# Chapter 13
# Graphical Data Exploration in QT Model Building and Cardiovascular Drug Safety

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**Abstract** Graphical data exploration of clinical trial results is an imperative step prior to any model-based analyses. Thorough understanding of the raw data and the biological and statistical significances will certainly increase the likelihood of constructing a useful model and evade excessive complex data representation and overfitting. In this work, we use graphical data exploration to assess the cardiovascular safety of Drug X by estimating the propensity for the drug to alter the duration of the QT interval. We also identify model building strategies and the potential models that may be tested incrementally. Insights gained from this exercise will improve the efficiency of the model building process, communicate a clear and simple representation for complex data, and provide a useful decision making instrument for the drug development program.

## 13.1 Introduction

Advancements in mathematical modeling and simulation in drug development can be attributed to much of what has been accomplished in engineering and applied physics. The concept of modeling a real life scenario through a computer prior to building a working prototype has been the cornerstone for much of the advancement in engineering. For example, in aerospace industry, a major part of the development of airplanes, missiles, and spacecrafts relies on aerodynamics 3D modeling (computational fluid dynamics, CFD) through solutions to Navier–Stokes equations, the basic governing equations, written down in the nineteenth century, for fluid mechanics (Girgis et al. 2006).

Unlike some of the physics-based models, biological modeling does not possess a unique set of differential equations to describe or link different drugs to the efficacy

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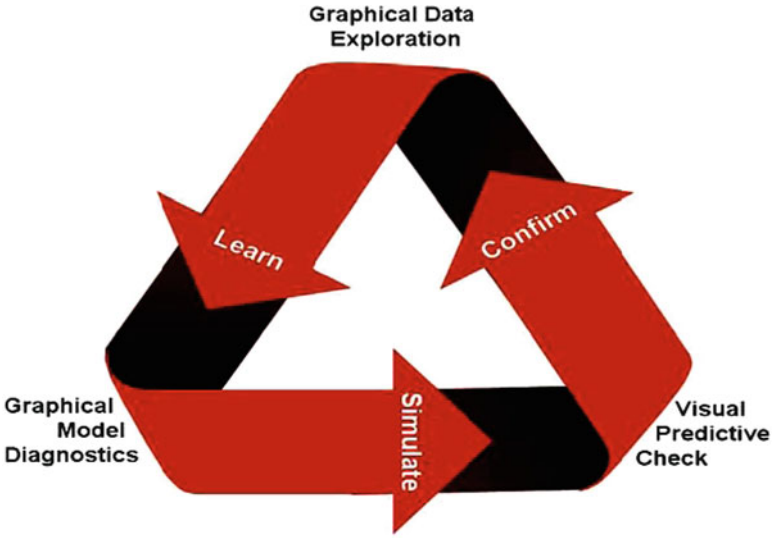


**Fig. 13.1** Graphical data presentation cycle in modeling

and safety endpoints. Consequently, pharmacometrics (drug and disease modeling) requires a high level of art and proficiency in combining experimental evidences, biological fundamentals, and scientific reasoning in order to analyze various observations. This is particularly true in modeling of biological phenomena since it usually has a high level of complexity, large variability, and numerous degrees of freedom. Therefore, graphical visualization and exploration is a crucial element of biological model building. It provides a powerful tool for scientific data exploration as well as for communicating quantitative information. In addition, it uncovers many quantitative and qualitative relationships and confounding information inherent in the data.

## 13.2 Graphical Data Exploration

Graphical data presentation is the backbone of pharmacometrics in all its different phases (data exploration, modeling building, model validation, and simulation scenarios) (Dykstra et al. 2010). These modeling phases (Fig. 13.1) mirror, in a local level, the Learn and Confirm Paradigm in drug development (Sheiner 1997). While graphical data presentation plays a different role in each of these phases, graphical data exploration is the first essential step, and perhaps the most important step, to better understand the data and identify potential models. It provides a meaningful visual view of multidimensional data, clues for the clinical significance of various variables and its trends, key relationships, and sanity check on the quality of the data and trial conduct. We provide one such case study where graphical data exploration was utilized to build a useful model.

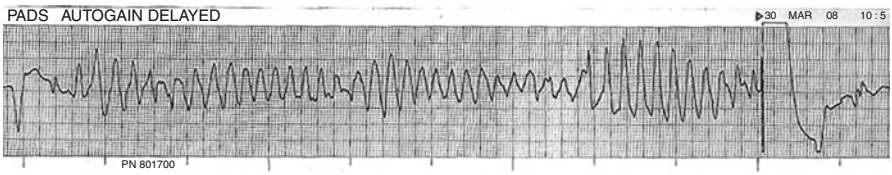


**Fig. 13.2** Lead II ECG of TdP and cardioverter-defibrillator shock at end of the strip

## 13.3 Objective

Detecting drug-induced effects on cardiac repolarization, measured by the length of the QT interval on an ECG, is a closely monitored safety element in drug development. Drug-induced prolongation of the QT interval has been linked to cardiotoxic risk and the occurrence of torsades de pointes (TdP), a polymorphous ventricular life-threatening arrhythmia. An ECG of a patient with TdP is shown in Fig. 13.2. Every compound is required to demonstrate absence of QT prolongation beyond a predefined safety margin. A regulatory guidance document (U.S. Department of Health and Human Services 2005) provides justification for a thorough QT (TQT) study and suggests a level of rigor required for conducting such a trial to support a regulatory submission in the US. A TQT study is designed to determine the drug cardiovascular safety by detecting the magnitude of the QT changes caused by the drug. A mean time-matched QT prolongation of 5 ms, with the upper bound of the 95% one-sided confidence interval excluding 10 ms, is considered a threshold level by regulatory bodies (U.S. Department of Health and Human Services 2005).

QT intervals can be influenced by a number of factors, such as heart rate, administration of placebo, gender, and natural circadian rhythm (Piotrovsky 2005; Girgis et al. 2007). The objective of this work is to provide an example in utilizing graphical visualization to understand and help the model building in pharmacokinetics and pharmacodynamics (PK and PD); namely, the change of the individual QT interval following administration of Drug X, a noncardiac drug, or Moxifloxacin (PK/PD relationship) in connection with different covariate effects, such as gender, placebo effect, RR interval (RR = 60/HR, HR is the heart rate), and circadian rhythm. This approach is valuable for future nonlinear mixed-effects population modeling development, if needed. A schematic presentation of the durations and intervals of a typical ECG is shown in Fig. 13.3.

## 13.4 Data Used

To ensure a thorough assessment of the potential electrocardiographic effects of Drug X (half-life of 10–15 h), precise measurements of ECGs in healthy adults, with particular attention to the QT interval duration, were collected when Drug X is administered twice a day at therapeutic and supratherapeutic doses (4 times the therapeutic dose).

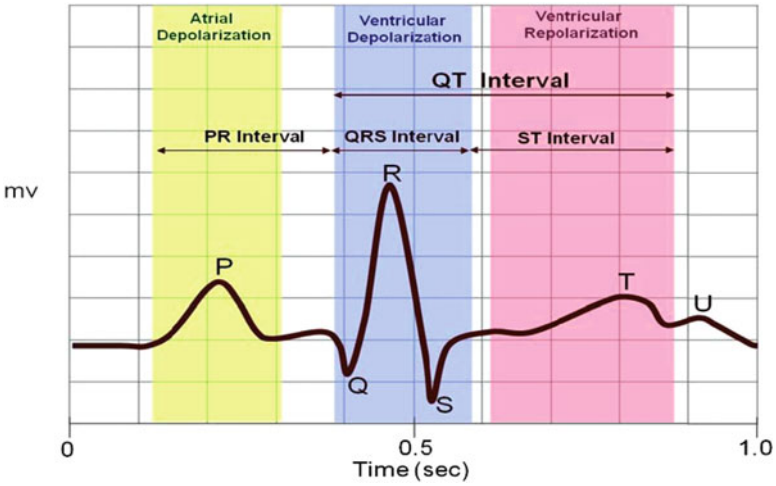


**Fig. 13.3** Schematic for the ECG trace and the QT interval

This TQT study is a double-blind, randomized, placebo- and positive-controlled, 3-way crossover study in 40 healthy subjects (22 M, 18 F, age 30 ± 8 years, BMI 24 ± 2) between 18 and 50 years of age. The study consisted of 3 phases: a screening phase of up to 21 days, a double-blind treatment phase with three 11-day (days −2 to 9) treatment periods, and end of study/early withdrawal assessments. During the double-blind phase, each treatment period was separated by a washout period of at least 10 days, but not more than 14 days, between the last dose in a treatment period and the first dose in the next treatment period. A placebo control was used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. Subjects received all 3 treatments, one during each of the 3 treatment periods. Moxifloxacin (400 mg single oral dose) was used as a positive control for evaluation of the sensitivity to detect changes in the QT interval.

The study is also designed to evaluate the steady-state of the Drug X effect (Day 7), and the assay sensitivity (Day 8, moxifloxacin). On Days −1, 7, and 8 in each treatment period, 13 h continuous 12-lead ECG recordings are obtained for each subject. Each of these continuous collection periods initiated 30 min before the time of the morning dose (including days when no drug is given). On Days 7 and 8 in each treatment period, blood samples are collected predose and within 5 min after each time point to measure the plasma concentrations of Drug X and moxifloxacin (Table 13.1).

Subject time point measurements, for each treatment period, are obtained at the same time point on the baseline day (Day −1). The dataset used in this analysis contains 2,350 time points for baseline, 738 time points for placebo (Day 8 placebo observations are not included due to residual drug effect), 557 time points for Moxifloxacin, and 1,318 time points for Drug X. The clock time data, 7 A.M. to 9 P.M., was imputed from the time relative to dosing and dosing window, where the

**Table 13.1** Overview of study design

| Arm | Period 1 | | Period 2 | | Period 3 |
|---|---|---|---|---|---|
| 1 | D(−1): Baseline | Washout 10–14 days | D(−1): Baseline | Washout 10–14 days | D(−1): Baseline |
| | D1–7: Placebo | | D1–7: Low dose Drug X | | D1–7: High dose Drug X |
| | D8: Moxifloxacin | | D8: Placebo | | D8: Placebo |
| 2 | D(−1): Baseline | | D(−1): Baseline | | D(−1): Baseline |
| | D1–7: Placebo | | D1–7: High dose Drug X | | D1–7: Low dose Drug X |
| | D8: Moxifloxacin | | D8: Placebo | | D8: Placebo |
| 3 | D(−1): Baseline | | D(−1): Baseline | | D(−1): Baseline |
| | D1–7: Low dose Drug X | | D1–7: High dose Drug X | | D1–7: Placebo |
| | D8: Placebo | | D8: Placebo | | D8: Moxifloxacin |
| 4 | D(−1): Baseline | | D(−1): Baseline | | D(−1): Baseline |
| | D1–7: Low dose Drug X | | D1–7: Placebo | | D1–7: High dose Drug X |
| | D8: Placebo | | D8: Moxifloxacin | | D8: Placebo |
| 5 | D(−1): Baseline | | D(−1): Baseline | | D(−1): Baseline |
| | D1–7: High dose Drug X | | D1–7: Placebo | | D1–7: Low dose Drug X |
| | D8: Placebo | | D8: Moxifloxacin | | D8: Placebo |
| 6 | D(−1): Baseline | | D(−1): Baseline | | D(−1): Baseline |
| | D1–7: High dose Drug X | | D1–7: Low dose Drug X | | D1–7: Placebo |
| | D8: Placebo | | D8: Placebo | | D8: Moxifloxacin |

morning dose was taken between 8:00 A.M. and 10:00 A.M., and the corresponding evening doses, which were taken 12 h later.

## 13.5 Data Overview

Data set preparation is performed using S-PLUS™ 8.0 for Windows (Tibco Software Inc, Palo Alto, CA). Data exploration and data visualization are carried out by Prism™ 5.01 (GraphPad Software, Inc, La Jolla, CA). There are many factors that make the data highly variable across population. Analysis of such data is complex. A boxplot of the data stratified by the treatment group (Fig. 13.4) is presented to give first insights about the data quality, variability, and trend. The horizontal line in the interior of the box is located at the median of the data. The height of the box is equal to the interquartile distance, or IQD, which is the difference between the 3$^{rd}$ and 1$^{st}$ quartiles of the data. Approximately 95 percent of the data fall inside the whiskers (the lines extending from the top to the bottom of the box). The outliers are presented in a staggered format. Compared to the median of the placebo arm (407 ms), Drug X low dose shows a QT shortening of 4 ms, while the high dose shows a shortening of 10 ms. Additionally, the positive control (Moxifloxacin) has

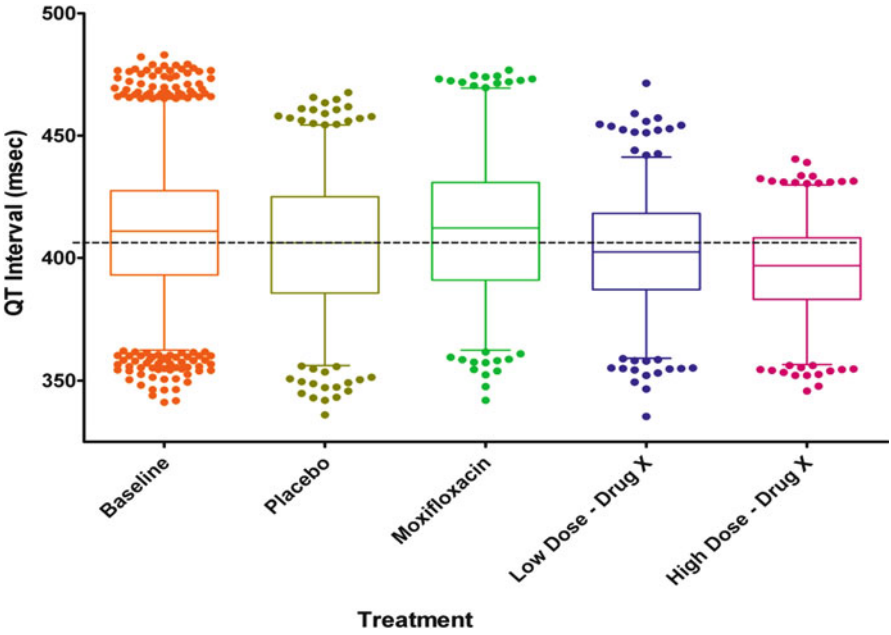


**Fig. 13.4** Overview of QT data stratified by treatment group

a QT prolongation effect of 6 ms. This naive estimate agrees with previous results from literature and shows a preliminary evidence to establish the ability of the study to detect the effect of the study drug.

The lowess smoother curve is one of many useful exploratory graphical tools. It follows the trend of the data, using an algorithm developed by Chambers et al. (1983) and implemented by Prism™. It is a robust, local smooth regression of scatterplot data using weighted linear least squares without computationally expensive methods. In this work, coarse lowess curves, with 5 points smoothing window, are used. Figure 13.5 shows a temporal overview of all the data stratified by the treatment group. Significant circadian rhythm variation can be seen with a similar pattern along all treatment groups. Such an effect is important to be taken into consideration in the modeling since it may interfere with the drug effect.

## 13.6 Baseline Data

Accurate modeling and understanding of baseline QT is the initial step in evaluating effects of drugs. Changes to this baseline model after the administration of the investigational drug will reflect the effect on the QT interval. Data variability has mixed-effects (random and fixed) components. Random (unexplained) variability is difficult to relate to controllable variables. However, it may be identified on different levels; namely, intra-individual variability (IIV, i.e., measurement error),

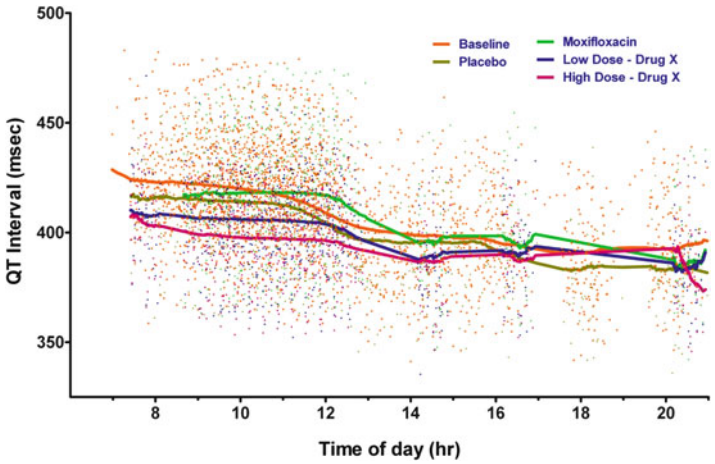


**Fig. 13.5** Temporal overview of QT data stratified by treatment group

between-individual variability (BIV, i.e., individual difference), and between-occasion variability (BOV, i.e., different day). On the other hand, fixed effects (variability) are associated with changes in known covariates (variables). Among the most important fixed effects on QT, besides the drug effect, are placebo effect, heart rate (presented with RR interval), gender effect, and time effect (circadian rhythm) (Dykstra et al. 2010).

### *13.6.1 Placebo Effect*

Since, in some cases, placebo effect (response) is substantial and can vary substantially, understanding and correcting this effect is important to qualify the drug effect. Figure 13.6 shows a column scatter plot of the baseline and placebo data where all the individual data points are shown and stacked into different columns according to their values. The scatter plot shows a thorough view of the data density, its distribution, median, and the IQD range. Figure 13.7 shows the placebo effect across time of day, and a slight shortening of the QT interval by approximately 3 ms, during placebo treatment compared to baseline. Both baseline and placebo curves demonstrate similar daily temporal variation, consequence of a circadian rhythm, suggesting an additive placebo correlation model.

### *13.6.2 RR Effect*

As shown in Figs. 13.8 and 13.9, the QT interval is highly correlated with heart rate (or RR interval). The most conventionally used correction method for the heart rate

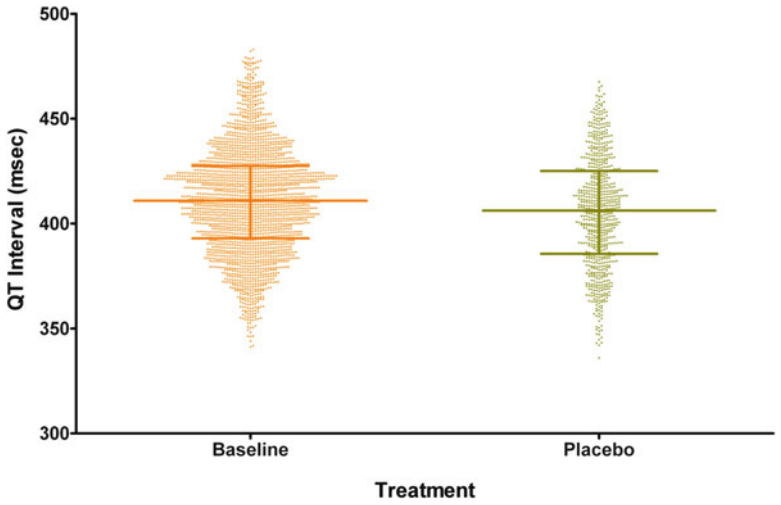


**Fig. 13.6** Column scatter plot of baseline and placebo QT interval data

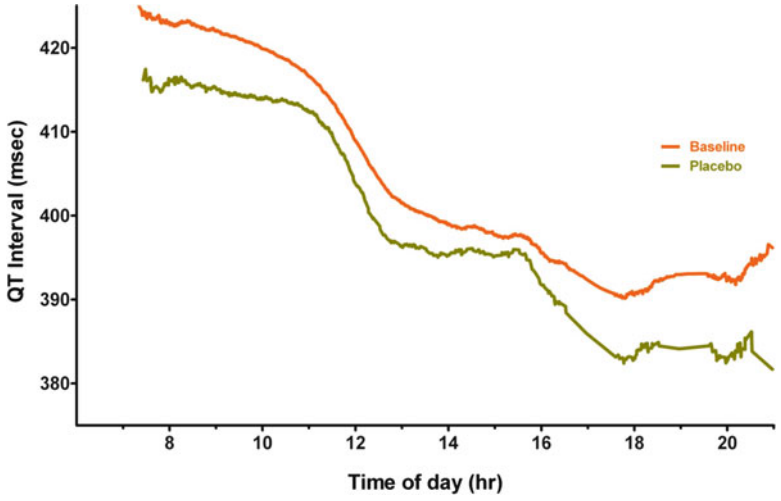


**Fig. 13.7** Lowess smoother curves of the daily temporal variation of the baseline and placebo QT interval data

effect on the QT interval has a general power formula of $QTc = QT/RR^n$, where the RR interval is in seconds. The value of the exponent ($n$) may be estimated based on the pool or subject-specific data. For the fixed correction method, $n = 0.5$ (Bazett's correction, QTcB) or $n = 0.333$ (Fridericia's correction, QTcF). Figure 13.10 shows that the power formula provides an adequate correction for changes in RR with a baseline RR-corrected QT (QTc) of 417 ms and $n$ of 0.375 (using naive fitting with no covariate effect).

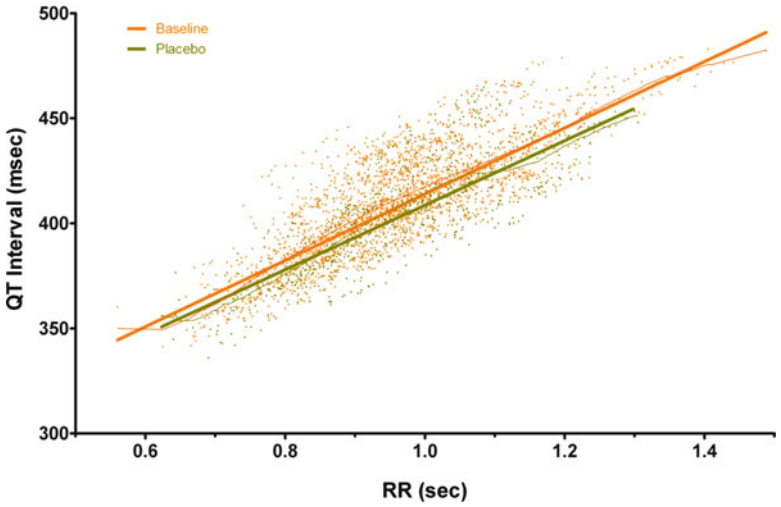


**Fig. 13.8** Linear fit and lowess smoother curves of QT interval vs. RR interval for baseline and placebo data

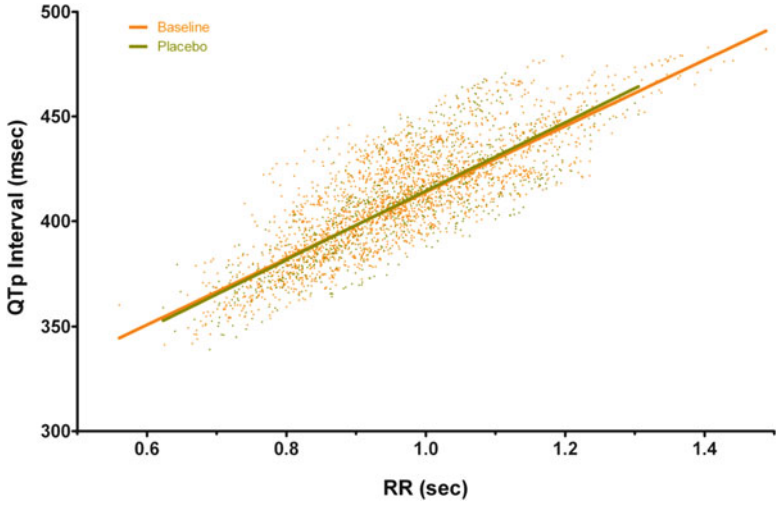


**Fig. 13.9** Linear fit of placebo-corrected QT (QTp) compared to the baseline QT

### *13.6.3 Gender Effect*

One of the important demographic factors that impacts the QT interval is the subject's gender. Females usually exhibit a longer QT interval than males. Figure 13.11 illustrates the gender effect on the baseline QT. As shown, females consistently exhibit a significantly longer QT interval than males by about 15 ms, which implies

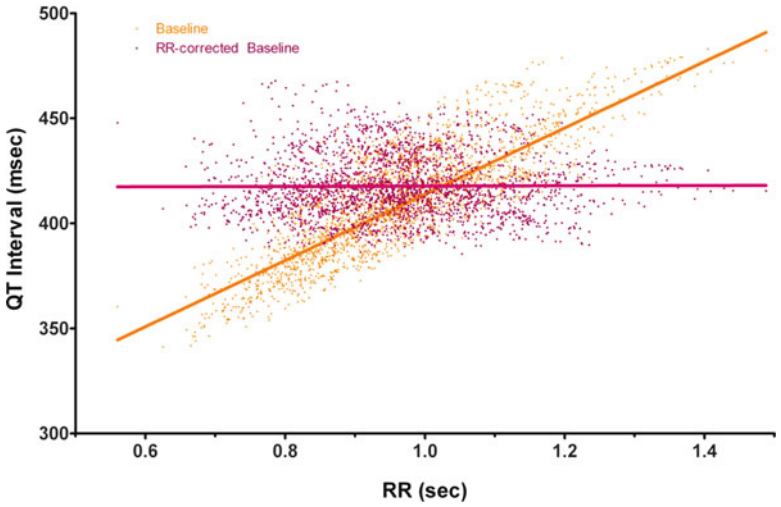


**Fig. 13.10** RR-corrected baseline QT (QTc) compared to the uncorrected QT

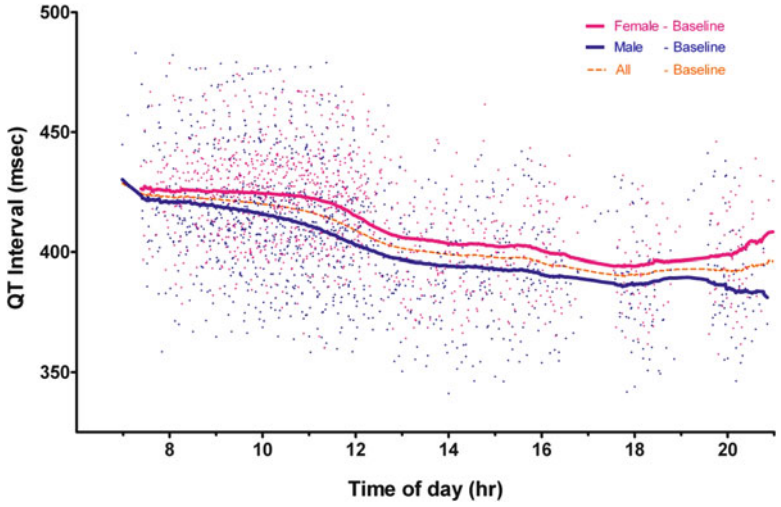


**Fig. 13.11** Temporal distribution of baseline QT and QTc intervals for males and females

that either an additive or a multiplicative simple gender effect model will be adequate to capture this difference.

It is intriguing to gain significant insights using a simple graphical presentation of the pooled data. Based on the above discussion, the effects of heart rate, placebo, and gender could be adequately captured by simple expressions, as follows:

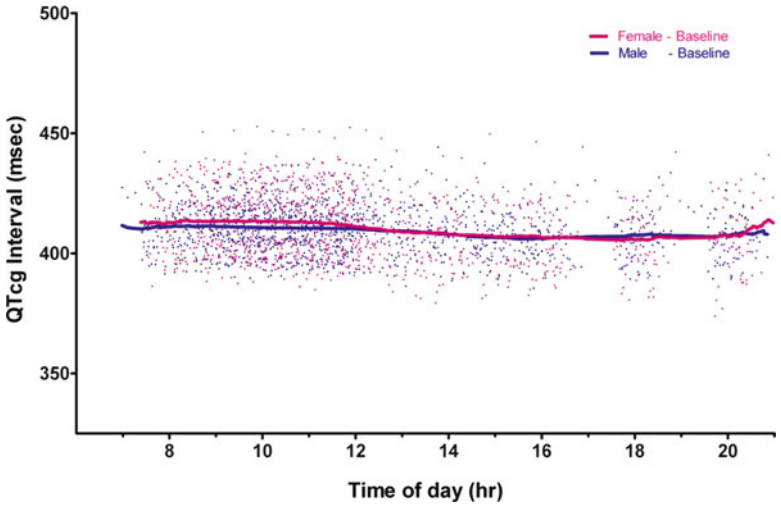


**Fig. 13.12** Temporal view of QTcg interval for the baseline data by gender

Corrected QT for heart rate (QTc):

$$QT_c = QT / RR^n$$

Corrected QT for heart rate and gender effect (QTcg):

$$QTcg = QT / RR^n + \Delta Gen$$

Corrected QT for heart rate, placebo effect, and gender (QTcgp):

$$QTcpg = QT / RR^n + \Delta Gen + \Delta Pla$$

where, as discussed earlier, $n = 0.375$, $\Delta Gen = -15$ ms, and $\Delta Pla = +3$ ms. Figure 13.12 shows the calculated QTcg of baseline data for males and females. Compared to Fig. 13.11, the used fixed-effects model for QTcg significantly reduces and explains the baseline data variability by deducing the relationships with heart rate and gender covariates. Similarly, Fig. 13.13 shows the calculated QTcg and QTcgp of baseline and placebo data. Figure 13.14, a box and whisker plot, contrasts the raw and corrected baseline and placebo data.

### *13.6.4 Circadian Rhythm*

Circadian Rhythm is an internally driven, 24 h cycle biological clock. It is influenced by a number of effects, such as light–dark cycles, timing of food

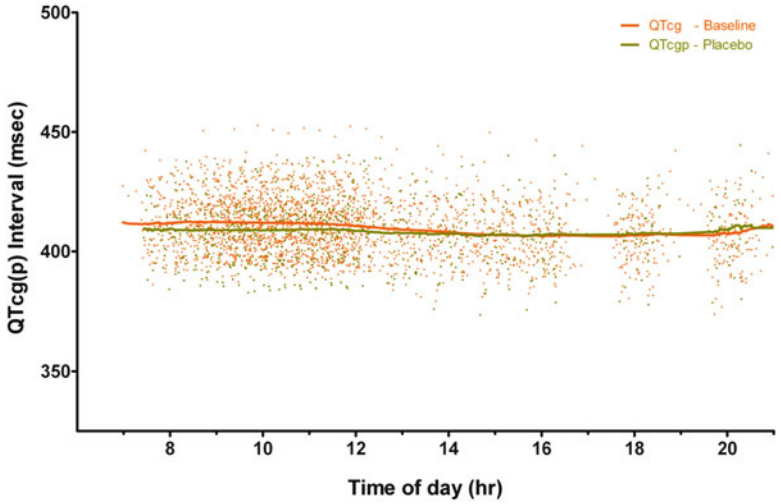


**Fig. 13.13** Temporal view of QTcg(p) interval of the baseline and placebo treatment groups

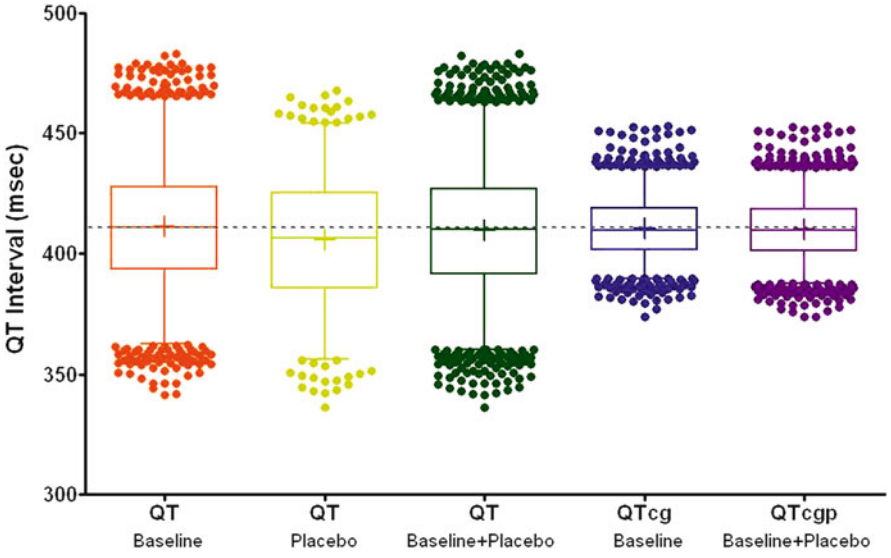


**Fig. 13.14** Uncorrected and corrected QT interval of the baseline and placebo treatment groups

intake, and temperature. Therefore, one key fixed effect on QT is day time. The impact of the day time on QT is critical to be quantified in order to be able to draw a conclusion about drug effects. The corrected QT (QTcg and QTcgp) interval for pooled baseline and placebo data show a circadian variation of about 5 ms, peaking during morning hours (Fig. 13.15). The same pattern is observed at the

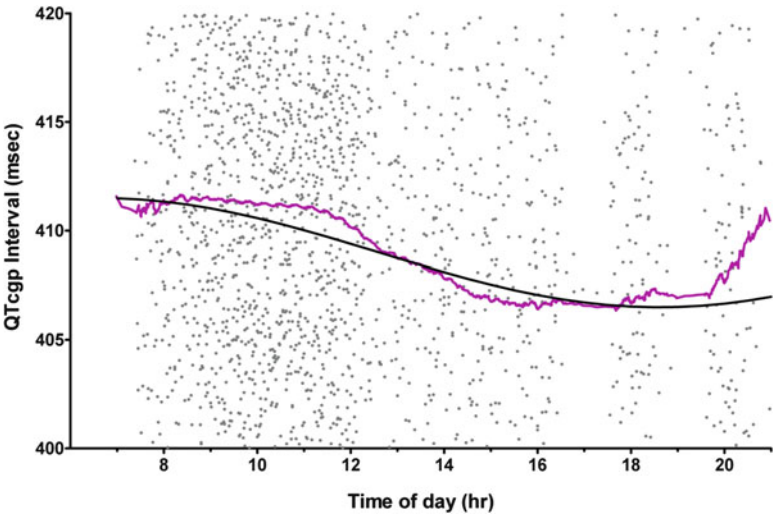


**Fig. 13.15** Circadian rhythm trend line and cosine model for baseline and placebo pooled data

individual level (Girgis et al. 2007). For our purpose, a simple, 24 h harmonic cosine function

$$( A \cos(2\pi / 24(\text{Time} - \varphi)) )$$

is used to describe the circadian rhythm (diurnal fluctuations) effect, where $A$ is the amplitude parameter and $\varphi$ is the phase shift parameter. The parameter values are estimated by trial and error. The corrected QT for heart rate, placebo effect, gender, and circadian rhythm (QTcgpt) can then be expressed as follows:

$$\text{QTcgpt} = \text{QT} / \text{RR}^n + \Delta\text{Gen} + \Delta\text{Pla} + A \cos(2\pi / 24(\text{Time} - \varphi))$$

where $\Delta\text{Gen} = -15$ ms, $\Delta\text{Pla} = +3$ ms, $n = 0.375$, $A = 2.5$ ms, and $\varphi = 6.6$ h.

## 13.7 Drug Effect

### *13.7.1 Moxifloxacin Drug Effect*

Since the effect of moxifloxacin is well known, it was administrated and included in this study as a positive (active) control. Active control is necessary in order to show the validity of the trial conduct and to help assess any false QT liability. Using pooled data from 20 studies, Florian et al. (2011) described the moxifloxacin concentration–QTc relationship by a linear model with a mean slope of 3.1 (2.8–3.3)

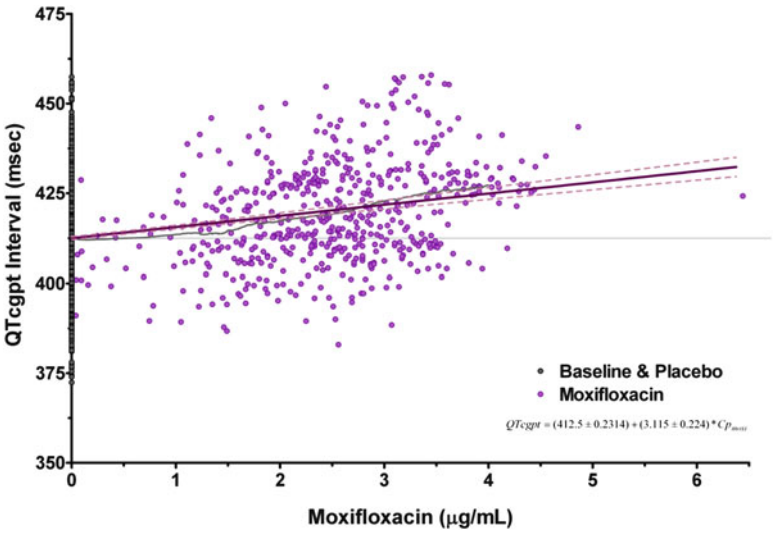


**Fig. 13.16** Lowess smoother and linear fit (with 95% confidence interval) of QTcgpt interval vs. moxifloxacin concentration

milliseconds per µg/mL of moxifloxacin. For the current data, corrected baseline and placebo data were combined with corrected moxifloxacin (QTcgpt) data to present the zero moxifloxacin concentration effect (model intercept). As shown in Fig. 13.16, the predicted mean slope is 3.12 ms per µg/mL. Thus, the result validates and gives credibility for the graphical data exploration process and technique used.

### *13.7.2 Drug X Effect*

Figure 13.17 shows that as the Drug X concentration increases, the QT interval decreases. The linear fit predicts a QT shortening with a negative slope of −0.45 ms per µg/mL. While a prolonged QT interval is linked to the risk for life-threatening events, little is known about shortened QT intervals. Nevertheless, QT interval shortening has previously been associated with sudden death (Gaita et al. 2003).

## 13.8 Modeling Results

Based on the above rationale, Girgis et al. (2007) used a hierarchical Bayesian approach to establish a population model for baseline and placebo data. The final structure model was similar to the current proposed corrections for the QT interval (QTcgpt). Figure 13.18 illustrates an example of the model fit for different subjects.

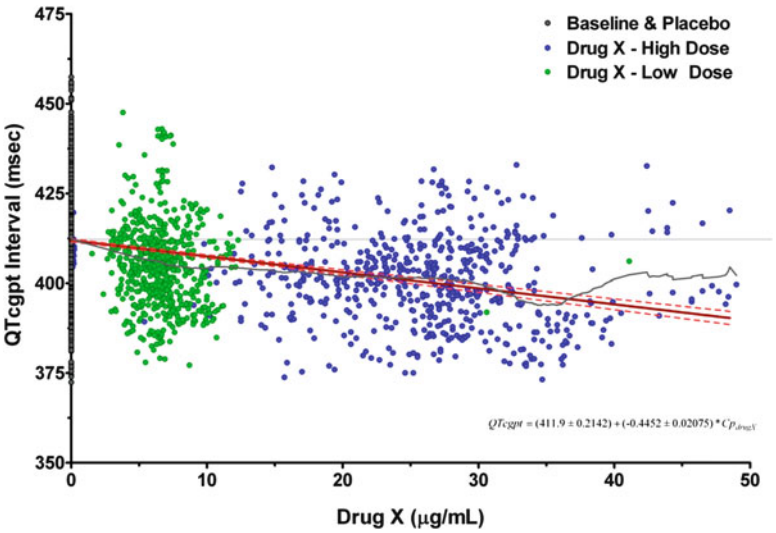


**Fig. 13.17** Lowess smoother and linear fit (with 95% confidence interval) of QTcgpt interval vs. Drug X concentration

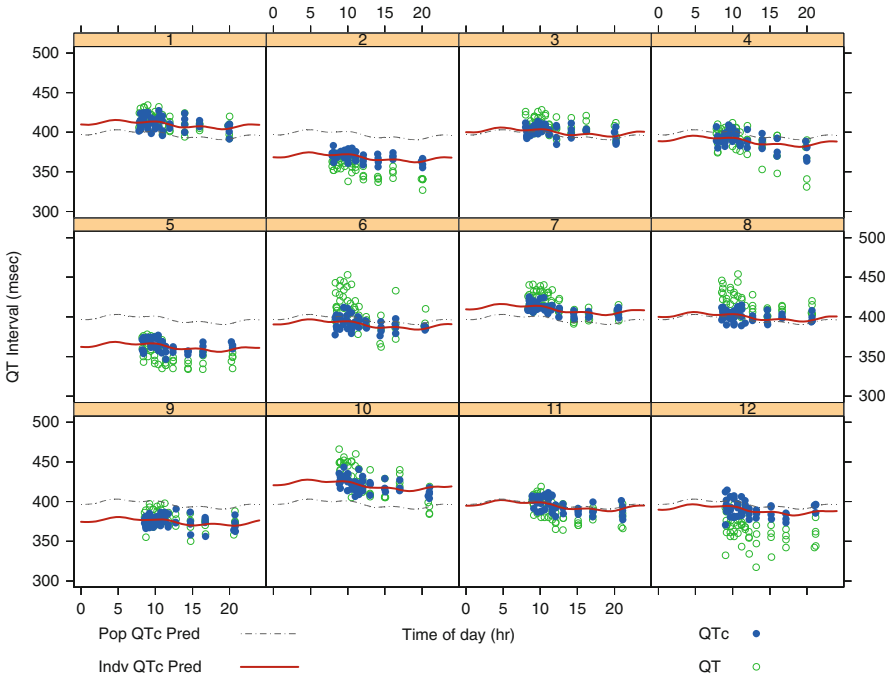


**Fig. 13.18** Example of model fit for individual QT baseline data

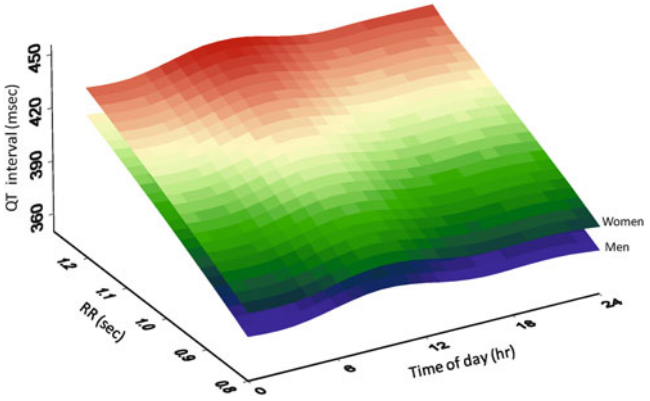


**Fig. 13.19** Three dimensional plot of the modeled QT interval

It shows the time course of the measured QT (open green circles), individually corrected QT, (QTic = QT/RRni, filled blue circles), QTic individual predictions (red solid line), and QTic population predictions for a typical male (dashed gray line) for 12 subjects. As shown, QT measurements are well described by the final model. Figure 13.19 shows the 3-dimensional plot of the QT Interval and its relationship to heart rate, gender, and circadian rhythm based on the Girgis et al. baseline model (Girgis et al. 2007).

## 13.9 Summary

Data from a thorough QT study were used as an example to illustrate the benefits of graphical data exploration to assess the cardiovascular safety of a Drug X. As shown, graphical data exploration of clinical trial results greatly helps to better understand the data and increase the likelihood of constructing a useful model. It also could improve the efficiency of the model building process and provide a useful decision making instrument for the drug development program.

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## References

Chambers JM, Cleveland WS, Tukey PA, Kleiner B (1983) Graphical methods for data analysis. Wadsworth and Brooks, Pacific Grove

Dykstra K, Pugh R, Krause A (2010) Visualization concepts to enhance quantitative decision making in drug development. J Clin Pharmacol 50:130S–139S

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

Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, Grossi S, Richiardi E, Borggrefe M (2003) Short QT syndrome: a familial cause of sudden death. Circulation 108:965–970

Girgis IG, Shneider MN, Macheret SO, Brown GL, Miles RB (2006) Creation of steering moments in supersonic flow by off-axis plasma heat addition. J Spacecraft Rockets 43(3):May–June

Girgis IG, Schaible T, Nandy P, De Ridder F, Mathers J, Mohanty S (2007) Parallel Bayesian methodology for population analysis. PAGE 16:Abstr 1105. www.page-meeting.org/?abstract=1105

Guidance for industry: e14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. U.S. Department of Health and Human Services, Food and Drug Administration, Oct 2005

Piotrovsky V (2005) Pharmacokinetic-pharmacodynamic modeling in the data analysis and interpretation of drug-induced QT/QTc prolongation. AAPS J 7(3):E609–E624

Sheiner LB (1997) Learning versus confirming in clinical drug development. Clin Pharmacol Ther 61:275–291