

Current and future assessment of cardiotoxicity beyond the TQT

N Stockbridge

Division of Cardiovascular and Renal
Products, FDA/CDER

Outline

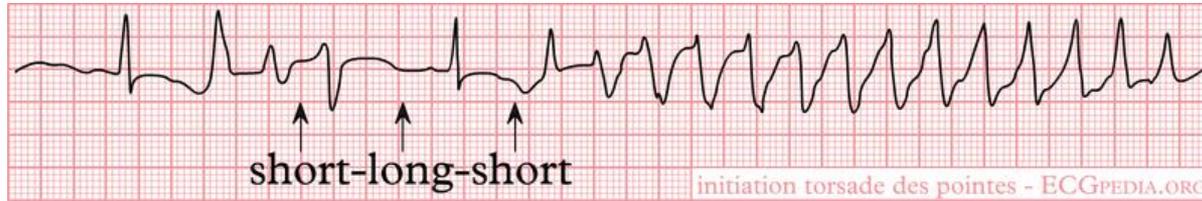
- How we got here
- Why we should not be happy
- Exposure-response data to assess QT
- Why we should still not be happy
- Getting at risk through the ECG
- Getting at risk through non-clinical assessment

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Torsade de Pointes

(Twisting of the points)



Drugs Removed From Market for Arrhythmia Risk

- Encainide (Enkaid[®]) 1991 (1986)
- Terfenadine (Seldane[®]) 1998 (1985)
- Astemizole (Hismanal[®]) 1999 (1988)
- Grepafloxacin (Raxar[®]) 1999 (1997)
- Cisapride (Propulsid[®]) 2000 (1993)
- Levomethadyl (Orlaam[®]) 2003 (1993)

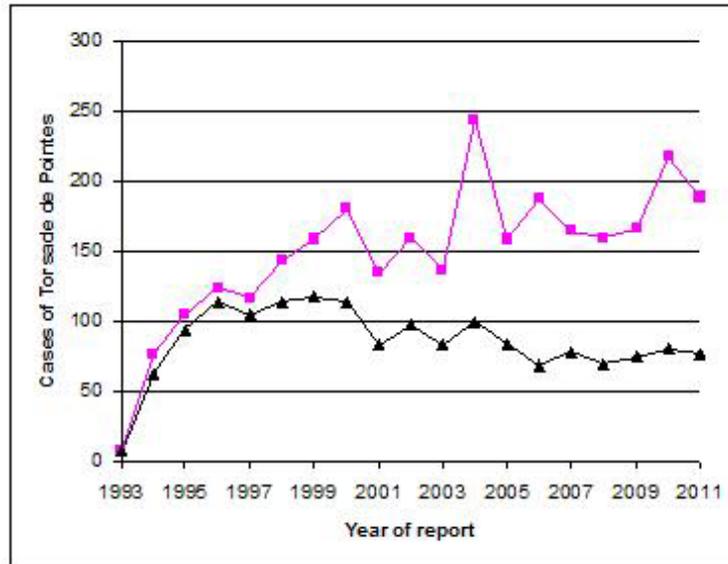
* year of removal (year of approval)

Responses to TdP crisis

- Regulatory
 - ICH S7B, E14 guidances
 - FDA QT interdisciplinary review team
- Technical
 - HL7 ECG data standard
 - ECG Warehouse
- Community & Research
 - Specialized QT study vendors
 - ECG Metrics Consortium
 - Cardiac Safety Research Consortium

Success!

- No new withdrawals
- Decline in TdP as a reported adverse event



All drugs

Excluding
anti-arrhythmics

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Direct costs

- Since 2005
 - Around 300 TQT studies reported to FDA
 - Estimated 450 TQT studies performed
 - Estimated cost per study is few \$M
- Total of ~\$1B over 9 years

Timing of TQT study

- Not usually the first clinical study, so if there is a significant problem, you may not know until you have further investment in a compound.

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Use exposure-response data

- From early-phase clinical study
- TQT-like attention to collecting ECGs and PK data
- Minimal interference with other aspects of phase I study
- Fully pre-specified methods to model exposure-QTc relationship
- Predict QTc at some dose's Cmax

- FDA agreed...but wanted a prospective study to demonstrate validity

ORIGINAL ARTICLE

The IQ-CSRC Prospective Clinical Phase 1 Study: “Can Early QT Assessment Using Exposure Response Analysis Replace the Thorough QT Study?”

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Charles Benson, M.D., Ph.D.,^{4,†} Corina Dota, M.D.,^{5,*} Georg Ferber, Ph.D.,^{6,‡}
Venkateswar Jarugula, Ph.D.,^{7,†} Lars Johannesen, M.Sc.,^{8,9} James Keirns, Ph.D.,^{10,†}
Kevin Krudys, Ph.D.,¹¹ Catherine Ortemann-Renon, Pharm.D., Ph.D.,^{12,*}
Steve Riley, Pharm.D., Ph.D.,^{13,‡} Danise Rogers-Subramaniam, Ph.D.,^{4,†}
and Norman Stockbridge, M.D., Ph.D.¹⁴

Design

- 20 healthy male subjects underwent 3 treatments
 - Incomplete block design: 9 on each drug, 6 on placebo
- Drugs:
 - Positive: Ondansetron, quinine, dolasetron, moxifloxacin and dofetilide
 - Negative: levocetirizine
- Each period consisted of 2 days
 - Day 1: Low dose intended to give ~ 10 to 12 ms QTc
 - Day 2: High dose intended to give ~ 15 to 20 ms QTc

Criteria for QT Assessment

Positive QT assessment :

1. The QT effect is detected:

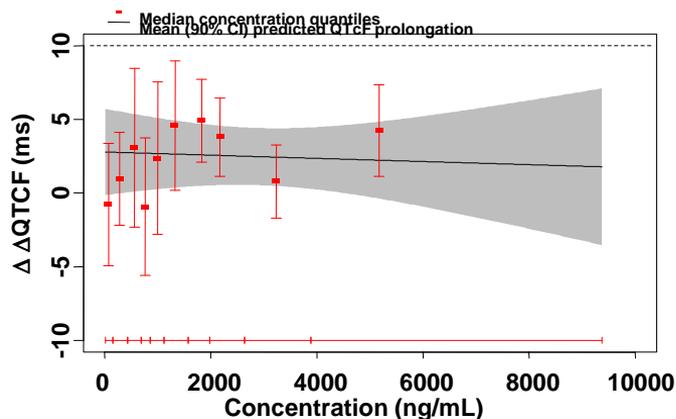
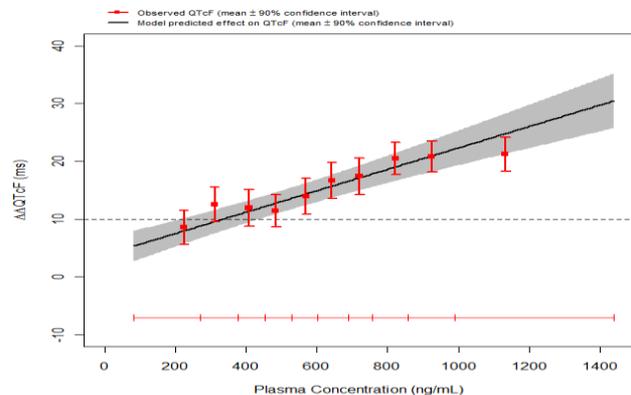
The upper bound of the 2-sided 90% confidence interval (CI) of the projected placebo-corrected ΔQTcF is above 10 ms at the observed geometric mean C_{max} of the drug.

2. The slope of the ER relationship is statistically significant:

The lower bound of the 90% confidence interval for the slope of $\Delta\Delta\text{QTcF}$ vs. concentration is above zero.

Negative QT assessment :

- The upper bound of the confidence interval of the predicted placebo-corrected ΔQTcF at the observed geometric mean C_{max} of the drug is below 10 ms.



Results



Cardiac Safety Research Consortium
www.cardiac-safety.org



INTERNATIONAL CONSORTIUM *for*
INNOVATION & QUALITY
in PHARMACEUTICAL DEVELOPMENT

Sharing Results from Novel Research Symposium

10903 New Hampshire Avenue, Silver Spring, Maryland 20993

White Oak Facility, FDA Headquarters • Silver Spring, MD • December 12, 2014

The results from the **IQ-CSRC prospective study 'CAN EARLY ECG ASSESSMENT USING EXPOSURE RESPONSE ANALYSIS REPLACE THE THOROUGH QT STUDY?'** will be presented at a meeting on FDA's White Oak campus. The study evaluates whether the QT effect of 5 marketed, mild QT-prolonging drugs can be identified in a study design typical for a phase 1 First-in-Man trial in healthy volunteers. The choice of the drugs and the design and the analysis plan of the study have been done in close collaboration with the FDA and the clinical phase of the study is now completed. The results of the study analyzed by the IQ-CSRC group and by FDA separately will be presented with comments from different stakeholders. The clinical and regulatory implications of the study will be discussed at the meeting with participation from FDA and other regulators, as well as from the ICH E14 Discussion group.

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What's wrong with that?

- False negatives, but other arrhythmias are detected in other assays (never were the problem).
- **Not all QT prolongation represents effects on hERG (false positives, parts 1 and 2).**
 - QRS prolongation from blocking Na, Ca (inward) currents
 - True repolarization effects can represent minor potassium currents (we see negative hERG and then a plateau effect on QT of 10 ms or so)

What's wrong with that?

- Not all proarrhythmic risk attributes to hERG blockade (false negatives).
- Not all QT prolongation represents effects on hERG (false positives).
- **Some true hERG blockers are *anti*-arrhythmic, because of effects on inward currents, too (worse false positives).**
 - Verapamil
 - Ranolazine
 - Amiodarone

What's wrong with that?

- Not all proarrhythmic risk attributes to hERG blockade (false negatives).
- Not all QT prolongation represents effects on hERG (false positives).
- Some true hERG blockers are anti-arrhythmic, because of effects on inward currents, too (worse false positives).
- **Optimizing against hERG can be a bad bargain**
 - **Reduced affinity for target receptor**
 - **New off-target effects**
 - **No drug candidate**

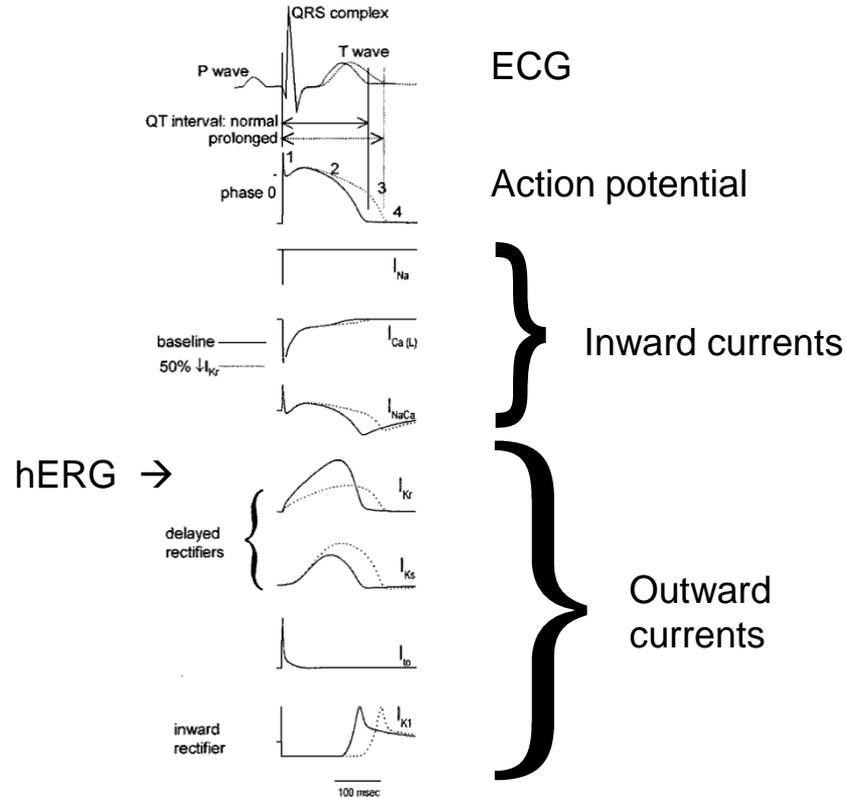
What's wrong with that?

ICH S7B and E14 were well-intentioned responses to a public health issue, but they had costs that were wildly out of proportion to the problem we were trying to solve, most importantly in the form of fewer safe and effective drugs entering development.

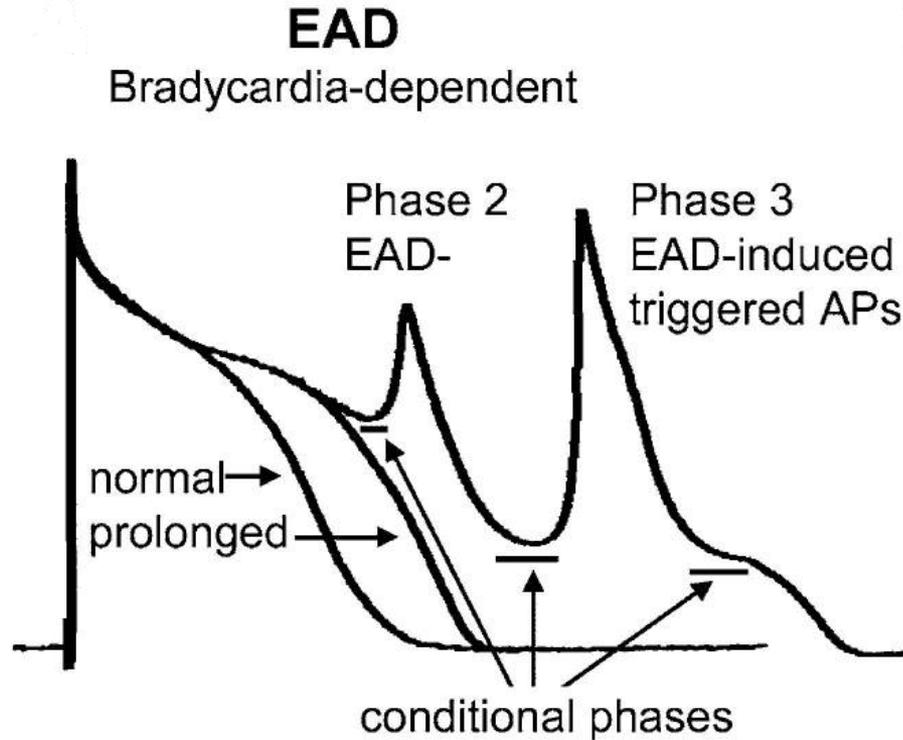
Basis for optimism

- We deeply understand what makes one drug proarrhythmic and another not, as well understood as any toxicity
 - Proarrhythmia requires reduction in repolarizing relative to depolarizing forces, and ...
 - Regional heterogeneity in the heart to set up a circuit. This is why you can go decades with impaired repolarization.
- The ion channel effects, but not heterogeneity, are amenable to study
 - Through effects on the human ECG
 - Through effects on isolated human cardiac ion channels

Cardiac ionic currents



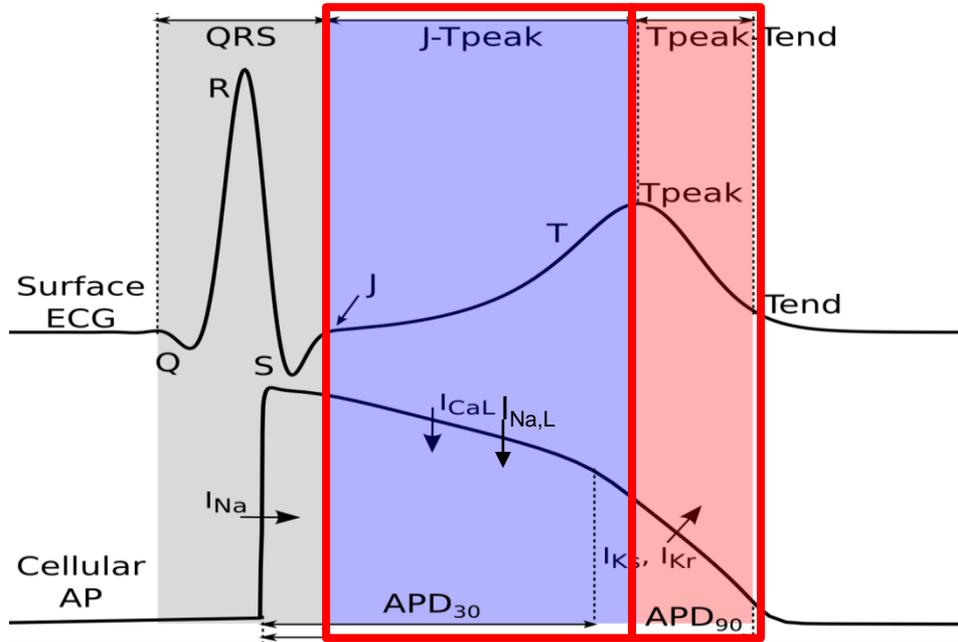
Vulnerability during repolarization



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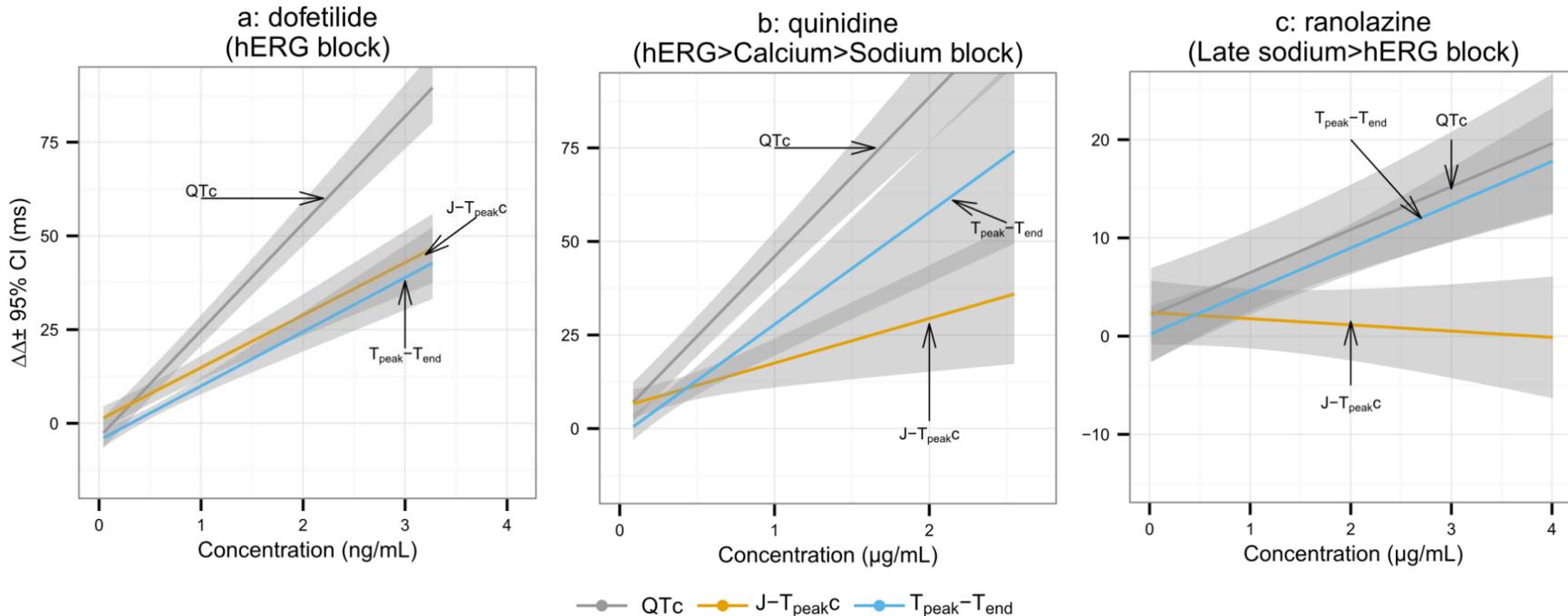
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ECG reflects channel effects



- David G. Strauss
- Lars Johannesen
- Jay Mason
- Jose Vicente
- Martin Ugander
- Jeffrey Florian
- Kristin Waite-Labott
- Staff at Spaulding Clinical Research and Frontage Laboratories

Signatures for dofetilide, quinidine, and ranolazine



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Comprehensive in vitro

Proarrhythmia Assay



- Assess drug effects on each cardiac ion channel type individually, using a high-throughput assay
- Compute net effect on refractoriness of the action potential to EADs
- Check to see if you missed something important
 - Action potentials in stem cell derived human cardiac myocytes
 - Signature of drug effects on the morphology of the ECG

CiPA Organization

- Ion Channel Work Stream led by SPS/Fermini & Abi Gerges
- In Silico Work Stream led by FDA/Colatsky
- Myocyte Work Stream led by HESI/Gintant & Zhang
- Compound Selection Work Stream led by CSRC/Sager
- Steering Committee / above plus various academics and regulators at EMA, Japan, and FDA.

Progress note

- Large international enterprise (pharma, technology vendors, academics, regulators) underway to define protocols
- Pilot studies getting underway
- Validation plan coordinated with various regulatory agencies and ICH
- Probably 18 months from fruition