

# End of T Wave Determination by Polynomial Curve Fitting on a Vector Magnitude Lead

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## Abstract

**Background:** A key issue associated with any computer-based tool for QT interval measurement is accurate determination of the end of the T-wave (Tend). Both noise resistance and accuracy with complex T-wave morphologies are of great importance, but many existing methods are unreliable in the presence of substantial noise or T-wave morphology changes. Moreover, existing methods do not include algorithms for self-assessment of the quality of Tend determination.

**Methods:** We developed a method for Tend determination that is based on a single measurement on a single lead for every beat of an ECG recording. To achieve this goal, a single vector magnitude lead is first synthesized. This single lead representation has as many beats as 12-lead recording. Once appropriate baseline is established this waveform is used to determine Tend by iterative curve fitting of a third order polynomial function to the actual falling edge of the T-wave. A function was developed to determine which iteration offered the best fit to the actual T-wave. Once the results were determined to guarantee best available fit, Tend is determined as the minimum of the third-order polynomial function.

**Results:** A study was performed on 104 ECG tracings from a well known pro-arrhythmic drug that causes a substantial QT prolongation and T-wave morphology changes. The "gold standard," a set of fully manual readings by 3 qualified cardiologists, was compared to results from QTinno, a fully automated quantitative ECG analysis tool using above described T-wave end determination method. QTinno returned a mean time-matched change in QTcF ( $\Delta$ QTcF) that was <0.5msec different from the gold standard. In addition, the curve fitting quality function was of great value in helping QTinno identify those readings that were of poor quality and/or had large T-wave morphology changes and thus had to be over read by a manual reader.

**Conclusions:** The method described here offers excellent noise resistance and accuracy in the presence of complex T-wave morphologies, and also provides a reliable tool for separating computer-generated QT measurements that should be overread from those that have a high-quality curve fit and thus do not need a human overread. Excellent agreement with best available gold standard was achieved for time-matched change in QTcF, a key cardiac safety metric.

## Introduction

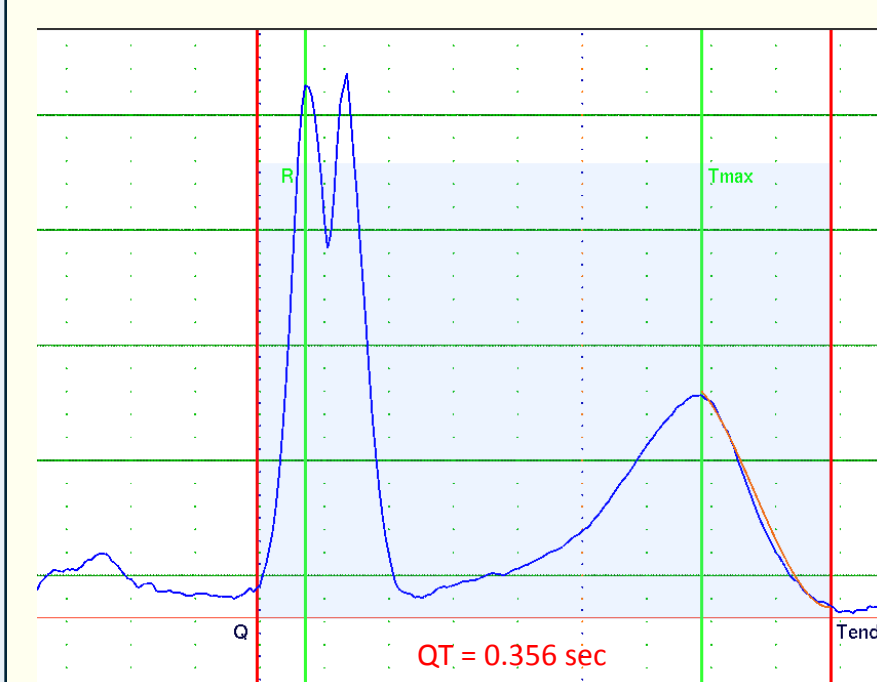
- Main goal of ECG assessment of drug cardiac safety is to detect and characterize the drug effect on:
  - any ECG parameters, including but not limited to interval duration measurements and wave voltages, of
  - all ECG waveforms (P, Q, R, S, T, J, and U waves) with a special focus on:
    - Duration and morphology of ventricular repolarization
    - QT/QTc interval prolongation and ST-T segment changes
    - Arrhythmogenic potential – for torsades de pointes and other arrhythmias
- Need for reliable, fully automated ECG analysis in drug cardiac safety studies
  - Regulatory guidance now requires Thorough QT Study (TQTS) for all new drugs in development
  - TQTS is a single, highly-powered study to assess drug effects on cardiac repolarization, focusing on QT interval prolongation, and routinely requiring full analysis of 30K or more ECGs
  - At present, ECGs are analyzed using manual or "semi-automated techniques (automated interval duration measurements followed by human overread and adjustment)

## QTinno Key Features

- Fully automated software technology for measuring and adjudicating QT interval and other ECG based intervals
- Accepts ECG files from standard ECG equipment
- Converts 12L ECG into heart vector representation

### Use of Vector Magnitude Lead

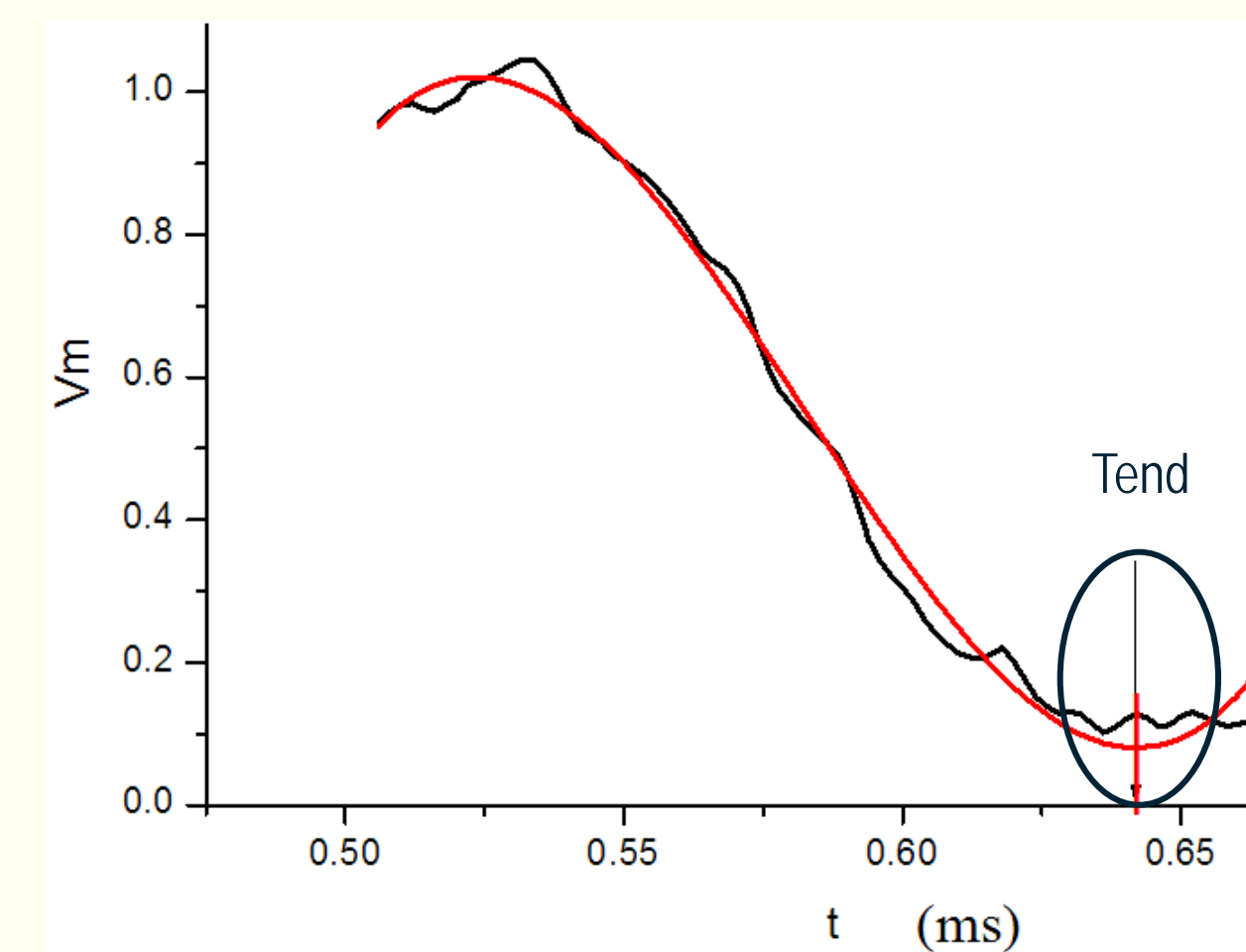
- Interval measurements made on vector magnitude lead provide excellent noise resistance and full QT intervals



- Wave shape similar to a traditional lead
- Contains information from all 12 leads and thus represents an electrically well-founded single lead representation of global cardiac electrical activity

## QTinno Key Features

### Iterative Algorithms Define Cardiac Electrical Events



- Proprietary, iterative curve fitting algorithms optimize accuracy and precision in fiducial point placement
  - Fitting of third-order polynomial function to VM data by least-squares, with multiple iterations until difference between function and recorded data falls below pre-defined threshold
  - Minimum of the fitted function represents the T<sub>end</sub>
  - Approach is noise-resistant and baseline-independent
  - Fully applicable to other key cardiac electrical events

### Viewing Function Provided by QTClient



- Convenient, user-friendly interface to allow visualization of all key results
- Although program is designed to be fully automated, overread feature is provided to allow human adjudication if desired

## QTinno Key Features

### Confidence Factor Identifies Problematic ECG Files

- Each automated reading self-assessed by QTinno for quality and assigned a Confidence Factor (CF). Assesses presence of:
  - Base line wander (LF)
  - High frequency (HF) noise
  - Power line noise (50/60Hz)
  - Muscle tremor related noise
  - Random noise (disturbance)
  - Missing leads
  - Arrhythmia and heart rate instability
- CF is comprised of 3 components
  - CFR – confidence factor for the overall ECG recording
  - CFT – confidence factor for a triplet
  - CFF – confidence factor that reflects existence of a problem that will automatically make CF=0
- Dominant weight given to CFT as it measure the quality of the selected triplet
- CFR reflects the quality of the ECG recording itself and is used as the "incoming inspection" ECG quality gauge
- CFF = 0 or 1, and used as the multiplier for all other components i.e. if CFF=0 it will force the overall CF=0

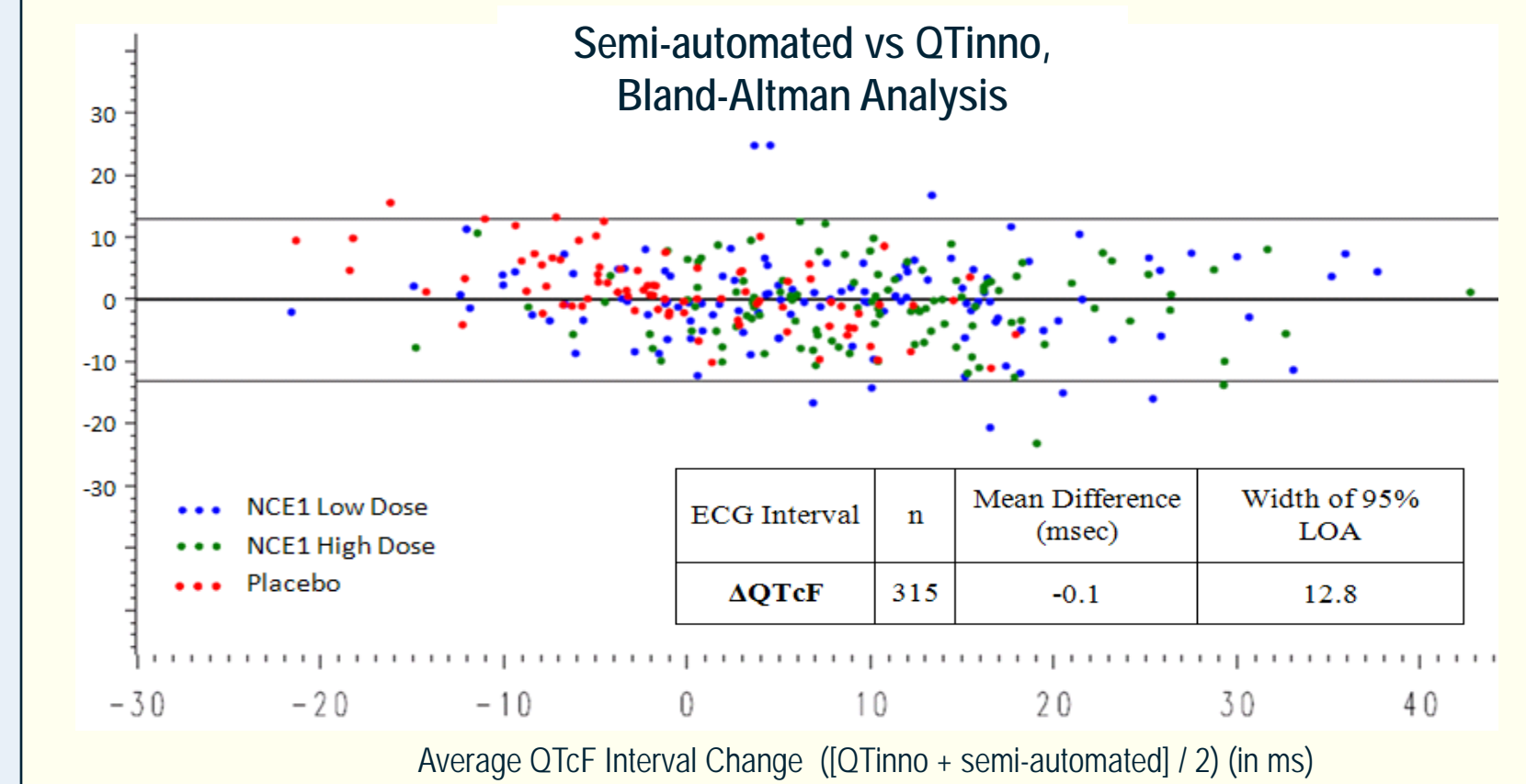
- User may set a CF threshold below which human review of automated interval duration measurements is suggested

## Results and Discussion

### Key Data from NCE1 Clinical Validation Study

- Placebo-controlled, double-blind, Phase I multiple ascending dose study of quinolone antibiotic
- Subjects: 23 healthy subjects receiving placebo (6 subjects), low-dose (8), or high-dose (8) NCE1
- Serial time-matched triplicate ECGs at multiple time points (1-24 hrs) (Total of 1963 ECGs)
- QTinno compared to semi-automated results overread and adjusted by 3 cardiologists

## Results and Discussion



### Intrinsic Variability of 2 semi-automated methods vs. QTinno

Intrinsic variability determined using mixed statistical model including factors for age, gender, subject, day and all interactions. SLT = single-lead tangent semi-automated method with human overread; GRB= Global Representative Beat semi-automated method with human overread

Method	Mean Difference (msec)	Width of 95% LOA
SLT	6.4 ms	
GRB	5.6 ms	
<b>QTinno</b>	<b>4.0 ms</b>	
SLT	9.0 ms	
GRB	7.4 ms	
<b>QTinno</b>	<b>4.8 ms</b>	

### Overview of results from all clinical validation studies

Study	CPU time	Mean $\Delta$ QTc (ms)	Std Dev (ms), 95% Limits of Agreement	Intrinsic Variability (ms)	% of flagged ECGs (CF < 80)
<b>Totalol</b> (n=104)	<2 min	QTinno vs Manual Global <0.5	<7 =13.1	ND	<4
<b>NCE1</b> (n=1963)	<15 min	QTinno vs semi-automated global <0.1	<7 =12.8	Between: 4.0 vs 5.6 Within: 4.8 vs 7.4	<2
<b>NCE2</b> (n=7039)	<60 min	QTinno vs Manual Global <1	<8 =14.2	Between: 4.4 vs 4.4 Within: 8.3 vs 9.1	<2
<b>NCE3</b> (n=2523)	<30 min	QTinno vs Manual Global <1	<10 =19.1	Between: 8.0 vs 9.5 Within: 11.9 vs 11.4	<10

- QTinno™ closely matched results from CROs and cardiologist readers using state-of-the-art semi-automated and computer-assisted manual tools
- Intrinsic variability of QTinno™ as good or better than semi-automated or manual methods in all instances
- Semi-automated and manual techniques labor-intensive and time-consuming
- In contrast, QTinno™ finished each study with <1 hr of CPU time, without human overread or adjustment