

Evolution of testing pharmaceuticals for proarrhythmic potential

An example of applied regulatory science

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Regulatory *Science*?

- Science as *organized knowledge*
 - Well, if political science is science, we qualify.
- Science as set of *testable* ideas
 - Well, testable doesn't say we test, just that we can
 - Our tests are (always?) historically controlled, and seldom if ever have predefined metrics of success
 - Still looks like political science
- Science as method for advancing knowledge through *hypothesis testing*
 - Our musings along these lines are pure natural philosophy
 - To be wished for when my administration wants to impose some change upon my business practices

Proarrhythmia assessment

- History and net result
- What's wrong with that?
- Science-based approaches to improve state
- Regulatory science or science in regulation

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)

Torsade de Pointes

(Twisting of the points)



Responses to TdP crisis

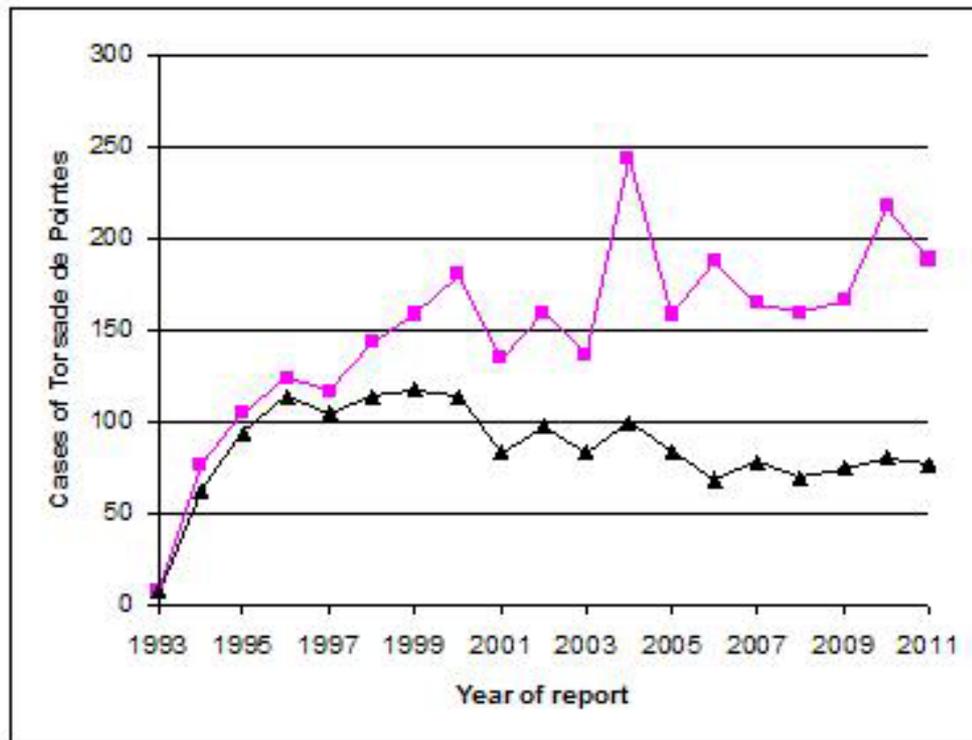
- Regulatory
 - ICH S7B, E14 guidances
 - FDA QT interdisciplinary review team
- Technical
 - HL7 ECG data standard
 - ECG Warehouse
- Community & Research
 - Specialized QT study vendors
 - ECG Metrics Consortium
 - Cardiac Safety Research Consortium

Direct costs

- Since 2005
 - Around 300 studies 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?

- **Not all proarrhythmic risk attributes to hERG blockade (false negatives).**
 - For example, anti-epileptic drugs are mostly sodium channel blockers
 - Felbamate- SVT, TdP, AF
 - Pregabalin- VF
 - Not a big deal—we have other assays to pick up these types of arrhythmias

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, part 1).**
 - 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

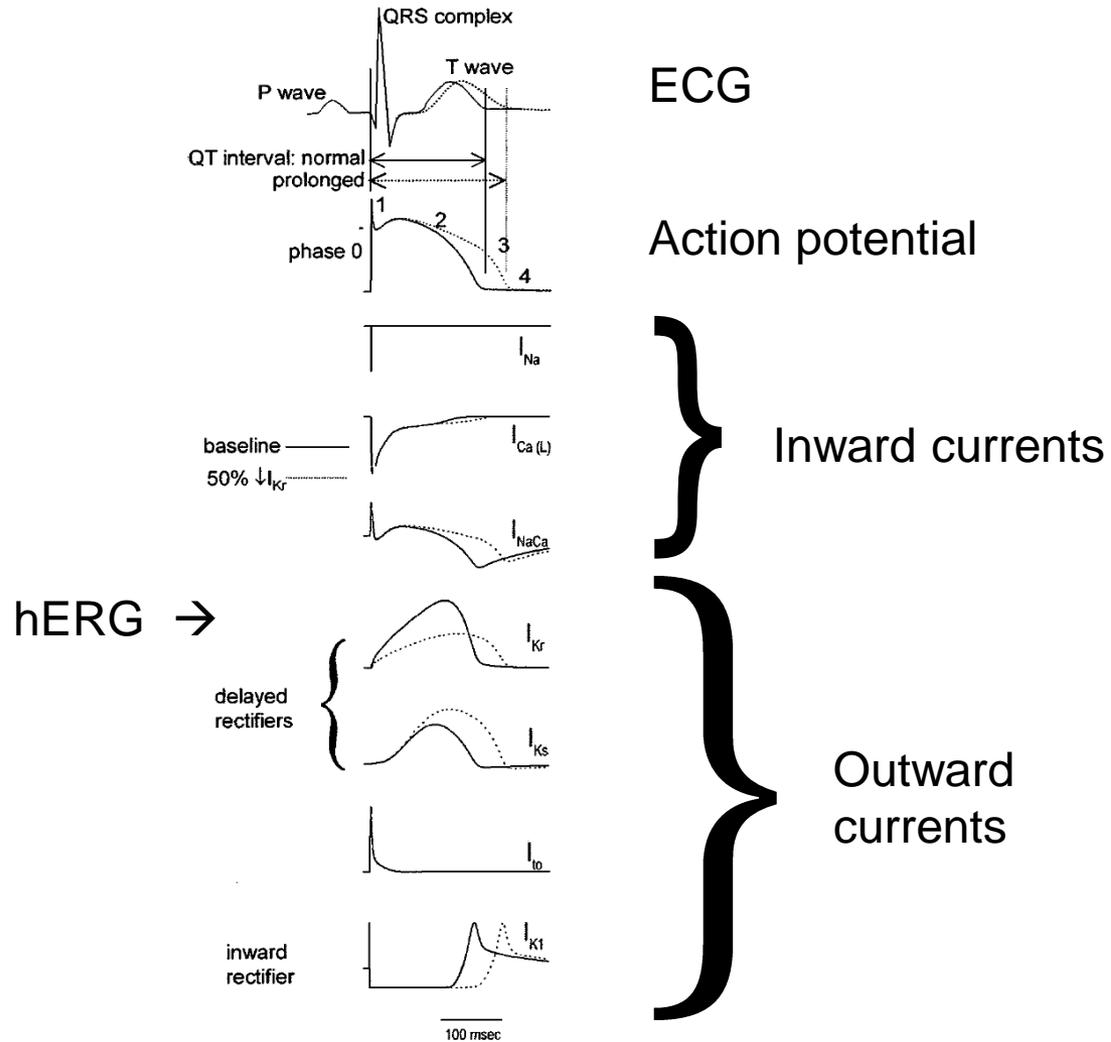
What's wrong with that?

Well-intentioned response to a public health issue 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.

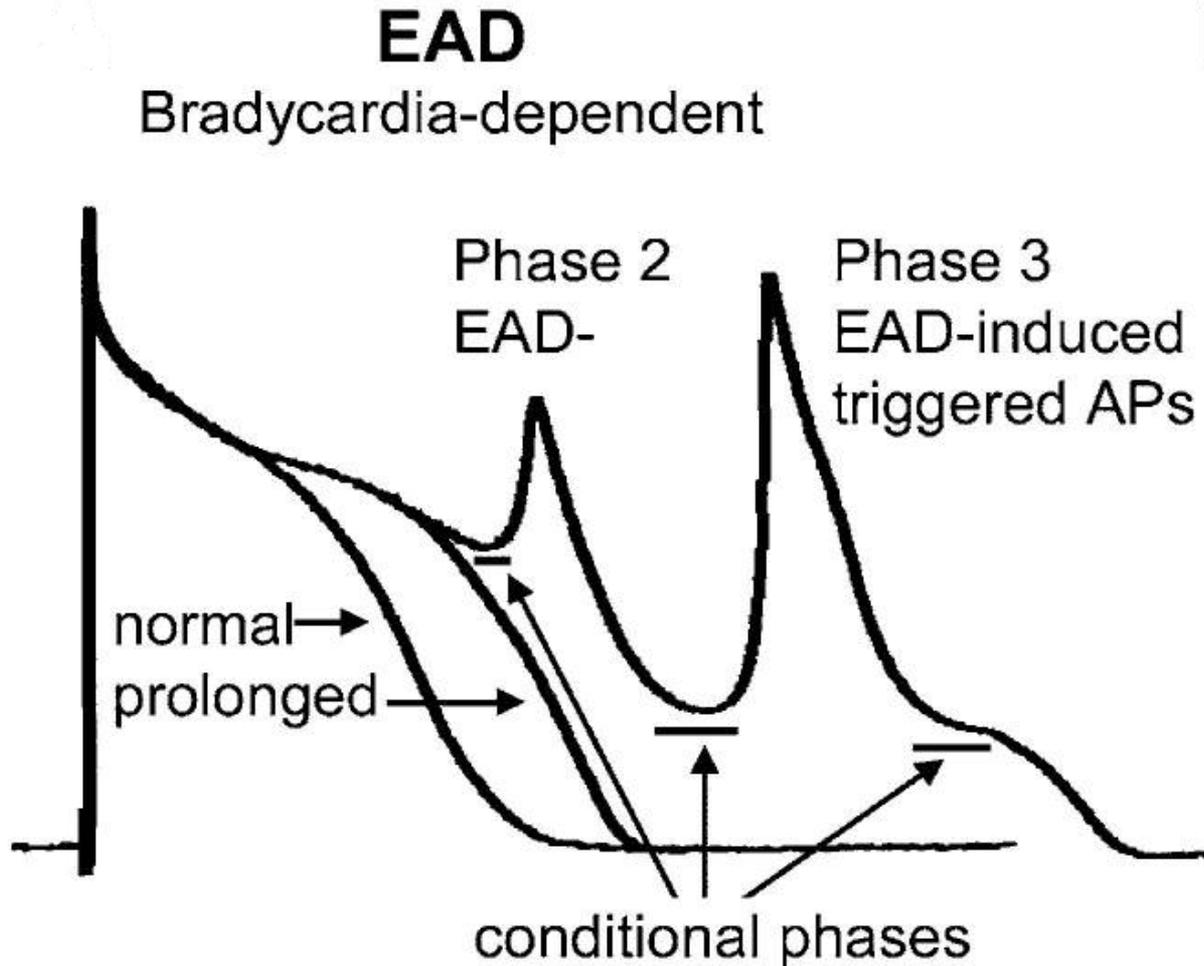
The fix

- We almost certainly can do much better than the current hERG/QT paradigm
- We deeply understand what makes one drug proarrhythmic and another not, as well understood as any toxicity
- We can isolate the 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



Multiple ion channel effects matter

- Because hERG effects are dramatic, it used to be thought that hERG was especially poorly designed for the pharmacologist, but now other ion channels are known to be fairly often the target—or one of the targets—for small molecule drugs.
- These other ion channel effects can make matters worse or better
 - Need relatively intact inward current to generate an EAD, so verapamil and ranolazine (both hERG blockers plus) are antiarrhythmic

Comprehensive in vitro Proarrhythmia Assay (CiPA)

- Assess drug effects on each cardiac ion channel type, 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

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

Regulatory science

- Properly, ought to be base policy on (testable) theories of how actions affect parameters of interest
 - Right mix of safety and efficacy
 - Foster drug development

I don't think we do this much at all!
- More often, as with CiPA, we achieve some incorporation of science in how we make decisions