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The Need for a New Paradigm to Assess Proarrhythmic Effects of Drugs

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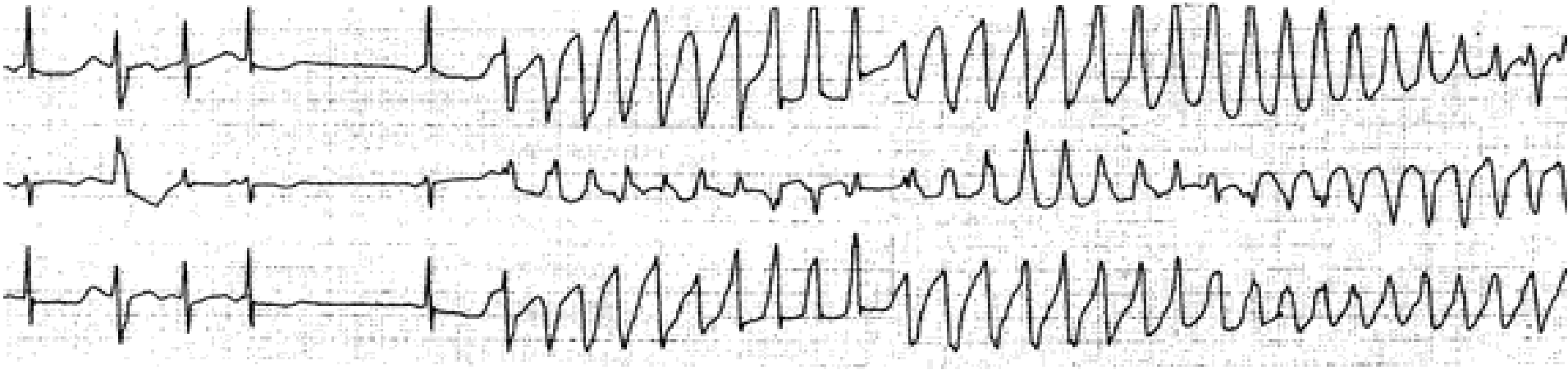
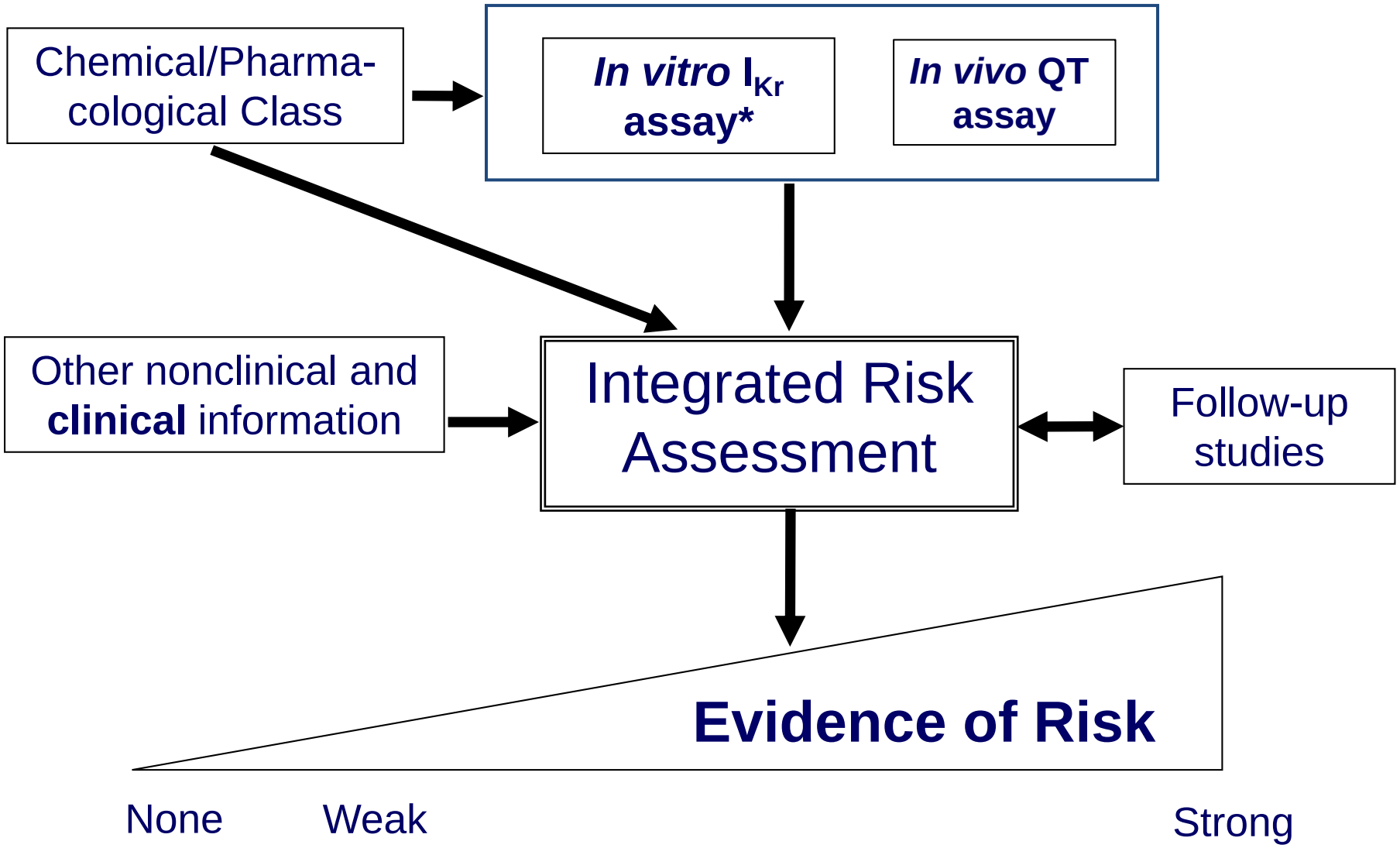
Drug-Induced Torsade de Pointes



QT Prolonged/Drug-Induced Torsade

- QT prolongation/TdP – single most common cause of withdrawal or restriction on marketed drugs
  - Terfenadine, astemizole, cisapride, droperidol, grepafloxacin, levomethadyl, lidoflazine, sertindole, terodiline
- This has resulted in the need for regulatory guidance.
- TdP rarely observed during clinical development
- Focus on surrogates- HERG and QTc testing
  - QTc- sensitive but not very specific

S7B: Nonclinical Testing Strategy

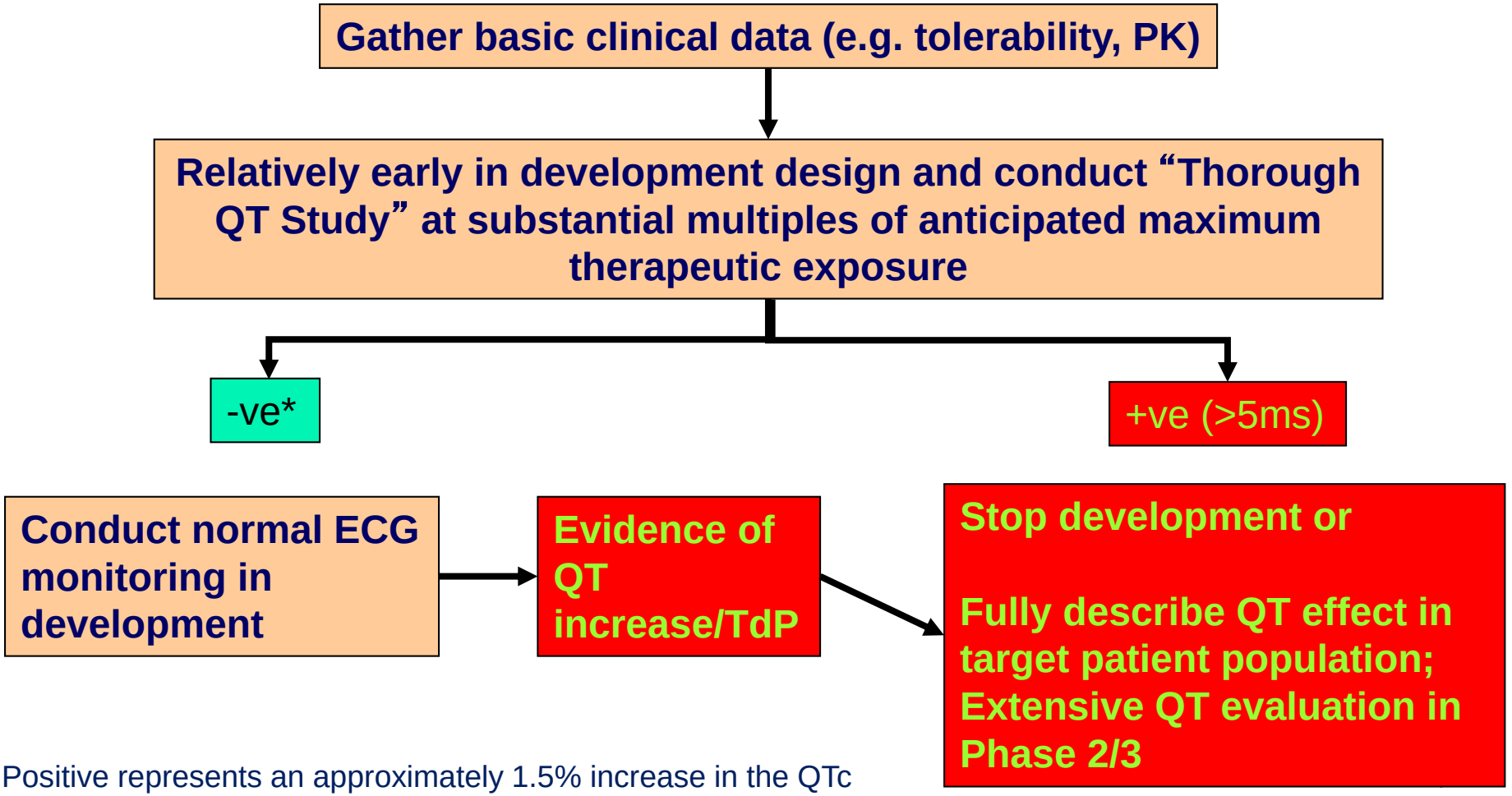


*The hERG (gene for K_v11.1 alpha subunit of I_{Kr}) related current is used

Clinical QT Update

Guidance document – ICH E14

Applicable to all new drugs with systemic bioavailability



* Positive represents an approximately 1.5% increase in the QTc

Consequences: Compound with QT effect

Consequences of developing a compound with QT effect

- Significant development burden
- Increased perceived risk = increased burden to demonstrate benefit
- Increased costs
- Delays in filing and/or approval
- Label warnings and competitive implications
- Licensing/partnering issues
- **Often leads to termination of development**

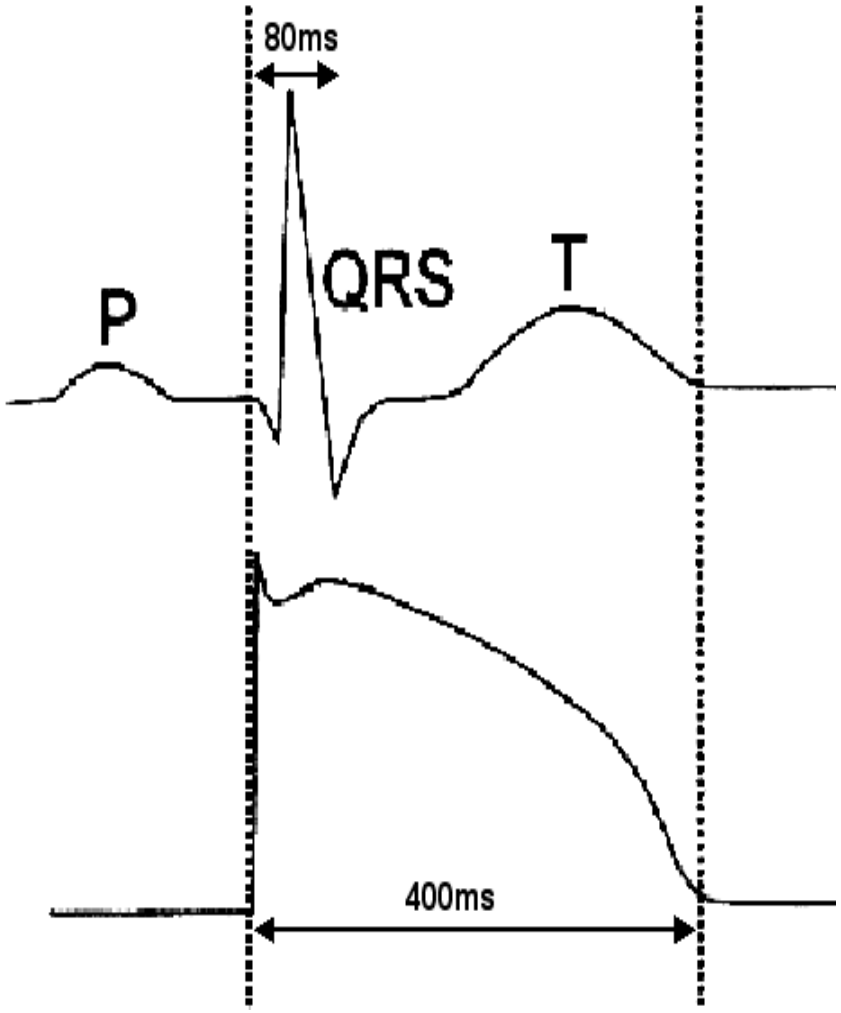
Torsadogenic Drugs

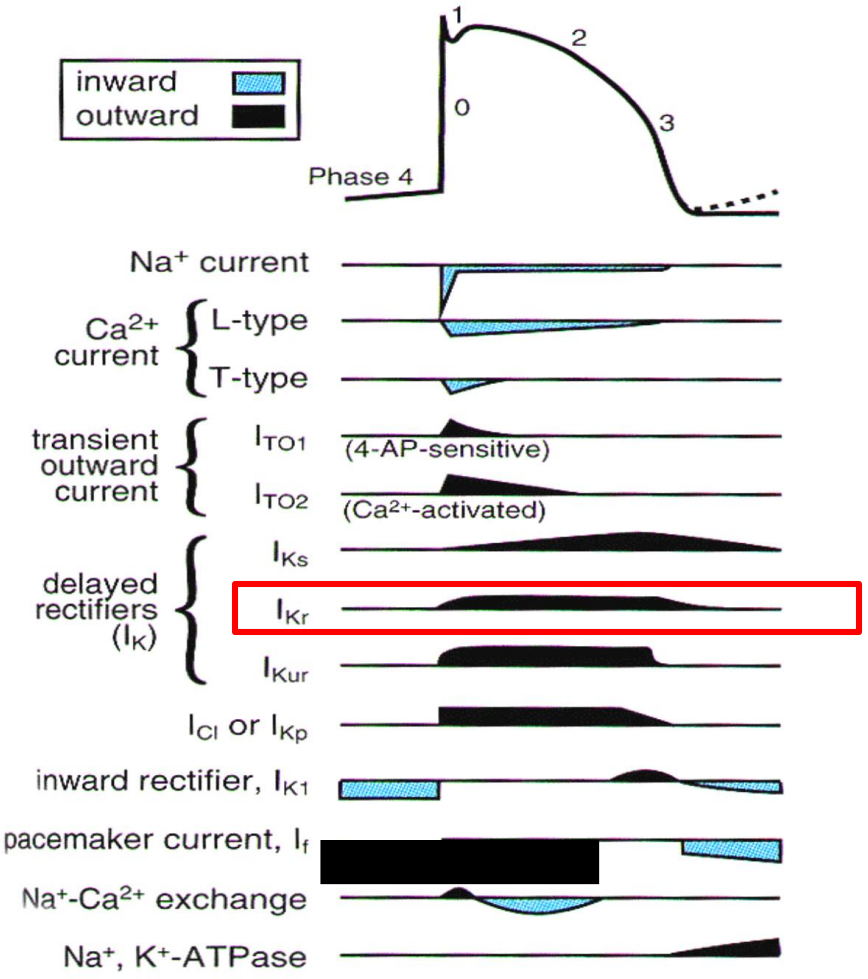
- ICH E14/S&B have resulted in no drugs with unrecognized risk being approved

- **Success!**

- Negative impact on drug development
  - Premature discontinuation due to hERG or QT “signal”
    - (Inaccurate) perception of risk leading to drug discontinuation
      - Estimates of up to 60%
    - Concerns regarding development burden, costs, labeling
    - Many potentially good compounds never get evaluated in humans due to a hERG effect
  - Drug development in specific areas- CNS
  - Many drugs with QT labeling are unlikely proarrhythmic
  - Engineering-out hERG- applicability/other effects

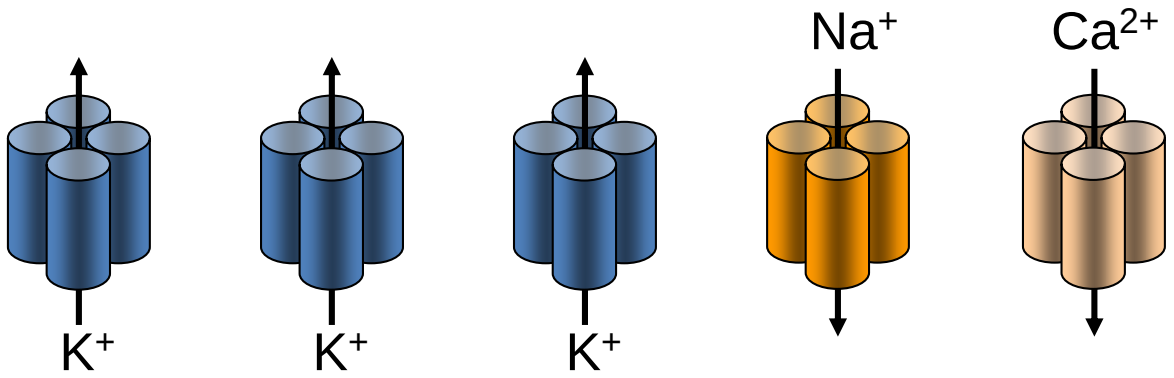
Ventricular Repolarization





Evidence of Alternative Mechanisms

Strong genetic data illustrating potential impact of non-hERG-mediated changes in QT interval with drug examples for most



Current	I_{Kr}	I_{Ks}	I_{K1}	I_{Na}	$I_{Ca,L}$
Loss of function	QT↑	QT↑	QT↑		QT↓
Gain of function	QT↓	QT↓	QT↓	QT↑	QT↑

C. Pollard

QT Prolongation: Dissociation from TdP

- Sodium Pentobarbital
  - Prolongs QT but no TdP
  - Inhibits I_{kr}, I_{ks}, and late I_{Na}

- Amiodarone
  - TdP very rare
  - Inhibits I_{kr}, I_{ks}, late I_{Na}, and I_{ca}

- Verapamil
  - Inhibits I_{Kr} but also Ca influx

- Ranolazine
  - Prolongs QT but no TdP
  - Inhibits late I_{Na}, I_{kr}, and I_{NaCa}

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- Verapamil
  - Inhibits I_{Kr} but also Ca influx
  - No QT prolongation or TdP
- Ranolazine
  - Prolongs QT but no TdP
  - Inhibits late I_{Na}, I_{kr}, and I_{NaCa}
  - No EAD's, reduces dispersion;
  - Suppresses E4031 induced TdP

Thus QTc Prolongation need not cause TdP

Issues

- QT prolongation ≠ Proarrhythmia
- HERG block ≠ Proarrhythmia
- Negative impact on drug development
- New paradigm

New Paradigm

A new cardiac safety paradigm focused on non-clinical measurement of proarrhythmia proclivity

Focus on the real issue: Proarrhythmia

- Reduce the premature termination of drugs with favourable benefit:risk profiles
- Make drug development more efficient
  - Move the bulk of proarrhythmic assessment to the discovery phase
  - Use the assays to potentially guide candidate selection
  - Obviate the TQT study
- Enhance the accuracy with which existing and/or new drugs are labelled relative to actual proarrhythmic risks

American Heart Journal

Rechanneling the cardiac proarrhythmia safety paradigm: A meeting report from the Cardiac Safety Research Consortium

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- Proarrhythmic risk can be determined by pre-clinical assessments
- Proclivity to develop EAD's
  - Ionic Currents
    - in silico modeling
  - Cell-Based Approach
  - Focus on high throughput approaches
- ECG Phase 1 Assessment

American Heart J 2014

Collaborators

- Drs. Stockbridge, Gintant, Petit, and the Steering Comm.
- FDA
- EMA
- PMDA
- Health Canada
- CSRC
- HESI
- SPS
- In Silico Modelers
- Pharmaceutical and Device Companies
- CRO’s
- Numerous Academic Groups

Thank you

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