Novel ECG Biomarkers – Practical Implications, Workflow, and Open Source Code

Robert B. Kleiman, M.D.
Chief Medical Officer, ERT

ERT®
Innovating Better Health™

Disclosures

- I am a full time employee of ERT
- ERT provides ECG core lab services and other solutions to the pharmaceutical industry
- I provide consulting services to the pharmaceutical industry
- No other disclosures

Why Novel ECG Biomarkers?

- Real concern – avoiding drug induced TdP
- CiPA : ex-vivo evaluation of risk of drug induced TdP
- Clinical ECGs still needed – but alternative biomarkers to complement (rather than replace) QTc are desirable
  - QTc: known shortcomings as a biomarker
  - Novel biomarker use to help confirm/contradict concordance between clinical and preclinical data
  - Multichannel block a main concern, but not the only one

TdP is only one of many cardiac safety issues

Use Case for Novel Biomarkers?

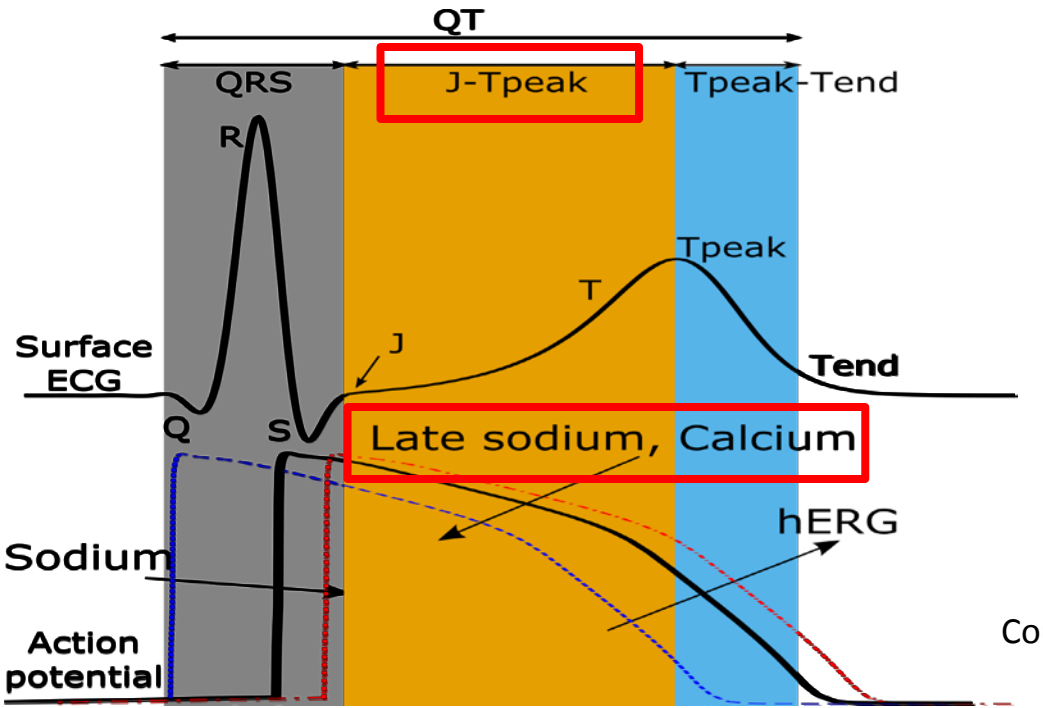
- **CiPA assessment low risk:**
  - ~~**Phase I QTc UCI < 10 ms**~~ *(very low risk)*
  - **Phase I QTc UCI ≥ 10 ms: novel ECG biomarkers useful**
- **CiPA assessment intermediate or high TdP risk:**
  - ~~**Phase I QTc UCI < 10 ms**~~ (*reexamine preclinical and clinical data*)
  - ~~**Phase I QTc UCI ≥ 10 ms**~~ *(agreement that risk is high)*
- **Threshold effect – could help understand magnitude of risk**
- **May help inform go/no go decisions**

Speculation: needed only for one scenario as above

Implementation – Operational Points

- Generally no need to assess novel biomarkers in real time
  - Exception could be for a high risk compound, in order to inform dose escalation decisions
- Easiest to run as a batch after study completion
- Digital ECGs only
- Methodology will be absolutely critical

Ion channels and ECG: Theory



Courtesy of Jose Vicente

J-Tpeak and Tpeak-Tend: Some Issues

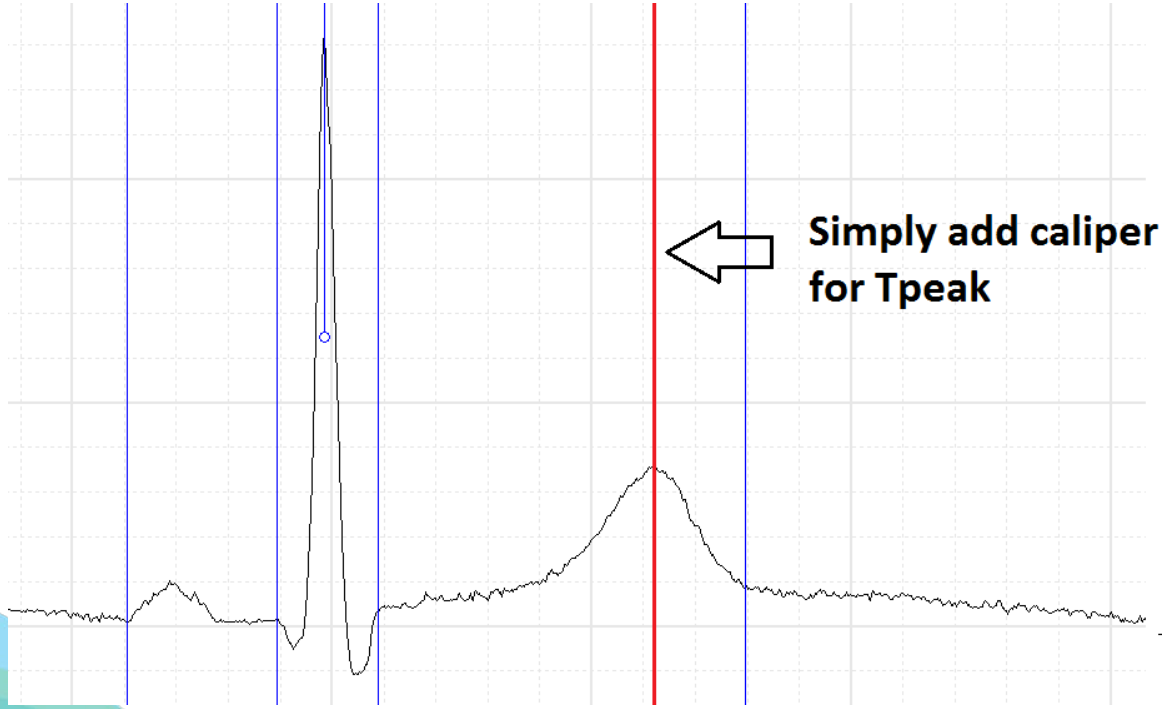
- Definition of J point – less straightforward than QRS onset
- Definition of Tpeak:
  - Visual (point at which amplitude is greatest)
  - Algorithmic
  - What about notched, bifid or biphasic T waves?
- Still need to measure QRS onset and T wave offset
  - QRS onset: relatively simple
  - T wave offset: no universal consensus
- Standardization of HR correction method

J-Tpeak and Tpeak-Tend: Many Methods

- FDA method – open source code – uses vector magnitude lead
- GE QT Guard Plus – proprietary – uses vector magnitude lead
- Measurement in a single lead
- Measurement on a superimposed global median beat

Different methods will likely produce different results

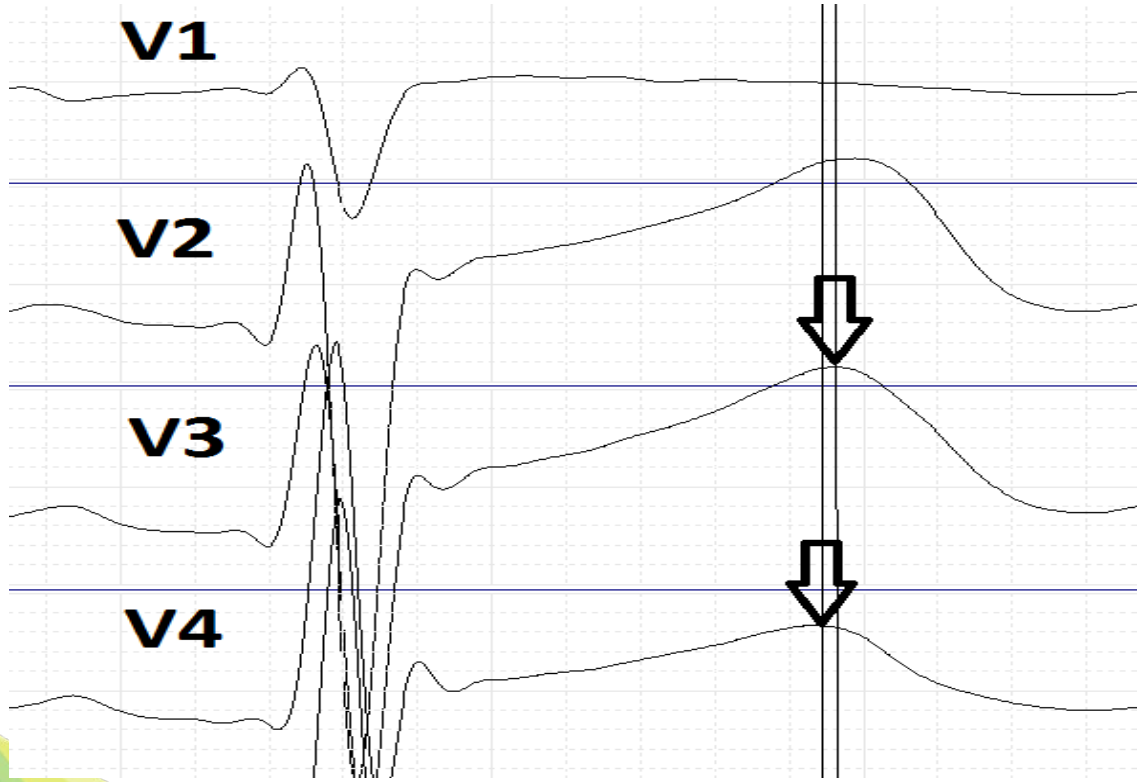
Example: Single Lead Measurement



But – which lead?

ERT Innovating Better Health™

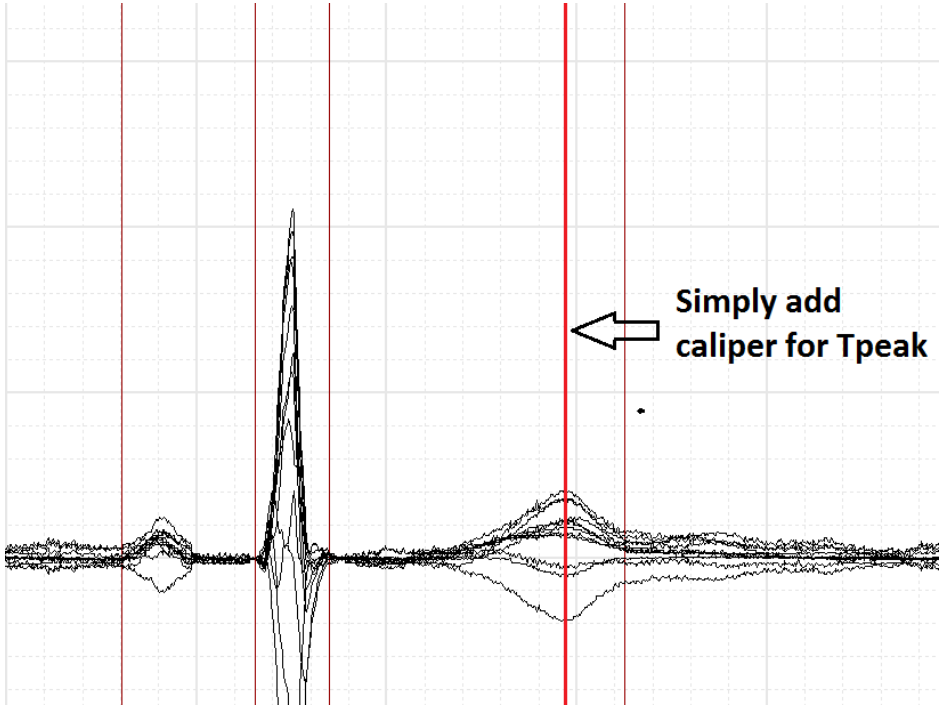
Single Lead Measurement



10 ms difference between peak of T wave in V3 and V4

ERT Innovating Better Health™

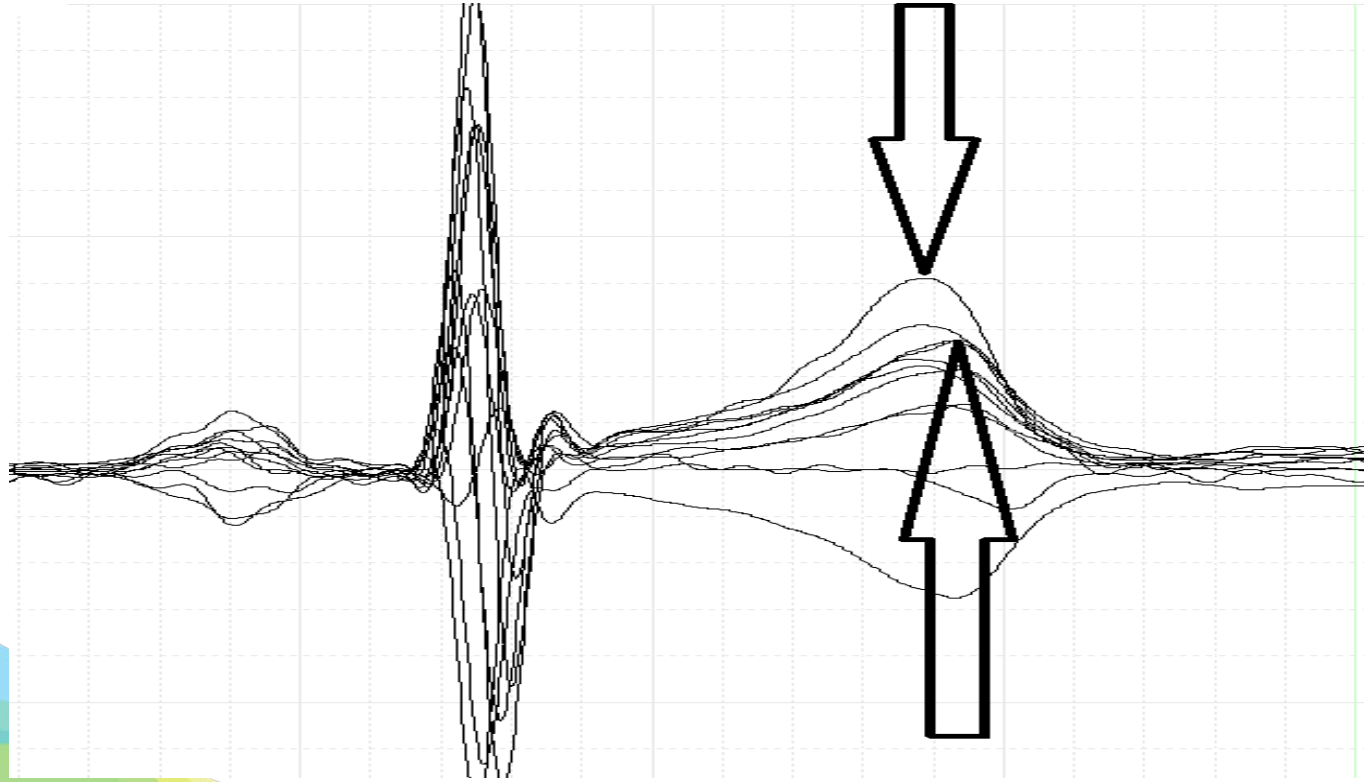
Measurement from Superimposed GMB



But - the peak of the T wave varies between leads

ERT Innovating Better Health™

Superimposed GMB



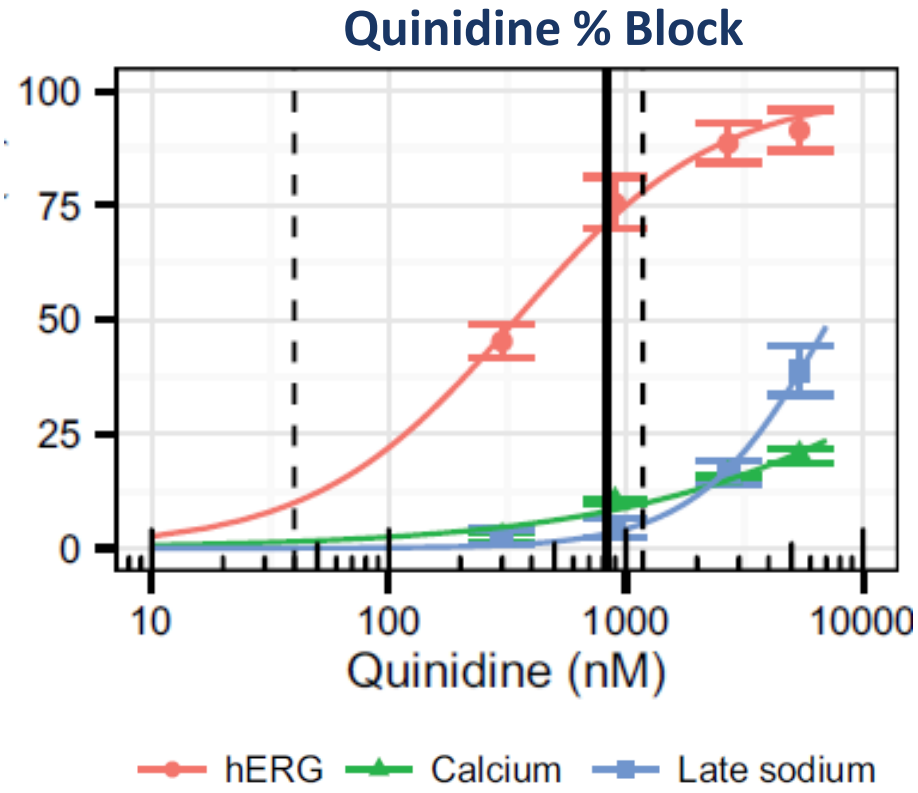
20 ms difference between peak of T wave in different leads within the superimposed beat

ERT® Innovating Better Health™

Methods must be standardized!

- Unless methodology is standardized, high risk of flawed data submissions
- How to assess quality?
  - In TQT, positive control insures assay sensitivity
  - How will validity of J-Tpeak and Tpeak-Tend measurements be assessed?
- Best solution: agree on a standardized methodology for new biomarkers
- FDA will make their algorithms available as open source code
- To date, validation has been entirely based on the FDA methodologies
- Proposal: any alternative to FDA methodology should undergo equivalent validation before being accepted for regulatory submission

Concentration Dependence of Quinidine Ion Channel Effects



As concentration changes, relative contribution of inward/outward current block changes

Courtesy of Jose Vicente

ERT Innovating Better Health™

Challenges for Core Labs

- Different core labs use different platforms for measurements
  - Some core labs use external proprietary software platforms which may not allow for any code changes
  - Pressure to adapt their methods (single lead or GMB) to perform JTpeak and Tpeak-end measurements in a nonstandard fashion?
  - If external manufacturer updates software, will it use the exact methods described by the FDA open source release?
  - Will platform updates be properly validated, regulatory compliant?

Challenges for Sponsors

- When to request novel ECG biomarker analysis?
- ECGs must be collected digitally – no retrospective analysis of paper ECGs
- Format of collected ECGs must be accepted by the core lab
- ECGs collected by a CRO without any core lab involvement may not be in correct format
- Sponsors must understand methodology issues in order to understand core lab capabilities

Challenges for Regulators

- Regulators will need to understand when novel biomarkers are useful, and when irrelevant
- Regulators must be able to confirm methodology used to measure J-Tpeak and Tpeak-Tend
- Will the ECG Warehouse be able to accept these additional caliper placements?
- Should data measured with alternate methods be rejected?
- Any concerns about wagging the dog? (FDA involved in the research and publication of the software)

Summary

- Some biomarkers (esp. J-Tpeak and Tpeak-Tend) can be measured with different methods
- Consensus required about what to measure, specific methods
- Validation and standardization of methods are necessary
- ECG Core Labs will need to modify methods to allow introduction of new measurements and properly validate
- Sponsors will need to choose when to use novel biomarkers
- Regulators need to be ready for novel biomarker data