Analysis comparing different ECG biomarkers approaches to detect drug effects on ion channels beyond hERG

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Disclaimer

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)
ECG biomarkers developed to detect hERG block

a: QT and subintervals

b: Flatness, asymmetry and notching

<table>
<thead>
<tr>
<th>Flat</th>
<th>Asymmetric</th>
<th>Notched</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>LRD30%</th>
<th>ERD30%</th>
</tr>
</thead>
</table>

c: 30% of repolarization duration

d: Vectorcardiographic biomarkers

e: Gaussian modeling

Adapted from Vicente et al. J Am Heart Assoc. 2015
Ion channels and ECG

- CiPA proarrhythmic risk score is based on drug effects on multiple ion channel currents

![Diagram of the QT interval and ion channel currents](Image)

- **Surface ECG**
- **Sodium**
- **Ventricular Action Potential**
- **Late sodium Calcium**
- **hERG**
- **Depolarization**
- **R**
- **S**
- **J-Tpeak**
- **Tpeak-Tend**
- **Repolarization**
- **Early**
- **Late**
- **Tpeak**
- **Tend**
Beyond QT interval and hERG block

• To detect drug-induced ion channel effects beyond hERG on the ECG
  – How does multichannel block affect QT subintervals and T-wave morphology?
  – Can we use these ECG biomarkers to detect presence of inward current block?
FDA-sponsored clinical studies

- **Study 1:**
  - To evaluate the effect of selective hERG block vs. multichannel block on QTc, $J - T_{peak}$, $T_{peak} - T_{end}$ and T-wave morphology biomarkers

- **Study 2:**
  - To assess which ECG biomarkers are useful to detect inward current block on the ECG, in particular in presence of QTc prolongation caused by hERG block
FDA-sponsored clinical studies

• Study 1:
  – To evaluate the effect of selective hERG block vs. multichannel block on QTc, J-\(T_{\text{peak}}\)c, \(T_{\text{peak}}-T_{\text{end}}\) and T-wave morphology biomarkers

• Study 2:
  – To assess which ECG biomarkers are useful to detect inward current block on the ECG, in particular in presence of QTc prolongation caused by hERG block
Study 1

- Exposure response analysis of 12 ECG biomarkers

Adapted from Vicente et al. J Am Heart Assoc. 2015
Results:

QTc, $J-T_{\text{peak}c}$ and $T_{\text{peak}}-T_{\text{end}}$

Dose dependent QTc prolongation by dofetilide, quinidine and ranolazine

Adapted from Vicente et al. J Am Heart Assoc. 2015
Results:

QTc, J-T<sub>peak</sub>c and T<sub>peak</sub>-T<sub>end</sub>

- hERG block prolongs both J-T<sub>peak</sub>c and T<sub>peak</sub>-T<sub>end</sub>
- Balanced late sodium and hERG block prolongs T<sub>peak</sub>-T<sub>end</sub> but not J-T<sub>peak</sub>c

Results: 30% of early and late repolarization duration

Dose dependent ERD$_{30\%}$ and LRD$_{30\%}$ prolongation

Adapted from Vicente et al. J Am Heart Assoc. 2015
Results: flatness

Dose dependent increase in T-wave flatness and asymmetry
Dose dependent decrease in T-wave amplitude

Adapted from Vicente et al. J Am Heart Assoc. 2015
Results: Notched T-waves

- Dose dependent increase of probability of developing notched T-wave in PCA1 (notch score by Andersen, Xue et. al J Electrocardiol. 2008)
- However, only 0.8 % notched ECGs in vector magnitude lead
- No notches in Study 2 (lower dose of dofetilide)

<table>
<thead>
<tr>
<th>Treatment</th>
<th># ECGs</th>
<th>Notched (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dofetilide</td>
<td>1056</td>
<td>2 (0.2 %)</td>
</tr>
<tr>
<td>Quinidine</td>
<td>1008</td>
<td>40 (4.0 %)</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>1056</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>1056</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1056</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5232</td>
<td><strong>42 (0.8 %)</strong></td>
</tr>
</tbody>
</table>

Adapted from Vicente et al. J Am Heart Assoc. 2015
Heart Rate Dependency

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

- 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
## Study 1: ECG signatures summary

<table>
<thead>
<tr>
<th>ECG biomarker</th>
<th>hERG</th>
<th>Balanced hERG &amp; late sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT and subintervals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTcF (ms)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>J-(T_{peak}c) (ms)</td>
<td>↑</td>
<td>No effect</td>
</tr>
<tr>
<td>(T_{peak}-T_{end}) (ms)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td><strong>T-wave morphology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-wave flatness (d.u.)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>T-wave asymmetry (d.u.)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>ERD(_{30%}) (ms)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>LRD(_{30%}) (ms)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>T-wave amplitude (µV)</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
Study 1: Conclusions

- hERG block prolongs QTc by prolonging both $J-T_{peakc}$ and $T_{peak}-T_{end}$ intervals
- Balanced late sodium and hERG block prolongs QTc by prolonging $T_{peak}-T_{end}$ but not $J-T_{peakc}$
- Strong dose-response relationship between hERG block and T-wave morphology changes
- Balanced late sodium and hERG block still has dose dependent relationship with T-wave morphology
FDA-sponsored clinical studies

• Study 1:
  – To evaluate the effect of selective hERG block vs. multichannel block on QTc, $J-T_{\text{peak}}$, $T_{\text{peak}}-T_{\text{end}}$ and T-wave morphology biomarkers

• Study 2:
  – To assess which ECG biomarkers are useful to detect inward current block on the ECG, in particular in presence of QTc prolongation caused by hERG block
Study 2

- Dofetilide alone
- Dofetilide + mexiletine
- Dofetilide + lidocaine

Exposure response analysis of eight ECG biomarkers
- ROC-AUC to rank the ECG biomarkers by their ability to detect late sodium current block

Adapted from Johannesen et al. Clin Pharmacol Ther. 2015
Results:

**QTc, J-T_{peak c} and T_{peak-T_end}**

Dofetilide + mexiletine/lidocaine

Late sodium current block (mexiletine, lidocaine) shortens QTc prolongation induced by hERG block (dofetilide) by shortening the J-T_{peak c} interval

Adapted from Johannesen et al. Clin Pharmacol Ther. 2015
Results: 30% of early and late repolarization duration

Late sodium current block did not cause significant effects on ERD$_{30\%}$ and LRD$_{30\%}$
Results: flatness and asymmetry

Late sodium current block did not cause significant effects on T-wave flatness and asymmetry
Results:

Detection of late sodium current block

• Classification of any time-point of any subject as multichannel block (dofetilide+mexiletine and dofetilide+lidocaine) vs. selective hERG block (dofetilide and moxifloxacin)

• $J-T_{\text{peak}C}$ is the best ECG biomarker to detect late sodium current block

• Threshold in this study: $\Delta\Delta J-T_{\text{peak}C} < 9\text{ms} \rightarrow \text{LateNa}$

• Similar results with machine learning approach

Vicente et al. 2016 (submitted)
Study 2: Conclusions

- Late sodium current block shortens QTc prolongation induced by hERG block by shortening the $J-T_{\text{peak}}c$ interval

- $J-T_{\text{peak}}c$ was the best of the eight studied ECG biomarkers for detecting late sodium current block in presence of QTc prolongation caused by hERG block
Summary

• How does multichannel block affect these ECG biomarkers?
  – Selective hERG block
    • Prolongs QTc by prolonging both J-T_{peak}c and T_{peak}-T_{end}
    • Causes dose dependent changes in T-wave morphology
  – Balanced late sodium and hERG block
    • Prolongs T_{peak}-T_{end} but not J-T_{peak}c
    • hERG effects on T-wave morphology are present

• Can we use these ECG biomarkers to detect presence of inward current block?
  – J-T_{peak}c is the best ECG biomarker for detecting late sodium current block in presence of QTc prolongation caused by hERG block
Conclusion

• Methodologies assessing drug effects on ion channels should use $J-T_{\text{peak}}c$ to detect inward current block on the ECG
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