exp Ther 310(2):599–605

Yang W, Zilov A, Soewondo P, Bech O, Sekkal F, Home P (2010) Observational studies: going beyond the boundaries of randomized controlled trials. Diabetes Res Clin Pract 88(Suppl 1):S3–S9

Yano Y, Beal SL, Sheiner LB (2001) Evaluating pharmacokinetic/pharmacodynamic models using the posterior predictive check. J Pharmacokinet Pharmacodyn 28:171–192

Yasunari K, Maeda K, Nakamura M, Watanabe T, Yoshikawa J (2005) Benidipine, a long-acting calcium channel blocker, inhibits oxidative stress in polymorphonuclear cells in patients with essential hypertension. Hypertens Res 28(2):107–112

Zaręba W (2007) Drug induced QT prolongation. Cardiol J 14:1897–5593