New ECG biomarkers and their role under CiPA

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The opinions expressed in this presentation are mine and do not necessarily reflect the official views of the U.S. Food and Drug Administration (FDA)
CiPA Phase 1 ECG Assessment

- **Goal:** Use human phase 1 ECG data to determine if there are unexpected ion channel effects in humans compared to preclinical ion channel data
  - Human specific metabolite, protein binding
- **Role:** New ECG biomarker(s) would need to add additional information beyond PR/QRS/QTc
  - Differentiate multi-ion channel effects during repolarization
  - Can be corrected for heart rate (if needed)
  - Sufficient power to detect changes in small sample sizes with exposure-response analysis
  - Available for wide-spread use
Analysis of 12 ECG Biomarkers

• Assessed 12 biomarkers
• Exposure response relationship present for many of them
• However, most paralleled changes in QTc without adding additional information

Vicente et al. *Journal of the American Heart Association* 2015;4:e001615
Analysis of 12 ECG biomarkers: Results

- J-T\textsubscript{peak\text{c}} identified as the best biomarker for differentiating QT prolonging drugs with predominant hERG block from drugs with hERG and late sodium/calcium block
  - Retrospective analysis of 34 drugs
  - Two FDA-sponsored prospective clinical trials
  - Additional ongoing analysis of TQT studies

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Ion channels and ECG

- CiPA proarrhythmic risk score is based on drug effects on multiple ion channel currents.
Retrospective Analysis of TQT Studies

Retrospective analysis of 34 thorough QT studies revealed patterns of QTc prolongation.

**Selective hERG block**
- Prolongs QTc, J-Tpeakc and Tpeak-Tend

**hERG + calcium and late sodium block**
- Prolongs QTc and Tpeak-Tend
- Shortening or having no effect on J-Tpeakc

Prospective Clinical Study 1

Dofetilide % block

Quinidine % block

Ranolazine % block

Dofetilide (hERG block)

Quinidine (hERG>Calcium>Sodium block)

Ranolazine (Late sodium>hERG block)

Vicente et al. *JAHA* 2015;4:e001615
Late sodium current block shortens QTc

Late sodium current block shortens $J-T_{peakc}$

Late sodium current block has no effect on $T_{peak} - T_{end}$

Prospective clinical study in 22 healthy volunteers receiving: dofetilide, dofetilide + mexiletine, dofetilide + lidocaine, moxifloxacin + diltiazem or placebo.

Prospective Clinical Study 2

J-T_{peakc} separates predominant hERG block from balanced ion channel block

- J-T_{peakc} 10 ms cut off separates predominant hERG block from balanced ion channel block (hERG + late sodium)
- Other measurement methods (e.g. from other leads) may result in different thresholds
Differentiating Predominant hERG Block from Multichannel Block

- ROC-AUC analysis for the ability of each biomarker to discriminate individual ECGs from
  - Multichannel block vs.
  - Predominant hERG block
- $J-T_{\text{peak}c}$ is the best discriminator for the presence of late sodium current block
  - $\Delta \Delta J-T_{\text{peak}c} < 9\text{ms} \rightarrow \text{Late Na}$

Heart Rate Dependency of Biomarkers

Biomarker-RR relationship for two different subjects (red vs. blue) at baseline

- QT, J-Tpeak & T-wave flatness are all heart rate dependent
- QT and J-Tpeak rate dependency is consistent with low inter-subject variability
- T-wave flatness rate dependency is highly variable between subjects

<table>
<thead>
<tr>
<th>For 22 Subjects</th>
<th>QT Mean Slope</th>
<th>J-Tpeak Mean Slope</th>
<th>T-wave Flatness Mean Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Slope</td>
<td>0.29</td>
<td>0.53</td>
<td>0.50</td>
</tr>
<tr>
<td>SD of Slope</td>
<td>0.07</td>
<td>0.12</td>
<td>0.30</td>
</tr>
<tr>
<td>SD/Mean (%)</td>
<td>24%</td>
<td>23%</td>
<td>60%</td>
</tr>
</tbody>
</table>

\[
J - Tpeak_{adj} = \frac{J - Tpeak}{RR^{0.58}}
\]
Exposure-response analysis in small sample size studies

• Resampling analysis suggests that 9 subjects on active study drug and 6 subjects on placebo will be sufficient to detect QTc prolongation for “predominant hERG” drugs and exclude J-T_{peak}c prolongation for “balanced ion channel” drugs.

• Prospective Phase 1 clinical study using exposure-response analysis in small sample size planed for completion in 2017
Measuring J-Tpeak: Computation of a global lead

Traditional 12-lead 10 s ECG

Semi-automatic measurement of $J-T_{\text{peak}}$

- The $J-T_{\text{peak}}$ interval was measured semi-automatically in the vector magnitude lead
  - Peak: fitting a parabola to a user defined region
  - Offset: fitting a tangent to descending limb identified by user

- For both the peak and offset the location identified could be overwritten manually

*Vicente et al, Comput Cardiol 2013*
J-T_{peak} and T_{peak}-T_{end} automation

• The semi-automated approach using the vector magnitude lead was used successfully in analysis of data from two clinical trials
  – However, this semi-automated approach is associated with manual overread

• Therefore, an algorithm using a different approach and no need for manual input was developed

Automated reproduces primary results

Automated reproduces primary results

Publicly available resources

- ECG signals and clinical data from 2 FDA-sponsored clinical trials
    - Vicente et al. J Am Heart Assoc. 2015. doi: 10.1161/JAHA.114.001615
  - **FDA Study 2** (NCT02308748) data are available at PhysioNet's PhysioBank [https://physionet.org/physiobank/database/ecgdmmld/](https://physionet.org/physiobank/database/ecgdmmld/) (doi:10.13026/C2D016)

- Automated algorithm for J-T<sub>peak</sub> and T<sub>peak-T<sub>end</sub></sub>
  - **Open source code** available at: [https://github.com/FDA/ecglib](https://github.com/FDA/ecglib)
Summary

• Analysis of 12 ECG biomarkers showed J-T_peakc as the best biomarker to differentiate QT prolonging drugs with predominant hERG block from QT prolonging drugs with hERG and late sodium or calcium block

• Heart rate correction method for J-T_peak available

• Resampling analysis suggests that exposure-response analysis can differentiate predominant hERG block from balanced ion channel block in small sample size clinical studies
  – Prospective clinical study planned for completion in 2017

• Data and methods freely-available:
  – ECG signals and clinical data from 2 FDA-sponsored clinical studies
  – Open source software for J-T_peak and T_peak-T_end assessment
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Results: QTc, J-\(T_{\text{peakc}}\) and \(T_{\text{peak}} - T_{\text{end}}\)

- hERG block prolongs both J-\(T_{\text{peakc}}\) and \(T_{\text{peak}} - T_{\text{end}}\)
- Balanced late sodium and hERG block prolongs \(T_{\text{peak}} - T_{\text{end}}\) but not J-\(T_{\text{peakc}}\)