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Applied Translational Medicine

Cardiovascular Safety In Evolution

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Thorough QT Studies and Cardiovascular Safety

- Is the Thorough QT (TQT) study and ICH E14 guidance a relic or still relevant in 2015?
- What are the alternatives to ICH S7B and what initiatives are occurring to update this approach?
- Are there alternatives to the TQT study and what are the potential advantages and costs?
- What is driving the shift from cardiac safety to cardiovascular safety in early drug development?

Quinidine Syncope - Torsades de Pointes

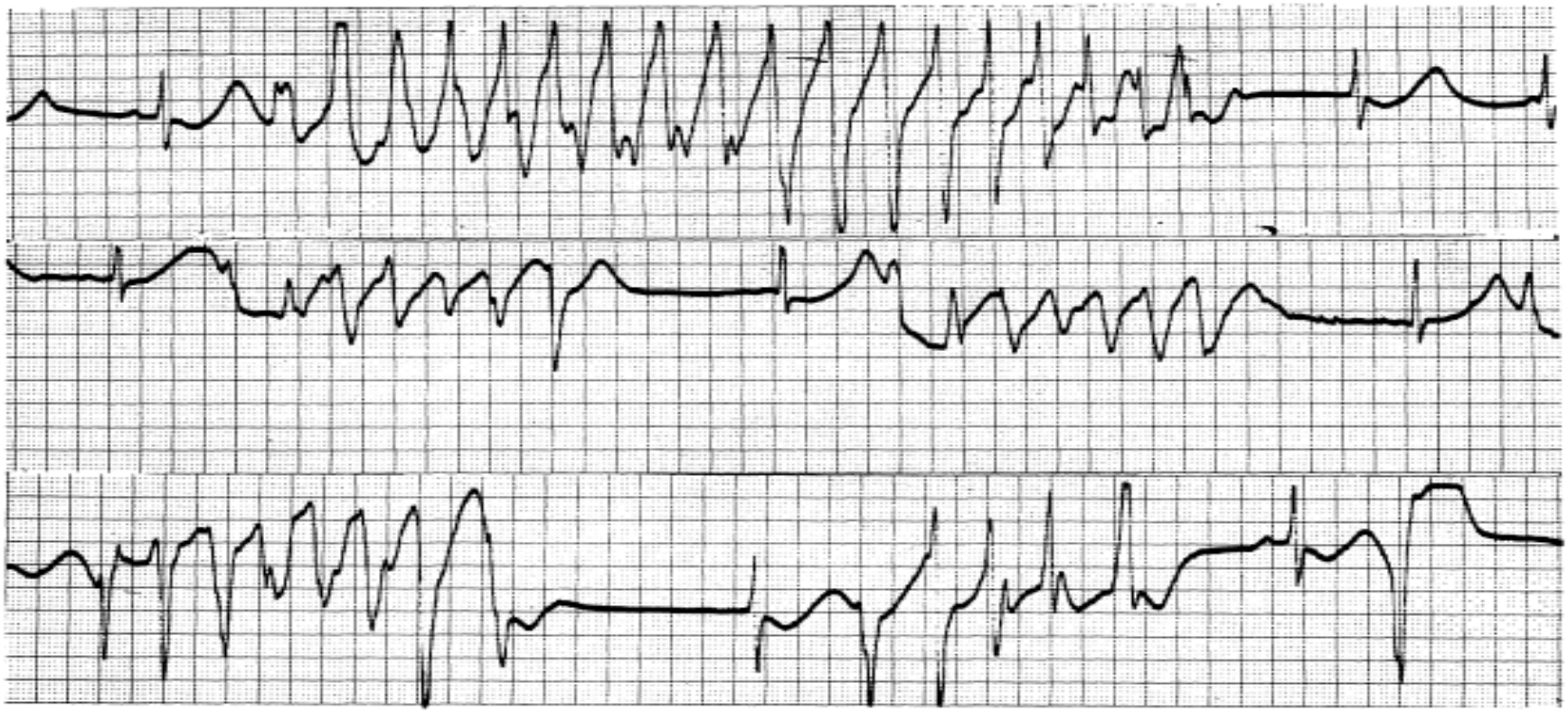

Figure 1

Electrocardiographic tracing of lead II in case 1 during postsyncopal stage of ventricular irritability.

Circ: 1964,30:17-26

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Torsades de Pointes Pathogenesis

Tulane School of Medicine: Pharmwiki

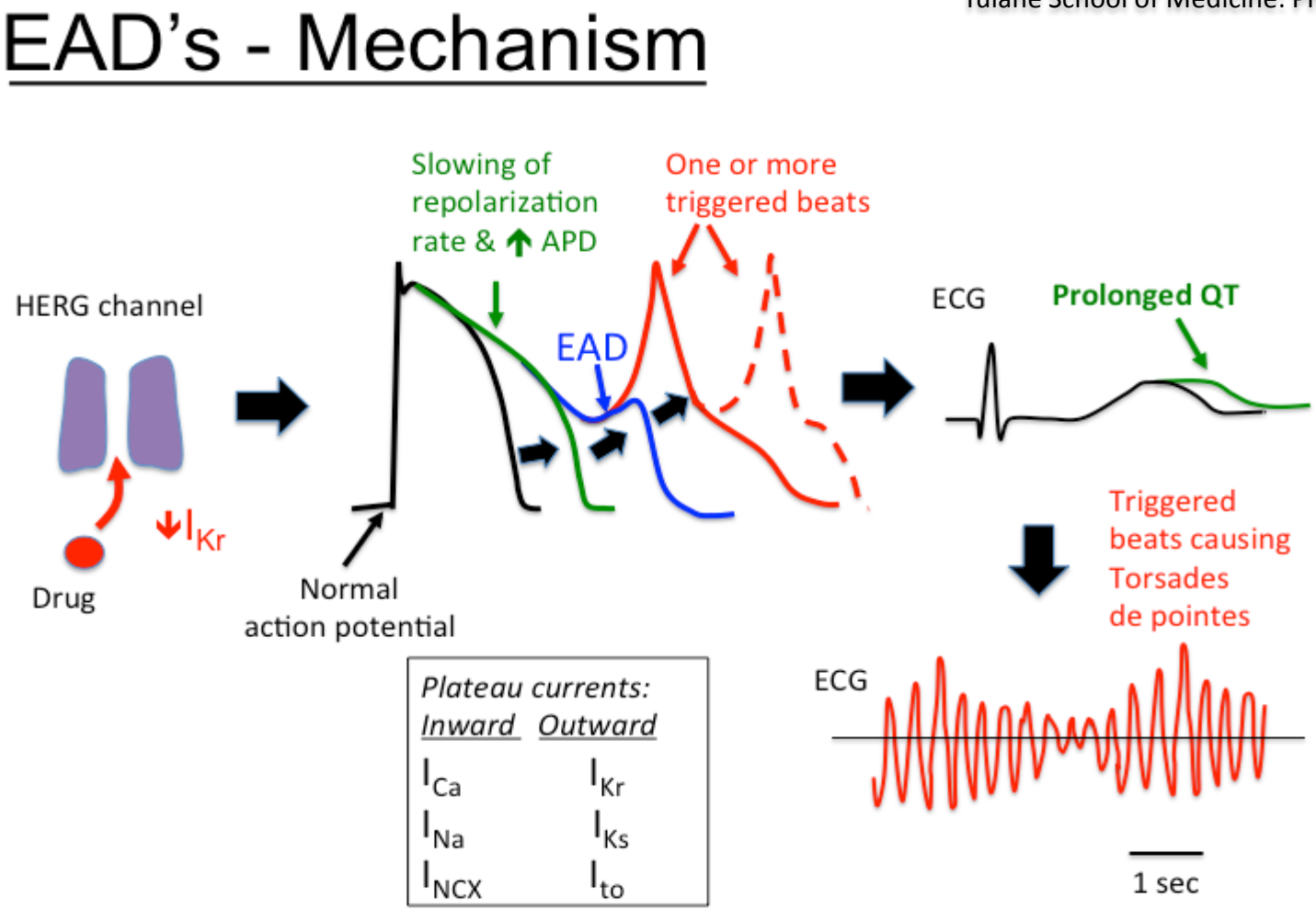
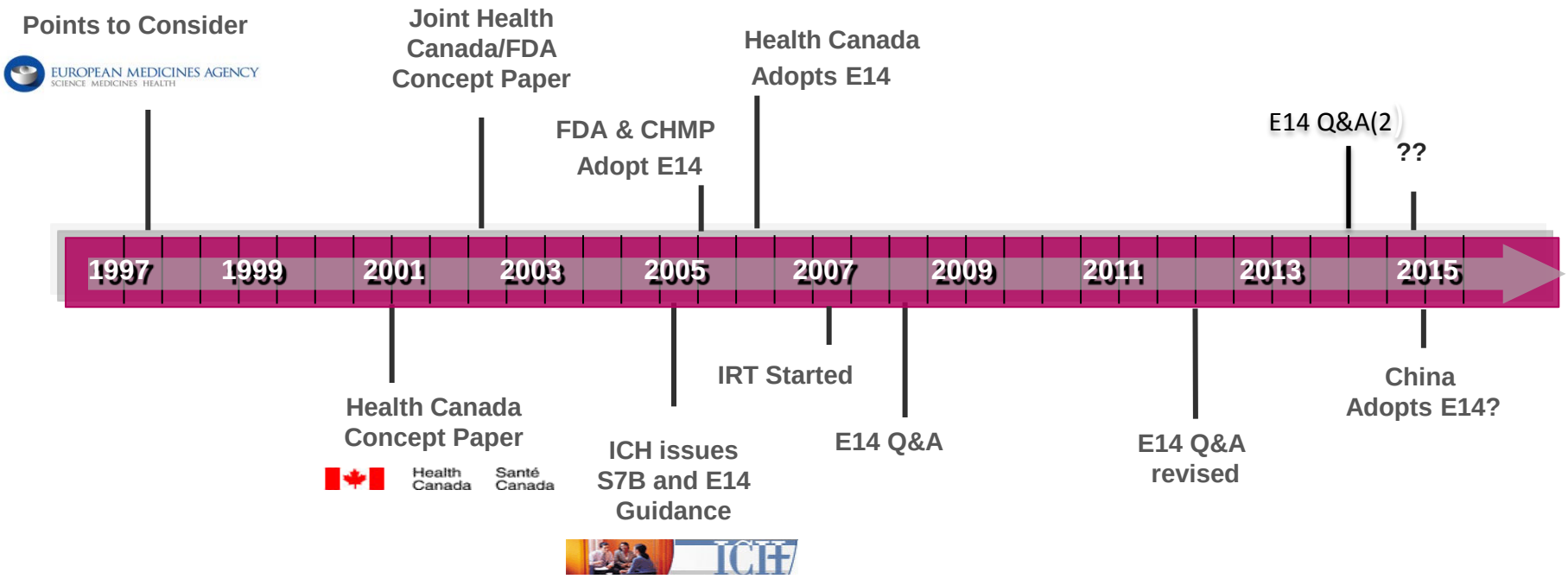


Figure 9. Mechanism of EAD formation & initiation of Torsade de pointes. Drug-induced blockade of the HERG channel reduces IKr amplitude, which in turn reduces net outward current during the plateau, and prolongation of the ventricular APD and QT interval in

Evolution of ICH E14



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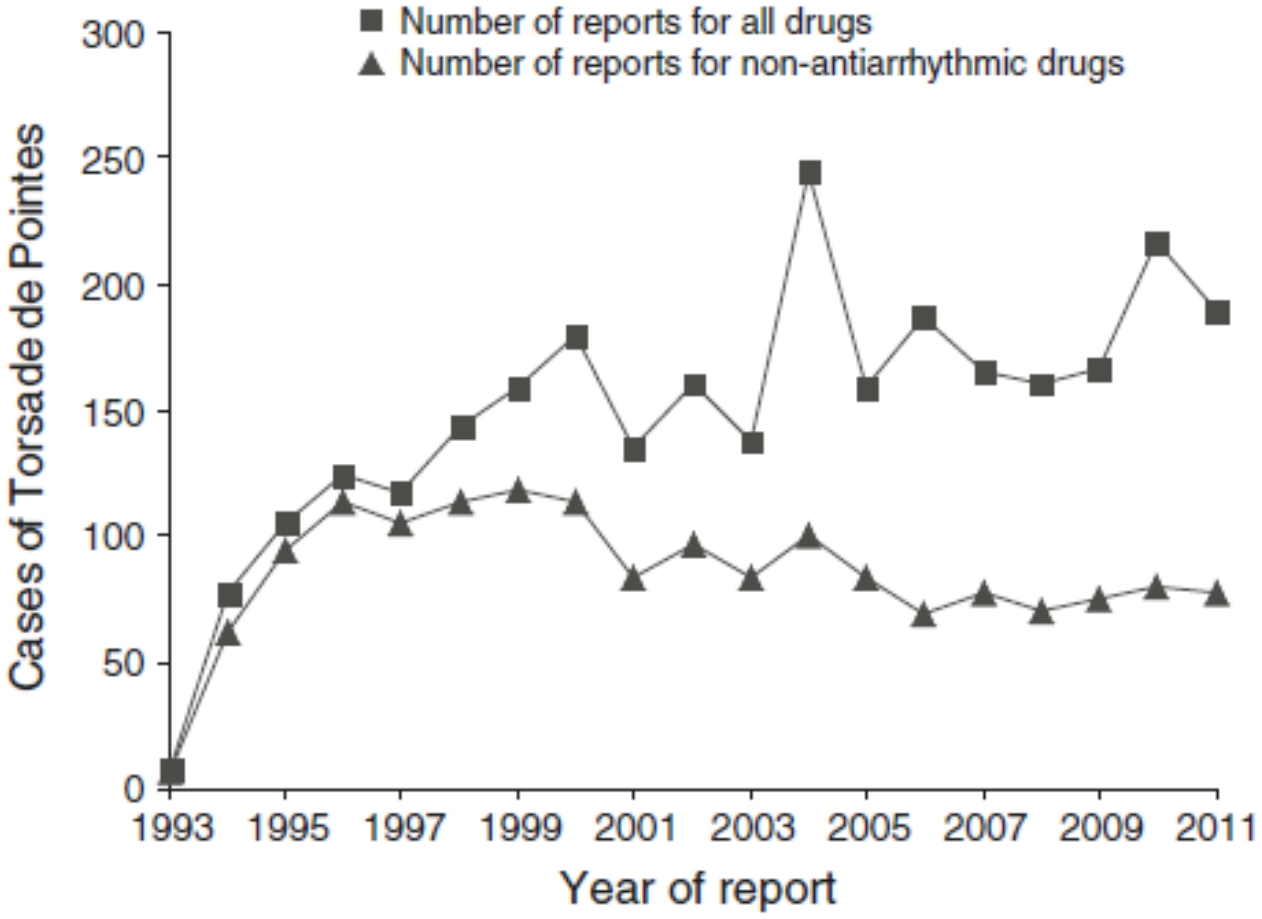
Cases of Torsades de Pointes



Annual number of spontaneous reports of Torsade de Pointes received by the US FDA Adverse Event Reporting System, Stockbridge et al. Drug Safety 2013;36:167-182

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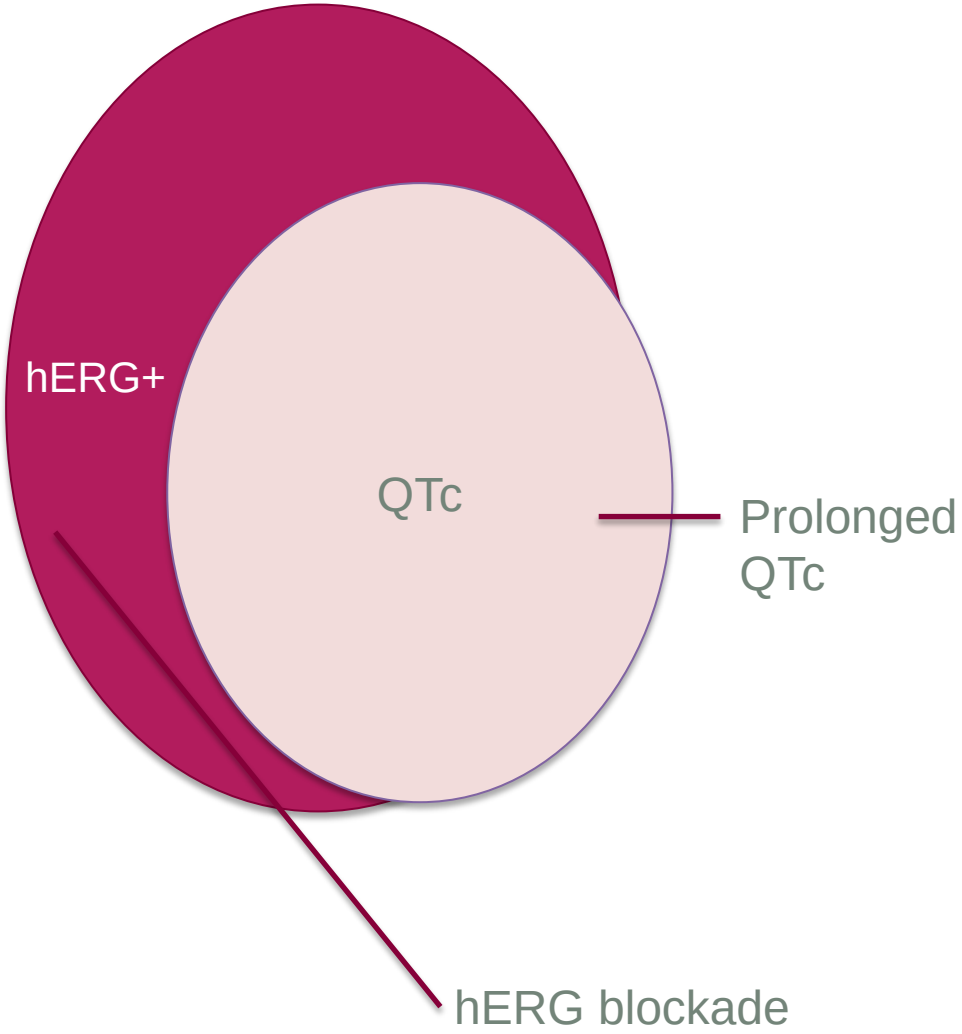
ICH E14 and TQT Studies - Limitations

- **Success?**
  - Qualified success but…
- **Limitations/unintended consequences**
  - Too restrictive in focus on QT
  - Criteria for + study may be too conservative
  - Resource intensive
  - Non mechanistic assessment of TdP
  - Binary approach to drug development
  - Premature termination/black box warning

There is no “gold standard” biomarker for TdP prediction

QT and hERG Centric Limitations



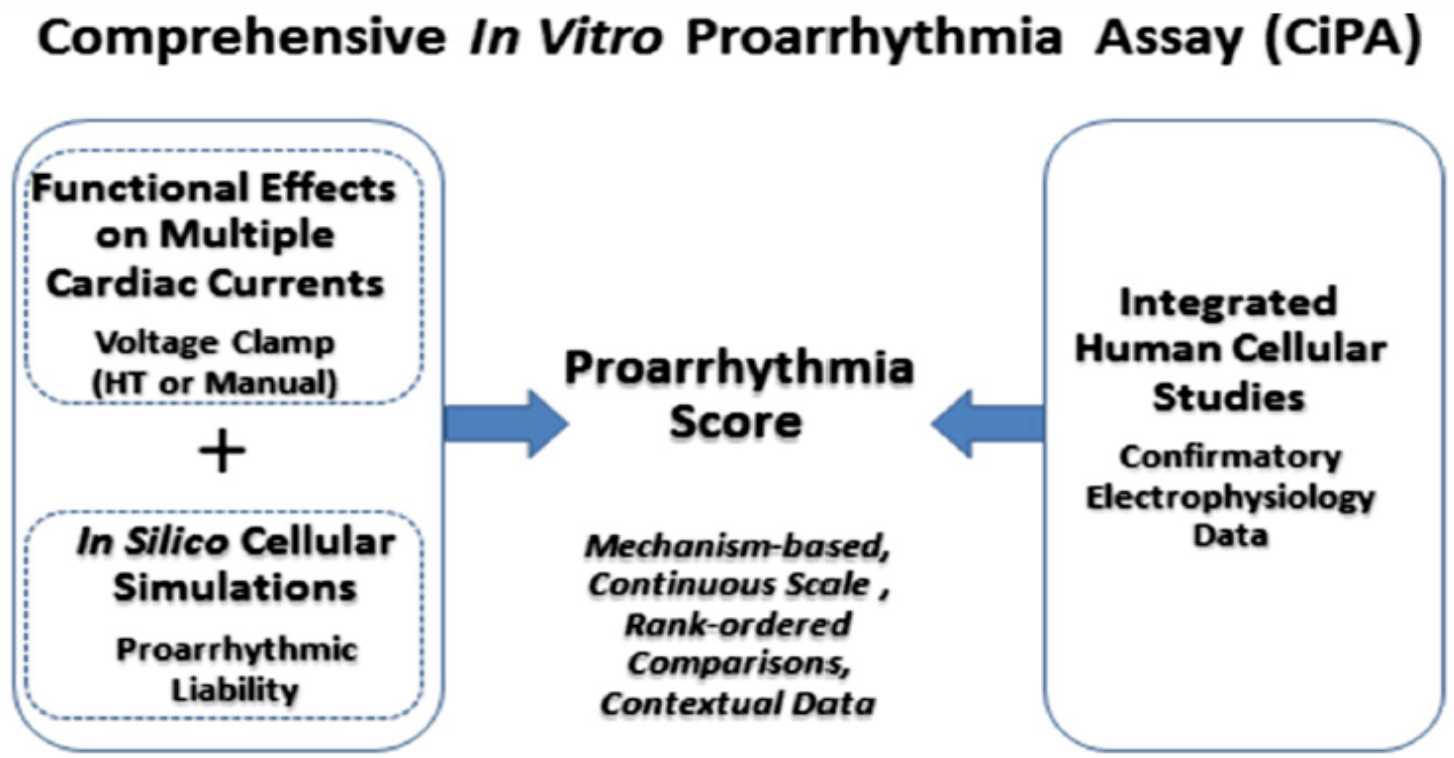
hERG:

- Lack of assay standardization
- Dissociation of hERG and QT
- Binary interpretation
- False positives:
  - hERG blockers which are antiarrhythmic (Verapamil, Vanoxirene, Amiodarone)
- False negatives:
  - Multiple Ion Channel Effects (MICE) including L-type Ca^{++} /late Na^{+} blockade, abnormal trafficking ► proarrhythmia/TdP
  - Metabolites, IKs, confounding physiology with FIH studies

QT:

- Variability of methodology

What is CiPA?.....Pre-clinical Paradigm



NOT DESIGNED TO PRODUCE TdP/ARRHYTHMIAS

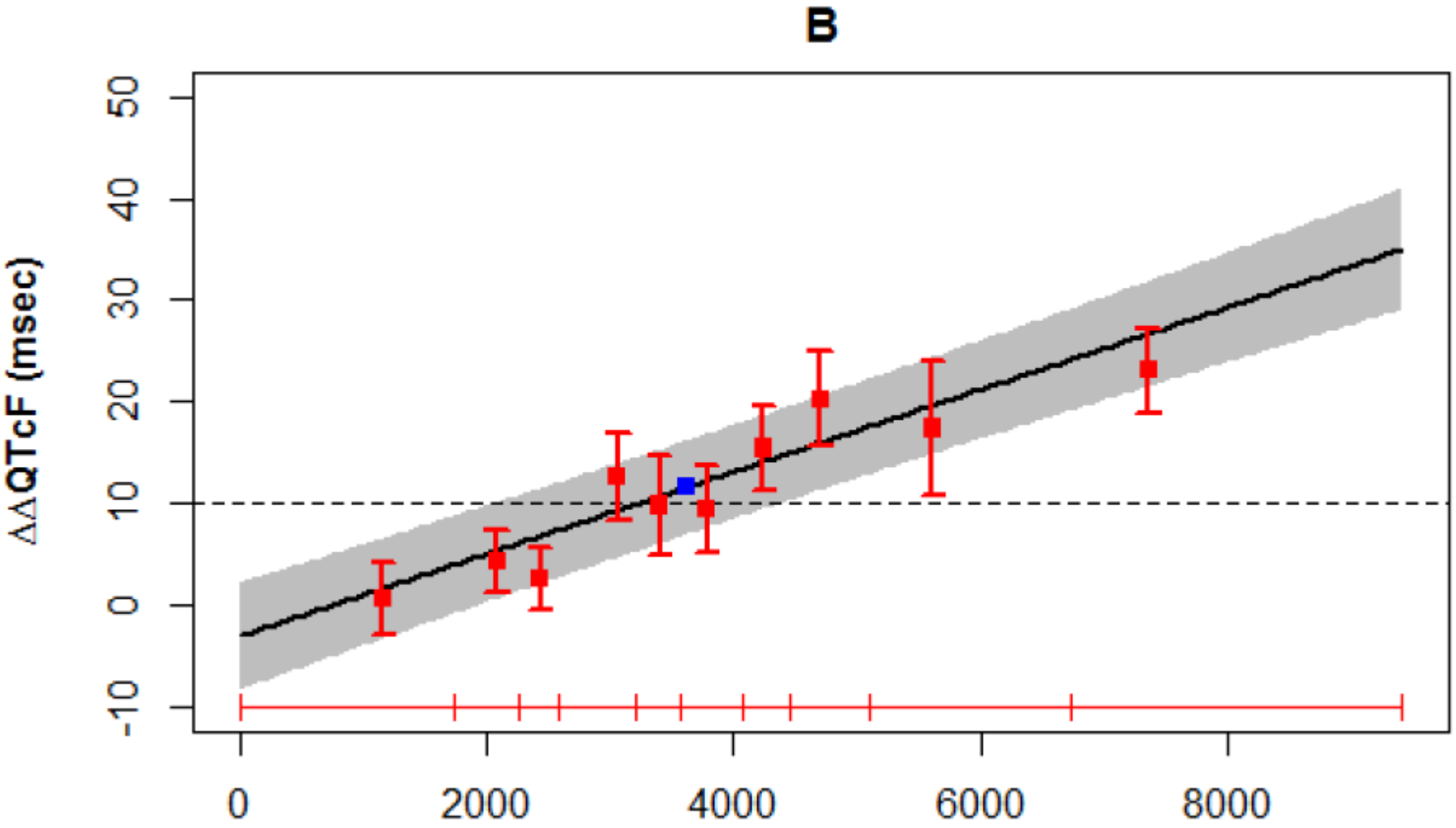
WILL NOT REPLACE IN VIVO ECG STUDIES

Philip T. Sager , Gary Gintant , J. Rick Turner , Syril Pettit , Norman Stockbridge. **Rechanneling the cardiac proarrhythmia safety paradigm: A meeting report from the Cardiac Safety Research Consortium.** American Heart Journal null 2013 null. http://dx.doi.org/10.1016/j.ahj.2013.11.004

Early Clinical/Intense ECG Paradigm

- IQ/CSRC
  - Looked at five marketed drugs with a positive QT signal and one with a negative signal
    - Ondansetron, dofetilide, quinine, dolasetron, moxifloxacin
    - Levocetirizine
  - SAD-like study with two doses…
  - Three pre-dose/nine post-dose ECGs for each dose....PK/QT exposure response

Quinine……"Positive" Drug



IQ-CSRC Accepted Article', doi: 10.1002/cpt.60

Major Reasons for Drug Attrition

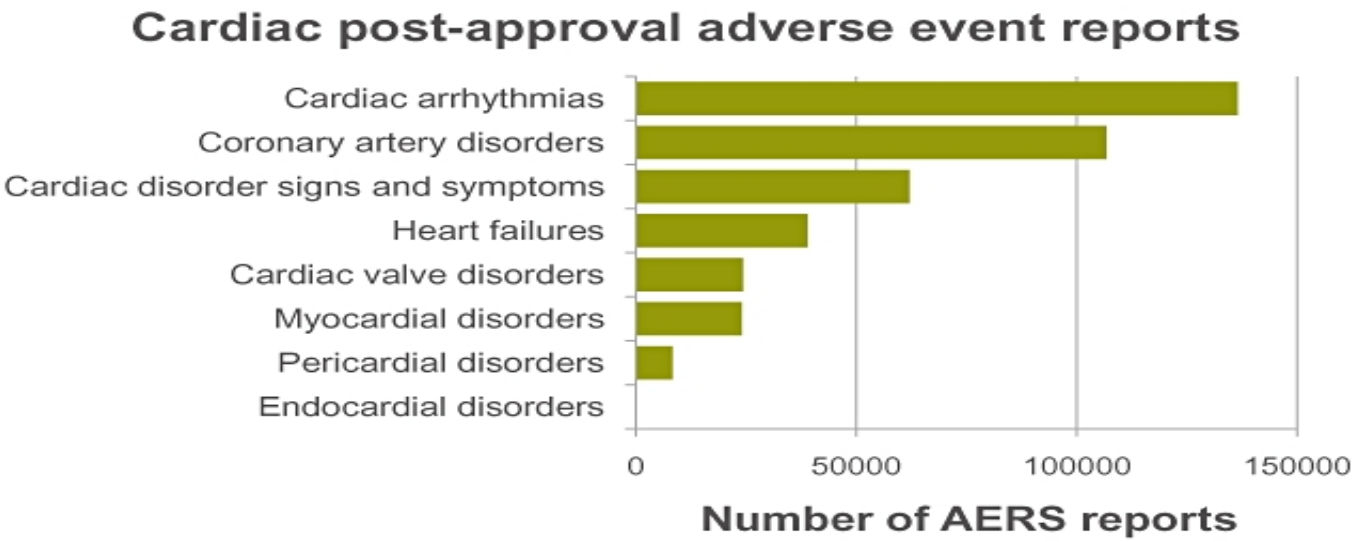
PMC Full Text: Br J Pharmacol Jun 2011: 163(4):675-693
Doi: 10.1111/j.1476-5381.2011.01255x

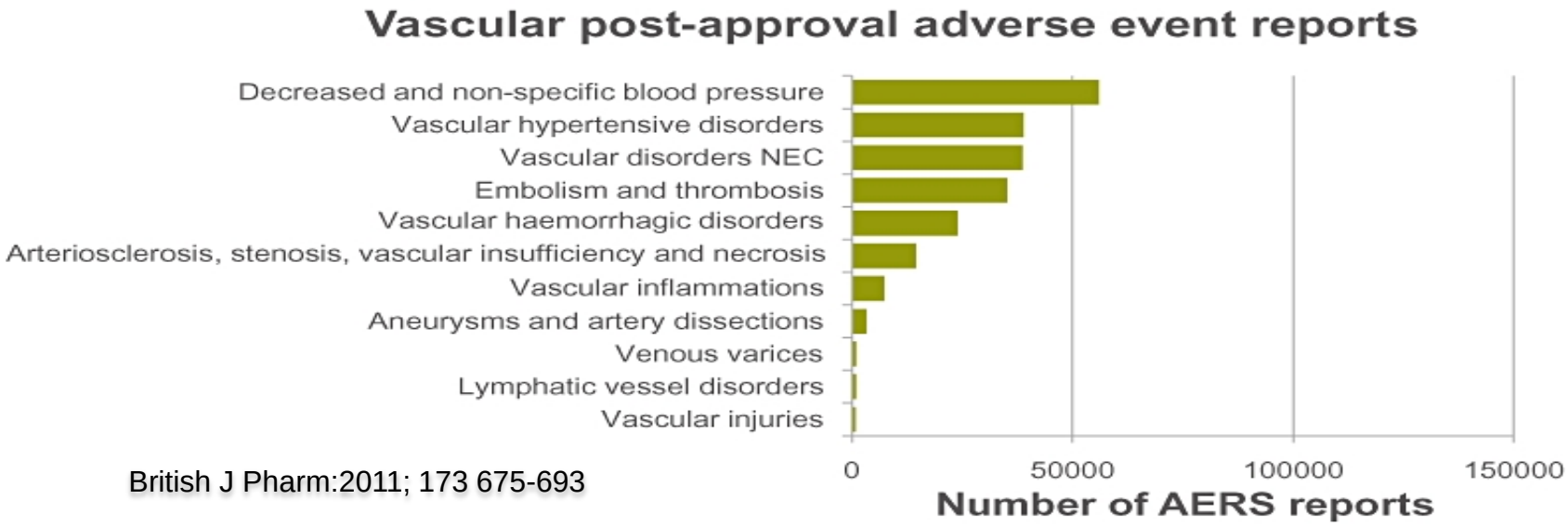
Figure 2

Phase	Non-clinical	Phase I	Phase I-III	Phase III/ post-approval	Post-approval	Post-approval	Post-approval
Information	Causes of attrition	Serious ADRs	Causes of attrition	ADRs on label	Serious ADRs	Withdrawal from sale	Withdrawal from sale
Source	Car (2006)	Sibille et al. (1998)	Olson et al. (2000)	BioPrint®	Budnitz et al. (2006)	Fung et al., (2001)	Stevens & Baker (2009)
Sample size	88 CDs stopped	1,015 subjects	82 CDs stopped	1,138 drugs	21,298 patients	121 drugs	47 drugs
Cardiovascular	27%	9%	21%	36%	15%	9%	45%
Hepatotoxicity	8%	7%	21%	13%	0%	26%	32%

0% 1 - 10% 10-20% >20%

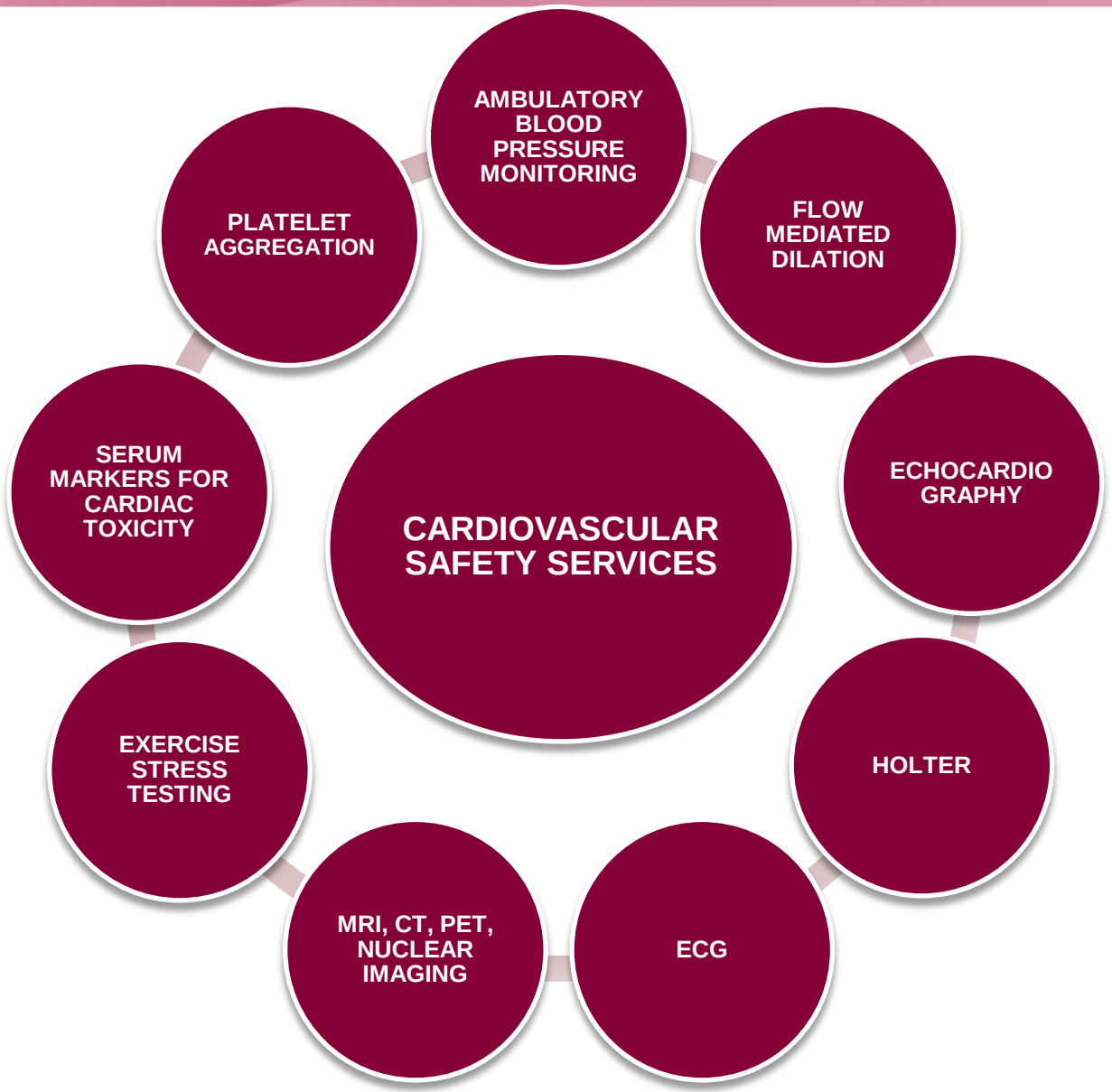
Adverse Cardiovascular Events



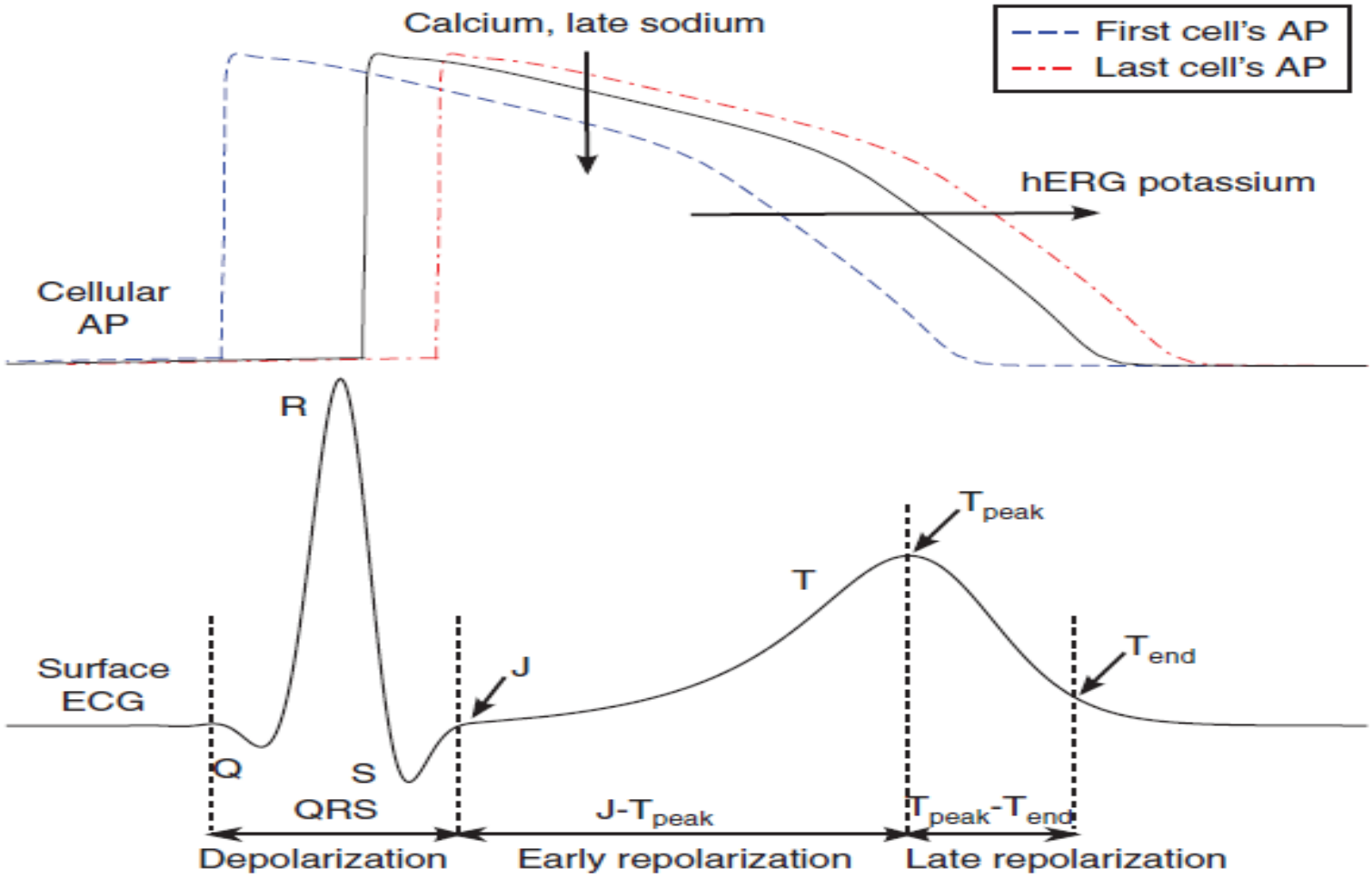


British J Pharm:2011; 173 675-693

Cardio*VASCULAR* Safety Diagnostic Tests



Future Direction…..ECG Biomarkers and MICE



Clinical Pharmacology and Therapeutics 96:5, 2014 549-558

Conclusions

- TQT studies are still required for NCEs and 2005 ICH guidelines still in effect
- Intensive ECG evaluation in SAD/MAD studies with ER analysis integrated with CiPA preclinical data may justify a TQT waiver - "**an alternative**"
- The spectrum of off-target cardiovascular effects of non-cardiovascular agents should be considered in early drug development programs
- Drug development liability is more than the QT/QTc interval