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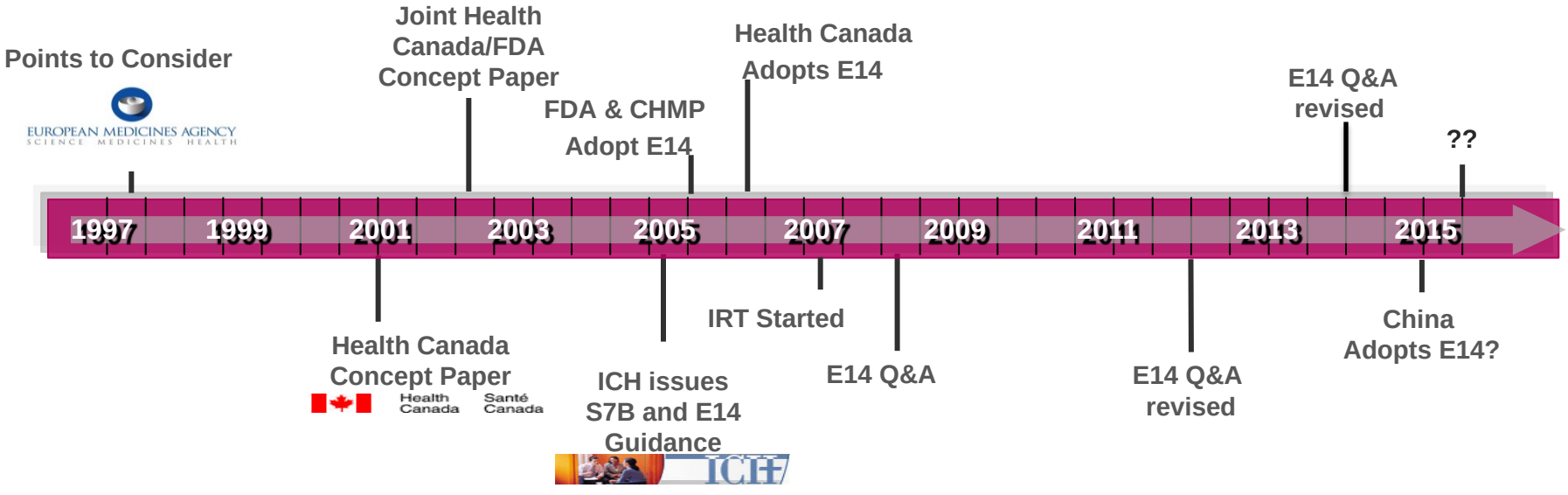
Applied Translational Medicine

QT Assessment: The new paradigm, but now what?

Joy Olbertz PharmD, PhD

Senior Director, Cardiovascular Safety Services

The Evolution of ICH E14



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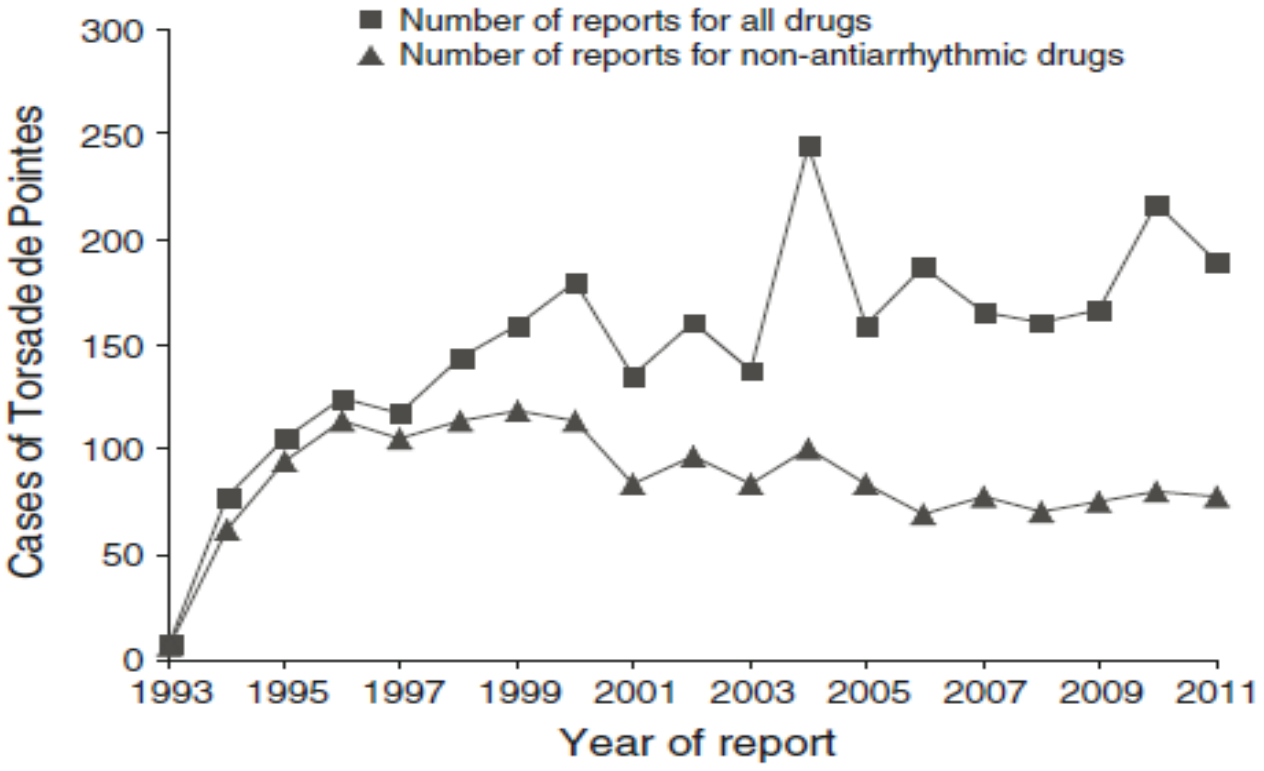
Cases of Torsades de Pointes



Annual number of spontaneous reports of Torsade de Pointes received by the US FDA Adverse Event Reporting System, Stockbridge et al. Drug Safety 2013;36:167-182

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The Future of ICH E14

- Movement to assess QT prolongation risk in early clinical studies rather than a dedicated TQT
- IQ-CSRC study completed to provide scientific rationale for this approach
  - International Consortium for Innovation & Quality in Pharmaceutical Development (IQ)
  - Cardiac Safety Research Consortium (CSRC)
- Likely not revising ICH E14 but rather updating the Q&A

IQ-CSRC Study

- 3 period, randomized, placebo-controlled study
- 20 healthy subjects
- 6 study drugs: 5 “QTc-positive”, 1 “QTc-negative”
- Incomplete block design used
  - Each study drug administered to 9 subjects and placebo to 6
- Exposure response analysis performed
  - Evaluate relationship between plasma concentration and placebo corrected, change-from-baseline QTc (ΔΔQTc)
- “QT positive” if the UB of the 2-sided 90% CI of the predicted placebo-corrected ΔQTcF is above 10 ms at the observed geometric mean Cmax of the lower dose of the studied drugs

Darpo, Borje, et al. *Annals of Noninvasive Electrocardiology* 19.1 (2014): 70-81.

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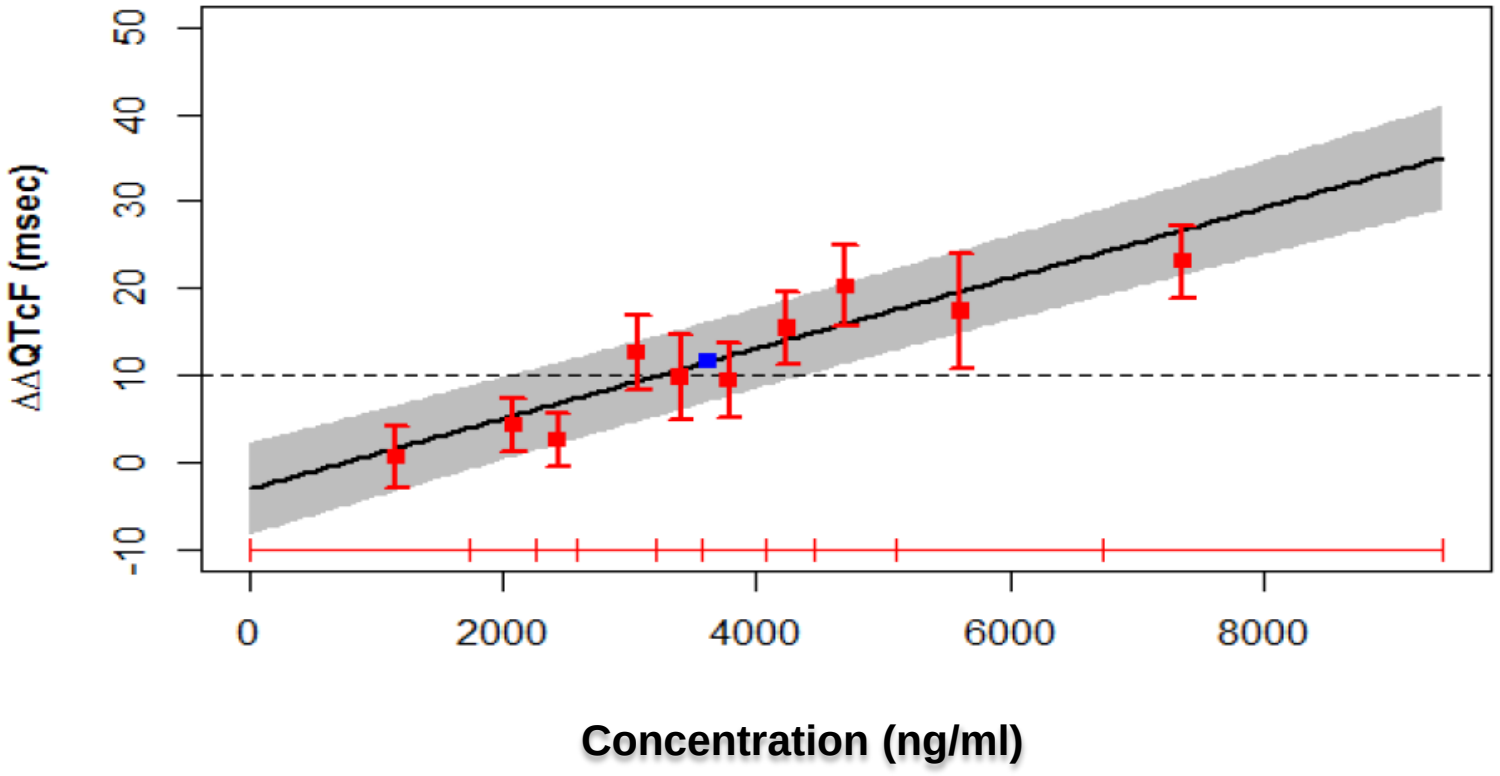
IQ-CSRC Study

Quinine



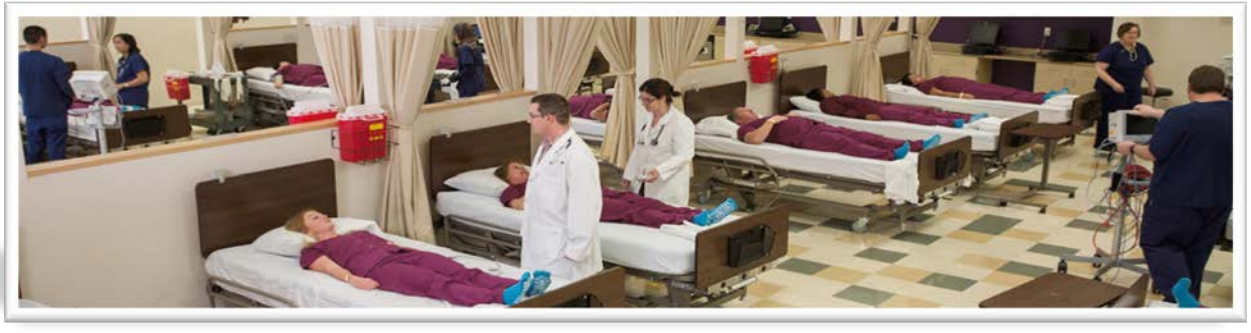
Darpo, Borje, et al. *Clinical Pharmacology & Therapeutics* (2014).

Intense ECG Data Collection in Early Studies

- TQT “like” ECG data collection
  - Holter monitors
  - Triplicate measurements
  - Baseline and post-dose ECG extractions
  - Low data variability is key
- Data collected at ***multiple dose levels*** then exposure response (QTcF/PK) modelling performed to determine trend if any for QTcF prolongation

Sounds Promising but…

- When I go to submit my TQT waiver what will be required for my preclinical package?
- How high does the SAD or MAD dose need to be? How does this impact the potential success of my TQT waiver?
- I want to add a patient cohort to the end of my SAD/MAD study. Should I include intense ECG monitoring?
- I am uncertain that early TQT like data collection is the right fit for my program, do I have to do this?



Comparison of Semi-Automated vs. Highly Automated ECG Analysis

Objective

- Automation suggests the potential for data sets with reduced variability and consequently, greater power per subject vs. the SA method

- Can Highly Automated (HA) methodology give results similar to Semi-automated (SA) methods?

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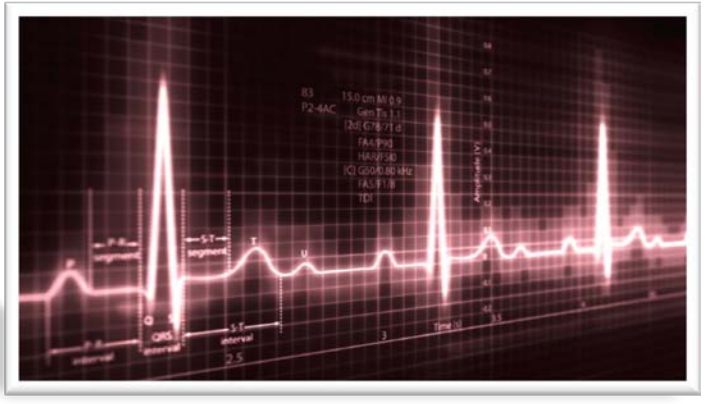
Overview

- Five vendors participated, using three ECG analysis algorithms – unknown to each other
- Semi-automated (SA): ECG interval measurements are all reviewed and confirmed by a cardiologist
- Highly automated (HA): Varied methods were used to extract and measure ECG interval measurements with the majority of interval measurements automated with some varying degree of cardiologist oversight

Methods

- Vendors were supplied raw Holter data from a TQT study previously analyzed using SA approach
- Analysis assessed:
  - Scientific validity of the vendor algorithm (alignment with prior SA analysis)
  - Variability of key ECG parameter intervals
  - Overall rank order of vendor performance at these tasks as judged by Clinical Utility Index



Conclusions

- All automated QTc analysis results aligned to the SA analysis results
  - Systematic differences in the absolute value of raw data do not substantially alter outcome across all effect sizes
    - Unlikely to have a false positive result for small drug effects
    - Unlikely to have a false negative result for marginal moxi effects
- SA analysis is analytically competitive with HA analysis
  - Variability was similar so HA methodology does not necessarily reduce enrollment needs
  - However, typically timelines are longer and costs higher with SA
- Vendor rankings identified by CUI were based on small differences

Automated ECG Analysis

Available online at www.sciencedirect.com

SciVerse ScienceDirect

Journal of Electrocardiology 46 (2013) 118 – 125

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Pattern recognition analysis of digital ECGs: Decreased QT measurement error and improved precision compared to semi-automated methods☆

Olivier Meyer, MS,[a,*] Georg Ferber, PhD,[b] Gerard Greig, MD,[c] Henry H. Ho

[a]Institute of Clinical Pharmacology, F. Hoffmann-La Roche, Strasbourg, France
[b]Statistik Georg Ferber GmbH, Riehen, Switzerland
[c]Clinical Pharmacology, F. Hoffmann-La Roche, Basel, Switzerland
[d]Department of Toxicology, Charles River Laboratories, Reno, NV, USA

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Comparative TQT analysis with three fully-automated platforms Comparison to core laboratory semi-automated results☆

Olivier Meyer, MS,[a,*] Gerard Greig, MD,[b] Henry H. Holzgrefe, BA[c]

[a]Institute of Clinical Pharmacology, F. Hoffmann-La Roche, Strasbourg, France
[b]Pharma Development Safety Licensing and Early Development, F. Hoffmann-La Roche, Basel, Switzerland
[c]Department of Toxicology, Charles River Laboratories, Reno, NV, USA

Clinical Pharmacology & Therapeutics **86**, 503-506 (November 2009) | doi:10

Comparison of Manual and Automated Measurements of the QT Interval in Healthy Volunteers: An Analysis of Five Thorough QT Studies

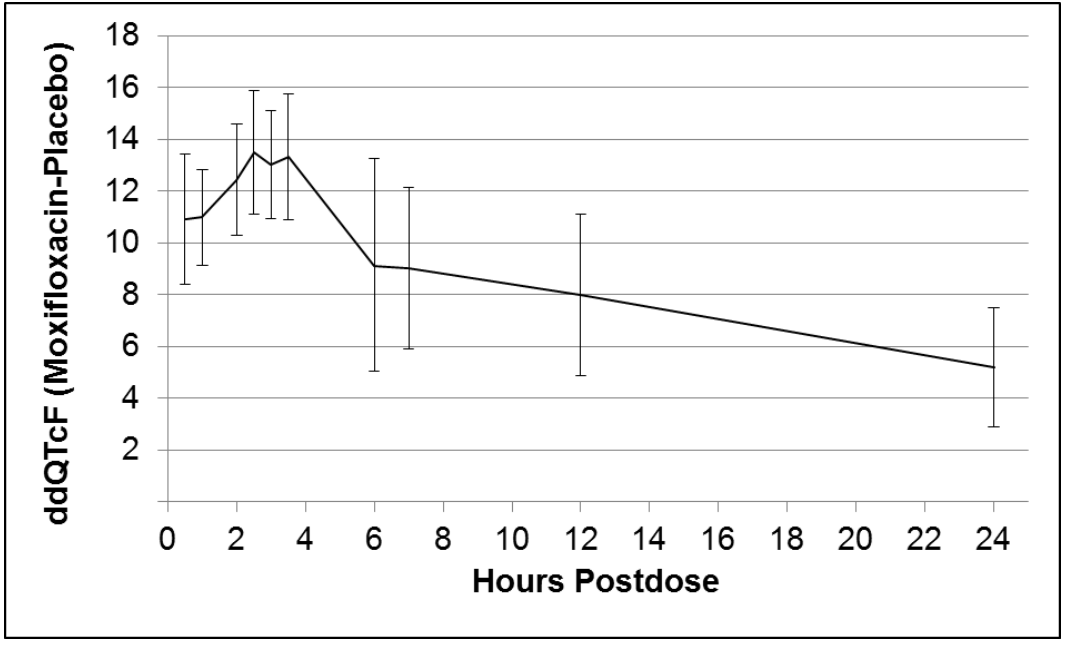
C Fosser, G Duczynski, M Agin, P Wicker and B Darpo

We analyzed five crossover, thorough QT (TQT) studies to compare automated, manual, and computer-assisted (CA) measurement methods. All the methods detected moxifloxacin-induced, baseline-adjusted, placebo-subtracted mean changes in Fridericia-corrected QT interval (QTcF), with peak effect ranging from 10 to 21 ms. The variability associated with manual and CA measurements was generally 5–28% greater than that associated with automated methods. The performances of automated, manual, and CA measurements were comparable for the purpose of demonstrating assay sensitivity in TQT studies with healthy volunteers.

George, S., Rodriguez, I., Ipe, D., Sager, P. T., Gussak, I. and Vajdic, B. (2012), Computerized Extraction of Electrocardiograms From Continuous 12-Lead Holter Recordings Reduces Measurement Variability in a Thorough QT Study. Journal of Clinical Pharma, 52: 1891–1900.

Case Study #1: HA analysis of TQT

Highly Automated and Automated Data has been Accepted by Regulatory Agencies for TQT



Results from a Thorough QT (TQT) study demonstrating assay sensitivity using moxifloxacin as a positive control. ECG data was analyzed using a highly automated approach in a TQT study with only 36 subjects.

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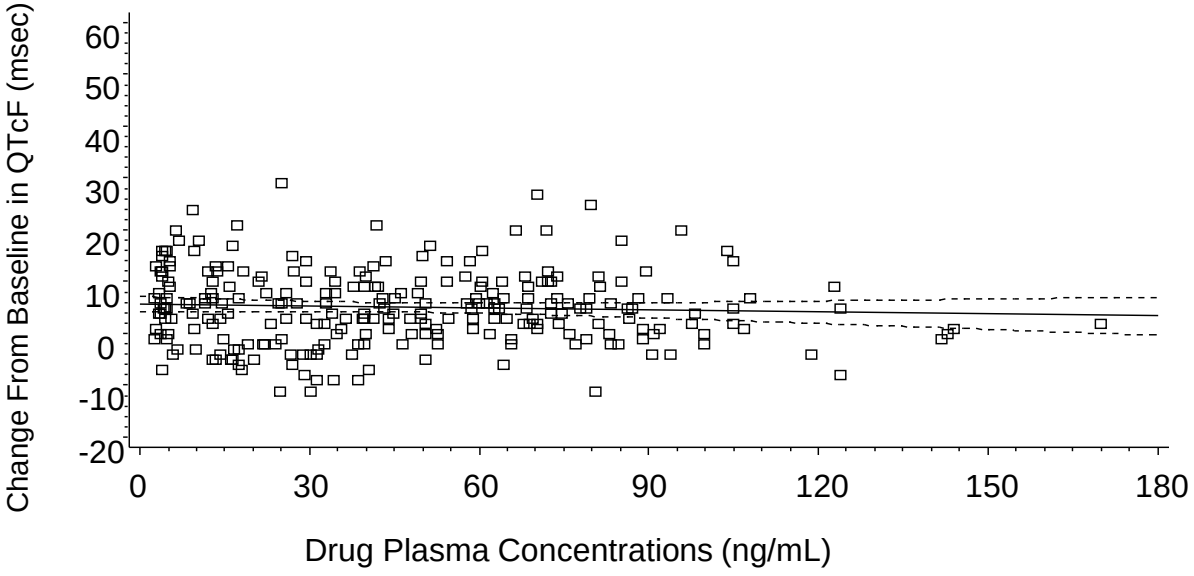
Case Study #2: HA analysis of DDI study

- Drug-Drug Interaction study (N=16)
  - Period 1: Single dose study drug
  - Period 2: dosing with inducer
  - Period 3: inducer + study drug
- ECG extractions: 3 pre-dose timepoints + 7 post-dose timepoints in Period 1, 2 & 3

Case Study #2: HA analysis of DDI study



Slope = **-0.01264 (95% CI: -0.039488, 0.014209)**
Intercept= **5.60 (95% CI: 4.07, 7.12)**
R^2= **0.0034**

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Questions