

Shifting Gears to Non-Clinical Pro- Arrhythmia Models

Rationale and Scope of the Proposed CiPA Paradigm

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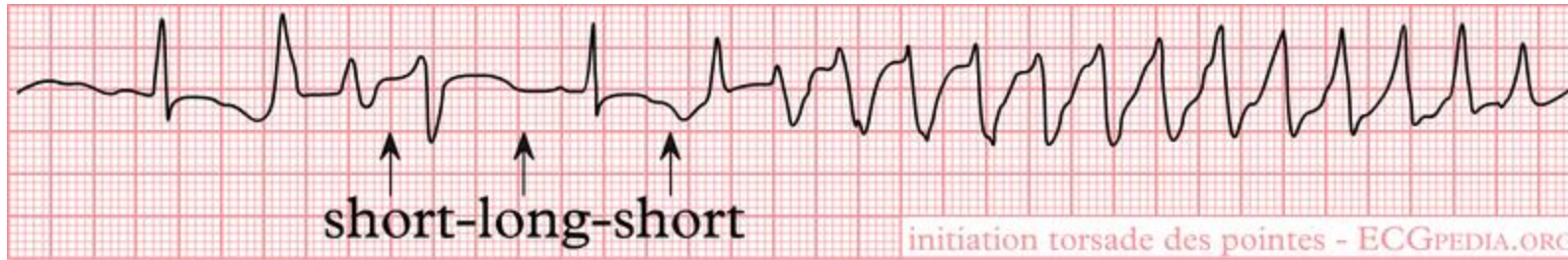
Division of Cardiovascular and Renal Products

FDA/CDER



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

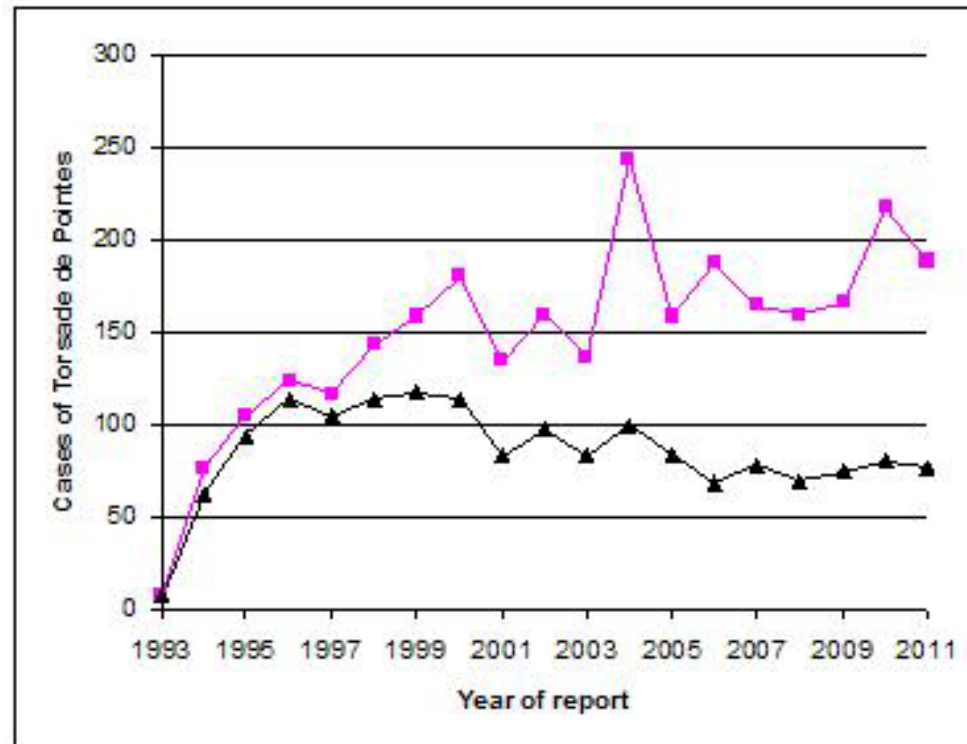
- Regulatory
 - ICH S7B, E14 guidances
 - FDA QT interdisciplinary review team
- Technical
 - HL7 ECG data standard
 - ECG Warehouse
- Community & Research
 - Specialized QT study vendors
 - ECG Metrics Consortium
 - Cardiac Safety Research Consortium

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

Success?

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



All drugs

Excluding
anti-arrhythmics

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.

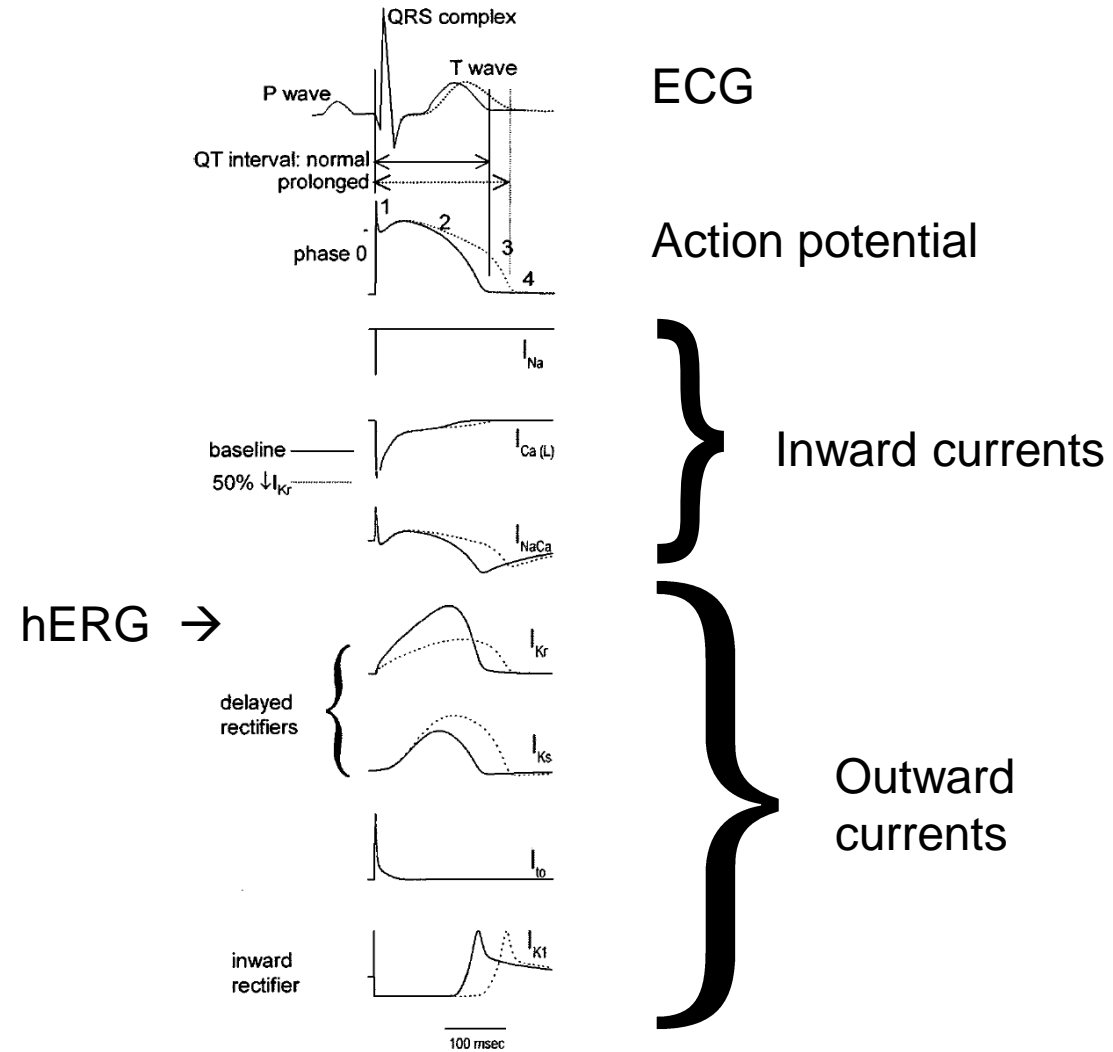
Solutions

- TQT cheaper
 - IQPharma project to get TQT-quality data from early phase clinical studies, utilizing best methods learned from TQT—data collection, data processing, exposure-response modeling, etc.
- Drug effects on multiple ion channels
 - Various efforts to wring more information from the human ECG about which ion channels are likely to be involved
 - Comprehensive in vitro proarrhythmia assay

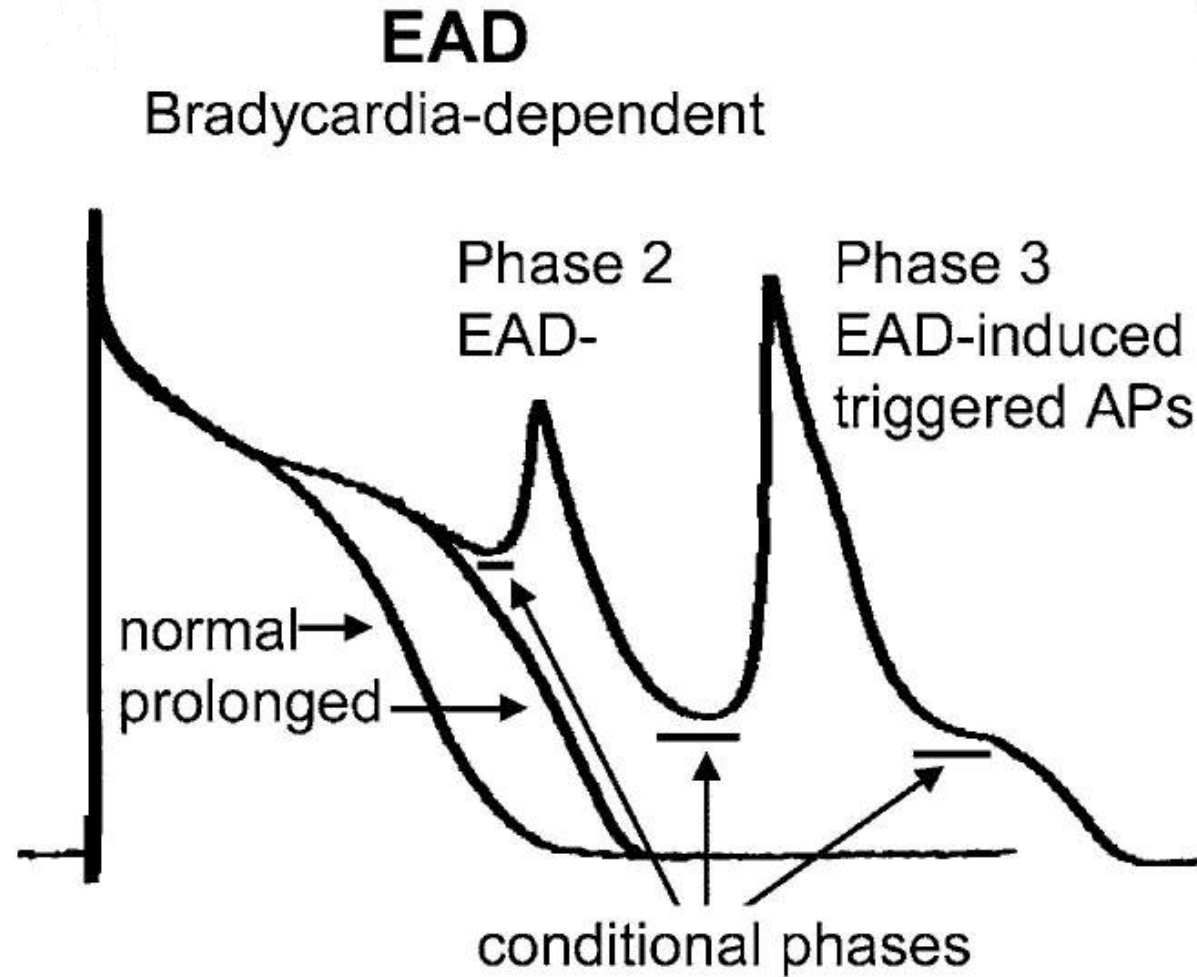
Basis for CiPA

- 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
 - We can isolate the relevant machinery of the human heart
 - There are commercially available high-throughput techniques, so an improved assay can be implemented early, at compound screening

Cardiac ionic currents



Vulnerability during repolarization



Comprehensive in vitro Proarrhythmia Assay (CiPA)

- 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/Collatsky
- 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

Summary

- CiPA is possible because the proarrhythmia science is well understood and the technological requirements can be met on a commercial scale.
- CiPA may be unique in toxicology.
 - Failure modes can be enumerated and tested.
 - CiPA uses human machinery and cells
 - Reconstruction of net effects on proarrhythmic potential is complex, but the model is fully specified and has no unmeasurable parameters
- CiPA is highly likely
 - To preserve the sensitivity of the current paradigm
 - To improve specificity over the TQT
 - To rehabilitate the labels of numerous marketed drugs
 - To widen the choice of molecules fit for clinical development.