# QTc Prolongation Liability: Prospective Use of Not-In-Trial Simulations

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## Introduction

Previously, the concept of Not-In-Trial Simulations was introduced to describe QTc-interval measurements in a real life cohort using a model-based approach [1]. The model consisted of *QTc = age-dependent baseline value + drug effects + effects from various co-morbidities and concomitant medications.* However, variability descriptors need to be considered in order to apply this approach prospectively in drug development. The aim of this investigation is to further evaluate the effect of age on QTc-interval and to explore the interactions between age and the other covariates. Ultimately, this should lead to a suitable setting for Not-In-Trial-Simulations for the assessment of cardiovascular risk of new compounds.

## Method and Data

### Method

The relationship between age and baseline QTc observations was modelled using NONMEM VI. The age-effect model was developed using data from healthy subjects and patients without co-morbidities or co-medications. An interaction model was then created by including patient data with co-morbidities and concomitant medications. Model comparisons were made using ΔOBJF with the criteria of $p<0.05$, while model performance was tested using diagnostic plots, VPCs and NPDEs. After model validation, we used a QT-prolonging drug (*d,l*-sotalol) to mimic a drug development scenario, which has been modelled previously according to a two-compartment model with weight as a covariate on clearance. Drug-induced QT-prolongation was added to the underlying effect of the covariates.

### Data*

Age 18 – 50: repeated obs. from healthy-volunteer clinical trial studies
Age 55 – 96: longitudinal obs. from the Rotterdam Cohort Study

| | Healthy | Sick | Total | HF | DIA | AMI | ARR |
|---|---|---|---|---|---|---|---|
| Male | 6425 | 2524 | 8949 | 34 | 350 | 390 | 6 |
| Female | 9000 | 3777 | 12777 | 54 | 451 | 265 | 9 |

## Model Estimates and Validation

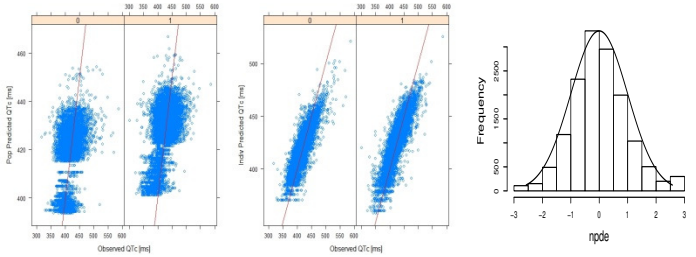
### Final Model

$$QTc = \{SLP+(AMIa*AMI+DIAa*DIA)\} \times AGE^{EXP} + \{INCPT+(ARRb*ARR+DIAb*DIA+AMIb*AMI+HFb*HF)\}$$

### Model Estimates*

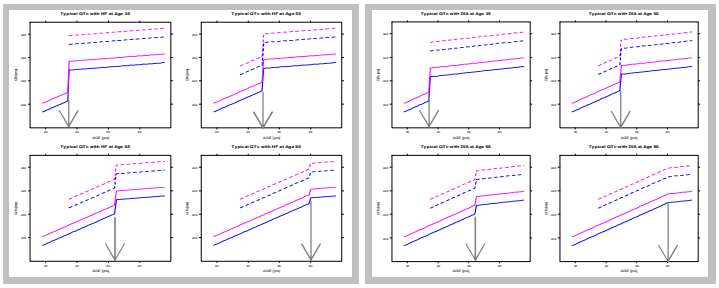
| SLP | BSVslp | INCPT | BSVincpt | EXP | Gen Factor | ARR on B | DIA onB | AMI on B | HF on B | DIA on A | HF on A | Res |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.583 | 0 (fixed) | 383 | 305 | 1 (fixed) | 7.42 | 1.74 | 35.4 | 2.92 | 42.6 | -0.44 | -0.479 | 240 |

### Model Diagnostics and Validation




* HF = heart failure, DIA = diabetes, AMI = myocardial infarction, ARR = arrhythmia

## Results from Simulation Model



***Figures 1 & 2.*** *Model predicted QTc values from age 18-96 with onset of heart failure (fig 1) and diabetes (fig 2) at age 35, 50, 65, and 80. The dash and solid lines represent the QTc values with and without drug respectively.*

### Prospective Model

The QTc vs. age relationship can be described with a linear model. Gender, arrhythmia, myocardial infarction, diabetes and heart failure were found to be covariates on the intercept of the relationship. In contrast, diabetes and heart failure were found to be covariates on the slope of the linear equation. BSV for the intercept was also estimated. QTc values with the onset of heart failure at the various ages are shown in figure 1 while the same is displayed for diabetes in figure 2.

### Not-In-Trial Simulation

Figures 3A, B and C demonstrate the prolongation of QTc values from a simulated cohort with disease-free baseline at various ages (A) to the same subjects with heart failure (B) and finally with the added effects of a QTc-prolonging drug (C). The prolongation due to co-morbidity is 20 ms, while the prolongation due to sotalol effects alone is 22 ms in both genders.

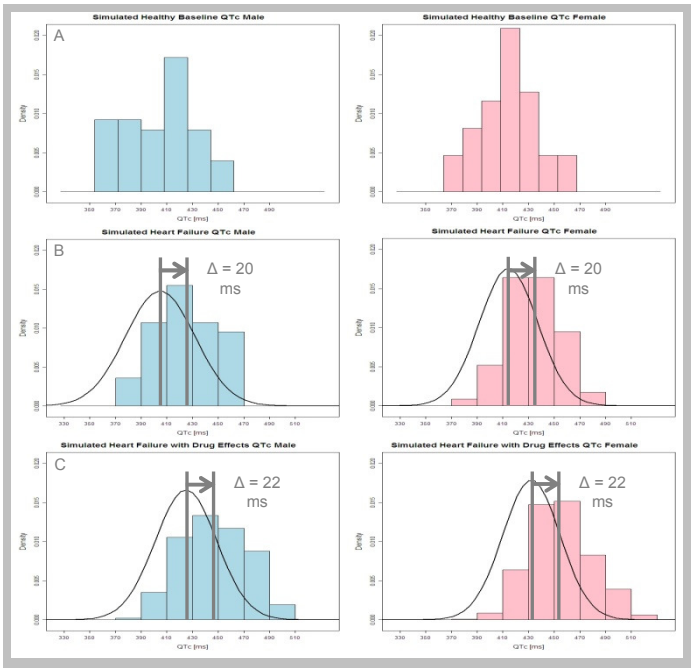



***Figure 3.*** *A) Simulation of a hypothetical phase IV study population with disease-free baseline QTc values. B) Simulation of the same population with heart failure. C) Simulation of the same population with the effects of a QTc-prolonging drug.*

## Discussions

Baseline QTc values are known to be age and gender dependent. This correlation plays an important role in that observed QTc values will always increase over time irrespective of drug treatment. From a previous study, it was shown on a population level, that co-morbidity conditions and concomitant medications also contribute to further increase in QTc values. In the present investigation, individual patient behaviours can now be described with variability estimations. The improvements made in the description of baseline QTc values are also dependent on the various health conditions where they impact the slope or intercept of the relationship. Furthermore, with the incorporation of all factors affecting the baseline QTc relationship, it can now be used to prospectively assess the overall cardiovascular safety issues.

*Ref: [1] Chain et al., PAGE 18 (2009) Abstr 1512 [www.page-meeting.org/?abstract=1512]*

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