Relevance of QT-RR correlations in the assessment of QTc-interval prolongation in clinical trial simulations

Francesco Bellanti[1], Anne Chain[1], Meindert Danhof[1], Oscar Della Pasqua[1,2]

[1]LACDR, Division of Pharmacology, Leiden University, Leiden, The Netherlands
[2]Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, Stockley Park, United Kingdom

Introduction

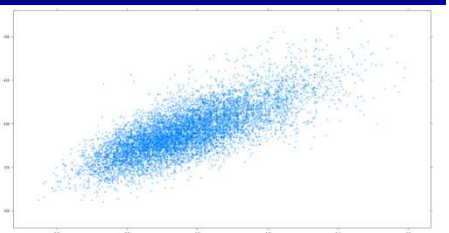
Correction for changes in heart rate is a fundamental step to the evaluation of QTc-interval prolongation. Yet, clinical trial simulations for thorough QT (TQT) studies often rely on re-sampling or empirical correlations to evaluate drug effect and design factors such as group size. The aim of the investigation was to develop a model-based approach to describe the correlation between QT and RR intervals in healthy volunteers.

Method and Data

Data (mean and sd)

QT (ms)	390.5 (27.8)
RR (sec)	0.96 (0.15)
AGE (years)	31.1 (9.4)

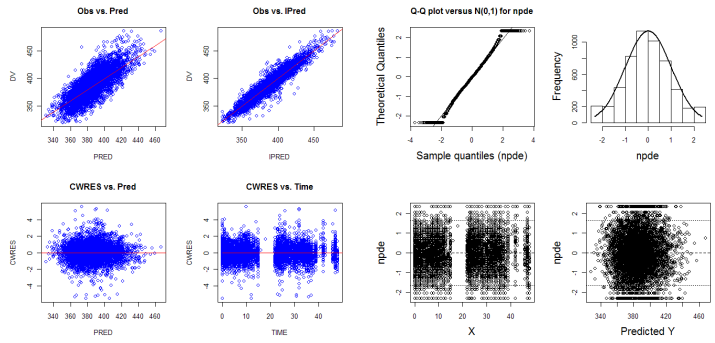
A large pool of healthy volunteer ECG data (Males=339 /Females=437) was used for the analysis. Data were split into two subsets to allow for the external validation of the final model. The analysis was performed using a non-linear mixed effects approach as implemented in NONMEM VI. Model building was based on changes in the objective function (OFV) and goodness of fit plots (GOF). Statistical and graphical diagnostics were used for internal and external validation. QT vs. RR values of the overall population are shown on the right panel.



Model Estimates and Internal Validation

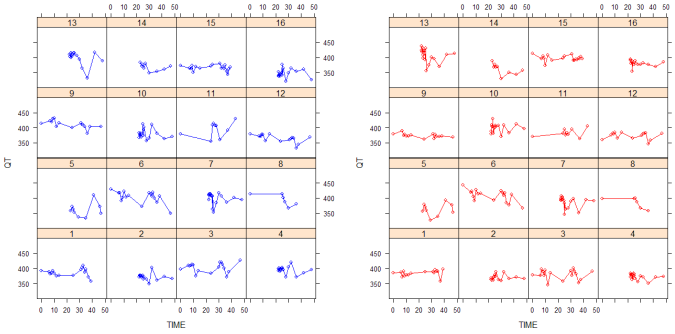
QT/RR correlation: $QT = SLP * RR^{EXP} + INTC$

	SLP females	SLP males	EXP females	EXP males	INTC	IIV SLP	IIV EXP	IOV	Residual
Model estimate	181	166	0.85	0.74	221	0.0059	0.046	0.012	0.0004
Bootstrap mean	180.2	165.3	0.87	0.76	222.3	0.0062	0.0459	0.013	0.0004
CV	12.3%	13.7%	13.7%	13.1%	10.1%	29%	17.4%	38%	5%

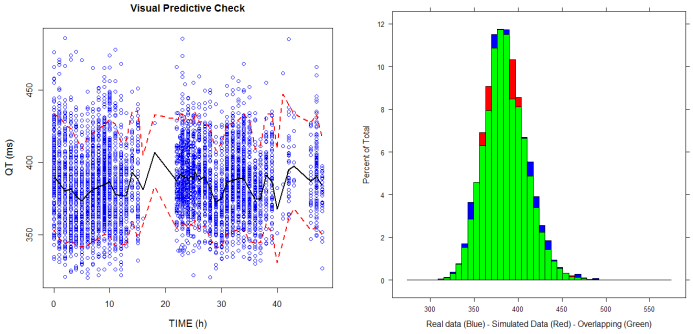


QT/RR final model: Among the different functions used in the evaluation of the QT-RR correlation [1], a power function yielded the best model performance. Age and gender were the only available covariates; gender was found to be significant both on slope and exponent. Inter-occasion variability on slope and exponent was also identified as a significant random effect.

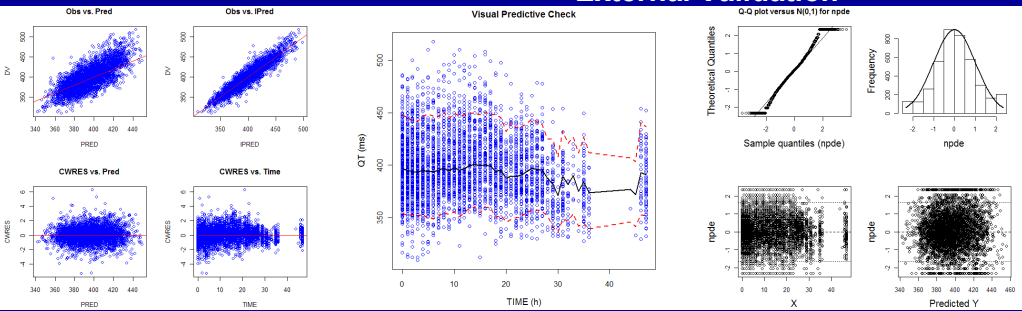
QT: Real vs. Simulated



Simulation: Model performance is demonstrated by the comparison of simulated and observed data. (above) QT-interval *vs.* time profiles (real data in blue and simulated data in red), and (below) Visual Predictive Check and QT-interval distributions.



External Validation



Goodness of fit, VPC and NPDE plots(on the left) show appropriate model performance with regard to the predictions for a different subset of studies. In this case, it is worth noticing that inter-occasion variability was not a significant random effect in this subset of data.

Conclusions

Our model describing the QT-RR relationship allows accurate simulation of QT-interval profiles starting from a physiological set of RR values. Parameter estimates have been subsequently used as part of a thorough QT study simulation. In the context of clinical trial simulations, the availability of such a model offers considerable advantages as compared to re-sampling methodologies. The use of a model-based approach allows one to generate an infinite number of realistic individual QT profiles, enabling the prediction of potential drug effects on QTc-interval for patients who do not meet inclusion criteria.

Ref: [1] Malik M, Färbom P, Batchvarov V, Hnatkova K, Camm AJ, Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. Heart, 2002 Mar;87:220-228.

Leiden /Amsterdam Center for Drug Research

GlaxoSmithKline

Universiteit Leiden