Cardiovascular Safety In Evolution

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Cardiovascular Safety Services
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
**EAD's - Mechanism**

- **HERG channel**
- **Drug** → ↓$I_{Kr}$
- Normal action potential
- **Slowing of repolarization rate & ↑APD**
- **One or more triggered beats**
- **ECG**
- **Prolonged QT**
  - Triggered beats causing Torsades de pointes

**Plateau currents:**

<table>
<thead>
<tr>
<th>Inward</th>
<th>Outward</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{Ca}$</td>
<td>$I_{Kr}$</td>
</tr>
<tr>
<td>$I_{Na}$</td>
<td>$I_{Ks}$</td>
</tr>
<tr>
<td>$I_{NCX}$</td>
<td>$I_{to}$</td>
</tr>
</tbody>
</table>

**ECG**

1 sec

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**Figure 9.** Mechanism of EAD formation & initiation of Torsade de pointes. Drug-induced blockade of the HERG channel reduces $I_{Kr}$ 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

Points to Consider

1997
- Health Canada Concept Paper

1999
- Joint Health Canada/FDA Concept Paper

2001
- FDA & CHMP Adopt E14

2003
- Health Canada Adopts E14

2005
- IRT Started

2007
- ICH issues S7B and E14 Guidance

2009
- E14 Q&A

2011
- E14 Q&A revised

2013
- China Adopts E14?

2015
- E14 Q&A (2)
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
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\(^{2+}\) /late Na\(^{+}\) blockade, abnormal trafficking proarrhythmia/TdP
  - Metabolites, IKs, confounding physiology with FIH studies

### QT:
- Variability of methodology
What is CiPA?.....Pre-clinical Paradigm

Comprehensive *In Vitro* Proarrhythmia Assay (CiPA)

**Functional Effects on Multiple Cardiac Currents**
- Voltage Clamp (HT or Manual)

**In Silico Cellular Simulations**
- Proarrhythmic Liability

**Integrated Human Cellular Studies**
- Confirmatory Electrophysiology Data

**Proarrhythmia Score**
- Mechanism-based, Continuous Scale, Rank-ordered Comparisons, Contextual Data

**NOT DESIGNED TO PRODUCE TdP/ARRHYTHMIAS**

**WILL NOT REPLACE IN VIVO ECG STUDIES**

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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

**Figure 2**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Non-clinical</th>
<th>Phase I</th>
<th>Phase I-III</th>
<th>Phase III/ post-approval</th>
<th>Post-approval</th>
<th>Post-approval</th>
<th>Post-approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information</td>
<td>Causes of attrition</td>
<td>Serious ADRs</td>
<td>Causes of attrition</td>
<td>ADRs on label</td>
<td>Serious ADRs</td>
<td>Withdrawal from sale</td>
<td>Withdrawal from sale</td>
</tr>
<tr>
<td>Sample size</td>
<td>88 CDs stopped</td>
<td>1,015 subjects</td>
<td>82 CDs stopped</td>
<td>1,138 drugs</td>
<td>21,298 patients</td>
<td>121 drugs</td>
<td>47 drugs</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>27%</td>
<td>9%</td>
<td>21%</td>
<td>36%</td>
<td>15%</td>
<td>9%</td>
<td>45%</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>8%</td>
<td>7%</td>
<td>21%</td>
<td>13%</td>
<td>0%</td>
<td>26%</td>
<td>32%</td>
</tr>
</tbody>
</table>


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

Cardiac post-approval adverse event reports
- Cardiac arrhythmias
- Coronary artery disorders
- Cardiac disorder signs and symptoms
- Heart failures
- Cardiac valve disorders
- Myocardial disorders
- Pericardial disorders
- Endocardial disorders

Number of AERS reports

Vascular post-approval adverse event reports
- Decreased and non-specific blood pressure
- Vascular hypertensive disorders
- Vascular disorders NEC
- Embolism and thrombosis
- Vascular haemorrhagic disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis
- Vascular inflamations
- Aneurysms and artery dissections
- Venous varices
- Lymphatic vessel disorders
- Vascular injuries

Number of AERS reports

British J Pharm:2011; 173 675-693
CardioVASCULAR Safety Diagnostic Tests

- Ambulatory Blood Pressure Monitoring
- Flow Mediated Dilation
- Platelet Aggregation
- Serum Markers for Cardiac Toxicity
- Echocardiography
- Exercise Stress Testing
- MRI, CT, PET, Nuclear Imaging
- Holter
- ECG
Future Direction.....ECG Biomarkers and MICE

[Diagram showing ECG waveforms and their corresponding cellular events]

- Calcium, late sodium
- hERG potassium
- First cell’s AP
- Last cell’s AP

Surface ECG:
- R
- QRS
- Q, S
- Depolarization
- Early repolarization
- Late repolarization

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