

CSRC White Paper: QT/QTc Evaluation for Drugs with Autonomic Effects

THEW Annual Meeting
April 29, 2009

Christine Garnett, PharmD
christine.garnett@fda.hhs.gov

Agenda

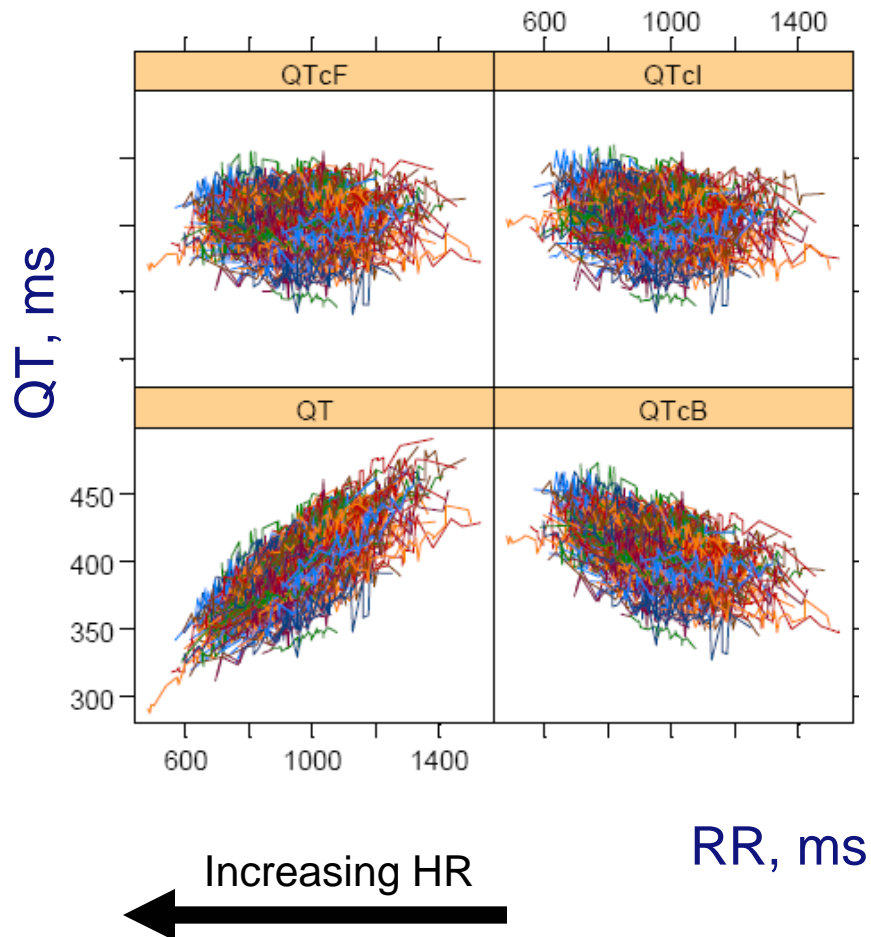
- Computation of QTcl
 - Current approach
 - Application to drug that increases heart rate
- CSRC white paper objectives
- THEW opportunities

Current Practice for Computing QTcI

- Collect resting, drug-free ECGs at pre-specified time points
- Individual correction computed from RR and QT data
 - $QT_c = QT + \beta(1 - RR)$
 - $QT_c = QT / RR^\beta$
- Apply individual QT-RR relationship to on-treatment ECGs

Evaluation of QT-RR Method

On-Treatment ECGs

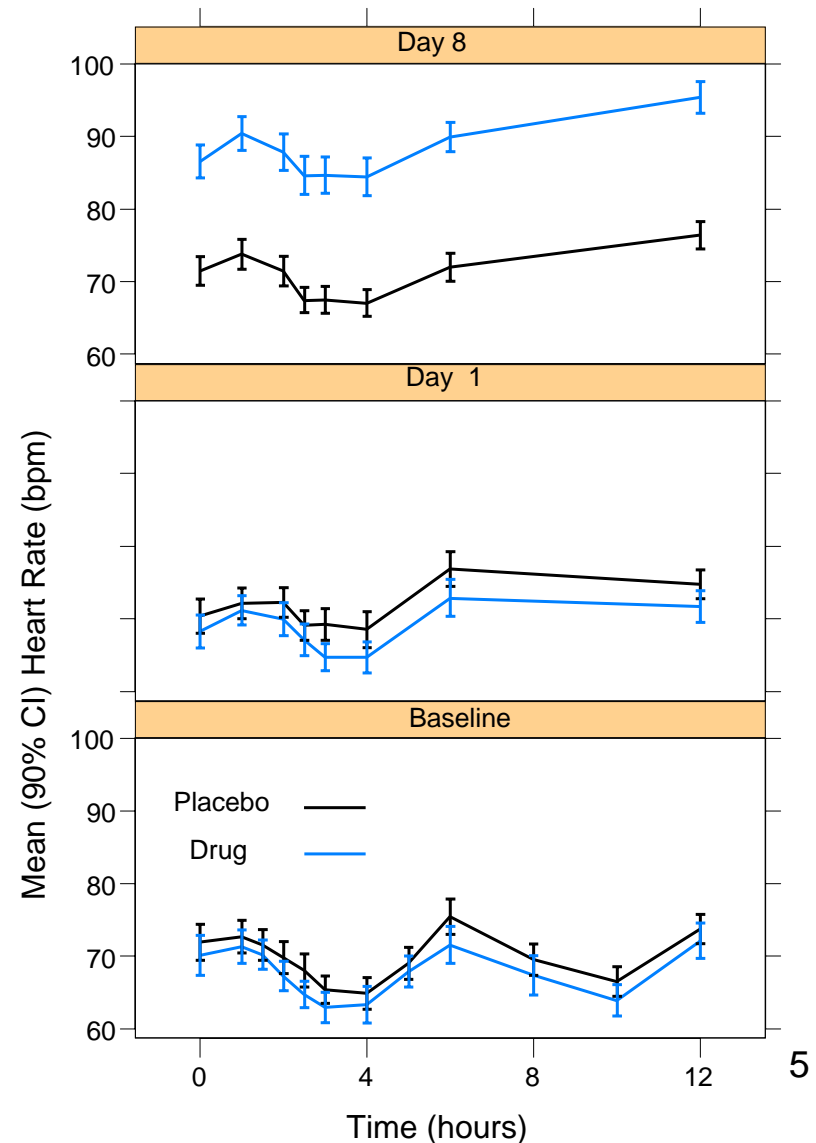


Sum of Square Slopes		
	QTcl	QTcF
Drug	0.003	0.002

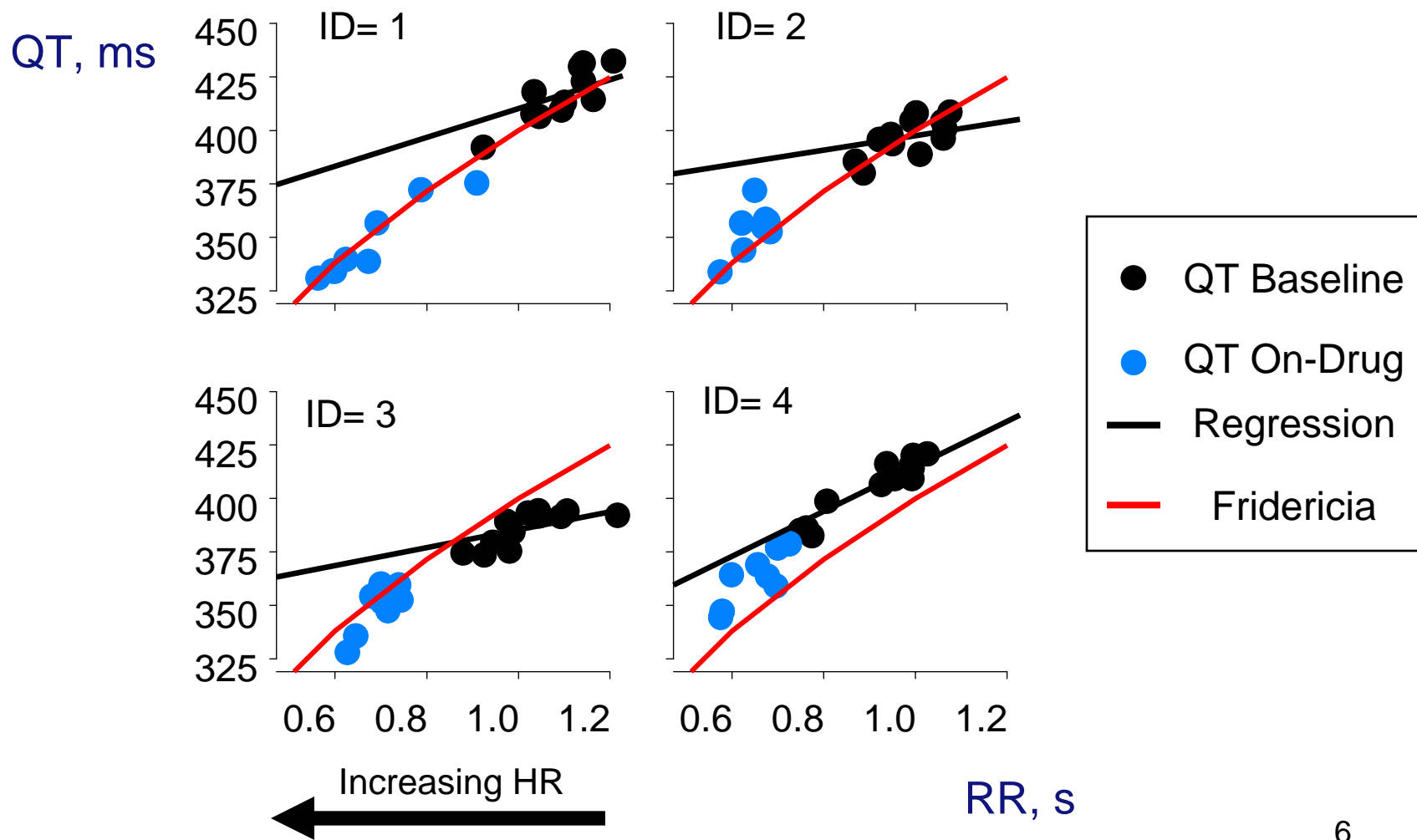
The smaller the value,
the better the QT-RR method

Example: Drug Increases HR by 20 bpm

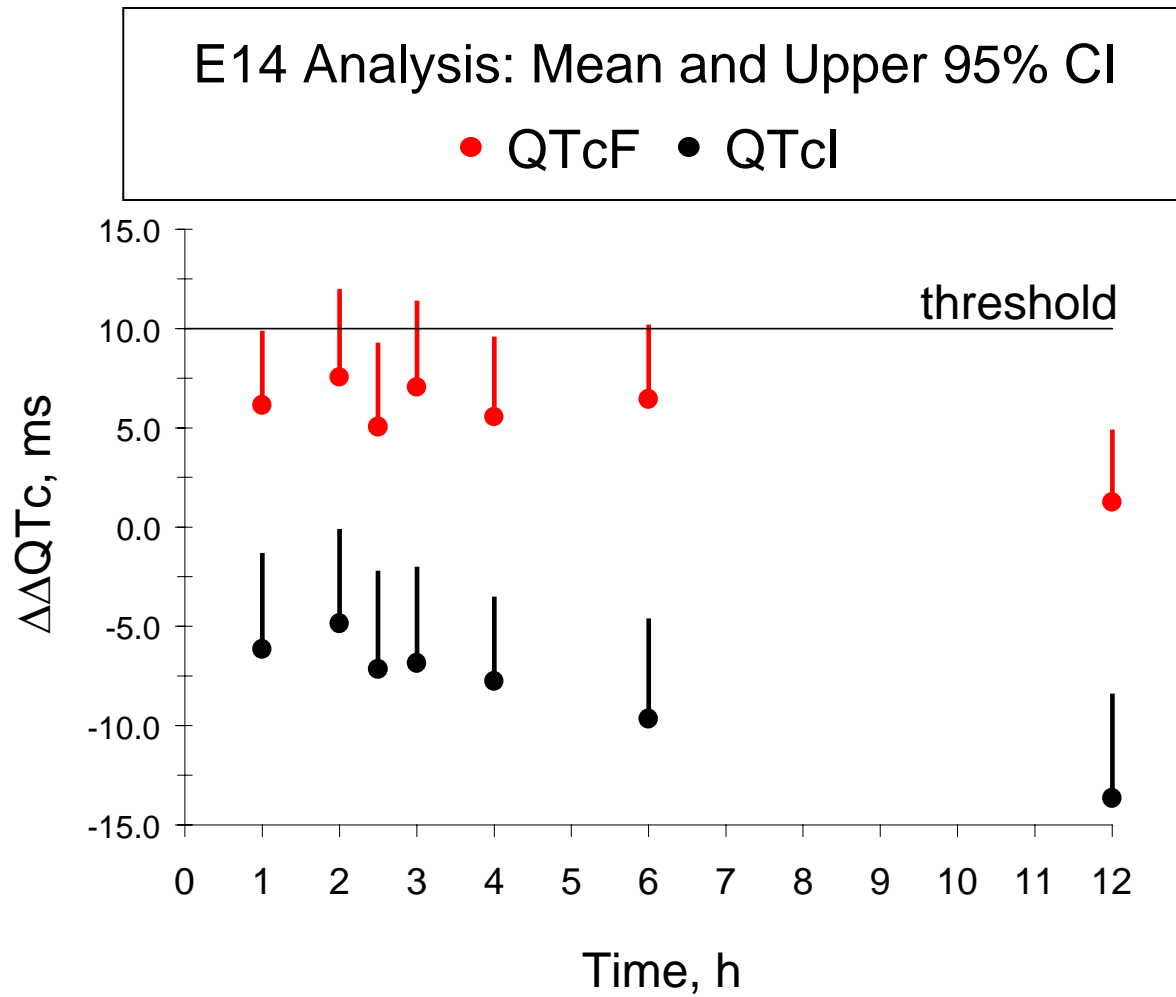
- Parallel TQT study
- Baseline & On-Treatment ECGs
 - 12-Lead Holter ECGs
 - Resting ECGs extracted at specified times



QTcI Computed from Baseline QT-RR Data Using Linear Model



QTcI and QTcF Give Different Answers



CSRC White Paper

- Develop white paper that outlines a strategy to evaluate QT/QTc for drugs with autonomic effects
 - Based on published methodologies
- Benefits: Increase efficiency of clinical development
 - Obtain less biased estimate of QT effect
 - Avoid falsely designating drug as a QT prolonger
 - Reduce re-analysis or repeat TQT studies

Approaches to Assess QT for Drugs Having Autonomic Effects

- QT-RR Correction (QTcI)
 - Increase range of HR at Baseline
 - Use on-treatment ECGs
 - PKPD Modeling
- Holter Bin Method
- Beat-to-Beat Method
- Pacing

THEW Opportunities

- Methodologies proposed to evaluate drugs with autonomic effects are based on Holter technology
 - Research purposes
 - Compare methods using common data
 - TQT studies
 - Warehouse to store Holter ECG data