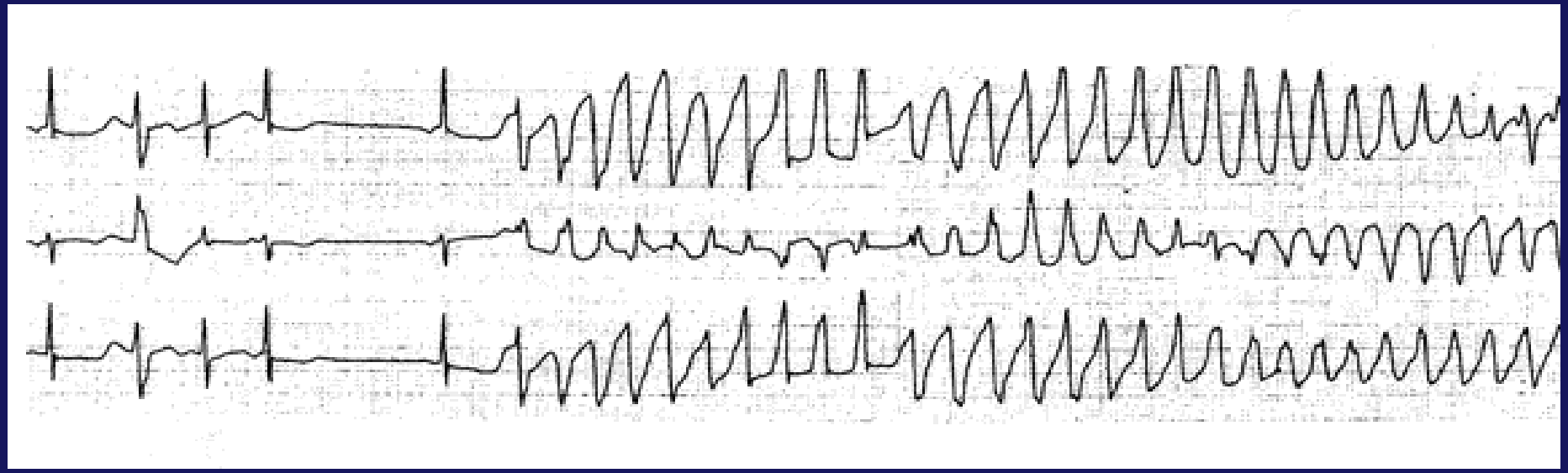
Proarrhythmic Assessment of Drugs: The Need For a New Paradigm

Philip Sager, MD, FACC, FAHA, FHRS
Consulting Professor of Medicine
Stanford University School of Medicine
Chair, Scientific Programs Committee,
Cardiac Safety Research Consortium
Psager@Stanford.edu



Industry Relationships

Member of DSMB, Adjudication Committee, or Consultant

- Genentech
- Orexo
- Aerpio
- Akebia
- Balance
- Medtronic
- Biomedical Systems
- ICardiac
- Heart Metabolics
- Milestone
- Theravance
- Lilly
- Viamet
- Shire
- Helsinn
- Celgene
- SNBL
- Pharmacyclics
- Anthera

Drug-Induced TdP

- Quinidine syncope with drug-induced LQTS (Selter and Wray, 1964)
- Ventricular arrhythmia Torsades de Pointes – TdP (Dessertenne, 1966)
- Terfenadine

  Mean QT change over 12 hours: 6ms
  Mean change at Tmax: 12ms
  Mean change with metabolic inhibition: ≥82ms

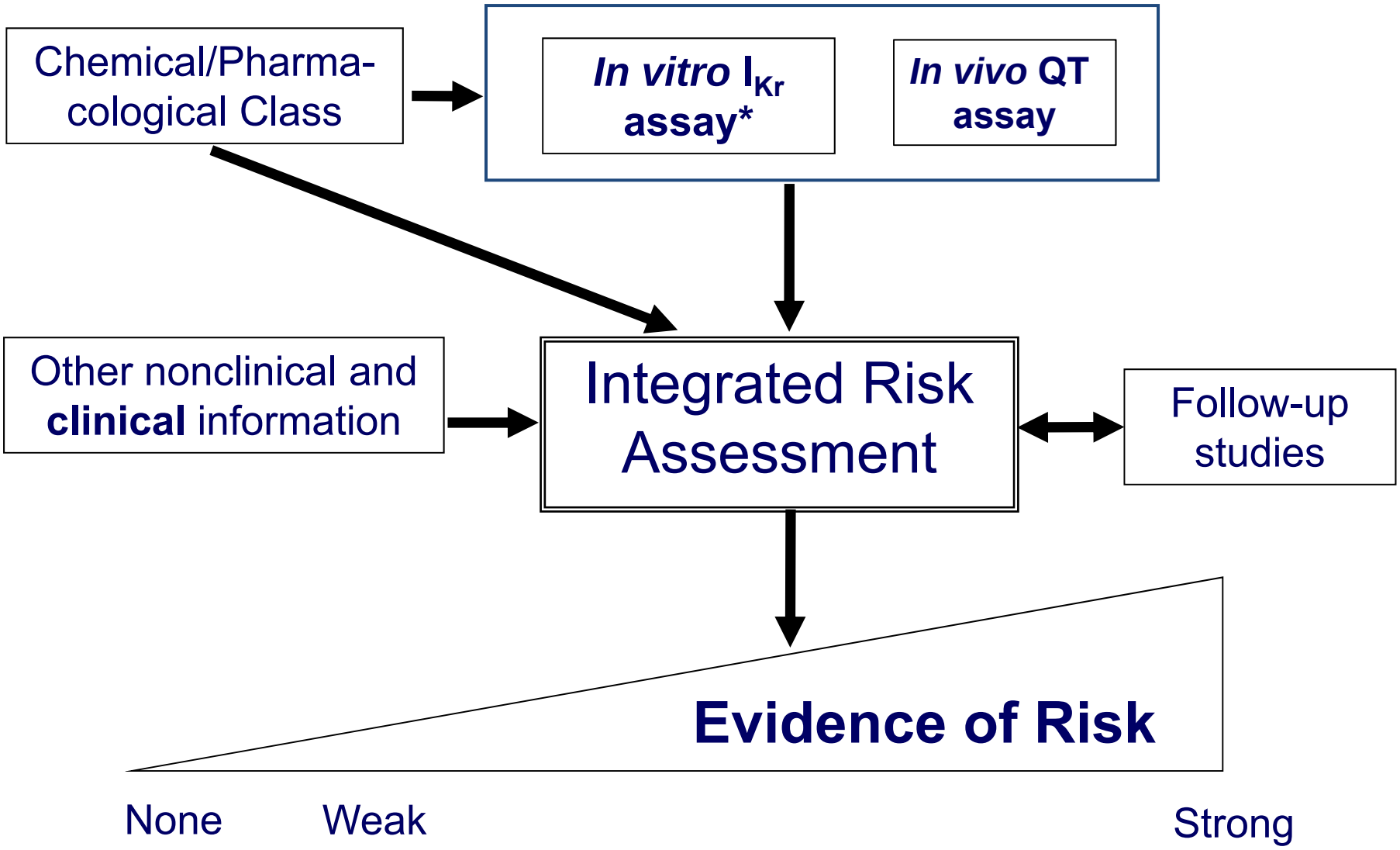
  Problem not clearly identified after 100,000,000 prescriptions

- Quinidine, d,l-sotalol, dofetilide, ibutilide 1-4% TdP incidence

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

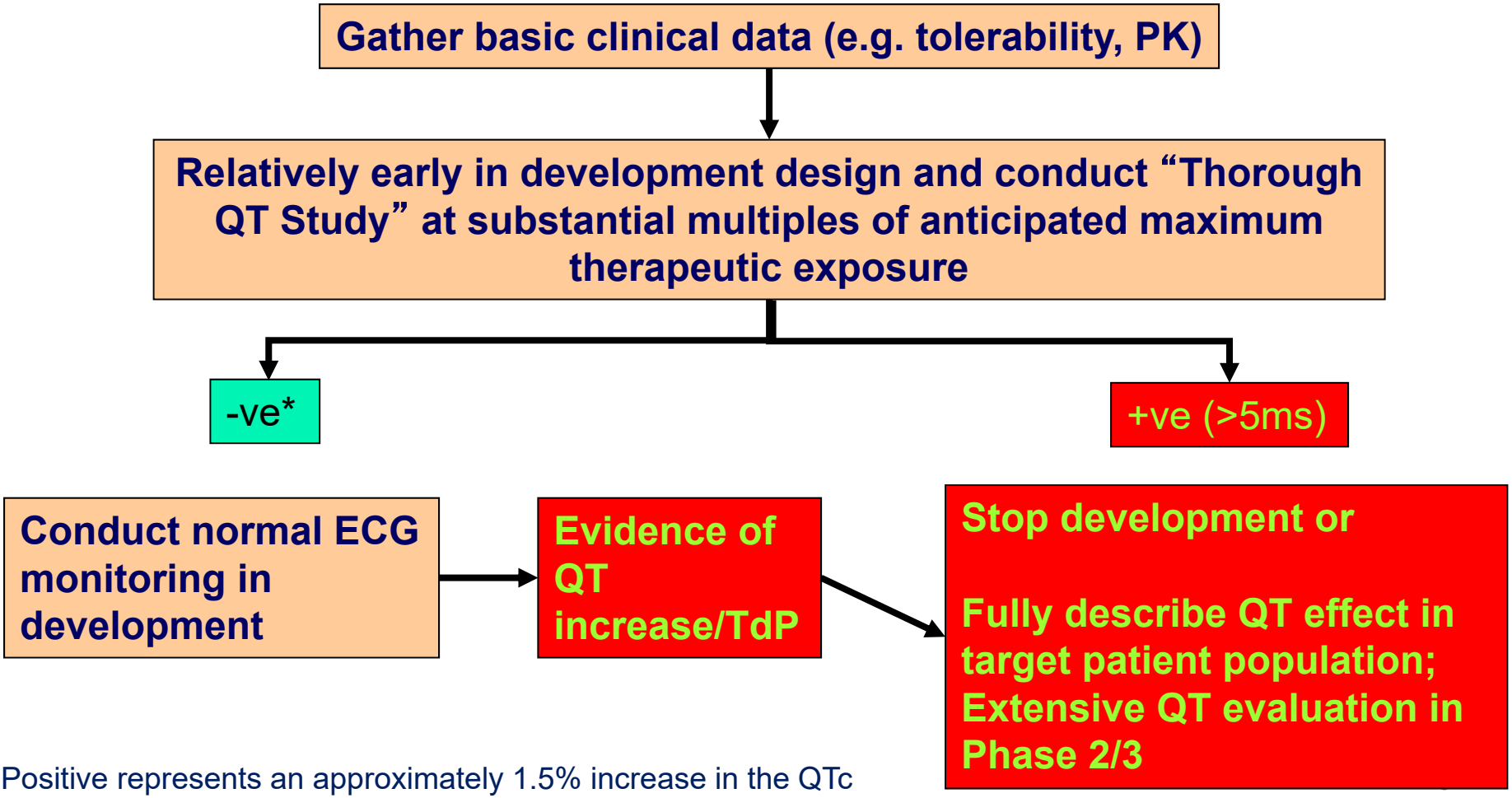


*The hERG (gene for K_v11.1 alpha subunit of I_{Kr}) related current is used

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

Examples of Label Implications of a QT Signal

- Alfuzosin
  - This observation [mild QT prolongation] should be considered in clinical decisions to prescribe UROXATRAL for patients with a known history of QT prolongation or patients who are taking medications known to prolong QT
- Ziprasidone
  - [has a] greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs. …raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs ...
  - In many cases this would lead to the conclusion that other drugs should be tried first

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**

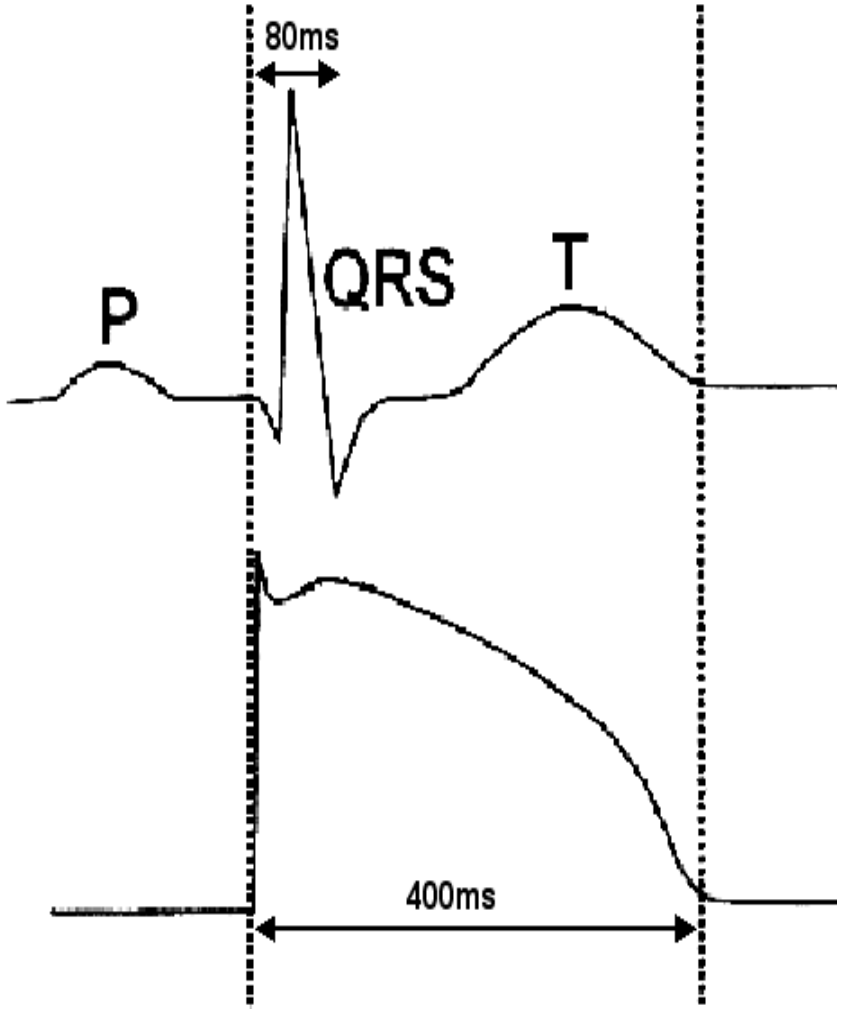
Torsadogenic Drugs

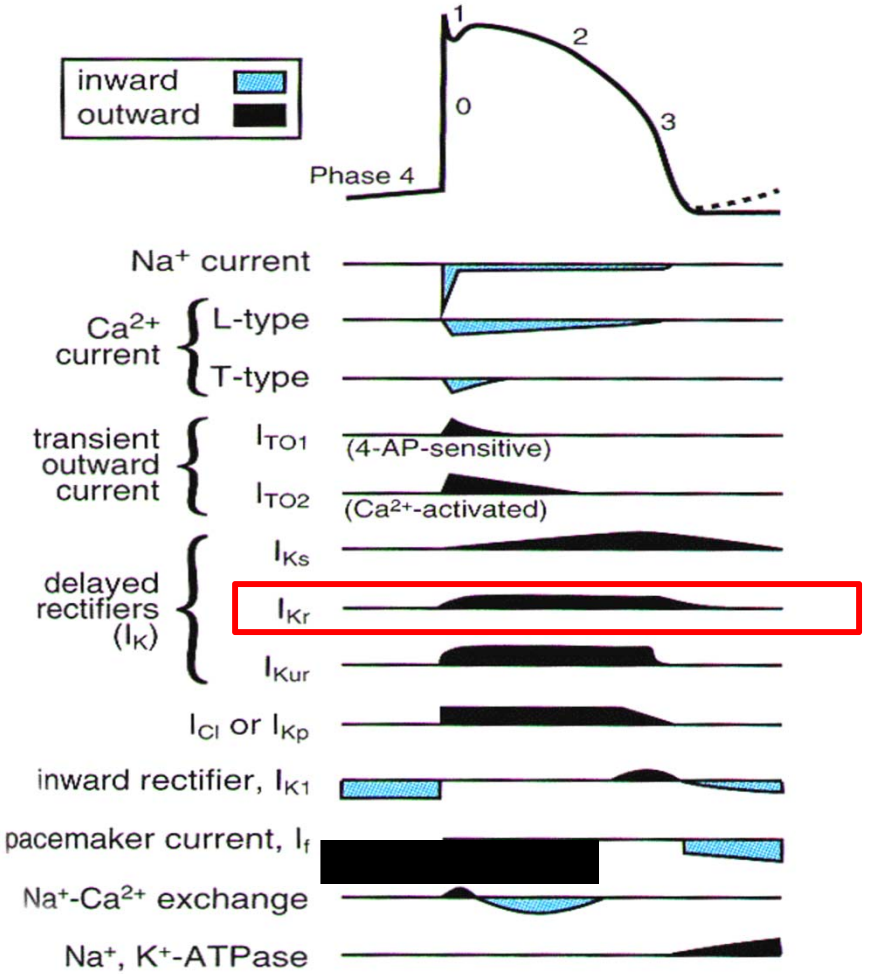
- ICH E14/S7B have resulted in no drugs with unrecognized risk being approved

- **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

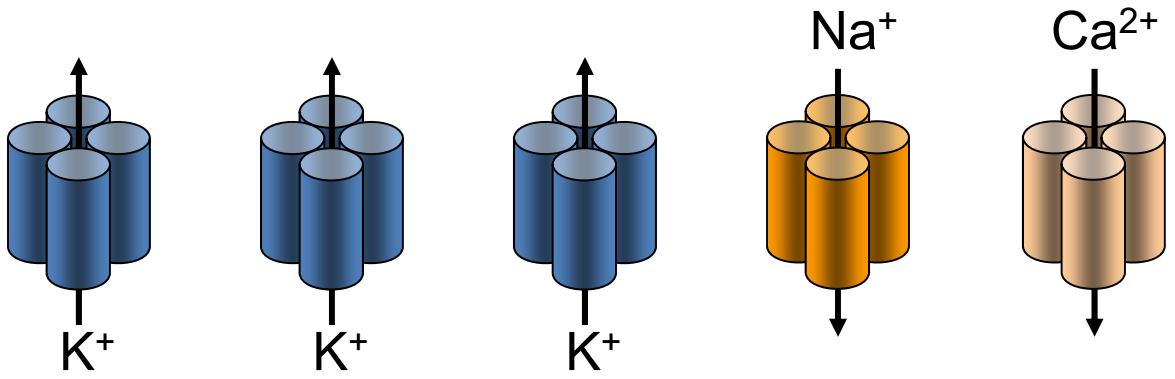
Ventricular Repolarization





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

Acquired LQTS: APD/EAD/QT Interval Prolonging Models

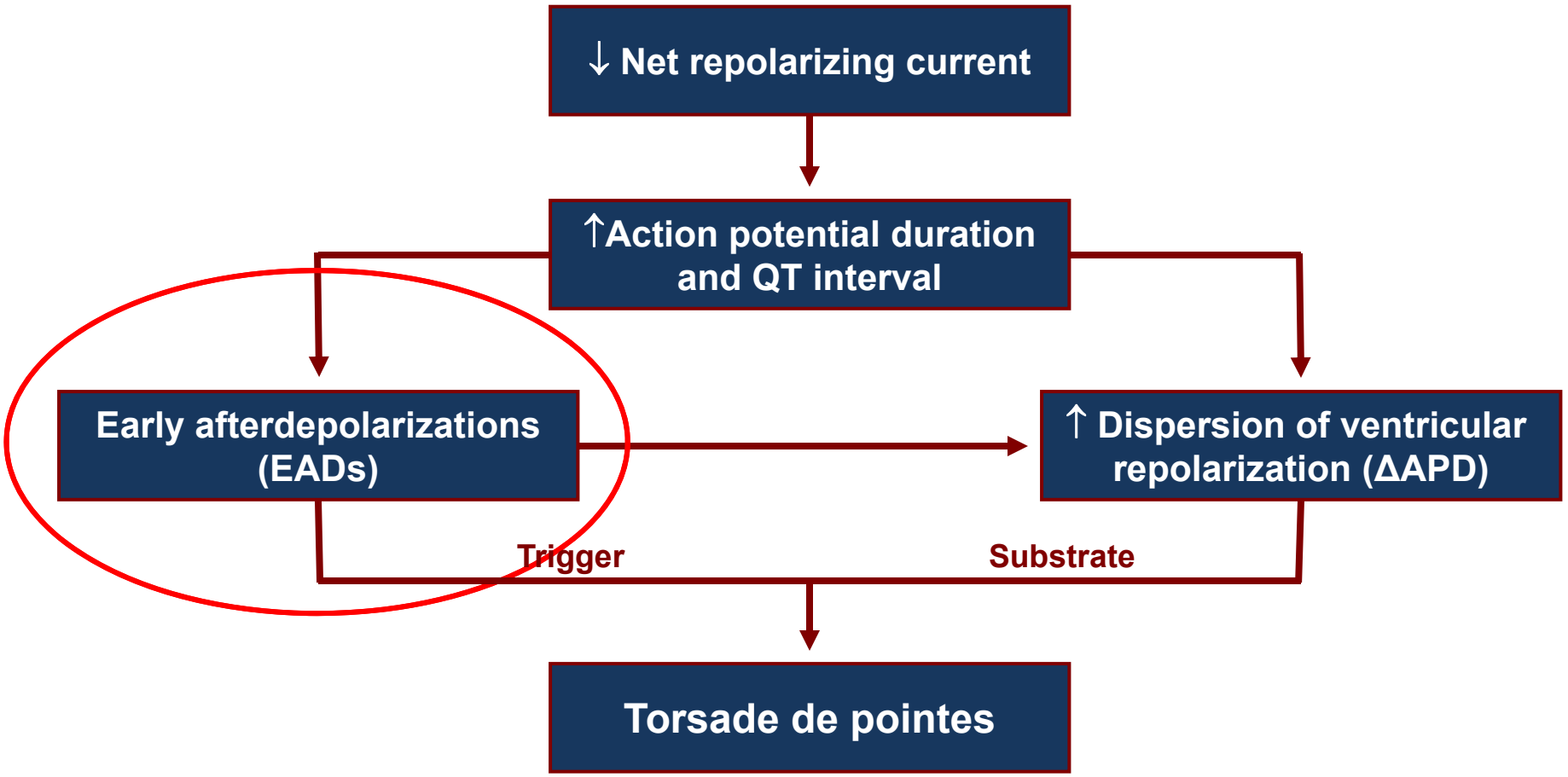
Drug/Gene Defect/Intervention	Principal Target
Veratridine, ATX II, anthopleurin A, alfuzosin, (*mutations in Na^+ channels*)	Enhance late I_{Na}
Bay K 8644 (*mutations in Ca^{2+} channels*)	Enhance $I_{Ca\text{-}L}$
Cs^+, quinidine, procainamide, bepridil	Suppress K^+ currents
E-4031, dofetilide, ibutilide, sotalol, terfenadine, astemizole, desmethylastemizole, cisapride, haloperidol, droperidol, halofantin, erythromycin, fluoxetine, etc. (*mutations in Kv11.1 K^+ channels*)	Suppress I_{Kr}
Azimilide, Chromanol 293B (*mutations in Kv7.1 K^+ channels*)	Suppress I_{ks}

Conclusions:

- **Most LQTS drugs cause rapid direct channel block of I_{kr}, but this is not the exclusive mechanism**

Modified from January: CSRC Mtg 2013

Development of TdP



Antzelevitch C et al. *J Cardiovasc Pharmacol Therapeut.* 2004;9(suppl 1):S65-83.

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

Philip T. Sager, MD, FACC, FAHA,[a] Gary Gintant, PhD,[b] J. Rick Turner, PhD,[c] Syril Pettit, MEM,[d] and Norman Stockbridge, MD, PhD[e] *Palo Alto, CA; North Chicago, IL; Durham, NC; Washington, DC; and White Oak, MD*

- **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

CiPA: Two Component Proposal

Ionic Currents / In Silico Based Approach

Effects on Multiple Cardiac Currents (Voltage Clamp Studies)

+

Reconstruction of Cellular Electrophysiology (*In Silico* Studies)

Myocyte-Based Approach

Effects on Human Ventricular Myocytes (*In Vitro* Studies)

- Complementary approaches
- Not designed to reproduce arrhythmia

Define a gradation of risk instead of a binary approach

Comprehensive *In Vitro* ProArrhythmia Assay (CIPA)

- Potential to make drug development more efficient
- Move arrhythmia risk assessment to the discovery phase
- Reduce the premature termination of drugs with favorable benefit:risk ratios

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

Philip Sager, MD, FACC, FAHA
Psager@Stanford.edu
Ph 650.450.7477