

Comparison of QTinno, a Fully Automated ECG Analysis Program, to Semi-Automated Methods in a Drug Safety Study in Healthy Subjects

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Abstract

Background: Several drugs have been shown to prolong cardiac repolarization and increase risk of torsades de pointes arrhythmia. Early identification of a drug's proarrhythmic potential is essential, but current ECG-based methods are labor-intensive and subject to reader variability. Reliable fully automated ECG analysis methods are needed. The objective of this study was to compare a novel fully automated method for cardiac time interval measurement (QTinno) to 2 computer-assisted, manually-adjusted (semi-automated) methods in common use: Global Representative Beat (GRB) and Single Lead Tangent (SLT).

Methods: QTinno performs fully automated cardiac interval measurements on a virtual ECG lead derived from heart vector movement in 3D space (vector magnitude). GRB measures QT from the earliest QRS-onset to the latest T-wave offset on representative beats superimposed from 12 standard leads. SLT measures 3 consecutive sinus rhythm beats in one lead using the raw ECG signal. Annotations made by both semi-automated methods were manually adjusted where necessary by 3 cardiologists, whereas no adjustments were made in the QTinno measurements. All methods were applied to 1422 digital 12-lead ECGs from a Phase 1 drug study.

Results: Using <2 hrs of CPU time, QTinno returned QTcF change from time-matched baseline (Δ QTcF) that differed minimally from both GRB and SLT methods (mean pairwise difference, 0.1 ms between QTinno and GRB, and 1.1 ms between QTinno and SLT). The average absolute QT and QTc intervals by QTinno were approximately 5 ms longer than GRB and 25 ms longer than by SLT. QTinno had lower intrinsic variability for Δ QTc than either GRB or SLT (QTinno between-subject SD 4.0 ms, GRB 5.6 ms, SLT 6.4 ms; QTinno within-subject SD 4.8 ms, GRB 7.4 ms, SLT 10.6 ms).

Conclusions: The methods show satisfactory agreement in detecting drug-induced QTc prolongation, with QTinno markedly accelerating the process and reducing the need for human labor. QTinno's lower intrinsic variability for Δ QTcF could increase study power or reduce sample size in thorough QTc studies.

Introduction

Many drugs have been shown to prolong cardiac repolarization and increase risk of torsades de pointes arrhythmia. Early identification of such effects is a critical priority. The ICH E14 Guidance for Industry states that virtually all new chemical entities should have a "thorough QT study" (TOTS) early in clinical development. The TOTS is a single highly powered trial designed to identify drugs that prolong cardiac repolarization, by evaluating the effect on heart rate-corrected QT interval (QTc) at multiple drug doses and time points after drug administration.

At present, QT measurement for drug development is routinely performed using digital ECGs and electronic caliper systems on a high-resolution computer screen. Measurements may be fully manual or "semi-automated", that is, automated QT determination by computerized algorithm followed by human overread and correction. These approaches yield acceptable results in skilled hands, but are relatively slow and labor-intensive, and subject to intra- and inter-reader variability.

Study Objective

The objective of this study is to compare the performance of QTinno, a novel fully automated program for determining electrocardiographic time intervals, with the performance of 2 semi-automated methods commonly used by clinical research organizations and central ECG core labs for detection of drug-induced QT/QTc prolongation. The methods were compared using serial digital 12-lead ECG triplicates acquired during robust QT/QTc assessment in healthy subjects enrolled in a Phase 1 multiple ascending dose study with an investigational drug.

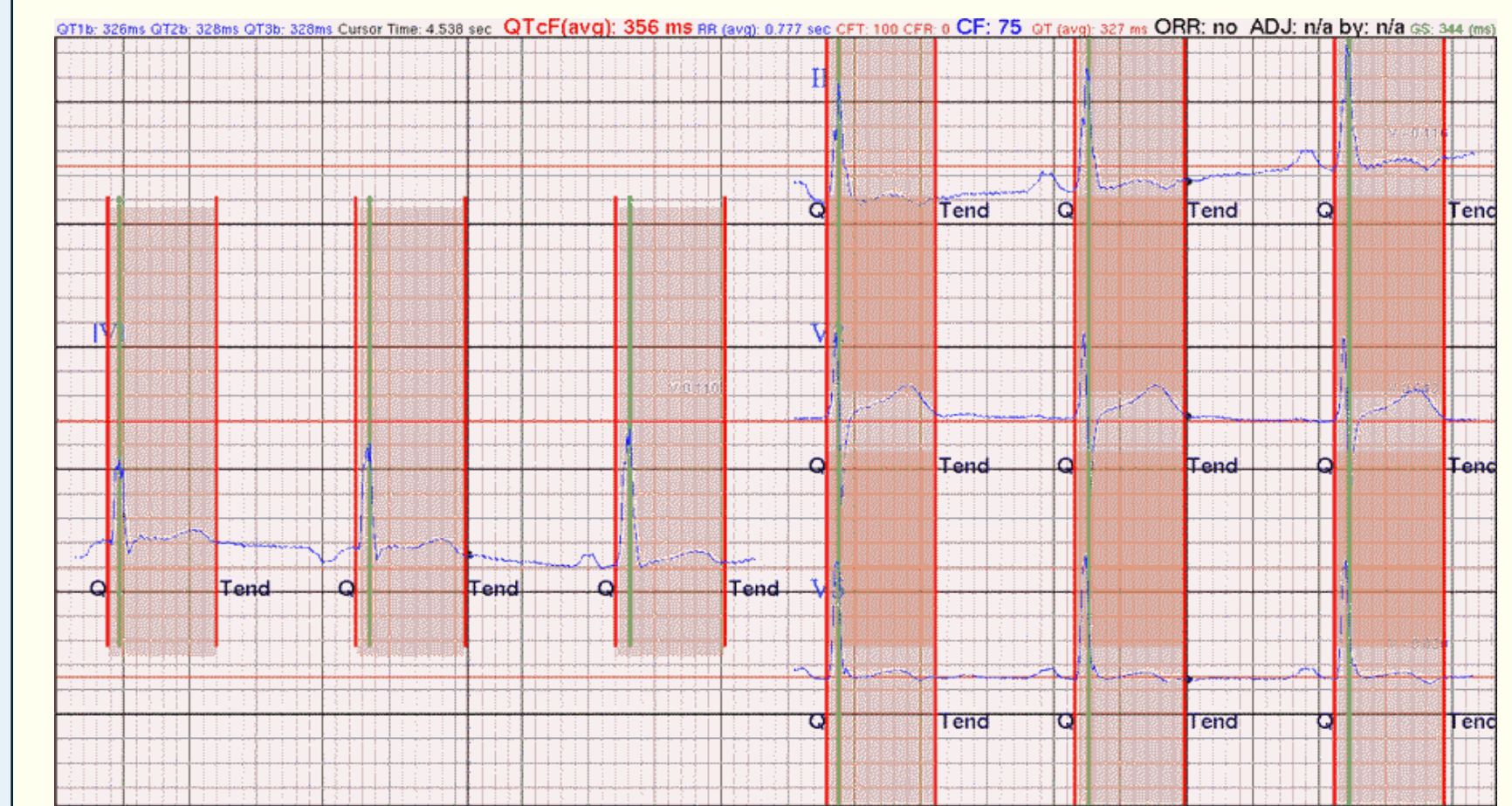
Methods

Study Design

- Phase 1, double-blind, randomized, placebo-controlled, multiple ascending dose study of a new chemical entity (NCE1), given as a 2 hr IV infusion, in 23 healthy volunteers, in 2 cohorts: *Cohort 1*, NCE1 lower-dose (9 subjects) or placebo (3 subjects); *Cohort 2*, NCE1 higher-dose (8 subjects) or placebo (3 subjects).
- ECGs were obtained at 1, 2, 4, 6, 8, 12, and 24 hours after the infusion start on Day 1 and Day 15. Baseline ECGs were obtained on Day -1 at corresponding times
- At each time, triplicate ECGs 2 min apart were obtained as 10-sec digital recordings after 10 min of rest in a fully supine position (total 1428 ECGs)

ECG Analysis by QTinno

- QTinno™ (NewCardio, Inc, Santa Clara, CA) is a software suite that provides fully automated analysis of key cardiac time intervals.
- QTinno key features include: use of a Vector Magnitude lead (V) for measurements (see Figure below); iterative curve-fitting to a 3rd order polynomial function to identify cardiac electrical events; and features to identify problematic ECGs for possible human overread.
- In each ECG, QTinno determined PR, RR and QT intervals, and QRS duration on all complete PQRS complexes, with QT intervals corrected using the immediately preceding RR interval according to the Fridericia formula ($QTcF = QT/RR^{1/3}$)
- In this study, all QTinno results are fully automated: no manual adjustments were made.



ECG Analysis by Semi-Automated Methods

- GRB Method:** Trace 3.6.3 software (Cardionics, Brussels, Belgium) annotated P- and Q-wave onset, and QRS complex and T-wave offset on the globally-presented representative PQRS complexes. The cardiologists manually adjusted annotations where necessary. The latest T-wave offset in any lead was determined as the intersection between the end of the T-wave and the isoelectric line.
- SLT Method:** The cardiologists selected three consecutive sinus rhythm PQRS complexes in limb lead II. Trace 3.6.3 software annotated the isoelectric baseline, P- and Q-wave onset, and QRS offset, and placed the tangent on the steepest part of the descending limb of the T-wave. The cardiologists reviewed the annotations and manually adjusted them where necessary. The end of the T-wave was the intersection of a tangent on the descending part of the T-wave and the baseline.

Statistical Methods.

- Bland-Altman plots of the individual pairwise differences in QTcF and Δ QTcF between methods were prepared.
- The intrinsic variability of QTcF and Δ QTcF (between-subject and within-subject error terms) was estimated for method by fitting a linear mixed model that included factors for treatment, age, sex, day, hour, age*day, age*hour, day*hour, and age*day*hour, with age treated as a continuous independent variable.

Results

1. Central Tendency Analysis

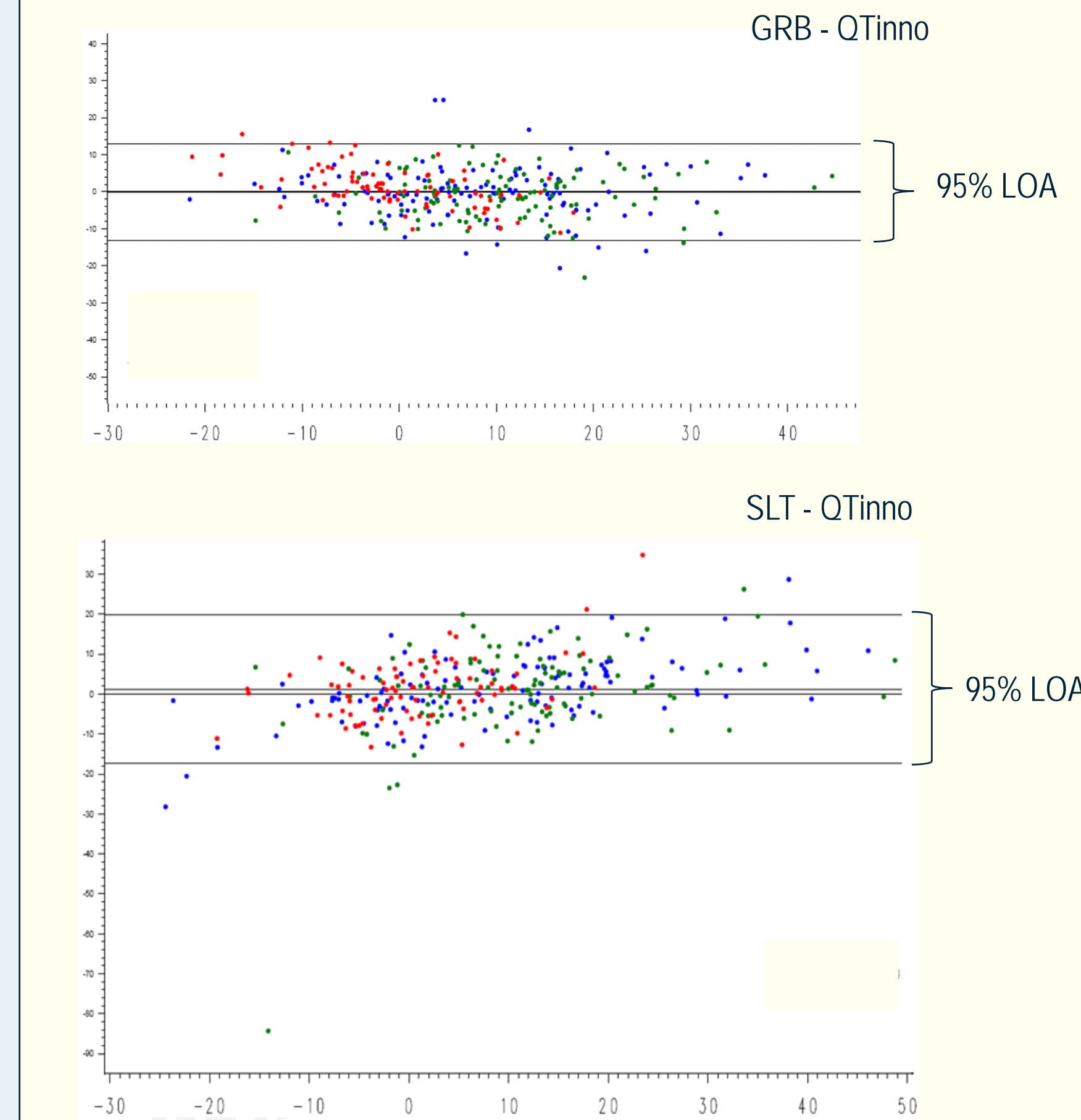


Fig 1. Bland-Altman plots comparing time-matched change in QTcF intervals measured by GRB and QTinno (top), and SLT and QTinno (bottom). 95% LOA = 95% Limits of Agreement.

			GRB - QTinno		SLT - QTinno	
ECG Interval	Treatment	n	Mean (msec)	Width of 95% LOA	Mean (msec)	Width of 95% LOA
	Untreated	245	-4.5	9.8	-26.5	28.2
	NCE1 Low-Dose	119	-5.0	12.4	-20.1	22.2
	NCE1 High-Dose	112	-5.1	13.2	-26.8	27.9
Δ QTcF	Pooled	315	-0.1	12.8	1.1	21.9
	Untreated	84	1.4	11.1	2.7	17.5
	NCE1 Low-Dose	119	-0.2	13.9	1.2	20.7
	NCE1 High-Dose	112	-1.1	12.4	-0.2	25.6

Table 1. Mean pair-wise differences and widths of the 95% limits of agreement (LOA; \pm [1.96 x standard deviation of the mean difference]) of the absolute QTcF interval and the QTcF change from baseline. Table compares summarized Bland-Altman results from the GRB and SLT methods to those obtained by QTinno. QTcF = Fridericia-corrected QT interval. Δ QTcF = time-matched change in QTcF.

Results

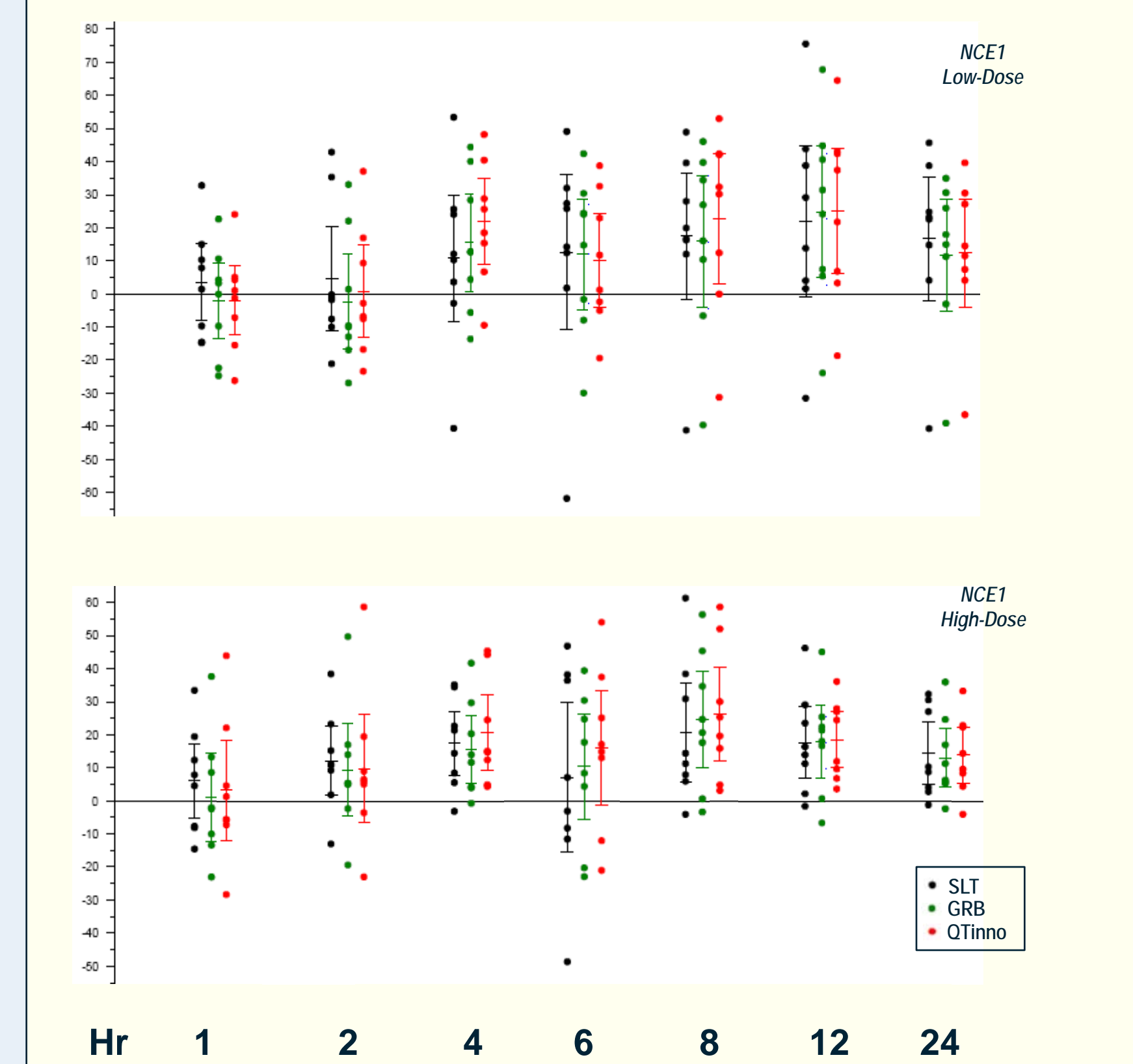


Fig 2. Hourly changes in time-matched, placebo-corrected QTcF ($\Delta\Delta$ QTcF) Day 15. For NCE1 Low-Dose, the largest $\Delta\Delta$ QTcF was at Hour 6 for SLT (point estimate 6.2 ms) and Hour 8 for GRB and QTinno (point estimates 9.9 and 13.5 ms, respectively). For NCE1 High-Dose, largest $\Delta\Delta$ QTcF was at Hour 8 for all methods (20.4 ms, 19.5 ms and 26.5 ms, for SLT, GRB, and QTinno, respectively).

2. Categorical Analysis

Measurement Method	Treatment	Number of subjects in category			
		Degree of QTcF Prolongation			Total
		<30 ms	30-60 ms	60-90 ms	
QTinno	Combined	466	10	0	476
	NCE1 low-dose	114	5	0	119
	NCE1 high-dose	107	5	0	112
	Untreated	245	0	0	245
Global	Combined	465	11	0	476
	NCE1 low-dose	113	6	0	119
	NCE1 high-dose	107	5	0	112
	Untreated	245	0	0	245
Tangent	Combined	455	20	1	476
	NCE1 low-dose	108	10	1	119
	NCE1 high-dose	105	7	0	112
	Untreated	242	3	0	245

Table 2. Categorical (outlier) analysis. Frequency of drug-associated QTcF prolongation detected by Tangent, Global, and QTinno measurement methods.

Results

3. Intrinsic Variability Analysis

Variability	Method	Δ QTcF
Between-Subject	SLT	6.4 ms
	GRB	5.6 ms
	QTinno	4.0 ms
Within-Subject	SLT	9.0 ms
	GRB	7.4 ms
	QTinno	4.8 ms

Table 3. Between- and within-subject variability for Δ QTcF, by measurement method and group. Mixed model including factors for age, sex, dose, subject, day and hour and all interactions.

Discussion

- Absolute QTcF intervals** measured by QTinno were similar to those measured by Global, whereas corresponding measurements by Tangent were about 25 ms shorter. The Tangent method uses a single ECG lead to measure cardiac time intervals; both Global and QTinno measure QT intervals from the earliest Q onset to latest T-offset. Kligfield et al. have recently shown that QT measurement from a single lead returns shorter values than global methods, an observation likely to explain the differences in absolute QTcF in this study.
- Time-matched change in QTcF.** All 3 methods showed close agreement in Δ QTcF. Thus, systematically shorter QTcF determinations by SLT (relative to GRB and QTinno) do not translate into differences in Δ QTcF, a key cardiac safety metric.
- Hourly changes in QTcF.** The methods were in reasonably close agreement in detecting the time and magnitude of maximum time-matched, placebo-corrected, QTcF change ($\Delta\Delta$ QTcF), another key cardiac safety metric.
- Categorical (outlier) analysis** results were similar for the QTinno and Global methods, with the SLT method identifying more "outliers" than the other 2 methods.
- Intrinsic variability of QTinno for Δ QTcF** was lower than either the Global or Tangent methods. Since the intrinsic variability of Δ QTcF affects study power and sample size calculations, this observation suggests that measurement by QTinno could enable robust QTc evaluation with smaller numbers of subjects or higher statistical power.

Conclusions and Clinical Implications

- Although SLT diverged from GRB and QTinno in some metrics, the three methods showed good agreement in detecting time-matched QTcF changes from baseline (Δ QTcF and $\Delta\Delta$ QTcF).
- QTinno exhibited lower intrinsic variability for Δ QTcF, which suggests that QTinno may be able to increase statistical power or reduce sample size for Thorough QT Studies.
- Key questions remaining include performance of QTinno on a fully powered TOTS database; and the impact of manual overread on semi-automated results, including possible data distortions or variability that might be associated with such an approach.