Statistical analysis of ECG signals with focus on QT

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Summary

In the process of drug development it is obligated, in many cases, to perform a study of potential prolongation of a particular interval of the electrocardiogram (ECG), the QT interval. The interval has gained clinical importance since a prolongation of it has been shown to induce potentially fatal cardiac arrhythmias. Because of correlation with heart rate, the length of the interval recorded at different heart rates can not be compared directly, a correction for heart rate is needed first. A number of formulas have been suggested for this purpose. Differences of opinion however rises regarding the most useful formula. In the thesis, data from a study designed to investigate potential QT prolongations from a certain drug, will be used to analyse the relationship between the QT interval and heart rate. Further, correction methods, that will allow QT intervals recorded at different heart rates to be compared, will be analysed. It will be shown that the most commonly used correction method in practice is inaccurate except under certain circumstances. Using the method that is found to be the optimum method of the ones discussed in the thesis, a possible drug induced QT prolongation of the drug in question will be analysed.
Preface

This master thesis was prepared at Informatics and Mathematical Modelling, the Technical University of Denmark as a partial fulfillment of the requirements for acquiring the degree, Master of Science in Engineering. The project was implemented in cooperation with H. Lundbeck A/S. The project corresponds to 35 ECTS points and was carried out in the period from March to October, 2005. The project was supervised by Professor Henrik Madsen, IMM, Anna Karina Trap Huusom, Lundbeck A/S and Judith L. Jacobsen, Lundbeck A/S.

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Anna Helga Jónsdóttir
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Introducction

1.1 Background

In the process of drug development it is required, in many cases, to perform a study of potential prolongation of a particular interval of the electrocardiogram (ECG), the QT interval. The QT interval can be used as a measure of delay of cardiac repolarisation of the heart, that can lead to potentially fatal cardiac arrhythmias [1]. A number of drugs have been reported to prolong the QT interval, both cardiac and non-cardiac drugs. Recently, previously approved, as well as newly developed drugs have been withdrawn from the marked or had their labeling restricted because of indication of QT prolongation [2].

The QT interval is highly correlated with heart rate and because of this correlation it is not possible to compare directly measurements of the interval recorded at different heart rates. The concept of heart rate corrected QT interval, or the QTc interval has therefore been developed. The idea of the QTc interval is to normalize the QT interval as it would have been gathered at a standard heart rate of 60 beats per minute.

Even though drug developers and regulatory agencies are giving the subject of drug induced QT prolongation a lot of attention, no formal guideline exist on how to perform such a study. However, while these words are written a draft on how to perform a QT/QTc study has been written by the European Medicines Agency (EMEA) [3]. The draft is supposed be taken into operation in November, this year. The draft concentrates more on the design of such study than how to correct the QT interval and analyse the resulting data which remains controversy.

The purpose of the thesis is to analyse the relationship between the QT interval and heart rate and to develop a correction method that can be applied to compare the measured QT interval gathered at different heart rates. Data used for the analysis is provided by H. Lundbeck A/S. Using the method developed, possible QT prolongation resulting from an intake of LU 35-138 (coded drug number) will be analysed.
1.2 Outline of thesis

A short overview of the cardiovascular system along with a description of a normal 12 lead electrocardiogram (ECG) will be given in Chapter 2. A definition of the QT interval and issues regarding QT prolongation measures will further be discussed.

Chapter 3 includes a description of the data and the design of the study performed by H. Lundbeck A/S. Some descriptive analysis will also be given in the chapter.

In Chapter 4, two articles found about QT interval prolongations will be summarised and discussed. Further, a draft of a guideline on how to perform and analyse a QT/QTc study written by the European Medicines Agency will be summarised.

Some statistical methods used in the thesis will be summarised in Chapter 5. A statistical method for deriving the correction parameter in different correction models will further be introduced in Chapter 6.

The data analysis will be divided into two chapters. In Chapter 7 only data gathered from the placebo subjects will be used to analyse the relationship between the QT interval and heart rate and to develop a correction method. In Chapter 8, the method developed in Chapter 7 will then be applied on the data for the subjects that were given the drug.

The results found will finally be summarised and discussed in Chapter 9.
A short description of the cardiovascular cycle will be given in the chapter. The electrocardiogram will further be described along with a brief discussion about the QT interval and problems regarding evaluation of QT prolongations. For information about the cardiovascular cycle and the electrocardiogram, references [4] and [5] were used.

2.1 The cardiac cycle

The human heart is composed primarily of cardiac muscle tissue. It has four chambers, the left and right ventricles, which are placed at the bottom of the heart and left and right atria placed at the top. The heart has four valves which control the flow of the blood in and out of the heart. The valves between the atria and the ventricles are called the tricuspid valve on the right and the mitral valve on the left. The third valve is placed between the aorta and the left ventricle, called aortic valve and the last valve between the pulmonary artery and the right ventricle, called the pulmonary valve. A drawing of the human heart is shown in Figure 2.1 where RA represent the right atrium, LA the left atrium, RV the right ventricle, LV the left ventricle, SVC the superior vena cavae, ICV the inferior vena cavae, PA the pulmonary artery and PV the pulmonary vein.

The cardiac cycle can be described as: Oxygenated blood is pumped from the left ventricle to the aorta which branches out to the whole body. The deoxygenated blood is then returned via the superior and inferior vena cavae to the right atrium and from there to the right ventricle. The blood is then expelled via the pulmonary artery from the right ventricle to the lungs where the blood is oxygenated. From the lungs the blood is returned to the left atrium by the pulmonary veins and finally through the
mitral valve, again to the left ventricle.

2.2 The electrocardiogram and the 12 lead system

An electrocardiogram (ECG) is a recording of the electric wave generation during heart activity. The electric activity starts at the top of the heart, spreads down and then up again causing the heart to contract. The electricity is produced by special cells in the heart called pacemaker cells. The cells change their charge by means of depolarisation and repolarisation. When the heart muscle is at rest the pacemaker cells are negatively charged but positively charged when the heart contracts. The heart rate is normally indicated in a group of pacemaker cells called the sinoatrial (SA) node, located in the right atrium near the superior vena cavae. From there, the action potential enters the ventricles through a cluster of cells called atrioventricular (AV) node placed in the region of the interatrial septum.

The electrical activity can be measured by an array of electrodes placed on the body. The most commonly used system is the 12 lead system. One wire is attached to each of the limbs (hands and legs), and six wires to the chest. From these ten wires, twelve leads or pictures are produced. The chest electrodes are named lead V1 and up to lead V6. The other six leads are lead VR, lead VL, lead VF, lead I, lead II and lead III. The placement of the leads and the relationship between the limb leads is shown in Figures 2.2 and 2.3.
The most common lead used in QT researches is lead II \cite{1}. It measures the potential difference between the right arm and left leg electrodes. A normal ECG, as recorded from lead II, along with definitions of the different waves and intervals is shown in Figure 2.4.

The P wave represents the wave of depolarisation that spreads from the SA node throughout the atria. The wave is normally 80-100 ms in duration. The wave is followed by a short zero voltage period that represents the time where the impulse is traveling within the AV node.

The distance between the beginning of the P wave to the beginning of the QRS complex is called the PR interval. Normal length of the interval is 120-200 ms. It represents the time between the beginning of atrial depolarisation and the beginning of ventricular depolarisation.

The QRS complex represents the ventricular depolarisation. The duration of the complex is normally only 60-100 ms. After the QRS complex a zero potential period appears, the ST segment, followed by the T wave that represents ventricular repolarisation. It is longer than the QRS complex meaning that the repolarisation of the ventricular is longer than its depolarisation.

The last interval marked on the figure is the QT interval which represents the time of both ventricular depolarisation and repolarisation. The interval is therefore a rough estimate of the duration of ventricular action potential. The interval normally ranges from 200-400 ms, depending upon heart rate.

There is no visible wave representing the atrial repolarisation. It occurs at the same time as the ventricular depolarisation and is therefore integrated in the QRS complex.

The ECG, as shown in Figure 2.4, is not as ceremonious in real life. A screen shot of a real ECG’s, measured in all leads is shown in Figure 2.5.

### 2.3 The QT interval

As stated above, the QT interval is defined as the time required for completion of both ventricular depolarisation and repolarisation. The interval has gained clinical importance since a prolongation of it has been shown to induce potentially fatal ventricular arrhythmia such as Torsade de Pointes \cite{1}. The arrhythmia causes the QRS
complexes to swing up and down around the baseline in a chaotic fashion which probably caused the name, which means "twisting of the points" in French.

The length of the QT interval is highly correlated with the RR interval, which is defined as the time duration between two consecutive R waves on the ECG. The RR interval and the heart rate are related inversely as

\[
\text{Heart rate}[\text{bpm}] = \frac{60}{\text{RR interval}[\text{sec}]} \quad (2.1)
\]

Because of this QT interval correlation with heart rate (and the RR interval), it is not possible to directly compare measurements of the interval, recorded at different heart rates. The concept of heart rate corrected QT interval, or the QTc interval has therefore been developed. The idea of the QTc interval is to normalize the QT interval to a standard RR interval, or standard heart rate of 60 beats per minute (RR interval = 1 sec). The resulting QTc interval should therefore be noncorrelated with heart rate.

Number of formulas have been suggested for this purpose. However, differences of opinion rises regarding the most useful correction formula. The most commonly used formula is the Bazett formula \[6\] where the QT interval is adjusted by dividing it by the square root of the corresponding RR interval or

\[
\frac{\text{QT}}{\sqrt{\text{RR}}}.
\]

The formula has been highly criticized for being inaccurate \[7\]-\[8\], even so it remains the most widely used correction in practise. Another widely used formula is the
2.4 Problems regarding QT prolongation analysis

Fridericia formula [9] where the QT interval is divided by the cube root of the RR interval or

$$QT_{c,Fridericia} = \frac{QT}{\sqrt[3]{RR}}.$$  \hfill (2.3)

Other types of correction have further been used, such as corrections resulting from linear regression. One of those is the Framingham correction [10] defined as

$$QT_{c,Framingham} = QT + 0.154(1 - RR)$$ \hfill (2.4)

Correction derived from a given study population are also used in practice. Instead of using a predefined value for the correction parameter, in the correction method used (as 0.154 in the Framingham correction), a correction parameter is derived from off-drug data and the resulting correction formula used to correct the data in the study.

2.4 Problems regarding QT prolongation analysis

The two procedures, the predefined correction and the correction derived from a given study data have a drawback. If the goal is to make the QTc interval noncorrelated
with heart rate in every subject, it needs to hold that the QT~RR relationship does not vary between subjects. For the predefined methods it must hold that all humans have a common QT~RR relationship, while for the study derived correction it must hold that all participants in the study share a common QT~RR relationship. Otherwise no single correction method can be estimated that would fit different subjects. Because of this drawback, other methods have been developed, such as subject specific corrections [11]. Off-drug data is used to estimate a correction parameter for every subject individually that leads to zero covariance, between QTc and RR, for that specific subject. The estimated correction parameter is then used in a correction formula that is applied on the data for the subject. Subject specific corrections however rely on another assumption. The QT~RR must be similar within every subject between days. In some cases it is difficult to attain subject specific methods, often because of too few off-drug data points.

When deciding what kind of correction method should be applied, the QT~RR relationship for the subjects of a study needs to be estimated using off drug data. Since the physiological relationship between the two variables is not obvious, (linear relationship is though often assumed) different kind of models should be applied. The models estimated should then be tested for equality both between (inter) subjects and within (intra) subjects. Finally, depending on the intra- and intersubject variability an appropriate correction method should be designed.
Chapter 3

The data

3.1 Data and design

The data used in the analysis comes from a study performed by H. Lundbeck A/S. It consists of data derived from about 50,000 ECG’s captured digitally using Mortara ELI\textsuperscript{TM} 200 Electrocardiographs. The purpose of the study, to investigate potential QTc prolongations in healthy subjects treated with multiple doses of LU 35-138 and placebo treated subjects [12].

H. Lundbeck A/S has provided two datasets for the analysis. The first set includes 42 variables including measurements of the RR, PR, QRS and QT intervals (see Figure 2.4). Some factor variables are also included in the dataset to discriminate between, for example, the patients and the leads used. Variables that state the time of the recording are further included in the set. The other dataset includes 39 variables that describe different characteristics of the subjects, for example gender, age and weight along with the number of the panel the subject belongs to. A description of the different variables in the sets is given in Appendix A.

The study is a randomized, double blind, multiple dose study in healthy male and female volunteers. The study is a parallel study meaning that while half of the group was given placebo the other half was given the drug. Total of 80 subjects were used in the study. All subjects, except one male subject, finished the study. The data available for the one subject is excluded from the analysis. A total of 79 subjects are therefore included in the analysis, 48 males and 31 females. 76 of the subjects are caucasians and three of other races. The mean age of the subjects is 29.7 years (st.dev = 7.6) and mean weight 71.7 kg (st.dev = 12.1).

The study was performed in five panels with 16 subjects per panel, named A-E. Within each panel half of the subjects were given placebo (A0-E0), while the other half was given the drug (A1-E1). A description of the panels is shown in Table 3.1.

For each subject, drug free 12 leads ECGs were taken the day before the dosing started
and regularly during dosing. After six days of dosing (on the seventh day), ECGs were recorded at the same time points as the day before the dosing started. The time points of the recording of the ECGs for the eight days is shown in Table 3.2.

<table>
<thead>
<tr>
<th>Day number</th>
<th>Intake</th>
<th>ECGs</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>-</td>
<td>8:00 10:00 12:00 14:00 20:00</td>
</tr>
<tr>
<td>1</td>
<td>8:00</td>
<td>8:00 (predose) 12:00</td>
</tr>
<tr>
<td>2</td>
<td>8:00</td>
<td>12:00</td>
</tr>
<tr>
<td>3</td>
<td>8:00</td>
<td>12:00</td>
</tr>
<tr>
<td>4</td>
<td>8:00</td>
<td>12:00</td>
</tr>
<tr>
<td>5</td>
<td>8:00</td>
<td>8:00 (predose) 12:00</td>
</tr>
<tr>
<td>6</td>
<td>8:00</td>
<td>8:00 (predose) 12:00</td>
</tr>
<tr>
<td>7</td>
<td>8:00</td>
<td>8:00 (predose) 10:00 12:00 14:00 20:00 8:00</td>
</tr>
</tbody>
</table>

Table 3.2: Time points of ECG recordings

From the recorded ECGs, the RR, PR, QRS and QT intervals (see Figure 2.4) were determined in each of the 12 leads. For the analysis only measurements from lead II will be used.

For each time point, three data points are given in the dataset (except for day 2, day 3 and day 4) where each point is based on the mean of three replicate recordings. The number of measurements from lead II given in the dataset, categorized by gender and treatments is shown in Table 3.3.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>off-drug</td>
<td>on-drug</td>
</tr>
<tr>
<td>Placebo</td>
<td>840</td>
<td>-</td>
</tr>
<tr>
<td>LU 35-138 50mg</td>
<td>120</td>
<td>328</td>
</tr>
<tr>
<td>LU 35-138 75mg</td>
<td>120</td>
<td>328</td>
</tr>
<tr>
<td>LU 35-138 100mg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>1080</td>
<td>656</td>
</tr>
</tbody>
</table>

Table 3.3: Number of measurements from lead II in the dataset

For a part of the analysis only off-drug data can be used. All the data from the placebo subjects will be considered off-drug. For every placebo subject a total of 56 data off drug data points are therefore available. Only 15 off drug data points are however
available for the subjects that were given the drug (data from day-1). In Figure 3.1, scatter plots of the QT-RR data available, categorized by days, for a single randomly chosen subject, is shown.

Figure 3.1: QT-RR data available for a single subject

\section*{3.2 Descriptive analysis}

From the datasets described above, the main variables are the measured RR interval and the QT interval. A histogram of the available data, both on-drug and off-drug, for the two variables measured in lead II is shown in Figure 3.2. The histograms for both variables are bell shaped, indicating a Gaussian distribution of the variables. It is though noticed that the distribution of the RR interval is somewhat skewed.

The mean length of the intervals among the subjects categorized by gender and treatment, measured in lead II, is shown in Table 3.4.

It is noticed by looking at the table that the male subjects have on average longer RR interval (slower heart beat) than the females. The difference between the genders is found to be significant (p-value < 0.001) by using a t-test described in Section 5.5. Since the QT interval is highly correlated with the RR interval it is not possible to compare the length of the QT intervals, a correction for heart beat is needed first.

It is of interest to visualize the relationship between the two variables. A scatter plot
The data

Figure 3.2: A histogram of the measured RR- and the QT intervals using all data available from lead II

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Females Mean RR</th>
<th>Females Mean QT</th>
<th>Males Mean RR</th>
<th>Males Mean QT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>930.51</td>
<td>385.13</td>
<td>1080.58</td>
<td>395.81</td>
</tr>
<tr>
<td>LU35-138/50 mg</td>
<td>943.15</td>
<td>399.94</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LU35-138/75 mg</td>
<td>936.33</td>
<td>398.82</td>
<td>1042.97</td>
<td>394.43</td>
</tr>
<tr>
<td>LU35-138/100 mg</td>
<td>-</td>
<td>-</td>
<td>1094.36</td>
<td>404.07</td>
</tr>
<tr>
<td>Total mean</td>
<td>935.27</td>
<td>392.49</td>
<td>1078.88</td>
<td>398.30</td>
</tr>
</tbody>
</table>

Table 3.4: Mean length of the RR and the QT intervals in ms measured in lead II

of the two variables categorized by gender using all data gathered in lead II (both on-drug and off-drug) is shown in Figure 3.3. A least square fitted linear regression models and lines are further included in the plots.

It can be seen, by looking the figure, that the line for the females is steeper than the one for the males. Another scatter plot of the two variables, now categorized by treatment, is shown in Figure 3.4. The data points plotted in the figure are the ones after the intake started.
3.2 Descriptive analysis

![Graph showing the QT-RR relationship categorized by gender using all data from lead II](image1)

Figure 3.3: The QT~RR relationship categorized by gender using all data from lead II

![Graph showing the QT-RR relationship categorized by treatment using data after intake started](image2)

Figure 3.4: The QT~RR relationship categorized by treatment using data after intake started
By looking at the regression models included in the plots, it can be seen that the value of the slope of the line for the placebo data is lower than the values of the slopes for the on-drug data. The slope of the line through the data where the subjects were given 50 mg of the drug is however a little steeper than the slope of the line where the subjects were given 100 mg of the drug. It should be kept in mind that only females were given 50 mg dose of the drug while only males were given 100 mg of the drug.
In the following chapter, two articles about QT interval prolongations will be summarised and discussed. The articles are written by Dr. Marek Malik and his associates at the Department of Cardiac and Vascular Sciences, St. George’s Hospital Medical School, London England. Dr. Malik and his associates have published a number of articles about the subject of QT prolongations. The names of the chapters below refer to the author and the placement of the article discussed, in the bibliography.

4.1 M. Malik and others [13]

The article Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate corrections of the QT interval was published in March 2002. The objective of the study discussed was to compare the QT~RR relation in healthy subjects in order to investigate the differences in optimum heart rate correction of the QT interval. 50 healthy subjects took part in the study, 25 males and 25 females. For each subject, 12 lead ECGs were gathered over 24 hours with a 10 second ECG obtained every two minutes. On average 671 ECGs were measurable in every subject (range 431-741). In the article, six different QT~RR relations are suggested and tested. Six different correction formulas are further converted from the QT~RR relation with the objective to make the QTc interval noncorrelated with the RR interval. The regression formulas and the corresponding correction formulas are written as:

For every QT~RR regression model, the slopes for the different subjects were compared pairwise, using "the regression related t-statistics test" (p.221) to investigate whether the regression curves between the subjects were parallel. Further the fit between the regression curves was investigated, using "the regression related F statistics test" (p.221) to investigate whether the regressions of different subjects were identical.
Type | QT~RR relationship | Heart rate correction
---|---|---
A: Linear | $QT = \beta + \alpha \cdot RR$ | $QTc = QT + \alpha \cdot (1 - RR)$
B: Hyperbolic | $QT = \beta + \alpha / RR$ | $QTc = QT + \alpha (1 / RR - 1)$
C: Parabolic | $QT = \beta \cdot RR^\alpha$ | $QTc = QT / RR^\alpha$
D: Logarithmic | $QT = \ln(\beta + \alpha \cdot \ln(RR))$ | $QTc = \ln(e^{QT} + \alpha \cdot (1 - RR))$
E: Shifted logarithmic | $QT = \beta + \alpha \cdot e^{RR}$ | $QTc = QT + \alpha (e^{RR} - 1 / e)$

Therefore a total of 14700 ($2 \cdot 50 \cdot (49 / 2) \cdot 6$) comparisons were made.

In the analysis a p-value of $p < 10^{-6}$ was considered significant in the regression comparisons. This is explained with: "Since these tests were not mutually independent (investigating the relation between 50 separate data sets) and the standard corrections of p values for multiple tests were not appropriate, and since the regression tests are rather sensitive, $p < 10^{-6}$ was considered significant in the regression comparisons." (p. 221)

Even though a very low critical p-value was used when testing whether it can be assumed that the regression lines for the different subjects are parallel, and further if the regressions could be assumed to be identical, a number of significant differences between subjects were found. The number of significant differences between subjects for the test of parallel lines ranged from 17 to 49 and the test for identical regression resulted in number of significant differences from 41 to 49. That is, for some of the subjects no other subject was found to have the same value of regression coefficients. The regression parameters were compared between females and males by using a Mann-Whitney test. Significant differences were found for both parameters for all the regression models. The regression parameters were not found to be related to age.

In order to compare the different regression types, the root mean square of the error (RMSE) resulting from the different models were compared. The number of subjects the different regression types gave the optimum results were further gathered. Regression models of type A and E, that is the linear and the exponential models, resulted in lowest RMSE (11.08 ms and 11.07 ms respectively). Regression type A was however found to be the optimum type for 20 subjects while regression type E only for 12 subjects.

In order to find the optimal $\alpha$ in the correction formulas, the formulas were applied to the QT/RR data of each subject, varying the value of the parameter $\alpha$ from 0 to 1 in steps of 0.001. The optimal $\alpha$ would be the one giving the lowest correlation between the RR interval and the QTc interval.

The value of the optimal $\alpha$ from the heart rate correction formulas was shown to differ between subjects. As an example, the range of $\alpha$ from the parabolic model was found to be [0.233, 0.485]. By using the mean optimal $\alpha$ among the subjects, as an overall correction, the range of the correlation between the RR interval and the resulting QTc interval (using the parabolic model) was found to be [-0.712, 0.578] indicating that no optimal overall correction can be found that fits different subjects.

The results of the authors are clear, no optimum heart rate correction formula can be found that would permit accurate comparisons of QTc intervals between subjects. Or by using their own words: "When a precise determination of QTc interval is needed, the heart rate correction should be optimized for the given person." (p. 227)
4.1.1 Discussion

After reading the article, some principal questions arise. It is not stated what kind of method is used to estimate the parameters in the QT$\sim$RR regression models. It is however stated that the "regression related t test" has been used to test if the parameters for the different subjects can be assumed to be identical, indicating that an ordinary least square method has been applied to estimate the parameters. Using the same symbol, $\alpha$, for the parameters in the regression models and the corresponding correction is misleading since it can be shown (derived in Chapter 6) that the parameters are, in some cases the same, but others not. If it is assumed that the parameters are the same, when they are in fact not, the QTc resulting from the derived correction formulas are not independent of the RR interval as it should be. Also by inserting the QT$\sim$RR relation for the hyperbolic and the exponential model into the corresponding correction formulas does not result in expression for the QTc interval that is independent of heart rate. In order to achieve that, the terms in the parenthesis needs to be switched.

No attempt is made to derive an expression for the parameters. It is only stated that the optimal $\alpha$ in the correction formulas is the one giving the lowest correlation between QTc and RR and is found by varying the value of the parameter in steps of 0.001.

The main purpose of the article seems to be to show that there is a significant difference in the QT$\sim$RR relationship between subjects and therefore the right way to go is to use subject specific corrections. No tests are however made regarding if the QT$\sim$RR relationship can be assumed to be constant within the subjects, which must be an important assumption when using subject specific corrections. The authors however refer to another study using an independent set of data where the QT$\sim$RR relationship was found to be stable within each person over time.

4.2 M. Malik and others [11]

The article, Differences Between Study-Specific and Subject-Specific Heart Rate corrections of the QT interval in Investigations of Drug Induced QTc Prolongation was published in June 2004. The article documents the analysis of a computational study designed to investigate the differences between study-specific and a subject-specific heart rate corrections of the QT interval. From 53 healthy subjects, serial 10 second ECG were obtained during day time hours. From each subject 200 ECG’s were selected that represented the QT$\sim$RR relationship. From the population, 30000 different subgroups of 16 subjects were produced and their data used to model drug induced QT interval prolongation by 0, 5, 10, 20 ms combined with drug induced heart rate acceleration and deceleration. Fifteen different correction methods were used in the analysis, six study-specific heart rates corrections with data pooled from all subjects, six subject-specific heart rate corrections from the data for each subject individually, subject optimized correction, where the best regression method was selected for every individual and used for the correction and finally using the Bazett and Fridericia corrections.

The same six regression models and derived correction models are used as in [13]
but the authors are now using different symbols for the parameters in the regression models and the correction models. The models are now defined as:

<table>
<thead>
<tr>
<th>Type</th>
<th>QT~RR relationship</th>
<th>Heart rate correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Linear</td>
<td>$QT = \eta + \xi \cdot RR$</td>
<td>$QTc = QT + \alpha (1-RR)$</td>
</tr>
<tr>
<td>B: Hyperbolic</td>
<td>$QT = \eta + \xi / RR$</td>
<td>$QTc = QT + \alpha(1/RR - 1)$</td>
</tr>
<tr>
<td>C: Parabolic</td>
<td>$QT = \eta \cdot RR^\xi$</td>
<td>$QTc = QT / RR^\alpha$</td>
</tr>
<tr>
<td>D: Logarithmic</td>
<td>$QT = \eta + \xi \cdot \ln(RR)$</td>
<td>$QTc = QT - \alpha \cdot \ln(RR)$</td>
</tr>
<tr>
<td>E: Shifted logarithmic</td>
<td>$QT = \ln(\eta + \xi \cdot RR)$</td>
<td>$QTc = \ln(e^{QT} + \alpha(1-RR))$</td>
</tr>
<tr>
<td>F: Exponential</td>
<td>$QT = \eta + \xi \cdot e^{-RR}$</td>
<td>$QTc = QT + \alpha(e^{RR} - 1/e)$</td>
</tr>
</tbody>
</table>

Again it is stated that the $\alpha$ in the correction formulas was optimized to get a zero correlation between the QTc interval and the RR interval. To study the relationship between study specific and subject specific correction of the same type of regression model, the $\alpha$ resulting from the pooled correction was compared to the average of the $\alpha$ resulting from the individualized correction. The correlation between the study- and subject specific $\alpha$s from the 30000 subgroups was found to be very weak for the six model types ($r = 0.215, 0.447, 0.056, 0.197, 0.222, 0.172$).

All 15 heart rate corrections (6 study specific + 6 subject specific + subject optimized + Bazett + Fridericia) were used to calculate the difference between the baseline and on-treatment QTc values for each individual. These QTc values were compared with the initially introduced QTc prolongation. Differences between the reported QTc values and the true simulated QTc prolongations were taken as the error of the given heart rate correction method. This was done separately for the simulated data for treatment related heart rate deceleration and acceleration. The errors were found to be larger with heart rate acceleration on model treatment than with deceleration. In both cases the optimized correction and the individual correction using the exponential model gave the smallest error. The distribution of the errors from the subject specific models was found to be much tighter than for the study specific models. The worst performance was observed with the Bazett and the Fridericia formulas.

Again the conclusion of the authors is clear: "Precise subject-specific corrections should therefore be used in the intensive and definite studies aimed at providing the final answer on the ability of a drug to prolong the QT interval." (p. 800)

### 4.2.1 Discussion

Similar questions arise when reading the article as when reading [13]. Now the authors however use different symbols for the parameters in the regression formulas and in the correction formulas. Again the correction parameter is estimated iteratively to give zero correlation between RR and QTc.

The authors choose to use the RMSE from the regression models to decide what correction should be chosen for the subjects. Whether this is the correct way to go will be looked at in Section 7.2.

As before, the results of the article is clear, subject specific methods should be used to get accurate results. The important assumption about stable QT~RR relationship within a subject is however neither tested or discussed in the article.
4.3 The European Medicines Agency [3]

A thorough QT/QTc study is a study dedicated to evaluate a drug effect on cardiac repolarisation. *The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs* is a draft on guidelines for sponsors, concerning the design, conduct, analysis and interpretation of such a study. The draft summarised here is the fifth draft from the 12th of May 2005. The first draft was written in July 2003.

It is suggested that a thorough QT/QTc study is made early in the clinical development by using electrocardiographic evaluation. It should be carried out in healthy volunteers, if possible. The study should be adequate and well controlled and should be able to deal with potential bias with the use of randomization, appropriate blinding and a placebo control group. It is recommended to use a positive control group to assay sensitivity.

Pros and cons of using parallel or crossover studies are listed in the draft. Crossover studies usually need fewer subjects than parallel group studies and might advance heart rate corrections based on individual subject data. For drugs with long elimination half lives, parallel studies might be preferable as when multiple doses or treatment groups are to be compared.

The timing of the ECG’s is suggested to be guided by the available information about the pharmacokinetic profile of the drug. Care should be taken to perform a ECG recordings around the time points of the maximal observed concentration of the drug.

A negative thorough QT/QTc study is defined in the draft, as one which the upper bound of the one sided 95% confidence interval on the time matched mean effect on the QTc interval excludes 10 ms. This is done to provide reasonable assurance that the mean effect on the QTc interval is not greater than 5 ms which is the threshold level of regulatory concern. When the time-matched difference exceeds the threshold, the study should be termed positive. A positive study influences the evaluation carried out during later stages of the drug development. Additional evaluation in subsequent clinical studies should then be performed.

Regarding collection, assessment and submission of the ECG’s, it is suggested in the draft to use 12 lead surface ECG’s where the different intervals are measured by few skilled readers. The readers should be blinded with time, treatment and subject identifier. The same reader should read all the ECG recordings from a given subject.

What kind of QT interval correction formulas and how to analyse QT/QTc interval data is shortly discussed in the draft. It is stated that in order to detect small effects in the QTc, it is important to apply the most accurate correction method available.

Since the best correction approach is a subject of controversy, uncorrected QT and RR interval data, heart rate data as well as QT interval data corrected using Bazett’s and Fridericia’s corrections should be submitted in addition to QT interval corrected using any other formula. It is prevised that the Bazett formula overcorrects at high heart rates but under corrects at heart rates below 60 bpm while the Fridericia is more accurate in subjects with such altered heart rates. Regarding correction formulas derived from within subject data it says in the draft: "These approaches are considered most suitable for the 'thorough' QT/QTc study and early clinical studies, where it is possible to obtain many QT interval measurements for each study subject over a broad range of heart rates." (p. 12)

Considering how the QT/QTc interval should be presented it is stated that it should be presented both as analysis of central tendency (mean, medians) and categorial
analysis. The largest time matched mean difference between the drug and placebo over the collection period should be analysed along with changes occurring around Cmax for each individual. The categorial analysis of the QT/QTc should be based on number and percentage of subjects meeting or exceeding some predefined upper limit value. What this upper limit value should be is not decided but stated that multiple analysis using different limits are reasonable approach including absolute QTc interval prolongation of > 450, > 480 and > 500 and change from baseline of > 30 and > 60. Adverse events and how to handle them along with regulatory implications, labelling and risk management strategies are finally discussed in the draft. Since these factors are not of importance for the analysis performed in this theses they will not be summarised here.
An overview of the statistical methods used in the analysis will be given in the chapter.

5.1 Calculation rules for the expectation and the variance of random variables

The calculation rules given in this section are taken from [14]. The following calculation rules are valid for the first moment, or the expectation, of a random variable X:

\[ E(a + bX) = a + bE(X) \]  \hspace{1cm} (5.1)
\[ E(X + Y) = E(X) + E(Y) \]  \hspace{1cm} (5.2)
\[ E(X \cdot Y) = E(X) \cdot E(Y), X \text{ and } Y \text{ are independent} \]  \hspace{1cm} (5.3)

The second central moment of a random variable is the variance defined as

\[ V(X) = E((X - E(X))^2) = E(X^2) - (E(X))^2 \]  \hspace{1cm} (5.4)

The following calculation rules are valid for the variance

\[ V(aX) = a^2V(X) \]  \hspace{1cm} (5.5)
\[ V(X + b) = V(X) \]  \hspace{1cm} (5.6)
\[ V(X \pm Y) = \begin{cases} V(X) + V(Y) \pm 2Cov(X, Y) & \text{if } X \text{ and } Y \text{ are independent} \\ V(X) + V(Y), X \text{ and } Y \text{ are independent} & \end{cases} \]  \hspace{1cm} (5.7)

where Cov(X, Y) is the covariance between the two random variables X and Y defined as

\[ Cov(X, Y) = E(X - E(X))E(Y - E(Y)) \]  \hspace{1cm} (5.8)
The following calculation rules apply for the covariance:

\[
\text{Cov}((a_1X + b_1), (a_2Y + b_2)) = a_1a_2\text{Cov}(X, Y) \tag{5.9}
\]

and finally

\[
\text{Cov}(X + Y, U) = \text{Cov}(X, U) + \text{Cov}(Y, U) \tag{5.10}
\]

where \(X, Y\) and \(U\) are random variables.

### 5.2 Ordinary Least Squares

A multiple regression model with \(k\) independent variables can be written as

\[
y_i = \beta_0 + \beta_1x_{i1} + \beta_2x_{i2} + \cdots + \beta_kx_{ik} + \epsilon_i \quad i = 1, 2, ..., n \tag{5.11}
\]

where \(\epsilon \sim \text{NID}(0, \sigma^2)\)

The observations, \(y_i\), should be uncorrelated and the independent variables fixed (that is non random). The independent variables can be quantitative, transformations of quantitative variables, interaction between variables or factor variables with several levels.

In matrix notation the model can be written as

\[
y = X\beta + \epsilon \tag{5.12}
\]

where \(y\) is a \((n \times 1)\) vector of observations, \(X\) is a \((n \times p)\) matrix of independent variables \((p = k+1\) to allow for intercept), \(\beta\) is a \((p \times 1)\) vector of regression coefficients and \(\epsilon\) is a \((n \times 1)\) vector of independent random errors.

The vector of least square estimators, that minimizes

\[
L = \sum_{i=1}^{n} \epsilon_i^2 = \epsilon^T \epsilon = (y - X\beta)^T(y - X\beta) \tag{5.13}
\]

is found by solving

\[
\frac{\delta L}{\delta \beta} = 0 \tag{5.14}
\]

and can be written as

\[
\hat{\beta} = (X^T X)^{-1}X^T y \tag{5.15}
\]

According to the Gauss-Markov theorem, the least square estimates of the regression parameters have the smallest variance among all linear unbiased estimates [15]. There might however exist a biased estimator with smaller mean square error. In some cases it is not appropriate to use the least square estimator, for example when the independent variables are not fixed or autocorrelation is found in the data. In other cases it can’t be used for example when large multicolinearity is found in the independent variables which leads to singular inverse of the \((X^T X)\) matrix.
5.3 Regression related tests

5.3.1 Test on individual regression coefficients

The hypothesis to test whether a single parameter from the regression model has a certain value \( c \), can be written as

\[
H_0 : \beta_j = c \\
H_1 : \beta_j \neq c
\]  

(5.16)

The test statistic for the hypothesis is defined as [16]

\[
T_0 = \frac{\hat{\beta}_j - c}{\sqrt{\hat{\sigma}^2 C_{jj}}} = \frac{\hat{\beta}_j - c}{se(\hat{\beta}_j)}
\]  

(5.17)

where \( C_{jj} \) is the diagonal element of \((X^TX)^{-1}\) corresponding to \( \hat{\beta}_j \). The null hypothesis should be rejected if \(|t_0| > t_{\alpha/2, n-p}\).

A special case of the hypothesis is used to test whether a single parameter from the regression model is significant, and can be written as

\[
H_0 : \beta_j = 0 \\
H_1 : \beta_j \neq 0
\]  

(5.18)

Failing to reject the null hypothesis is an indication that the regressor \( x_j \) can be deleted from the model.

5.3.2 Test for lower dimension of the model space

Consider a regression model with \( k \) regressor variables

\[
y = X\beta + \epsilon
\]

The following test can be used to test if the mean vector can be assumed to lie in a true subspace of the model space. The test is taken from [16].

The hypothesis can be written as

\[
H_0 : \mu \in H \\
H_1 : \mu \in M \setminus H.
\]  

(5.19)

where \( M \) is a \( k \) dimensional sub-space and \( H \) is a \( r \) dimensional sub-space of \( M \) where \( k > r \).

Let the regression sum of squares for the full model be defined as

\[
SS_R(\beta_M) = \hat{\beta}^T X^T y
\]

and

\[
MS_E = \frac{y^T y - \hat{\beta}Xy}{n - p}
\]
where \( n \) is the number of observations of the dependent variable and \( p = k + 1 \). Let us define \( \beta_H \) as the regression coefficients in the reduced model and \( X_H \) the columns of \( X \) associated with \( \beta_H \). The sums of squares for the reduced model is then defined as

\[
SS_R(\beta_H) = \hat{\beta}_H^T X_H^T y.
\]

The null hypothesis, may be tested by the test statistic

\[
F_0 = \frac{(SS_R(\beta_M) - SS_R(\beta_H))/r}{MS_E}.
\]

The null hypothesis should be rejected if \( F_0 > F_{\alpha, r, n-p} \).

### 5.3.3 Test for identity of regressions

It is suggested in [13] that the individually fitted RR-\~QT regressions should be tested pairwise for identity. As is discussed in Section 4.1, "the regression related F statistics test" should be used to investigate identity of regressions.

Considering two different regressions

\[
Y_i = \beta_0 + \beta_1 x_i + \epsilon_i, \quad i = 1, \ldots, n
\]

\[
Y'_i = \beta'_0 + \beta'_1 x_i + \epsilon'_i, \quad i = 1, \ldots, n'
\]

where \( \epsilon \) and \( \epsilon' \in N(0, \sigma^2(I)) \)

The hypothesis can be written as

\[
H_0 : \text{The regressions are identical} \\
H_1 : \text{The regressions are not identical}
\]

The regression related F statistical test for testing identity of regressions can be written as [17] (using the same notation)

\[
Z = \frac{n + n' - 4}{2((n - 2)s^2 + (n' - 2)s'^2)},
\]

\[
(b - b')^T [(X^T X)^{-1} + (X'^T X')^{-1}]^{-1} (b - b')
\]

where

\[
b = (X^T X)^{-1} X^T Y,
\]

\[
S_e = Y^T (I - X (X^T X)^{-1} X^T) Y
\]

and

\[
s^2 = S_e / (n - 2)
\]

The test statistic should be rejected if \( Z > F_{2, n+n'-4} \).
5.4 Kolmogorov Smirnov test

The one sample Kolmogorov Smirnov test is used to test if a sample comes from a population with a specific distribution, for example the normal distribution. The hypothesis are

\[ H_0 : \text{The sampled data follows the specified distribution} \]
\[ H_1 : \text{The sampled data does not follow the specified distribution} \]

The test compares the hypothesized continuous distribution function \( F \) to the empirical distribution function \( F' \) of the samples. The test statistic \( D \) is defined as the largest absolute deviation between \( F(x) \) and \( F'(x) \) over the range of the random variable or

\[
D = \max_x |F'(x) - F(x)| \quad (5.23)
\]

where \( F'(x) \) is defined as

\[
F'(x) = \frac{\text{number of samples} \leq x}{N}
\]

and \( N \) is the number of data points. The null hypothesis is rejected if the test statistic \( D \) is greater than a critical value obtained from a table.

5.5 T-test for difference in means-variance unknown

The test can be used to test whether means of two normal distributions are equal when the variance is unknown. The two sided hypothesis are

\[ H_0 : \mu_1 = \mu_2 \]
\[ H_1 : \mu_1 \neq \mu_2 \]

Two different cases arise. First when the variances of the two populations can be assumed to be equal and latter when the variances are not necessarily equal. The appropriate test statistic when \( \sigma^2_1 = \sigma^2_2 = \sigma^2 \) is defined as [16]

\[
T_0 = \frac{\overline{X}_1 - \overline{X}_2}{S_p \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}} \quad (5.24)
\]

where \( \overline{X}_1 \) and \( \overline{X}_2 \) are the sample means, \( n_1 \) and \( n_2 \) are the sample sizes and \( S_p \) is the pooled estimator of \( \sigma^2 \) defined as

\[
S_p^2 = \frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2} \quad (5.25)
\]

where \( S_1^2 \) and \( S_2^2 \) are the sample variances.

The null hypothesis should be rejected when \( t_0 > |t_{\alpha/2, n_1+n_2-2}| \).

For the latter case when \( \sigma^2_1 \neq \sigma^2_2 \) there is not an exact t-statistic available but under
the null-hypothesis, the test statistic in (5.24) is approximately distributed as t, with
degrees of freedom given by

\[
v = \frac{\left( \frac{S_1^2}{n_1} + \frac{S_2^2}{n_2} \right)^2}{\frac{(S_1^2/n_1)^2}{n_1-1} + \frac{(S_2^2/n_2)^2}{n_2-1}}
\]

(5.26)

The null hypothesis, in this case, should be rejected when \( t_0 > |t_{\alpha/2,v}|. \)

### 5.6 The paired t-test

A special case of the two sample t-test described in Section 5.5 is the paired t-test which should be used if the observations on the two populations of interest are collected in pairs.

Let us define \( \mu_D = \mu_1 - \mu_2 \), the hypothesis about the difference between \( \mu_1 \) and \( \mu_2 \) can be written as

\[
H_0 : \mu_D = 0 \\
H_1 : \mu_D \neq 0
\]

(5.27)

The test statistic for the hypothesis is defined as [16]

\[
T_0 = \frac{\overline{D}}{S_D/\sqrt{n}}
\]

(5.28)

where \( n \) is the number of pairs, \( \overline{D} \) is the sample average of the difference between the \( n \) pairs and \( S_D \) is the sample standard deviation of the differences.

A 100(1 - \( \alpha \)) confidence interval on the difference in means \( \mu_D \), where \( \alpha \) is the level of significance can be written as [16]

\[
\bar{d} - t_{\alpha/2,n-1} s_D/\sqrt{n} \leq \mu_D \leq \bar{d} + t_{\alpha/2,n-1} s_D/\sqrt{n}
\]

(5.29)

### 5.7 Test for equality of two variances

Let \( X_1 \) and \( X_2 \) be two independent random samples from two normal distributions with mean \( \mu_1 \) and \( \mu_2 \) and variances \( \sigma_1^2 \) and \( \sigma_2^2 \) respectively. To test the null hypothesis

\[
H_0 : \sigma_1^2 = \sigma_2^2 \\
H_1 : \sigma_1^2 \neq \sigma_2^2
\]

the following test statistic should be used [16]

\[
F_0 = \frac{S_1^2}{S_2^2}
\]

(5.30)

where \( S_1 \) and \( S_2 \) are the sample variances.

The null hypothesis should be rejected if \( f_0 > f_{\alpha/2,n_1-1,n_2-1} \) or \( f_0 < f_{1-\alpha/2,n_1-1,n_2-1} \).
5.8 Linearization of nonlinear functions

A Taylor series linearization can be used to derive a linear approximation to nonlinear functions. Let \( f \) be a nonlinear function of two variables \( X \) and \( U \). A linearization of the function around its nominal point is defined as

\[
f(X, U) \approx f(X_0, U_0) + \frac{\delta f}{\delta X} \bigg|_{X=X_0, U=U_0} (X - X_0) + \frac{\delta f}{\delta U} \bigg|_{X=X_0, U=U_0} (U - U_0) \quad (5.31)
\]
In the analysis, six different regression and correction models will be applied and tested. The models are the same as used in [11] and [13] except that the order of the terms inside the parenthesis of the hyperbolic and the exponential correction models have been changed. The regression models can be written as (with a slight change in notation from [11])

\[
\begin{align*}
A & \text{ Linear} \quad QT = \eta_A + \xi_A \cdot RR \\
B & \text{ Hyperbolic} \quad QT = \eta_B + \xi_B / RR \\
C & \text{ Parabolic} \quad QT = \eta_C \cdot RR^{c_c} \\
D & \text{ Logarithmic} \quad QT = \eta_D + \xi_D \cdot \ln(RR) \\
E & \text{ Shifted logarithmic} \quad QT = \ln(\eta_E + \xi_E \cdot RR) \\
F & \text{ Exponential} \quad QT = \eta_F + \xi_F \cdot e^{RR}
\end{align*}
\]

and the corresponding correction models

\[
\begin{align*}
A_c & \text{ Linear} \quad QT_c = QT + \alpha_A(1 - RR) \\
B_c & \text{ Hyperbolic} \quad QT_c = QT + \alpha_B(1 - 1/RR) \\
C_c & \text{ Parabolic} \quad QT_c = QT / RR^{c_c} \\
D_c & \text{ Logarithmic} \quad QT_c = QT - \alpha_D \cdot \ln(RR) \\
E_c & \text{ Shifted logarithmic} \quad QT_c = \ln(e^{QT} + \alpha_E(1 - RR)) \\
F_c & \text{ Exponential} \quad QT_c = QT + \alpha_F(1/e - e^{RR})
\end{align*}
\]

It is noticed by looking at the regression models that models A, B, D and F are linear in their parameters while models C and E are nonlinear.

It has been suggested in the literature, [11] and [13], that the \( \alpha \)'s from the correction models should be determined by varying their values from 0 to 1 in steps of 0.001. When dealing with large amount of data it can be time consuming to estimate the
correction parameters iteratively as suggested. An attempt to derive an expression for the correction parameters for the models that are linear in their parameters will therefore be made in the chapter. An attempt will also be made, by the use of some approximations, to relate the correction parameters in the models that are nonlinear in their parameters to the correction parameter in the linear model.

6.1 Linear models

The desired characteristic of the QTc interval is zero covariance between the QTc and the RR intervals, or equivalent, the two vectors should be orthogonal. The condition is written as

$$\text{Cov}(QTc, RR) = 0.$$  \hfill (6.3)

By inserting, for example, the linear correction formula \( A_c \) from (6.2) into (6.3) gives

$$\text{Cov}(QT + \alpha A_c (1 - RR), RR) = 0.$$  \hfill (6.4)

Solving for \( \alpha_A \) and apply it to calculate QTc would therefore result in orthogonal vectors of QTc and RR intervals.

Applying covariance calculation rule (5.10), this can be written as

$$\text{Cov}(RR, QT) + \text{Cov}(RR, \alpha_A) + \text{Cov}(RR, -\alpha_A \cdot RR) = 0.$$  \hfill (6.5)

The covariance between a random variable and a constant is zero and using (5.9) leads to

$$\text{Cov}(RR, QT) - \alpha_A \cdot \text{Cov}(RR, RR) = 0.$$  \hfill (6.6)

or

$$\text{Cov}(RR, QT) - \alpha_A \cdot \text{Var}(RR) = 0.$$  \hfill (6.7)

Let us now define vectors of \( N \) measurements of the RR and the QT intervals, \( RR = [RR_1 \ldots RR_N]^T \) and \( QT = [QT_1 \ldots QT_N]^T \). The estimate of the covariance between \( RR \) and \( QT \), assuming that the data is centered around the mean, can be written as

$$\text{Cov}[RR, QT] = \frac{1}{N} \sum_{i=1}^{N} RR_i \cdot QT_i = \frac{1}{N} RR^T \cdot QT$$  \hfill (6.6)

and the variance of \( RR \) as

$$\text{Var}[RR] = \frac{1}{N} \sum_{i=1}^{N} RR_i \cdot RR_i = \frac{1}{N} RR^T \cdot RR$$  \hfill (6.7)

inserting into (6.5) gives

$$RR^T \cdot QT = \alpha_A \cdot RR^T \cdot RR.$$  \hfill (6.8)
It is noticed that this is the same as the LS estimator given in (5.15) with QT as the dependent variable and RR the independent variable as in regression type A in (6.1). Going through the same steps for the hyperbolic model B from (6.1) gives

\[ \text{Cov}(QT + \alpha_B(1 - 1/RR), RR) = 0 \] (6.9)

or

\[ \text{Cov}(RR, QT) - \alpha_B \cdot \text{Cov}(RR, 1/RR) = 0. \]

By considering \( X = 1/RR \) as a new random variable, and \( X = [1/RR_1 \ldots 1/RR_N] \) as the corresponding vector of observations. Using the estimates of the covariances results in

\[ RR^T \cdot QT = \alpha_B (RR^T \cdot X) \]

and finally solving for \( \alpha_B \)

\[ \alpha_B = (RR^T \cdot X)^{-1} RR^T \cdot QT. \] (6.10)

It is noticed that this is not the same as the LS estimator for the hyperbolic model B in (6.1), which can be written as

\[ \xi_B = (X^T \cdot X)^{-1} \cdot (X^T \cdot QT). \] (6.11)

The same can be done for the other two linear models form (6.2), models D and E. Defining \( Y = \ln(RR) \) and \( Z = e^{-RR} \) as new random variables and \( Y = [\ln(RR_1) \ldots \ln(RR_N)] \) and \( Z = [e^{-RR_1} \ldots e^{-RR_N}] \) as the corresponding vector of observations, respectively, an expression for their parameters can be written as

\[ \alpha_D = (RR^T \cdot Y)^{-1} \cdot RR^T \cdot QT \] (6.12)

and

\[ \alpha_E = (RR^T \cdot Z)^{-1} \cdot RR^T \cdot QT \] (6.13)

which are not the same as the least square fitted regression parameters in the corresponding regression models D and E which can be written as

\[ \xi_D = (Y^T \cdot Y)^{-1} \cdot Y^T \cdot QT \] (6.14)

and

\[ \xi_E = (Z^T \cdot Z)^{-1} \cdot Z^T \cdot QT. \] (6.15)

It has therefore be shown that the following is valid

\[ \alpha_A = \xi_A \] (6.16)

\[ \alpha_B \neq \xi_B \] (6.17)

\[ \alpha_D \neq \xi_D \] (6.18)

\[ \alpha_E \neq \xi_E. \] (6.19)
6.2 Nonlinear models

For the two models that are nonlinear in their parameters, models C and F, an approximation of their corresponding QTc function is needed to be able to solve (6.3). The functions are therefore linearized as is described in Section 5.8. Using (5.31), a linearization of correction type Cc from (6.2) is given as

\[
QT_c = \frac{QT}{RR^{\alpha_C}} \approx \frac{QT_0}{RR_0^{\alpha_C}} - \alpha_C \cdot QT_0 \cdot RR_0^{-\alpha_C - 1} (RR - RR_0) + RR_0^{-\alpha_C} (QT - QT_0)
\]

(6.20)

and correction type Ec as

\[
QT_c = \ln(e^{QT_0} + \alpha_E(1 - RR)) \approx \ln(e^{QT_0} + \alpha_E(1 - RR_0)) + \frac{e^{QT_0}}{e^{QT_0} + \alpha_E(1 - RR_0)} (QT - QT_0).
\]

(6.21)

Inserting (6.20) into (6.3) and applying the covariance rules leads to

\[
\frac{1}{RR_0^{\alpha_C}} \text{Cov}(RR, QT) - \frac{\alpha_C \cdot QT_0}{RR_0^{\alpha_C + 1}} \text{Cov}(RR, RR) = 0
\]

or

\[
\frac{\alpha_C \cdot QT_0}{RR_0^{\alpha_C}} \text{Cov}(RR, RR) = \text{Cov}(RR, QT).
\]

Again by considering RR and QT as vectors of observations and using the estimate of the covariances leads to

\[
\frac{\alpha_C}{RR_0^{\alpha_C}} = \frac{1}{QT_0} (RR^T \cdot RR)^{-1} (RR^T \cdot QT).
\]

Recognizing \((RR^T \cdot RR)^{-1} (RR^T \cdot QT)\) as the LS estimator for the linear regression model A and using (6.16) this can be written as

\[
\frac{\alpha_C}{RR_0^{\alpha_C}} = \frac{1}{QT_0} \alpha_A.
\]

(6.22)

Going through the same steps for correction type Ec gives

\[
\text{Cov}(RR, e^{QT_0} (QT - QT_0)) + e^{QT_0} \cdot \text{Cov}(RR, \frac{-\alpha_E (RR - RR_0)}{e^{QT_0} + \alpha_E (1 - RR_0)}) = 0
\]

or

\[
e^{QT_0} \cdot \text{Cov}(RR, QT) - \alpha_E \text{Cov}(RR, RR) = 0.
\]

Once again using the estimates of the covariances and solving for \(\alpha_E\) gives

\[
\alpha_E = (RR^T \cdot RR)^{-1} (RR^T \cdot QT) \cdot e^{QT_0}.
\]

Again by recognizing the LS parameter from the linear regression model A and using (6.16) this can be written as

\[
\alpha_E = \alpha_A \cdot e^{QT_0}
\]

(6.23)
It has been shown that by using an approximation to the nonlinear correction functions it is possible to relate the two correction parameters from the nonlinear models to the correction parameter in the linear correction model (type $A_c$). How well the approximation works depends on the behavior of the approximated function. It is therefore expected that the approximation used for the shifted logarithmic function will perform better than the approximation for the parabolic model.
Chapter 7

Analysis of QT correction methods based on placebo subjects

A correction method needs to be designed to normalize the QT interval as it would have been measured at a constant heart rate. Such a method needs to be estimated using pre treatment data. As can be seen in Figure 3.1, only 15 data points are available per subject before the intake of the drug started. 56 data points are however available for every placebo treated subject. Because of this lack of pre treatment data, the data for the placebo subjects will be used for some of the analysis where only off-drug data is needed. Since it was chosen randomly what kind of treatment the subjects were given, it will be assumed that the same principles apply to the placebo subjects and the subjects that were given the drug.

In the following chapter, only data from subjects that were given placebo will be used.

7.1 The QT∼RR relationship

In order to investigate the nature of the QT∼RR relationship, the six different models given in (6.1) are analysed and tested. The models all have two parameters to be estimated, $\xi$ and $\eta$. It is noticed that four of the models (A,B,D,F) are linear in their parameters, while the other two are nonlinear (C,E). Ordinary least squares method is used to estimate the parameters in the linear models. For the models that are nonlinear in their parameters, the built in Splus function nls that uses the Gauss-Newton method is used for the estimation.

For every placebo treated subject, the six different model types are fitted individually
to the data, that is, the two regression parameters in the six models are estimated for every subject. Bar plots of the individually fitted slopes for the six model types are shown in Figure 7.1. The estimated mean value along with the range of the parameters within each regression type is further included in the plots.

![Figure 7.1: The value of the individually fitted slopes for the six model types and the 39 placebo subjects](image)

To determine what type of model from (6.1) fits the subjects best, the root mean square error (RMSE) is used, that is, the optimum model, for a given subject, is the one resulting in the lowest RMSE among the models. The mean and range of the RMSE among the subjects is shown in Table 7.1. The number of times the particular model type results in the lowest RMSE is further listed in the table.

<table>
<thead>
<tr>
<th>Model</th>
<th>mean(RMSE) [ms]</th>
<th>range(RMSE) [ms]</th>
<th>Optimum cases (total/female/male)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>9.5443</td>
<td>[5.5240,12.4022]</td>
<td>16/4/12</td>
</tr>
<tr>
<td>B</td>
<td>9.6281</td>
<td>[5.6420,12.3761]</td>
<td>14/8/6</td>
</tr>
<tr>
<td>C</td>
<td>9.5481</td>
<td>[5.5492,12.3900]</td>
<td>0/0/0</td>
</tr>
<tr>
<td>D</td>
<td>9.5586</td>
<td>[5.5608,12.3862]</td>
<td>0/0/0</td>
</tr>
<tr>
<td>E</td>
<td>9.5462</td>
<td>[5.5254,12.4003]</td>
<td>4/1/3</td>
</tr>
<tr>
<td>F</td>
<td>9.5547</td>
<td>[5.5600,12.3860]</td>
<td>5/2/3</td>
</tr>
</tbody>
</table>

**Table 7.1: Comparison of the six different regression models**

It is noticed by looking at the table that model type A, the linear model, is the optimal for a total of 16 subjects and model type B, the hyperbolic model, is the optimal one for 14 subjects. The RMSE for model type B is however the largest of the six model
types. Looking at the RMSE for regression type B more closely, it was found that when the type was not found to be the optimum it was usually the one resulting in the largest RMSE. It is also noticed that types A, C and E result in the lowest mean RMSE among the subjects.

It is of interest to test if the regression parameters differ significantly between males and females. Whether to use a parametric test or somewhat weaker nonparametric test depends on if it can be assumed that the distribution of the parameters is normal. In order to test this, a Kolmogorov Smirnov test is applied, described in Section 5.4. The p-values for the tests are listed in Table 7.2. The first column applies when the regression parameters for the males and females are pooled together and tested and the latter two when the distribution of the regression parameters are tested separately for normality. All p-values are larger than 0.05, as can be seen by looking at the table, indicating that the null hypothesis, stating that the distribution is normal, can not be rejected.

<table>
<thead>
<tr>
<th>Method</th>
<th>Pooled slope</th>
<th>Pooled intercept</th>
<th>Females slope</th>
<th>Females intercept</th>
<th>Males slope</th>
<th>Males intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.752</td>
<td>0.428</td>
<td>0.469</td>
<td>0.467</td>
<td>0.282</td>
<td>0.921</td>
</tr>
<tr>
<td>B</td>
<td>0.990</td>
<td>0.609</td>
<td>0.091</td>
<td>0.338</td>
<td>0.498</td>
<td>0.324</td>
</tr>
<tr>
<td>C</td>
<td>1.095</td>
<td>0.629</td>
<td>0.356</td>
<td>0.645</td>
<td>1.056</td>
<td>0.389</td>
</tr>
<tr>
<td>D</td>
<td>0.875</td>
<td>0.495</td>
<td>0.220</td>
<td>0.745</td>
<td>0.316</td>
<td>0.387</td>
</tr>
<tr>
<td>E</td>
<td>0.532</td>
<td>0.245</td>
<td>0.724</td>
<td>0.756</td>
<td>1.101</td>
<td>0.067</td>
</tr>
<tr>
<td>F</td>
<td>0.903</td>
<td>0.614</td>
<td>0.456</td>
<td>0.647</td>
<td>0.016</td>
<td>0.113</td>
</tr>
</tbody>
</table>

Table 7.2: P-values resulting from Kolmogorov Smirnov tests for Gaussianity

A t-test is used, described in Section 5.5, to test whether the regression parameters differ between males and females. It is the appropriate test for testing whether two normal distributions differ in mean when their variance is unknown. The test statistic differs however, depending on whether it can be assumed that the variances are equal or not. Therefore it needs to be tested whether the variances of the distributions for the males and the females, can be assumed to be equal. The p-values resulting from the tests are shown in Table 7.3.

<table>
<thead>
<tr>
<th>Model</th>
<th>Slope</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.3334</td>
<td>0.0021</td>
</tr>
<tr>
<td>B</td>
<td>0.2604</td>
<td>0.4569</td>
</tr>
<tr>
<td>C</td>
<td>0.0994</td>
<td>0.2566</td>
</tr>
<tr>
<td>D</td>
<td>0.2730</td>
<td>0.2576</td>
</tr>
<tr>
<td>E</td>
<td>0.4114</td>
<td>0.0021</td>
</tr>
<tr>
<td>F</td>
<td>0.2783</td>
<td>0.6212</td>
</tr>
</tbody>
</table>

Table 7.3: P-values resulting from a equal variance test between males and females

The variances of the distributions of the parameters for the males and the females can be assumed to be the equal, except for the intercept in models A and E, as can
be seen in the table. When testing whether the mean of the two distributions are the same, the test statistic in (5.24) is used. For the cases when the variances can be assumed to be equal the test statistic has a \( t \) distribution with 37 degrees of freedom \((n_1 + n_2 - 2)\) but 34.673 and 34.645 degrees of freedom for the test of the intercept in models A and E respectively, according to (5.25). The p-values resulting from the tests are given in Table 7.4.

<table>
<thead>
<tr>
<th>Model</th>
<th>Slope</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&gt;0.001</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>B</td>
<td>0.0828</td>
<td>0.0757</td>
</tr>
<tr>
<td>C</td>
<td>&gt;0.001</td>
<td>0.2754</td>
</tr>
<tr>
<td>D</td>
<td>&gt;0.001</td>
<td>0.2734</td>
</tr>
<tr>
<td>E</td>
<td>&gt;0.001</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>F</td>
<td>&gt;0.001</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

Table 7.4: P-values resulting from an equal mean t-test between males and females

By looking at the p-values, it can be concluded that for all types of regression models, except type B, either the slope or the intercept of the regression lines differ between males and females. Model type B is the only model where the difference between the slopes is not significant using 0.05 as the level of significance.

It is of interest to test if the QT\(\sim\)RR relationship varies significantly between subjects and also if it can be assumed to stay similar within a subject between days. Since the linear regression model, type A, is found to be the optimal model in most subjects and the one resulting in the lowest mean RMSE among the subjects it will be used to test for inter- and intrasubject variability.

7.1.1 Test of identical regression parameters between subjects

In order to test whether the regressions between the subjects are identical, it is suggested in [13], that the individually fitted regression parameters are compared pairwise for equality. The pairwise comparison will therefore provide, for every subject, the number of subjects that share a common QT\(\sim\)RR relationship with that given subject. However, since the goal here is to test whether it can be assumed that all the subjects in the study share a common QT\(\sim\)RR relationship, the pairwise comparison can be avoided and replaced with a classical test for a lower dimension of the model space, described in Section 5.3.2. It is decided to perform both test, first as it is done by Dr. M. Malik and his associates in [13] and then to use the test for lower dimension of the model space.

7.1.1.1 Pairwise comparison

When dealing with multiple comparison, the level of significance used needs to be lowered to account for the number of comparisons made. While the given level of significance is appropriate for each individual comparison, it is not for the set of all comparisons. It is suggested in [13] to consider p-values of \(p < 10^{-5}\) as significant
7.1 The QT∼RR relationship

when dealing with 14700 comparisons. Here, a total of 741 comparisons are made (39·(38/2)), or about 20 times fewer than in [13]. $p<2\cdot10^{-5}$ ($20\cdot10^{-6}$) will therefore be considered significant.

The test statistic given in (5.22) is used to test for the identity of the regressions, that is the slope and the intercept at the same time. The test statistic is applied on every pair of subjects and the number of significant differences counted. The result is shown in Figure 7.2.

By looking at the figure it is noticed that none of the subjects can be assumed to share a common regression line with all other subjects in the study. One of the subjects does not even share a common regression with any of the other subjects in the study.

7.1.1.2 Test for lower dimension of the model space

It is of interest to test whether it can be assumed that all the subjects in the study share a common QT∼RR relationship.

A linear model describing a common QT∼RR relationship among the subjects can be written as

$$ M1 : QT_i = \eta + \xi \cdot RR_i + \epsilon_i \ i = 1 \ldots N \tag{7.1} $$

where $N$ is the total number of data points available. A model allowing for different slopes and intercepts for the 39 different subjects can be written as

$$ M2 : QT_{i,j} = \eta_j + \xi_j \cdot RR_{i,j} + \epsilon_{i,j} \ i = 1 \ldots n, j = 1 \ldots 39 \tag{7.2} $$

Figure 7.2: The number of nonidentical regressions among the placebo subjects using pairwise comparison
where \( n \) is the number of data points available for the given subject. The hypothesis can be written as

\[
H_0 : \mu = M_1 \\
H_1 : \mu = M_2
\]  

(7.3)

The test statistic in (5.20) is used to test the hypothesis. The resulting test statistic from the test is calculated to be 80.90 (p-value << 0.001) and the null hypothesis therefore strongly rejected. It can therefore be concluded that the \( QT \sim RR \) relationship can not be assumed to be the same among the subjects.

### 7.1.2 Test of identical regression parameters within subjects

It is important that the assumption of similar \( RR \sim QT \) relationship within a subject, between days, is valid when subject specific correction methods are used. In order to test whether this assumption is valid, a test is generated to see if the slopes and the intercepts of the linear regression models are identical on day -1 and day 7. This can be done by estimating separately linear regression models for every placebo subject on the form (with a notation as is used in statistical software packages such as Splus and SAS)

\[
QT = \eta + \xi RR + \xi_2 day + \xi_3 RR \cdot day
\]  

(7.4)

where \( day \) is a factor variable with two factors, day -1 and day 7. If \( \xi_2 \) is found to be significant it means that the intercepts of the regression lines for the two days can not be assumed to be identical. If however \( \xi_3 \) is found to be significant, the slopes of the two regression lines representing the two days can not be assumed to be the same.

The test statistic defined in (5.24) is used to test the hypothesis of significant parameters. Only one subject, out of the 39 subjects, was found to have significantly different slopes and intercepts between days. A plot of the data points, for four subjects during the two days, along with the fitted regression lines is shown in Figure 7.3. The subject shown in the top left corner is the only subject found with significant difference between the two slopes and the two intercepts.

### 7.2 Estimation of the correction parameters

In order to see if the expressions for the correction parameters, \( \alpha_A, \alpha_B, \alpha_D \) and \( \alpha_E \), derived in Chapter 6 are correct, the parameters are estimated iteratively as suggested in [13] and using the derived expressions. The two methods were found to give the same results.

The expression for \( \alpha_C \) and \( \alpha_E \) were further compared to the corresponding iteratively estimated parameters to see if the approximation used in the derivation is accurate. The smallest difference between the two methods, for the parabolic model was found to be 0.21\% while the largest 21.35\%, indicating that the approximation of the function is not good enough. In the analysis, the iteratively estimated parameter in correction type \( C_c \) will therefore be used.

For the shifted logarithmic model, the expression in (6.23) is used to calculate the correction parameter and it compared to the corresponding iteratively estimated parameter. The largest difference between the two methods was found to be 0.4\%,
7.2 Estimation of the correction parameters

Figure 7.3: QT~RR relationship for four subjects for the two days, day -1 and day 7

indicating that the approximation is accurate.
Bar plots of the correction parameters, calculated using the appropriate expression ($\alpha_C$ though estimated iteratively), along with the estimated mean value and the range for the six correction types is shown in Figure 7.4.
It is noticed by looking at the figure that the value of the correction parameters differs somewhat between the subjects. It is further noticed that the Bazett parameter, corresponding to $\alpha_C = 0.5$ does not even lie in the range of the estimated correction parameters for model type $C_c$. As for the LS fitted regression parameters, Kolomogorov Smirnov test is applied to see if it can be assumed that the parameters are normally distributed. In all cases the p-values were larger than 0.05 indicating that the null hypothesis can not be rejected. The distribution of the correction parameters is therefore assumed to be normal.
The QTc intervals are estimated for every subject using the the six correction types shown in (6.2) and the appropriate expression for the correction parameter ($\alpha_C$ estimated iteratively). For the 39 subjects the optimal correction type is determined, defined as the one resulting in the smallest correlation between the QTc interval and the corresponding RR interval. The number of subjects each correction type was found to be the optimal is listed in Table 7.5 along with the number of times the corresponding regression formula was found to lead to the smallest RMSE, also shown in Table 7.1.
It can be seen in the table that the parabolic and the exponential models are the two types that leads most often to the lowest correlation between the two intervals. It can further be seen, that although a specific regression type is found to result in the lowest RMSE, it does not mean that the corresponding correction type results in the lowest correlation between the QTc and the RR intervals. By using the regression RMSE as
Figure 7.4: The values of the correction parameters for the 39 subjects and the six different correction types

<table>
<thead>
<tr>
<th>Type</th>
<th>Optimum cases LS</th>
<th>Optimum cases COR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Hyperbolic</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Parabolic</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Logarithmic</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Shifted logarithmic</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Exponential</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 7.5: The number of time the given correction type was found to be optimal, using $\min(RMSE)$ and $\min(|COR|)$

A criteria for choosing the optimal correction type, as is done in [13] might therefore lead to some bias in the analysis. How much influence this has will be looked at in Section 7.3.5.

### 7.3 QT correction

A method needs to be designed such that QT intervals recorded at different heart rates can be compared. Since it has been shown that the QT~RR relationship exhibits a variability between subjects, a correction formula that leads to zero RR-QTc covariance in one subject
7.3 QT correction

can lead to a large covariance in another. This means that when using the same correction formula in a number of subjects, some over correction and some under correction will occur. If the desired result is zero correlation between the QTc and the RR intervals within every subject, subject specific methods should therefore be used. If however only mean changes in QTc are of interest the same correction formula could be applied on numbers of subjects and it assumed that the over corrections and the under correction cancel each other out, leaving the mean change be caused by the drug affect.

In the chapter, both approaches will be looked at and the following questions answered

- Is the method leading to zero covariance between RR and QTc within every subject?
- When using the same correction formula for more than one subject, does the over and under corrections cancel each other out?

To answer the latter question an optimized subject specific correction will be applied to all the placebo subjects. That is, for every subject the correction formula from (6.2) that leads to the smallest covariance between RR and QTc is chosen. The correction parameter in the chosen formula is consequently estimated for the subject and the resulting correction formula applied on the data. Afterwards, other kinds of correction methods are applied and the resulting QTc intervals compared to the optimized individually estimated QTc intervals. The correction methods that will be compared to the individual optimized correction are

1. Predefined correction methods
   - Bazett
   - Fridericia

2. Study specific corrections, where the same correction parameter is applied on the whole study population. The correction parameter is further
   - estimated from the pooled data of the study - the pooled method.
   - estimated individually for every subject in the study and the mean of the estimated parameters used - the mean method.
   - estimated individually for every subject in the study and the median of the estimated parameters used - the median method.

3. Gender specific corrections, where two different correction parameters are applied, one on the females and another on the males. The correction parameters are further
   - estimated from the pooled data for females and pooled data for males - the pooled method.
   - estimated individually for every subject in the study and the mean of the estimated parameters for the females applied on the females and the mean of the estimated parameters for the males applied on the males - the mean method.
4. Panel specific corrections where five different correction parameters are applied, one for every panel in the study. The correction parameters are further

- estimated from the pooled data within every panel - the pooled method.
- estimated individually for every subject in the study and the mean of the estimated parameters within every panel used - the mean method.
- estimated individually for every subject in the study and the median of the estimated parameters within every panel used - the median method.

For the different methods, the six different correction types listed in (6.2) will further be applied. The difference between a subject specific correction using a fixed type of correction for all the subjects and the optimized subject correction will also be looked at.

As stated above, the idea behind the QTc interval is to normalize the QT interval as it would have been recorded at a standard RR interval of 1 sec (corresponds to heart rate of 60 bps). The resulting QTc interval should therefore be noncorrelated with heart rate. To visualize what happens if this fails and the QTc interval is correlated with heart rate, three figures are produced. The first figure shows a scatter plot of data where the QTc interval is not correlated with heart rate, the next where the QTc interval is positively correlated with heart rate and the last where the QTc interval is negatively correlated with heart rate. The figures are shown in Figure 7.5, 7.6 and 7.7 respectively.

It can be seen by looking at the figures that in the case of positive correlation between the RR and the QTc intervals, some over correction is expected to occur for RR intervals larger than 1 sec but some under correction for RR intervals smaller than 1 sec. The opposite is expected to happen in case of negative correlation. This behavior is summarised in figure 7.8.

### 7.3.1 Predefined correction methods

The simplest approach to heart rate correction of the QT interval is to use a predefined correction model. One of these models is the Bazett formula published in 1920 [6], defined as

\[
QTc = \frac{QT}{\sqrt{RR}}.
\]

Even though the method has been criticized frequently [7]-[8], it is still the most widely used correction method in practise.

Another commonly used method, published the same year as the Bazett correction, is the Fridericia formula [9] defined as

\[
QTc = \frac{QT}{\sqrt[3]{RR}}.
\]
Both correction methods are applied on the placebo data. In order to see how well the methods are performing regarding zero correlation between the RR and the QTc interval, the correlation of the two intervals is calculated for every subject separately. The size of the resulting correlation for the 39 subjects is shown in Figure 7.9. Due to the large correlation between the two intervals it can be concluded that the two formulas are not appropriate to use when a zero correlation within every subject is wanted. It can be seen by looking at the figure that the Bazett method leads
Figure 7.8: Expected over and under corrections

**Bazett**

Range = [-0.8457, -0.2959]
Median = -0.6153

**Fridericia**

Range = [-0.6684, 0.3413]
Median = -0.1553

Figure 7.9: Correlation between the QTc and the RR interval for the placebo subjects using the Bazett and the Fridericia correction methods
to negative correlation for all the subjects. The Fridericia method however results in negative correlation for almost all the male subjects but positive correlation for some female subjects and negative for others. To visualize what influence it has on the QTc~RR relationship, using these different methods, a scatter plot of the two intervals, for two subjects, one male and one female is produced for the two methods. The plots are shown in Figure 7.10.

Using Figure 7.8, it is concluded that the Bazett model is artificially prolonging the QTc interval when RR < 1 sec while it is shortened when RR > 1 sec. For the Fridericia model, the same is happening for the subjects with negative correlation between the RR and the QTc interval while the opposite is happening for the subjects with positive correlation between the two intervals.

It is of interest to see how much influence this over and under correction is having on the QTc interval. The range of the difference in QTc between the two methods and the QTc calculated by the optimized individual method, along with the mean of the difference is shown in Table 7.6.

<table>
<thead>
<tr>
<th>Method</th>
<th>Range</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bazett</td>
<td>[-57.1906, 38.8743]</td>
<td>-1.88</td>
</tr>
<tr>
<td>Fridericia</td>
<td>[-27.5184, 16.2916]</td>
<td>-1.43</td>
</tr>
</tbody>
</table>

Table 7.6: The range and the mean of the difference in ms from the optimized individual method
By looking at the table it is noticed that the largest under correction using the Bazett method is about 57 ms and the largest over correction about 38 ms. The under and over corrections are smaller using the Fridericia method or about 28 ms and 16 ms respectively.

In order to see if the under and over corrections are canceling each other out, among the subjects, the difference between the subject optimized corrected QTc interval and the QTc intervals resulting from the Bazett and the Fridericia models are looked at. Histograms of the difference, pooled for all the subjects, is shown in Figure 7.11 and categorized by gender in Figure 7.12. The sums of the differences is included in the figures. If the over and under corrections are canceling each other out completely, this sum would be equal to zero.

The sum of the error for the Bazett correction is -4068.44 ms while the sum is equal to -3094.44 ms for the Fridericia correction, as can be seen by looking at the figures. This means that both methods lead to an under correction of the QTc interval when summing the error for all the subjects.

It is also interesting to look at how the error is distributed when it is categorized by gender. The Bazett formula for the males is artificially prolonging the QTc interval for the females (sum = 4518.22 ms) while it is shortened for the males (sum = -8586.56). Since the females that were given placebo have on average RR interval of 0.930 sec while the males have on average 1.080 sec, as shown in Table 3.4 this does not come to a surprise since the correlation between the RR and the Bazett corrected QT interval is negative. Looking at the error for the Fridericia correction categorized by gender, it can be seen that the sum of the errors for the females is only -59.878 ms while it is -3034.562 ms for the males. This can be explained by noticing that the correlation for the males is always negative while for some of the females it is positive and others.
negative, allowing the error to cancel each other out to a certain point.

### 7.3.2 Study specific correction methods

When using study specific correction methods, the same correction parameter is applied on the whole study population. The applied correction parameter is estimated using the three different methods, described in Section 7.3 (the mean, the median and the pooled methods), for the six correction types. The estimated correction parameters used for the QTc calculations are listed in Table 7.7.

<table>
<thead>
<tr>
<th>Method</th>
<th>A_c</th>
<th>B_c</th>
<th>C_c</th>
<th>D_c</th>
<th>E_c</th>
<th>F_c</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>0.1155</td>
<td>-0.1151</td>
<td>0.2939</td>
<td>0.1149</td>
<td>0.1706</td>
<td>-0.3158</td>
</tr>
<tr>
<td>median</td>
<td>0.1085</td>
<td>-0.1152</td>
<td>0.2871</td>
<td>0.1117</td>
<td>0.1607</td>
<td>-0.3120</td>
</tr>
<tr>
<td>pooled</td>
<td>0.1272</td>
<td>-0.1402</td>
<td>0.3424</td>
<td>0.1360</td>
<td>0.1920</td>
<td>-0.3746</td>
</tr>
</tbody>
</table>

**Table 7.7: The correction parameters used for the study specific methods**

It can be seen by looking at the table that the correction parameters for the mean and the median methods are similar while the numerical value of the parameters for the pooled methods are higher than for the other two methods. The reason might be found by looking at how the correction parameter is calculated. Defining, $\mathbf{RR} = [RR_1 \ldots RR_N]^T$ and $\mathbf{QT} = [QT_1 \ldots QT_N]^T$, as vectors of $N$ observations of the intervals and considering, for example, correction type $A_c$, the correction parameter,
also given in (6.8) is calculated as
\[ \alpha_A = (RR^T \cdot RR)^{-1} RR^T \cdot QT. \]

Using the estimates of the covariance between \( RR \) and \( QT \) and the variance of \( RR \) given in (6.6) and (6.7) this can be written as
\[ \alpha_A = \frac{\text{COV}(RR, QT)}{\text{VAR}(RR)} \tag{7.7} \]

This means that the mean of the fraction between the individually estimated covariance between \( RR \) and \( QT \) and the individually estimated \( RR \) variance is lower than the corresponding ratio using pooled data.

The correlation between the estimated QTc interval and the RR interval, using the three methods and the six model types, is estimated within every subject to see how well the method is performing in zero correlation between the two intervals. The range of the estimated correlation for the three methods and six correction types is listed in Table 7.8.

<table>
<thead>
<tr>
<th>Type</th>
<th>Range</th>
<th>Type</th>
<th>Range</th>
<th>Type</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>median</td>
<td>pooled</td>
<td></td>
<td>mean</td>
</tr>
<tr>
<td>A</td>
<td>[-0.6598, 0.5769]</td>
<td>[-0.6239, 0.6115]</td>
<td>[-0.7295, 0.4813]</td>
<td>B</td>
<td>[-0.6035, 0.5493]</td>
</tr>
<tr>
<td>C</td>
<td>[-0.5905, 0.4750]</td>
<td>[-0.5782, 0.4917]</td>
<td>[-0.6894, 0.3016]</td>
<td>D</td>
<td>[-0.5916, 0.4954]</td>
</tr>
<tr>
<td>E</td>
<td>[-0.6601, 0.5796]</td>
<td>[-0.6250, 0.6128]</td>
<td>[-0.7345, 0.4782]</td>
<td>F</td>
<td>[-0.5913, 0.4935]</td>
</tr>
</tbody>
</table>

Table 7.8: Range of the correlation between QTc and RR for the placebo subjects using the study specific correction

By looking at Table 7.8, it can be concluded that the study specific method is not performing well in leading to zero correlation between the two intervals for individual subjects. A figure showing the size of the correlation for every placebo treated subject in the study, using the mean, the median and the pooled methods, for correction type Cc is shown in Figure 7.13.

By looking at the figure, it is noticed that the correlation resulting from the mean and the median methods are similar. The two intervals are negatively correlated for most of the males while they are positively correlated for all the females. For the pooled method, almost all the male subjects undergo negative correlation while the correlation is positive for some of the female subjects and negative for others.

In order to see how much influence this over and under corrections have on the QTc interval, the difference between the optimized individual correction and the QTc resulting from the study specific methods using the mean method and the pooled method is looked at (median method skipped because of similarity to the mean method). The range and the mean of the difference between the methods are listed in Table 7.9.

By looking at the range of the difference from the table, it is noticed that the largest under correction of a single QTc interval is found when using pooled data and correc-
Figure 7.13: The correlation between QTc and RR using the study specific method and correction type C.

<table>
<thead>
<tr>
<th>Type</th>
<th>Mean</th>
<th>Range</th>
<th>Pooled</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>A_c</td>
<td>-2.27</td>
<td>[-30.99, 14.31]</td>
<td>-2.60</td>
<td>[-37.98, 11.85]</td>
</tr>
<tr>
<td>B_c</td>
<td>0.45</td>
<td>[-15.95, 24.90]</td>
<td>0.49</td>
<td>[-23.72, 32.07]</td>
</tr>
<tr>
<td>C_c</td>
<td>-1.40</td>
<td>[-22.60, 15.62]</td>
<td>-1.62</td>
<td>[-29.41, 16.73]</td>
</tr>
<tr>
<td>D_c</td>
<td>-0.87</td>
<td>[-22.44, 20.25]</td>
<td>-1.09</td>
<td>[-30.29, 19.65]</td>
</tr>
<tr>
<td>E_c</td>
<td>-2.06</td>
<td>[-31.72, 16.41]</td>
<td>-2.40</td>
<td>[-38.64, 13.92]</td>
</tr>
<tr>
<td>F_c</td>
<td>0.84</td>
<td>[-21.93, 20.43]</td>
<td>-1.07</td>
<td>[-29.79, 19.58]</td>
</tr>
</tbody>
</table>

Table 7.9: The range and the mean of the differences (in ms) between the optimal correction and the subject specific methods shown in the table.

...
Analysis of QT correction methods based on placebo subjects

Figure 7.14: The difference in QTc between the optimized individual correction and study specific correction using the mean method

<table>
<thead>
<tr>
<th>Type</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-4930</td>
<td>-3051</td>
<td>-1879</td>
<td>-5629</td>
<td>-4590</td>
<td>-1040</td>
</tr>
<tr>
<td>B</td>
<td>991</td>
<td>668</td>
<td>302</td>
<td>1069</td>
<td>-1225</td>
<td>2294</td>
</tr>
<tr>
<td>C</td>
<td>-3042</td>
<td>-1775</td>
<td>-1268</td>
<td>-3501</td>
<td>-3550</td>
<td>49</td>
</tr>
<tr>
<td>D</td>
<td>-1889</td>
<td>-1014</td>
<td>-876</td>
<td>-2373</td>
<td>-2966</td>
<td>593</td>
</tr>
<tr>
<td>E</td>
<td>-4465</td>
<td>-2737</td>
<td>-1728</td>
<td>-5203</td>
<td>-4372</td>
<td>-831</td>
</tr>
<tr>
<td>F</td>
<td>-1831</td>
<td>-981</td>
<td>-850</td>
<td>-2310</td>
<td>-2954</td>
<td>645</td>
</tr>
</tbody>
</table>

Table 7.10: Sum of the difference (in ms) between the optimal correction and the study specific methods shown in the table

It is noticed by looking at the table that the mean method is performing better than the pooled method in leading to a total sum closer to zero. Looking at, for example, the sums for correction type C, using the mean method it is noticed that is is negative, both for the females and the males. Noting that the RR interval for the males is on average larger than 1 sec but smaller than 1 sec for the females and the fact that the correlation for the males is most often negative but positive for the females, as can be seen in Figure 7.13, rationalises this behavior. Looking at the sums for the pooled method, it can be seen that it is negative for the males but positive for the females.
Again by looking at how the correlations are distributed explains this. While the correlation is negative for the males it is positive for some of the females but negative for others, allowing the error to cancel each other out, up to a certain point.

### 7.3.3 Gender specific correction methods

For the gender specific correction methods, one correction parameter is estimated and applied on the female subjects and another one on the male subjects. The same three methods for estimating the correction parameters are used as for the subject specific correction and again using the six correction types. The estimated correction parameters, used to calculate the QTc interval, are listed in Table 7.11. The range of the estimated correlation between the QTc interval and the RR interval estimated for every subject, using the different gender specific corrections is shown in Table 7.12.

<table>
<thead>
<tr>
<th>Method</th>
<th>A_c</th>
<th>B_c</th>
<th>C_c</th>
<th>D_c</th>
<th>E_c</th>
<th>F_c</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean, females</td>
<td>0.1467</td>
<td>-0.1247</td>
<td>0.3516</td>
<td>0.1553</td>
<td>0.2157</td>
<td>-0.3714</td>
</tr>
<tr>
<td>median, females</td>
<td>0.1479</td>
<td>-0.1187</td>
<td>0.3620</td>
<td>0.1372</td>
<td>0.2217</td>
<td>-0.3798</td>
</tr>
<tr>
<td>pooled, females</td>
<td>0.1589</td>
<td>-0.1409</td>
<td>0.3841</td>
<td>0.1506</td>
<td>0.2355</td>
<td>-0.4128</td>
</tr>
<tr>
<td>mean, males</td>
<td>0.0954</td>
<td>-0.1084</td>
<td>0.2566</td>
<td>0.1015</td>
<td>0.1416</td>
<td>-0.2793</td>
</tr>
<tr>
<td>median, males</td>
<td>0.0964</td>
<td>-0.1041</td>
<td>0.2539</td>
<td>0.0997</td>
<td>0.1464</td>
<td>-0.2727</td>
</tr>
<tr>
<td>pooled, males</td>
<td>0.1384</td>
<td>-0.1694</td>
<td>0.3867</td>
<td>0.1546</td>
<td>0.2066</td>
<td>-0.4271</td>
</tr>
</tbody>
</table>

Table 7.11: The correction parameters used in the gender specific correction

<table>
<thead>
<tr>
<th>Type</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
</tr>
<tr>
<td>A</td>
<td>[-0.5302, 0.5256]</td>
</tr>
<tr>
<td>B</td>
<td>[-0.5485, 0.4910]</td>
</tr>
<tr>
<td>C</td>
<td>[-0.4970, 0.5189]</td>
</tr>
<tr>
<td>D</td>
<td>[-0.5043, 0.4818]</td>
</tr>
<tr>
<td>E</td>
<td>[-0.5328, 0.5127]</td>
</tr>
<tr>
<td>F</td>
<td>[-0.5048, 0.4758]</td>
</tr>
</tbody>
</table>

Table 7.12: The range of the correlation between QTc and RR for the placebo subjects using gender specific methods

It is noticed when looking at the table that the mean and the median methods are leading to similar range in the correlation while the pooled method is resulting in more negative correlations than the other two methods, as before. As for the study specific methods, the size of correlation resulting from using the mean method and correction type C_c is plotted in Figure 7.15. By looking at the figure it can be seen that for the mean and the median method the correlations are positive for some of the males and females and negative for others. This behavior is
Figure 7.15: The correlation between QTc and RR using the gender specific method and correction type $C_c$

expected since the mean and the median within the two groups were used. For the pooled method, the intervals for all males, except for one, are negatively correlated while the correlation is positive for some of the females but negative for others.

In order to see how much these correlations are influencing the QTc interval, the range and the mean of the difference for the mean and the pooled methods, are listed in Table 7.13.

<table>
<thead>
<tr>
<th>Type</th>
<th>Mean</th>
<th>Range</th>
<th>Pooled</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-0.46</td>
<td>[-22.65, 11.21]</td>
<td>-2.26</td>
<td>[-43.94, 14.36]</td>
</tr>
<tr>
<td>B</td>
<td>1.03</td>
<td>[-14.11, 22.25]</td>
<td>-0.48</td>
<td>[-32.54, 46.07]</td>
</tr>
<tr>
<td>C</td>
<td>-0.09</td>
<td>[-17.70, 12.07]</td>
<td>-1.81</td>
<td>[-36.44, 21.24]</td>
</tr>
<tr>
<td>D</td>
<td>0.31</td>
<td>[-17.88, 13.86]</td>
<td>-1.41</td>
<td>[-36.98, 25.42]</td>
</tr>
<tr>
<td>E</td>
<td>-0.29</td>
<td>[-23.29, 11.19]</td>
<td>-2.10</td>
<td>[-43.13, 16.64]</td>
</tr>
<tr>
<td>F</td>
<td>0.33</td>
<td>[-17.47, 14.14]</td>
<td>-1.42</td>
<td>[-36.58, 25.49]</td>
</tr>
</tbody>
</table>

Table 7.13: The range and the mean of the differences (in ms) between the optimal correction and the gender specific methods shown in the table

The largest under correction of a single QTc interval is found when using the pooled
method and the linear model, or about 44 ms. The largest over correction is further found to be about 46 ms using the pooled method and the hyperbolic model.

Figure 7.16: The difference in QTc between the optimized individual correction and gender specific correction using the mean method

To visualize how the difference is distributed, histograms of the difference using the mean method where the difference from all the subjects is pooled together is shown in Figure 7.16 and categorized by gender in Figure 7.17. A table showing the sums of the difference between the optimized subject correction and the gender specific corrections are further shown in Table 7.14.

<table>
<thead>
<tr>
<th>Type</th>
<th>Mean</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total</td>
<td>male</td>
</tr>
<tr>
<td>A_c</td>
<td>-998</td>
<td>-992</td>
</tr>
<tr>
<td>B_c</td>
<td>2234</td>
<td>1143</td>
</tr>
<tr>
<td>C_c</td>
<td>-204</td>
<td>-496</td>
</tr>
<tr>
<td>D_c</td>
<td>668</td>
<td>121</td>
</tr>
<tr>
<td>E_c</td>
<td>-638</td>
<td>-743</td>
</tr>
<tr>
<td>F_c</td>
<td>704</td>
<td>139</td>
</tr>
</tbody>
</table>

Table 7.14: Sum of the difference (in ms) between the optimal correction and the gender specific methods shown in the table

By looking at the table is is noticed that some of the total sums for the mean methods are positive while others are negative. The numerical value of the sums are further lower than the corresponding sums in the study specific corrections, except for cor-
Figure 7.17: The difference in QTc between the optimized individual correction and gender specific correction using the mean method categorized by gender.

7.3.4 Panel specific correction methods

For the panel specific correction methods, one correction parameter is estimated and applied within each of the five panels. The same three methods for estimating the correction parameters are used as for the other correction methods and again using the six correction types. The correction parameters used for calculation of QTc for the parabolic model, type Cc, are shown in table 7.15.

<table>
<thead>
<tr>
<th>Method/Panel</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>0.2422</td>
<td>0.2539</td>
<td>0.2756</td>
<td>0.3645</td>
<td>0.3368</td>
</tr>
<tr>
<td>median</td>
<td>0.2348</td>
<td>0.2820</td>
<td>0.2532</td>
<td>0.3664</td>
<td>0.3204</td>
</tr>
<tr>
<td>pooled</td>
<td>0.3662</td>
<td>0.3354</td>
<td>0.3912</td>
<td>0.4129</td>
<td>0.4854</td>
</tr>
</tbody>
</table>

Table 7.15: The correction parameters for the panel specific method and correction type Cc

It can be seen by looking at the table that there is some difference between the parameters used by the mean method and the median method. Again the parameters...
used by the pooled method are considerably higher than for the other two methods. It is further noticed that for all the methods, the parameters used in the two last panels are higher than the first three panels which can be explain by the fact that the first three panels consists of male subjects while the last two of female subjects.

The ranges of the estimated correlation between the QTc interval and the RR interval estimated for every subject, using the different panel specific corrections are shown in Table 7.16.

<table>
<thead>
<tr>
<th>Range</th>
<th>Type</th>
<th>mean</th>
<th>median</th>
<th>pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>[-0.5116, 0.4611]</td>
<td>[-0.5705, 0.5027]</td>
<td>[-0.6907, 0.0867]</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>[-0.5398, 0.5005]</td>
<td>[-0.6088, 0.5318]</td>
<td>[-0.8154, 0.0598]</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>[-0.4889, 0.4712]</td>
<td>[-0.5658, 0.5270]</td>
<td>[-0.6807, 0.0928]</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>[-0.5218, 0.4286]</td>
<td>[-0.5647, 0.4917]</td>
<td>[-0.7546, 0.0183]</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>[-0.5245, 0.4456]</td>
<td>[-0.5686, 0.4825]</td>
<td>[-0.7044, 0.0595]</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>[-0.5256, 0.4241]</td>
<td>[-0.5667, 0.4885]</td>
<td>[-0.7632, 0.0114]</td>
<td></td>
</tr>
</tbody>
</table>

Table 7.16: Range of the correlation between QTc and RR for the placebo subjects using panel specific methods

The size of the correlation for the 39 subjects, using the three methods and correction type C is shown in Figure 7.18.

Figure 7.18: The correlation between QTc and RR using correction type C.
By looking at Table 7.16 and Figure 7.18, it can be seen that there is a larger difference between the correlation for the mean and the median methods now, than for the study- and the gender specific methods. This does not come to a surprise since the correction parameters used for the two methods are somewhat different. The pooled method is once again is resulting in more negative correlation than the other two methods.

The ranges and the means of the difference between the optimized individual method and the panel specific corrections, using the mean, the median and the pooled methods, are listed in Table 7.17.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>range</td>
<td>mean</td>
</tr>
<tr>
<td>B</td>
<td>0.91</td>
<td>[-16.47, 22.66]</td>
<td>0.50</td>
</tr>
<tr>
<td>C</td>
<td>0.00</td>
<td>[-17.31, 11.56]</td>
<td>-0.22</td>
</tr>
<tr>
<td>D</td>
<td>0.34</td>
<td>[-18.73, 15.94]</td>
<td>0.26</td>
</tr>
<tr>
<td>E</td>
<td>-0.11</td>
<td>[-22.83, 12.28]</td>
<td>-0.12</td>
</tr>
<tr>
<td>F</td>
<td>0.36</td>
<td>[-18.46, 16.32]</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Table 7.17: The range and the mean of the differences (in ms) between the optimal correction and the panel specific methods shown in the table

The largest under correction of a single QTc interval is found when using the pooled method and correction type E, or 35.57 ms. The largest over correction is further found to be 44.44 ms when using the pooled method and correction type B.

Histograms of the difference using the mean method where the difference from all the subjects is pooled together is shown in Figure 7.19. To get an idea of how the difference is distributed within the panels, histograms of the difference categorized by panels for the mean method and correction type Cc is shown in Figure 7.20. It is noticed that the distribution of the difference is very different between the panels. For panels 1 and 3 it is tight, somewhat wider for panels 4 and 5 and very wide for panel 2. In order to explain what is happening, the value of the correction parameters for correction type C, for all placebo subjects, are shown in Figure 7.21. By looking at the figure it is noticed that the correction parameter for two of the subjects from panel 3 is much lower than for the other subjects explaining the wide distribution of the difference.

A table showing the sums of the difference between the optimized individual correction and the panel specific correction is finally shown in Table 7.18.

It is noticed by looking at the table that the mean method using correction type Cc almost manages to cancel the over- and under correction out and leads to a total sum of only 3 ms. It is further noticed that correction types Dc and Fc manage to do the same for the male subjects (panels 1, 2 and 3).
Figure 7.19: The sums of the difference between the optimized individual method and the panel specific method using the mean method.

Figure 7.20: The sums of the difference between the optimized individual method and the panel specific method using the mean method categorized by panels.
7.3.5 Subject specific correction methods

In this section, the optimized individual correction will be compared to subject specific methods using a fixed correction type. That is, instead of choosing the optimal correction for a single subject, all six correction types are applied on every subject and compared to the optimized correction. The difference between the two methods will therefore represent how much influence it has on the QTc interval when a wrong correction type is used.

In order to see what influence it has on the QTc interval, using previously chosen model type instead of choosing the optimum one, the estimated mean and range of the difference are shown in Table 7.19.

It is noticed by looking at the table that choosing correction type Bc is causing the
7.3 QT correction

<table>
<thead>
<tr>
<th>Type</th>
<th>range</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&lt;sub&gt;c&lt;/sub&gt; Linear</td>
<td>[-7.8086 , 3.5282]</td>
<td>0.09</td>
</tr>
<tr>
<td>B&lt;sub&gt;c&lt;/sub&gt; Hyperbolic</td>
<td>[-8.5076 , 9.2927]</td>
<td>-0.51</td>
</tr>
<tr>
<td>C&lt;sub&gt;c&lt;/sub&gt; Parabolic</td>
<td>[-5.4904 , 4.9040]</td>
<td>-0.10</td>
</tr>
<tr>
<td>D&lt;sub&gt;c&lt;/sub&gt; Logarithmic</td>
<td>[-4.0722 , 4.9842]</td>
<td>-0.20</td>
</tr>
<tr>
<td>E&lt;sub&gt;c&lt;/sub&gt; Shifted logarithmic</td>
<td>[-7.2774 , 3.7781]</td>
<td>0.06</td>
</tr>
<tr>
<td>F&lt;sub&gt;c&lt;/sub&gt; Exponential</td>
<td>[-5.0632 , 4.7988]</td>
<td>-0.23</td>
</tr>
</tbody>
</table>

Table 7.19: The range and the mean of the difference between the optimized subject method and the subject specific method

largest deviation from the optimal correction. Histograms of the difference between the two methods, using the six correction types are shown in Figure 7.22.

![Figure 7.22: The distribution of the difference between the optimized subject specific method and the subject specific method](image)

Finally, it is of interest to see how the value of the individually fitted correction parameters is dependent on the number of data points used to estimate it, since 56 data points were used in the analysis of the placebo subjects but only 15 data points are available for the on-drug subjects. In order to look at this possible dependency, the correction parameter, from correction type C<sub>c</sub>, is estimated for the 39 subjects, using 15 data points and up to 56 data points, adding one point at a time. Since some diurnal variations might be present in the data, the order of the points is chosen randomly. The result is shown in Figure 7.23. Looking at the figure it is noticed that the value of the correction parameters is not stable as more data points are used to estimate it. The difference in α<sub>c</sub>, using 15 and 56 data points is shown, for the 39 subjects in Figure 7.24.
Figure 7.23: The value of the correction parameter for correction type $C_c$ when adding one data point at a time for the estimation.

Figure 7.24: Difference of the value of the correction parameter for correction type $C_c$ when using 15 data points and using 56 data points.

By looking at the figure it is noticed that for some of the subjects the difference is very large indicating that using only 15 data points to estimate the individual correction parameter might be somewhat dangerous.
7.4 Summary of methods used for QT correction

By comparing the different methods in the chapter, it is noticed that the panel-specific correction, using the mean method and correction type Cc, performed best in canceling out the difference in QTc between the methods and the optimized individual method. The method is therefore assumed to give accurate results when mean changes in the QTc interval are looked at. When a zero correlation between the QTc interval and the RR interval is however wanted, predefined-, subject-, gender- and panel specific methods should be avoided. By looking at Tables 7.6, 7.9, 7.13 and 7.17 it is noticed that the mean difference in QTc between the methods and the optimized subject correction ranges from about -2.60 ms using the study specific correction with the mean method and the linear model and up to around 1.03 ms when using the gender specific correction with the mean method and the hyperbolic model.
Analysis of QT correction methods based on placebo subjects
Chapter 8

Analysis of possible drug induced QTc prolongation

Before possible QT prolongation resulting from intake of LU 35-138 can be analysed it needs to be decided what method to use for the QT correction. Since it has been shown in the previous chapter, that the QT~RR relationship varies between subjects, while it could not be rejected that it is different, within a subject, the subject-specific method seems to be the right method to use. However, there are only 15 off-drug data points available per subject to estimate the correction parameter. Since it has been shown, in Section 7.3.5, that using only 15 data points to estimate the correction parameter can be somewhat dangerous it is decided to do a subject specific correction but to use the panel specific correction using the mean method and correction type $C_c$, to estimate possible QTc prolongations. The Bazett, the Fridericia and the study specific correction, using the pooled method, will in addition be applied on the data since these are the most commonly used corrections in practise.

Since the design was done in parallel, the subjects that were given the placebo are not the same subjects that were given the drug. In order to make the analysis consistent, the parabolic correction is applied on all subjects when using the the subject specific and the study specific methods.

Both analysis of central tendency and categorial analysis will be given, as suggested in [3]. The increase from baseline will be analysed using the largest time matched mean difference between on- and off-drug data (on- and off placebo for the placebo subjects). The time matched difference is defined as

$$\Delta QT_{c_i} = QT_{c_{day 7, hours from intake i}} - QT_{c_{day -1, hours from intake i}}$$

Data is available right before the the drug is taken and then two-, four-, six- and twelve hours after the intake. For each of these five time points, three measurements are available. The mean of the three measurements will be used to represent the
\( \Delta QTc_i \) for the specific time point. The mean of the time matched difference is then calculated, that is for a fixed time point the mean of the \( \Delta QTc_i \) is calculated within the four doses groups, called \( \Delta QTc_{i,j} \) were the index \( i \) represents hours from intake and \( j \) the group the mean is calculated from. The largest time matched mean difference is then defined as,

\[
\Delta QTc_{\text{max},j} = \max(\Delta QTc_{00,j}, \Delta QTc_{02,j}, \Delta QTc_{04,j}, \Delta QTc_{06,j}, \Delta QTc_{12,j})
\]

For evaluating the safety of the dose levels, the difference between the largest time matched mean difference, and placebo at that same time, called the adjusted time matched mean difference, will be used as is suggested in [19] or

\[
\Delta QTc_{\text{max,adj},j} = \Delta QTc_{\text{max},j} - \Delta QTc_{@\text{max,placebo}}
\]  

(8.1)

Two sided 90% confidence intervals will be presented for this difference between the baseline adjusted mean difference between LU 35-138 and placebo using (5.29). The upper limit will correspond to the one sided 95% upper limit that is suggested to use in [3].

For the categorial analysis, percentages exceeding some upper limits, both of absolute changes and changes from baseline in the QTc interval will be given. As suggested in [3], absolute interval prolongations of

\[
QTc > 450\text{ms}
\]

\[
QTc > 480\text{ms}
\]

\[
QTc > 500\text{ms}
\]

(8.2)

and changes from baseline of

\[
\Delta QTc > 30\text{ms}
\]

\[
\Delta QTc > 60\text{ms}
\]

(8.3)

will be counted.

Before the different methods are applied on the on-drug data, the influence of the drug on the RR interval will be looked at. The adjusted time matched mean difference between the days along with the number of points exceeding the values defined in (8.2) and (8.3) will then be given for the different methods. The results found using different correction methods will finally be summarized in the end of the chapter.

### 8.1 Drug effect on the RR interval

In order to see what influence LU 35-138 has on the RR interval, measurements of the interval before dosing are compared with measurements performed seven days later. The mean length of the interval, for the subjects that were given LU 35-138, from day -1 (off-drug) and day 7 (on-drug) are given in Table 8.1.

It is noticed by looking at the table that the drug seems to be prolonging the RR interval. It is of interest to test whether this increase is significant or

\[
H_0 : \mu_{\text{day} -1} = \mu_{\text{day} 7}
\]

\[
H_1 : \mu_{\text{day} -1} \neq \mu_{\text{day} 7}
\]
8.2 The subject specific method

For every on-drug subject the correction parameters are estimated individually from the data before the dosing started, using the parabolic correction. The time matched mean difference between the two days for the different doses groups and the five time points are shown in Figure 8.1.

By looking at the figure it is noticed that the time matched mean difference in QTc between the two days, peaks 6 hours after intake of the drug for the males and for the females that were given 75mg of the drug. However, no measurements are available until 6 hours later or 12 hours after the intake, meaning that measurements around the true peak might be missing. For the females that were given 50mg of the drug, the peak is found 4 hours after the intake started.

On order to evaluate the safety of the dose levels, two sided 90% confidence intervals around $\Delta QT_{c_{max,adj,males}}$ are generated and show in table 8.2.

<table>
<thead>
<tr>
<th>$\Delta QT_{c_{max,adj,males}}$</th>
<th>mean</th>
<th>90% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>75mg</td>
<td>17.88</td>
<td>[ 9.66 , 26.11 ]</td>
</tr>
<tr>
<td>100mg</td>
<td>25.24</td>
<td>[19.39 , 31.09 ]</td>
</tr>
<tr>
<td>50mg</td>
<td>17.23</td>
<td>[10.08 , 24.38 ]</td>
</tr>
<tr>
<td>75mg</td>
<td>14.27</td>
<td>[ 6.27 , 22.27 ]</td>
</tr>
</tbody>
</table>

Table 8.2: $\Delta QT_{c_{max,adj,j}}$ using the subject specific method

By looking at the table it is noticed that for all the groups, the upper confidence interval around the mean exceeds the 10ms that are of regulatory concern. The largest mean prolongation of the QTc interval, among the subjects, occurs for the
Figure 8.1: *The time matched mean difference using the subject specific method*

male subjects that were given 100 mg of the drug or 25.24 ms. It is also noticed that the largest mean difference for the females that were given 50mg of the drug is larger than for the females that were given 75mg of the drug. Remembering that no measurements are available between 6 hours and 12 hours from intake might explain this.

The number and percentage of data points exceeding the limits given in (8.2) and (8.3), categorized by dose groups are given in Table 8.3.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Males 75mg</th>
<th>Males 100mg</th>
<th>Females 50mg</th>
<th>Females 100mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$QT_c &gt; 450$</td>
<td>0</td>
<td>0</td>
<td>3(2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>$QT_c &gt; 480$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$QT_c &gt; 500$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$\Delta QT_c &gt; 30$</td>
<td>7(5.8%)</td>
<td>33(13.8%)</td>
<td>11(9.2%)</td>
<td>4(3.3%)</td>
</tr>
<tr>
<td>$\Delta QT_c &gt; 60$</td>
<td>1(0.8%)</td>
<td>2(0.8%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 8.3: *Number of data points exceeding limits using the subject specific method*

### 8.3 The panel specific method

For the panel specific method, different correction parameters are applied within the panels, all estimated using the mean method and the parabolic model. The time matched mean difference between the two days for the different doses groups and the
five time points are shown in Figure 8.2. As before, it is noticed that the time matched mean difference in QTc between the two days, peaks 6 hours after intake of the drug for the males and for the females that were given 75mg of the drug. For the females that were given 50mg of the drug, the peak is found 4 hours after the intake started. On order to evaluate the safety of the dose levels, two sided 90% confidence intervals around $\Delta QT_{c_{\text{adj}},j}$ are generated and show in table 8.4.

| $\Delta QT_{c_{\text{max}},\text{adj,males 75mg}}$ | 15.78 | [10.62, 20.93] |
| $\Delta QT_{c_{\text{max}},\text{adj,males 100mg}}$ | 22.71 | [17.57, 27.86] |
| $\Delta QT_{c_{\text{max}},\text{adj,females 50mg}}$ | 15.31 | [8.56, 22.06] |
| $\Delta QT_{c_{\text{max}},\text{adj,females 75mg}}$ | 13.56 | [6.17, 20.94] |

Table 8.4: $\Delta QT_{c_{\text{max}},\text{adj},j}$ using the panel specific method

By looking at the table it is noticed that the upper confidence limits, for all dose groups, are much larger than the critical limit of 10ms. The number and percentage of data points exceeding the limits given in (8.2) and (8.3), categorized by dose groups are given in Table 8.5.
Analysis of possible drug induced QTc prolongation

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Males 75mg</th>
<th>Males 100mg</th>
<th>Females 50mg</th>
<th>Females 100mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc &gt; 450</td>
<td>0</td>
<td>0</td>
<td>1(0.8%)</td>
<td>1(0.8%)</td>
</tr>
<tr>
<td>QTc &gt; 480</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QTc &gt; 500</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ΔQTc &gt; 30</td>
<td>3(2.5%)</td>
<td>24(10%)</td>
<td>8(6.7%)</td>
<td>4(3.3%)</td>
</tr>
<tr>
<td>ΔQTc &gt; 60</td>
<td>2(1.7%)</td>
<td>1(0.4%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 8.5: Number of data points exceeding limits using the panel specific method

8.4 Study specific correction using the pooled method

For the study specific method, a correction parameter is estimated from off-drug data and applied on the whole study population. The time matched mean difference between the two days for the different dose groups and the five time points are shown in Figure 8.3.

Figure 8.3: The time matched mean difference using study specific correction and the pooled method

In order to evaluate the safety of the dose levels, two sided 90% confidence intervals around ΔQTc_{max, adj.j} are generated and shown in Table 8.6. By looking at the table it is noticed that the upper confidence interval is much larger than the critical value of 10ms, as before. The number and percentage of data points exceeding the limits given in (8.2) and (8.3), categorized by dose groups are finally given in Table 8.7.
8.5 Predefined methods

The most commonly used methods in practice, the Bazett and the Fridericia methods are applied on the data. Same kind of analysis will be carried out as for the methods above.

8.5.1 Bazett

The time matched mean difference between the two days for the different dose groups and the five time points are shown in Figure 8.4. In order to evaluate the safety of the dose levels, two sided 90% confidence intervals around $\Delta QT_{c_{max,adj,j}}$ are generated and shown in Table 8.8.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Males 75mg</th>
<th>Males 100mg</th>
<th>Females 50mg</th>
<th>Females 100mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$QT_c &gt; 450$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>$QT_c &gt; 480$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$QT_c &gt; 500$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$\Delta QT_c &gt; 30$</td>
<td>2 (1.7%)</td>
<td>26 (10.8%)</td>
<td>8 (6.7%)</td>
<td>4 (3.3%)</td>
</tr>
<tr>
<td>$\Delta QT_c &gt; 60$</td>
<td>2 (1.7%)</td>
<td>1 (0.4%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 8.7: Number of data points exceeding limits using the study specific method and the pooled method

By looking at the table, it is noticed that for the males that were given 75mg of the drug, the upper confidence interval is calculated to be only 10.94ms which is considerably lower than for the other methods used. The number and percentage of data points exceeding the limits given in (8.2) and (8.3), categorized by dose groups are finally given in Table 8.9.
Analysis of possible drug induced QTc prolongation

Figure 8.4: The time matched mean difference using the Bazett method

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Males 75mg</th>
<th>Males 100mg</th>
<th>Females 50mg</th>
<th>Females 100mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc &gt; 450</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1(0.8%)</td>
</tr>
<tr>
<td>QTc &gt; 480</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QTc &gt; 500</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ΔQTc &gt; 30</td>
<td>4(3.3%)</td>
<td>29(12.1%)</td>
<td>10(8.33%)</td>
<td>10(8.33%)</td>
</tr>
<tr>
<td>ΔQTc &gt; 60</td>
<td>0</td>
<td>0</td>
<td>3(2.5%)</td>
<td>2(1.7%)</td>
</tr>
</tbody>
</table>

Table 8.9: Number of data points exceeding limits using the Bazett method

8.5.2 Fridericia

The time matched mean difference between the two days for the different dose groups and the five time points are shown in Figure 8.5. In order to evaluate the safety of the dose levels, two sided 90% confidence intervals around ΔQTc_{max,adj,j} are generated and shown in Table 8.10.

<table>
<thead>
<tr>
<th>ΔQTc_{max,adj,j}</th>
<th>mean</th>
<th>90% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔQTc_{max,adj,males 75mg}</td>
<td>11.35</td>
<td>[ 7.00 , 15.70]</td>
</tr>
<tr>
<td>ΔQTc_{max,adj,males 100mg}</td>
<td>21.41</td>
<td>[17.18 , 25.65]</td>
</tr>
<tr>
<td>ΔQTc_{max,adj,females 50mg}</td>
<td>15.58</td>
<td>[ 8.23 , 22.93]</td>
</tr>
<tr>
<td>ΔQTc_{max,adj,females 75mg}</td>
<td>16.55</td>
<td>[10.09 , 23.02]</td>
</tr>
</tbody>
</table>

Table 8.10: ΔQTc_{max,adj,j} using the Fridericia method

By looking at the table it is noticed that the upper confidence limit is much larger...
than the critical limit of 10ms. The number and percentage of data points exceeding
the limits given in (8.2) and (8.3), categorized by dose groups are finally given in
Table 8.11.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Males 75mg</th>
<th>Males 100mg</th>
<th>Females 50mg</th>
<th>Females 100mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$QT_c &gt; 450$</td>
<td>0</td>
<td>0</td>
<td>1(0.8%)</td>
<td>1(0.8%)</td>
</tr>
<tr>
<td>$QT_c &gt; 480$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$QT_c &gt; 500$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$\Delta QT_c &gt; 30$</td>
<td>2(1.7%)</td>
<td>28(11.7%)</td>
<td>4(3.3%)</td>
<td>8(6.7%)</td>
</tr>
<tr>
<td>$\Delta QT_c &gt; 60$</td>
<td>2(1.7%)</td>
<td>1(0.4%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 8.11: Number of data points exceeding limits using the Fridericia method

8.6 Summary of methods used for investigation of QTc prolongation

It is clear, by looking at the the tables in the chapter, that LU 35-138 causes prolonga-
tion of the QT interval. However, the size of the prolongation is different, depending
on the method used for the correction. By comparing Tables 8.1 and 8.4 it is noticed
that the subject specific method is resulting in higher adjusted time matched mean
difference than the panel specific method. Since it has been shown, that using only 15
data points to estimate the correction parameters used in the subject specific method,
can be somewhat dangerous, it is decided to use the results from the panel specific method to determine the safety of the dose levels.

It is of interest to compare the results from the different methods to the results from the panel specific method that is assumed to be the right method to use here. By looking at Tables 8.6, 8.8 and 8.10 it is noticed that for the females that were given 50mg of the drug, the study specific-, the Bazett- and the Fridericia methods are all leading to similar results as the panel specific method. It should be remembered that this group of females was the only group found not to cause significant prolongation of the RR interval. Looking at the same tables for the females that were given 75mg of the drug, it is noticed that the study specific correction and the Fridericia methods are resulting in higher adjusted time matched mean difference than the panel specific correction. Looking at Figures (7.9) and (7.13) it is remembered that the methods resulted in positive correlation between the QTc and the RR interval for most of the females that were given the placebo. The Bazett method is however found to result in lower adjusted time matched mean difference than the panel specific correction. Looking again at Figure 7.9 it is noticed that the method is expected to result in negative correlation between the QTc interval and the RR interval.

Looking at the same for the males, for both dose groups, the study specific-, the Bazett and the Fridericia methods are resulting in lower adjusted time matched mean difference than the panel specific method. Once again looking at Figures 7.9 and 7.13 it is noticed that all methods are resulting in negative correlation between the QTc interval and the RR interval for the males that were given placebo.
Chapter 9

Results and discussion

In the chapter, a short summary of the results found in the thesis will be given followed by a short discussion about the results and possible future work.

9.1 Summary of results

Data from a study designed to investigate potential QTc prolongations from a certain drug, has been used to analyse the QT~RR relationship in healthy subjects. Further, correction methods that allow QT intervals recorded at different heart rates to be compared have been analysed. Data gathered from subjects that were given placebo was used for this purpose. Six different regression types were used to describe the QT~RR relationship and six different types of QT corrections applied, shown below.

<table>
<thead>
<tr>
<th>Type</th>
<th>QT~RR relationship</th>
<th>Heart rate correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Linear</td>
<td>QT = \eta + \xi \cdot RR</td>
<td>QTc = QT + \alpha (1-RR)</td>
</tr>
<tr>
<td>B: Hyperbolic</td>
<td>QT = \eta + \xi / RR</td>
<td>QTc = QT + \alpha(1-1/RR)</td>
</tr>
<tr>
<td>C: Parabolic</td>
<td>QT = \eta \cdot RR^\xi</td>
<td>QTc = QT / RR^\alpha</td>
</tr>
<tr>
<td>D: Logarithmic</td>
<td>QT = \eta + \xi \cdot \ln(RR)</td>
<td>QTc = QT - \alpha \cdot \ln(RR)</td>
</tr>
<tr>
<td>E: Shifted logarithmic</td>
<td>QT = \ln(\eta + \xi \cdot RR)</td>
<td>QTc = \ln(e^{QT} + \alpha(1-RR))</td>
</tr>
<tr>
<td>F: Exponential</td>
<td>QT = \eta + \xi \cdot e^{RR}</td>
<td>QTc = QT + \alpha(1/e - e^{RR})</td>
</tr>
</tbody>
</table>

Most often, the linear relationship was found to be the optimal type of regression (using RMSE as a criteria) and was therefore used to test the relationship further. The QT~RR relationship was found to vary between different subjects while it could not be rejected that it is constant, between days, within the same subject. It was further tested whether the regression parameters differed between males and females. For the
linear model both the slope and the intercept were found to be significantly different between the genders.

Expressions to calculate the correction parameters in the models that are linear in their parameters were derived and the following found to be valid

\[ \alpha_A = \xi_A \]
\[ \alpha_B \neq \xi_B \]
\[ \alpha_D \neq \xi_D \]
\[ \alpha_F \neq \xi_F. \]

For the correction types that are nonlinear in their parameters, an attempt to relate the correction parameter to the correction parameter for the linear model was made. The following approximations were derived

\[ \frac{\alpha_C}{RR_0^{\alpha_C}} = \frac{1}{QT_0} \alpha_A \]

and

\[ \alpha_E = \alpha_A \cdot e^{QT_0}. \]

The approximation for the parabolic model, type \( C_c \), was found to be inaccurate while the approximation for the shifted logarithmic model, type \( E_c \), was found to be accurate.

The six different correction types were applied on every placebo subject and the correlation between the resulting QTc interval and the RR interval looked at. The optimal correction type was defined as the one that resulted in the lowest correlation between the two intervals. It was concluded that even though a certain regression type was found to be optimal in a given subject, the corresponding correction formula might not be the optimal one to use for that same subject.

An optimized correction was made by correcting every subject individually with the correction type that was found to be optimal for that given subject. A number of correction methods were then applied and compared to the optimized method, that is, a gender specific, a panel specific, a study specific, the Bazett and the Fridericia methods. In addition, three different methods were used to estimate the correction parameter for the six different correction types. None of the above mentioned methods was found to perform well in resulting in zero correlation between the QTc interval and the RR interval within the subjects. However, the panel specific method, using the parabolic model and the method using the means, was found to perform well in canceling out over and under correction in the QTc interval. The most commonly used method in practise, the Bazett method, was shown to perform very poorly both in leading to zero correlation between subjects and in canceling out over and under corrections.

After going through the different correction methods, possible QTc prolongations resulting from intake of the drug were investigated. It was decided to use the panel specific method using the parabolic model and the mean method to determine if the drug in question induced QTc prolongations. The difference in adjusted time matched mean difference between the on drug groups and the placebo subjects are shown below.

The threshold level of regulatory concern for this time matched mean difference is around 5ms evidenced by an upper bound of the one sided 95% confidence interval
around the mean effect of 10ms (corresponds to the upper limit of the two sided 90% confidence interval shown above). It can therefore be concluded that the drug induces QTc prolongations since the upper bound for all groups is much larger than 10ms.

The results using the most commonly used methods in practice, the study pooled method, the Bazett method and the Fridericia method were finally compared to the results from the panel specific method that was assumed to be the correct method to use. The methods were found to lead to similar results for the females that were given 50mg of the drug which was the only group where the RR interval was found not to be prolonged by the intake. For the other three dose groups, the RR interval was found to be prolonged by the intake of the drug. For the females that were given 75mg of the drug, study specific and the Fridericia methods were found to result in higher time matched mean difference than the panel specific method. The opposite was found for the Bazett method in that same group of females. For the two groups of males, the study specific, the Bazett and the Fridericia methods were all found to result in lower time matched mean difference than the panel specific method. These results were found to be consistent with the expected under and over corrections of the methods discussed in Chapter 7.

According to these results, the correction type used is not important when looking at the time matched mean difference, if the intake of the drug does not affect the RR interval. If however the intake of the drug is found to prolong the RR interval, methods that are found to result in positive correlation between the QTc interval and the RR interval are expected to result in higher time matched mean difference than a given optimal correction while methods that result in negative correlation between the two intervals are expected to result in lower time matched mean difference. When a drug is found to shortened the RR interval the opposite is expected to happen.

### 9.2 Discussion

The analysis of the different correction methods, using data gathered from placebo subjects, indicated that a subject specific corrections should be used to correct the QT interval because of large difference between the subjects. However, because of too few off drug data points for the subjects that were given the drug, it was decided not to use the method to determine the magnitude of drug induced prolongation of the QTc interval. Having more data points to work with, the issue of inter- and intrasubject variability could have been addressed more closely, possibly with the use of adaptive techniques. Further, possibly diurnal variation of the different intervals on the ECG could have been looked at. Using cross over designs in stead of parallel design in a QT study of this kind would result in more off drug data for every individual in the study, without having to measure more ECGs. It is therefore recommended to apply
cross over designs in stead of parallel designs when possible. Another issue that is interesting to look at more closely is the difference between males and females. For this population of subjects it is clear that the QT~RR relationship and the correction parameters used for the QT correction differs between males and females. Further, the mean RR interval was found to be significantly different between males and females. Even though, the correction methods used today are designed to normalize the QT interval as it would have been gathered at a constant RR interval of 1 sec for both genders. The author of this thesis would not be surprised if QT correction methods in the future will focus more on this difference between males and females.
Bibliography


APPENDIX A

Description of variables in data set
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