



## Comparison of QTinno, a fully automated electrocardiographic analysis program, to semiautomated electrocardiographic analysis methods in a drug safety study in healthy subjects<sup>☆</sup>

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### Abstract

**Background:** Improved automated methods for electrocardiographic (ECG) analysis are needed, particularly for drug development purposes.

**Objectives:** This study compared a novel fully automated method for ECG analysis (QTinno; NewCardio, Santa Clara, CA) to 2 semiautomated digital methods: global measurement from the earliest QRS onset to the latest T-wave offset on representative superimposed beats (global) and tangent measurement on 3 consecutive beats in one lead (tangent).

**Methods:** All 3 methods were used to determine uncorrected and rate-corrected QT interval duration (QT and QTcF) and related metrics in 1422 digital 12-lead ECGs from a phase 1 drug study. Global and tangent annotations were manually adjusted by the same 3 cardiologists wherever necessary. No adjustments were made in QTinno determinations.

**Results:** QTinno returned QTcF change from time-matched baseline ( $\Delta$ QTcF) that differed minimally from both global and tangent methods (mean pairwise difference: 0.1 millisecond between QTinno and global, 1.1 milliseconds between QTinno and tangent). The average absolute QT and QTcF intervals by QTinno were approximately 5 milliseconds longer than global and 25 milliseconds longer than by tangent. QTinno had lower intrinsic variability for  $\Delta$ QTcF than either global or tangent (between-subject SD: QTinno 4.0 milliseconds, global 5.6 milliseconds, tangent 6.4 milliseconds; within-subject SD: QTinno 4.8 milliseconds, global 7.4 milliseconds, tangent 10.6 milliseconds). All methods were robust in detecting the largest placebo-adjusted mean time-matched  $\Delta$ QTcF (15–25 milliseconds) induced by study drug.

**Conclusions:** The methods show good agreement for drug-induced QTc prolongation. Lower intrinsic variability of  $\Delta$ QTcF by QTinno could facilitate smaller sample sizes or increase study power in thorough QTc studies.

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### Keywords:

QT interval; Drug-induced QT prolongation; Automated ECG analysis

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### Introduction

A significant number of drugs have been shown to prolong cardiac repolarization and increase risk of torsades de pointes, a potentially lethal ventricular arrhythmia.<sup>1,2</sup> Early identification of such effects is a critical priority for the pharmaceutical industry and drug regulators.<sup>3–5</sup> The International Committee on Harmonization E14 guidance states that “almost all” new chemical entities with systemic availability

should have a “thorough QT study” (TQTS) early in clinical development.<sup>6</sup> The TQTS is typically a single highly powered trial that is designed to identify drugs that prolong cardiac repolarization, by evaluating the effect on heart rate (HR)–corrected QT interval (QTc) at multiple drug doses and time points after drug administration.<sup>6,7</sup>

The E14 guidance suggests that mean QTc prolongation smaller than 5 milliseconds (determined by ruling out an effect as large as 10 milliseconds at the 1-sided upper 95% confidence limit) is not associated with levels of risk of regulatory concern. In contrast, drugs with mean QTc effects of more than 5 milliseconds in TQTS may require extensive evaluation of QT effects in later-phase clinical trials.<sup>6</sup> Detecting or excluding such small effects requires careful attention to study design, conduct, and analysis. More reliable and reproducible QT interval measurement methods may enhance the accuracy and precision of TQTS results and may substantially reduce the number of electrocardiograms (ECGs), subjects required, cost, and work burden of a TQTS.

Determining the effect of a drug on QT interval is a complex task. Physiologic and methodology-related factors introduce substantial variability that can have a significant impact on the sample size, design of the study, and final results.<sup>8,9</sup> 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 “semiautomated,” that is, automated QT determination by computerized algorithm followed by overreading and manual correction by trained observers.<sup>10–12</sup> These approaches yield acceptable results in skilled and experienced hands but are relatively slow and labor-intensive and subject to intra- and interreader variability that may affect design of the study, statistical power, and overall results.<sup>9,13,14</sup> Fully automated QT measurement algorithms are available and their reliability for TQTS is currently under investigation.<sup>6,15,16</sup>

The objective of this study is to compare the performance of QTinno (NewCardio, Santa Clara, CA), a novel fully automated program for determining cardiac time intervals, with the performance of 2 semiautomated methods commonly used by clinical research organizations and central ECG core laboratories 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

### *Subjects and study design*

This was a phase 1, double-blind, randomized, placebo-controlled, multiple ascending-dose study of a new chemical entity (referred to herein as NCE1) in 23 healthy male and female volunteers. Two cohorts were randomized: cohort 1, NCE1 lower dose (9 subjects) or placebo (3 subjects); cohort 2, NCE1 higher dose (8 subjects) or placebo (3 subjects). Treatments were administered by a 2-hour constant-rate intravenous infusion on day 1 (single dose) and once daily on

days 3 to 15. All subjects gave written informed consent to the study protocol, which was conducted according to Good Clinical Practices, the Declaration of Helsinki, and all applicable regulatory guidance, approved by an independent institutional review board.

### *Electrocardiographic time-interval measurements*

On-treatment ECGs were obtained at 1, 2, 4, 6, 8, 12, and 24 hours after the start of the infusion on days 1 to 2 and days 15 to 16. A total of 1422 ECGs were analyzed. Baseline ECGs were obtained on day –1 and predose on day 1, at clock times corresponding to the scheduled times of postdose ECGs. At each time point, triplicate standard resting 12-lead ECGs (3 ECGs 2 minutes apart) were obtained as 10-second digital recordings after 10 minutes of quiet rest in a fully supine position with no ambient noise. The same 3 experienced cardiologists (from the same clinical research organization and applying the same standard operating procedures) performed both methods of QT interval measurement using the on-screen caliper system (Trace 3.6.3 software, Cardionics, Brussels, Belgium). Readers were blinded to treatment, sex, study day, and time point. The same cardiologist interpreted all ECG tracings from one subject in 1 day.

### *QTinno method*

QTinno is a software suite that provides fully automated analysis of key cardiac time intervals, including PR, RR, and QT intervals and QRS duration, has been described in detail elsewhere.<sup>17</sup> The software provides full numerical data and annotated ECGs at a rate of about 10 000 ECGs per hour using a standard desktop PC and Windows XP or Vista operating system. Briefly, key features of QTinno include:

1. *Use of vector magnitude lead for cardiac time interval measurements.* The QTinno algorithm processes the ECG input signal into a vectorial representation of cardiac electrical activity over time, using all ECG input leads. It then generates a single vector magnitude lead that it uses to determine all cardiac intervals.
2. *Use of an automated beat selection algorithm.* QTinno measures cardiac time intervals on all available complete cardiac electrical cycles (complete PQRST complexes) in an ECG, excluding the first complex and excluding those that are contaminated by electrical noise or substantially dissimilar from others in the ECG (eg, because of substantial variations in rate, QRS width, or QT interval). This analysis is done on the single vector magnitude lead generated in step 1. The preceding RR interval is used for individual rate correction on all QT complexes. For each ECG, reported values are the average obtained from all available PQRST complexes on the ECG.
3. *Use of third-order polynomial function to identify cardiac electrical events.* Key events, such as P-wave and QRS complex onset and QRS complex and T-wave offset, are identified and automatically annotated by novel, baseline-independent, proprietary algorithms. For the most part, these algorithms

identify key events by least-square fitting a third-order polynomial function to a defined segment of the vector magnitude function and identifying time at which the function reaches a local minimum. Curve fitting is optimized using an iterative process that determines the difference between the third-order polynomial function and vector magnitude over progressively smaller regions of interest and continues until the difference is less than a predefined boundary value.

The suite also includes features that identify defective ECGs (eg, those with missing leads or lacking a recognizable ECG signal) and features that tag potentially problematic ECGs (eg, high-frequency noise, baseline wander, arrhythmia) for possible human overreading. In each ECG, QT<sub>inno</sub> determined PR, RR and QT intervals, and QRS duration on all complete PQRST complexes, with QT intervals corrected individually using the immediately preceding RR interval according to the Fridericia formula ( $QTcF = QT/RR^{1/3}$ ). The reported QT and QTcF interval data from each ECG were the average of all complete PQRST complexes, with the exception of the first PQRST complex on the ECG. Each reported QT/QTcF interval is the mean of at least 3 PQRST complexes from the ECG under analysis. QT<sub>inno</sub> excluded 4 ECGs from its analysis because of signal quality inadequacies; in the instances of exclusion, the reported data are the mean of 2 ECGs from the same time point.

#### Global method

In each ECG, Trace 3.6.3 software (Cardionics) placed annotations marking P- and Q-wave onset and QRS complex and T-wave offset on the globally presented (ie, superimposed from all 12 leads) representative PQRST complexes. The cardiologists reviewed the annotations and manually adjusted them where necessary, with T-wave offset determined at the convergence of all superimposed T-wave offsets. The cardiologists then ungrouped the representative beats to individual 12 leads, visually inspected the placement of annotations on individual PQRST complexes in each lead, and manually adjusted them wherever necessary to capture the QT measurement from the earliest Q-wave onset to the latest T-wave offset in any lead. The latest T-wave offset in any lead was determined by visual determination of the intersection between the end of the T wave and the isoelectric line. A single mean QT value was reported from each ECG in the triplicate. The RR interval was computed as the mean of all RR intervals in that ECG.

#### Tangent method

In each ECG, the cardiologists visually inspected the raw ECG signal and selected 3 consecutive sinus rhythm PQRST complexes in limb lead II deemed suitable for QT interval measurement. Leads V<sub>2</sub> and V<sub>5</sub> were used as primary and secondary backup leads, respectively. If a backup lead was used for one of the subsequent serial ECGs, all tracings from that subject were remeasured in the backup lead. The Trace 3.6.3 software (Cardionics) annotated the isoelectric base-

line, onset of the P and Q waves, and QRS offset on the selected complexes and placed the tangent on the steepest part of the descending limb of the T wave. The cardiologists then reviewed placement of annotations and manually adjusted them wherever necessary. The end of the T wave was determined at the intersection between a tangent drawn upon the descending part of the T wave and the baseline. The average from 3 QT measurements on one ECG and the average from the RR intervals preceding the 3 selected beats were reported as the QT and RR values for that ECG, respectively.

For both semiautomated QT interval measurement methods, the same senior cardiologist performed a blinded review of all ECGs annotated by the primary cardiologists. In case of disagreement, ECGs were adjudicated for agreement of both observers to produce the final measurement. The Cardionics algorithm used the final annotation placement to determine the QT and RR interval duration (milliseconds), the QT corrected by Fridericia ( $QTcF = QT/RR^{1/3}$ ), and the HR (beats per minute).

A total of 5 ECGs were excluded from the global analysis and 2 were excluded from the tangent analysis because of signal quality problems. In each instance of ECG exclusion, the data point was reported as the average of the other 2 ECGs that were taken at the same time point.

#### Statistical methods

For all comparisons of measurement methods, an average of the 3 final QT, QTcF, and HR values from each ECG triplicate was used as a single observation at that ECG collection time point. The changes from the time-matched baseline in QT, QTcF, and HR ( $\Delta QT$ ,  $\Delta QTcF$ , and  $\Delta HR$ , respectively) were calculated for each subject at each postdose ECG collection time point on each study day by subtracting the averaged triplicate values for the corresponding time-matched baseline assessments on day -1 or predose on day 1. For the ECG time point at 24 hours on days 2 and 16, the baseline time-matched point was predose on day 1.

Bland-Altman plots of the individual pairwise differences in QTcF and  $\Delta QTcF$  between QT interval measurement methods were prepared for the data from each treatment group (NCE1 low dose, NCE1 high dose, and pooled placebo) and for the data pooled across all treatments on days 1 to 2 and days 15 to 16.<sup>18</sup> For each QT interval measurement method, the mean pairwise differences and the widths of the 95% limits of agreement (LOA) were tabulated for the differences between methods in QT/QTcF and  $\Delta QT/\Delta QTcF$ .

The intrinsic variability of QTcF and  $\Delta QTcF$ , as described by the between-subject and within-subject error terms (estimated SD), was estimated for each QT interval measurement 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 (SAS version 9.1, PROC MIXED procedure; SAS Institute, Cary, NC). This model was simplified in some instances because of sparse data caused by higher-order interactions or sex effects.

Table 1

Mean pairwise differences and widths of the 95% LOA  $\pm$  (1.96  $\times$  SD of the mean difference) of the absolute QT/QTcF interval and the QT/QTcF change from baseline, in milliseconds

ECG interval	Treatment	n	Global – QT <sub>inno</sub>		Tangent – QT <sub>inno</sub>	
			Mean (ms)	Width of 95% LOA	Mean (ms)	Width of 95% LOA
QT	Pooled	476	-4.6	10.9	-24.7	24.1
	Untreated	245	-4.4	9.4	-25.8	27.5
	NCE1 800 mg	119	-4.9	11.7	-21.5	21.3
	NCE1 1200 mg	112	-5.0	12.8	-25.5	27.1
QTcF	Pooled	476	-4.8	11.3	-25.6	24.8
	Untreated	245	-4.5	9.8	-26.5	28.2
	NCE1 800 mg	119	-5.0	12.4	-20.1	22.2
	NCE1 1200 mg	112	-5.1	13.2	-26.8	27.9
QT Change ( $\Delta$ QT)	Pooled	315	-0.1	11.9	1.6	20.6
	Untreated	84	1.4	10.6	3.0	16.9
	NCE1 800 mg	119	-0.1	12.8	1.6	18.7
	NCE1 1200 mg	112	-1.2	11.5	0.6	24.5
QTcF change ( $\Delta$ QTcF)	Pooled	315	-0.1	12.8	1.1	21.9
	Untreated	84	1.4	11.1	2.7	17.5
	NCE1 800 mg	119	-0.2	13.9	1.2	20.7
	NCE1 1200 mg	112	-1.1	12.4	-0.2	25.6

The table shows comparison of summarized Bland-Altman results from the global representative beat (global) and single lead tangent (tangent) methods to those obtained by QT<sub>inno</sub>.

Point estimates were obtained for the placebo-subtracted difference in  $\Delta$ QTcF for each NCE1 dose group by study time.

## Results

Twenty-three subjects (9 on NCE1 low dose, 8 on NCE1 high dose, and 6 on placebo) received at least one dose of study treatment. One subject on NCE1 low dose withdrew consent on day 10, with 22 subjects completing the study. The data set for QT interval measurement method comparisons included a total of 476 ECG data points. Each data point reflects the mean results from triplicate ECGs taken

within a 2-minute time window (total, 1428 ECGs). In a few instances, individual ECGs were excluded because of signal quality problems (for QT<sub>inno</sub>, 7 ECGs excluded; for global, 9 ECGs excluded; for tangent, 6 ECGs excluded). In these instances the reported data point is the mean of 2 ECGs rather than 3. There were 161 ECG data points from baseline (days -1 to 1), 161 from the first on-treatment day (days 1-2), and 154 from the last on-treatment day (days 15-16).

The corresponding means, minima, and maxima of QT and QTcF values at baseline were comparable between placebo and both NCE1 doses. The  $\Delta$ HR values in any treatment group did not exceed  $\pm$ 10 beats per minute at any time point on days 1 to 2 or 15 to 16, with no discernible differences in  $\Delta$ HR on placebo, NCE1 low dose, and NCE1

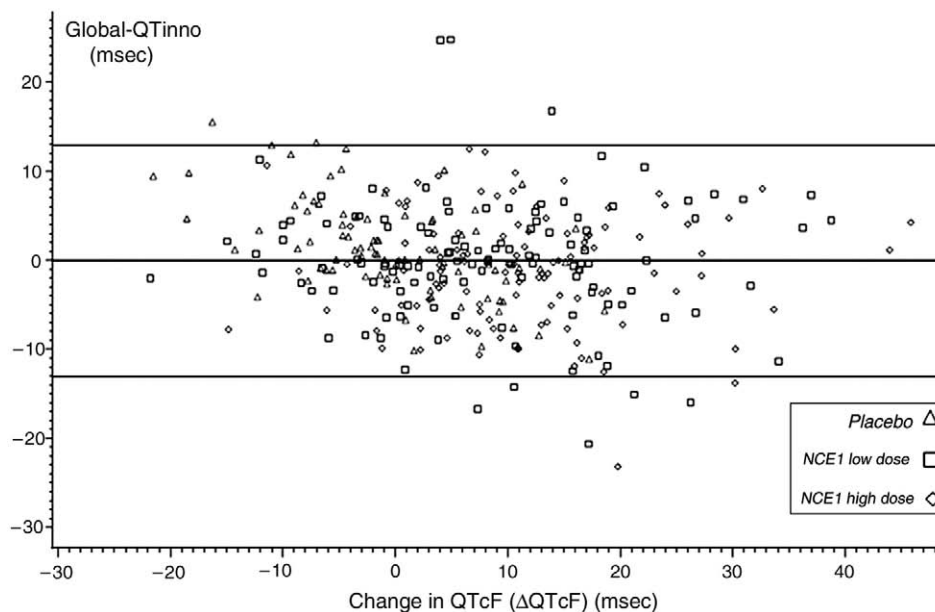


Fig. 1. Bland-Altman plots of change in QTcF intervals ( $\Delta$ QTcF) measured by global representative beat method (global) and QT<sub>inno</sub>.

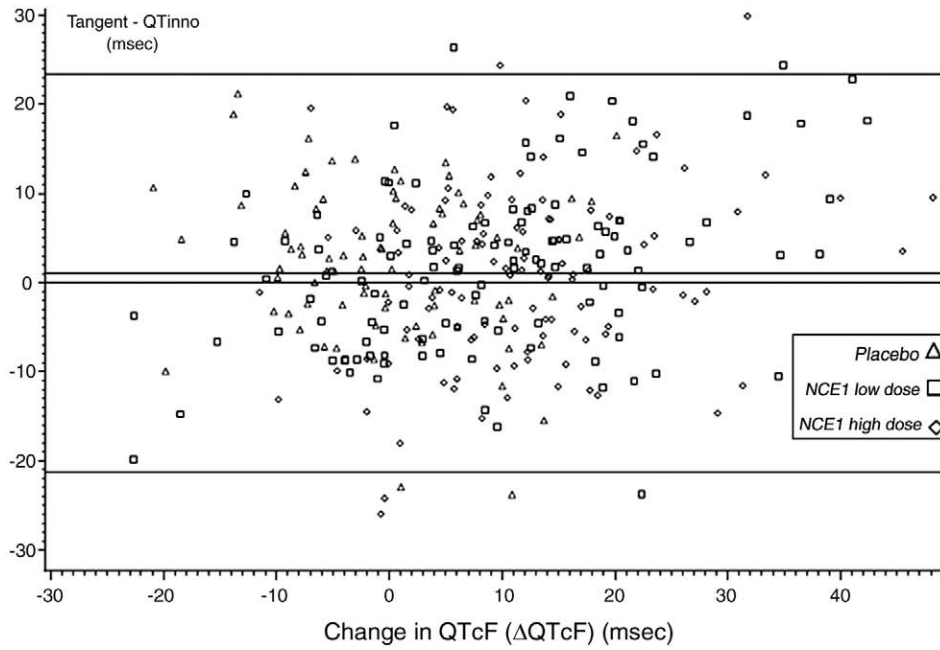


Fig. 2. Bland-Altman plots of change in QTcF intervals ( $\Delta$ QTcF) measured by single lead tangent method (tangent) and QTinno.

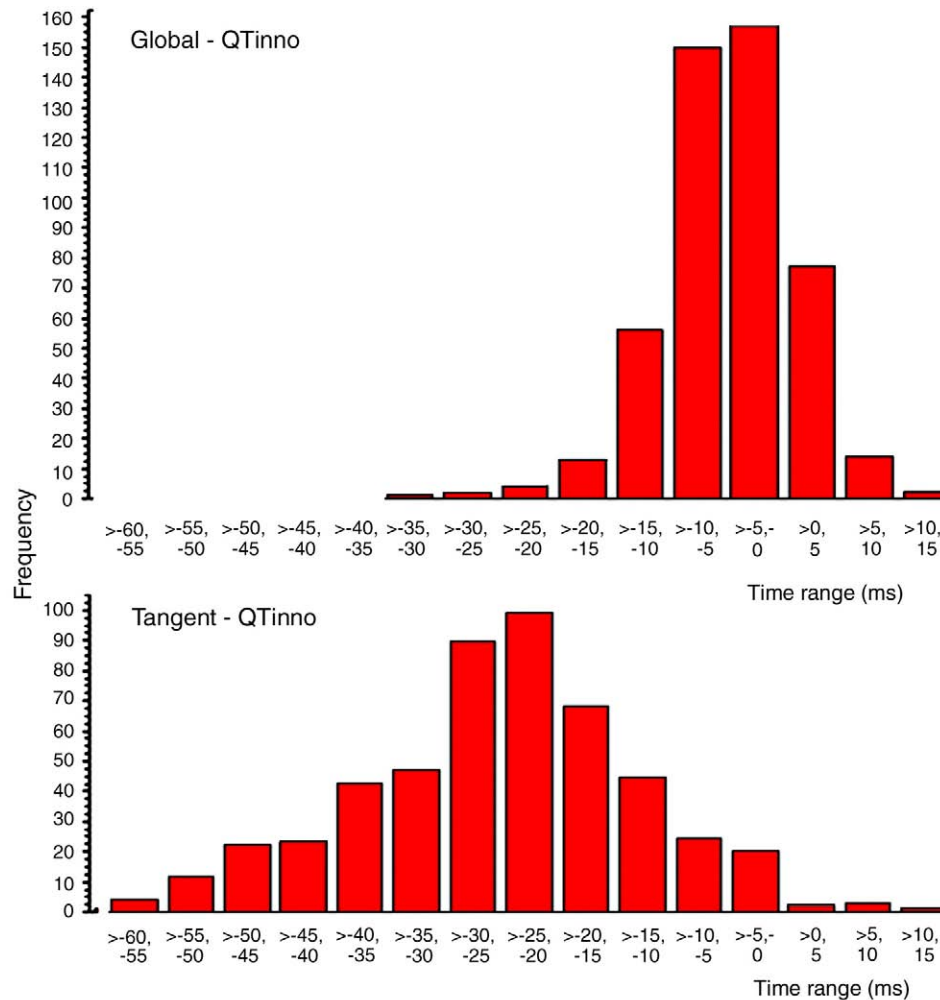


Fig. 3. Histogram showing distribution of categorical differences between the global representative beat (global) and QTinno methods (top), and the single lead tangent (tangent) and QTinno methods (bottom) for absolute QTcF. Paired measurements on the ECGs pooled from all treatments across all study days.

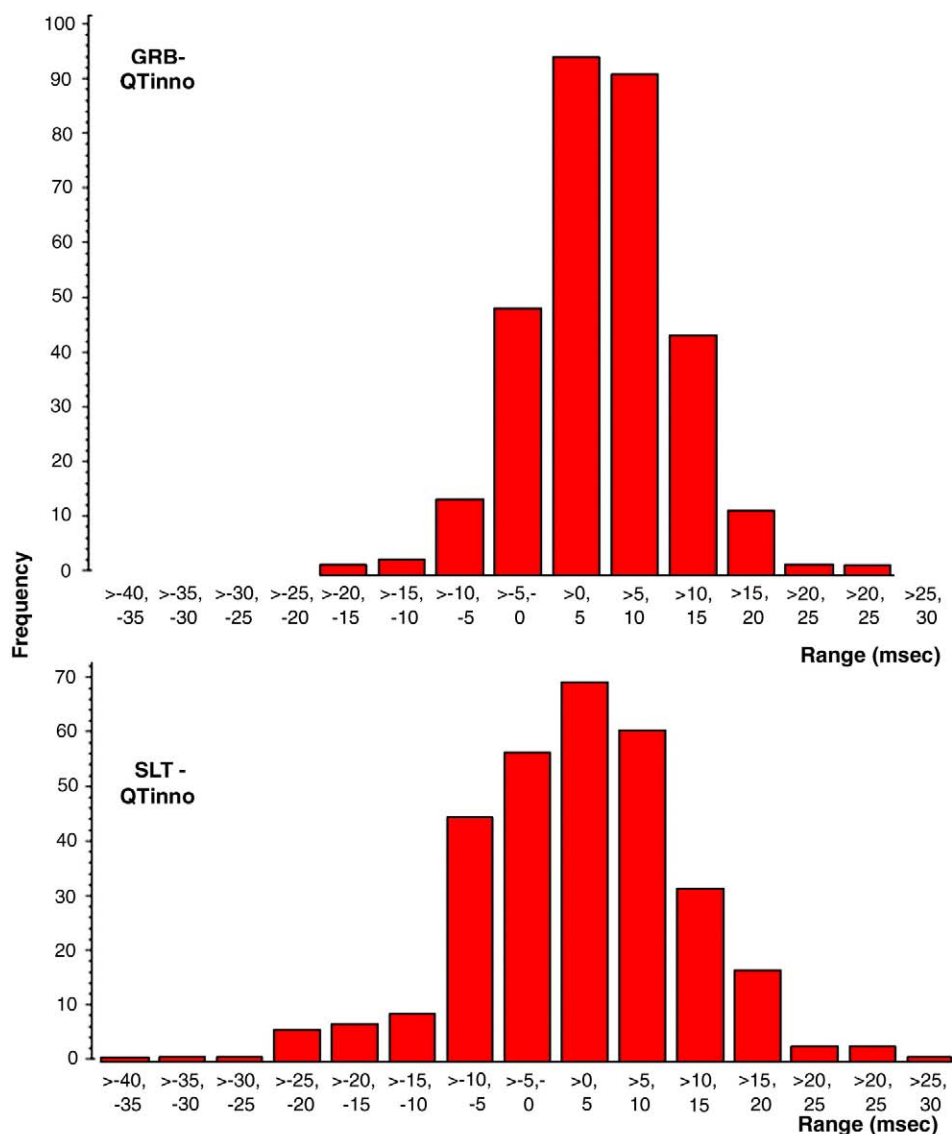


Fig. 4. Histogram showing distribution of categorical differences between the global representative beat (global) and QTinno methods (top), and the single lead tangent (tangent) and QTinno methods (bottom) for change in QTcF ( $\Delta$ QTcF). Paired measurements on the ECGs pooled from all treatments across all study days.

high dose. At each time point, the global, tangent, and QTinno methods produced comparable results for  $\Delta$ HR.

The QTinno and global methods showed reasonably close agreement for absolute values of QT and QTcF for the data pooled from all treatments (Table 1; mean pairwise difference,  $-4.6$  and  $-4.8$  milliseconds, respectively). For time-matched, placebo-corrected changes in QT and QTcF ( $\Delta$ QTc and  $\Delta$ QTcF, respectively), QTinno and global returned virtually identical results (mean pairwise difference,  $-0.1$  milliseconds for both metrics). Fig. 1 shows Bland-Altman plots for differences in absolute QTcF and  $\Delta$ QTcF intervals between global and QTinno, which confirms the similarity of the results produced by the 2 methods.

In contrast to reasonably close agreement between global and QTinno, the tangent method returned substantially shorter values for mean QT and QTcF than QTinno (mean pairwise difference in the pooled treatment group,  $-24.7$  and  $-25.6$  milliseconds, respectively). Shorter QT and QTcF values for tangent relative to QTinno were apparent in each

treatment group (Table 1). However, the tangent and QTinno methods showed much closer agreement for time-matched, placebo-corrected changes in QT and QTcF, both for pooled data and in each individual treatment group (mean pairwise difference for pooled data,  $1.6$  and  $1.1$  milliseconds,

Table 2

Estimated between- and within-subject variability for absolute QT and QTcF, and for time-matched changes in QT ( $\Delta$ QT) and QTcF ( $\Delta$ QTcF), by measurement method and group

Method	Variability	QTcF	$\Delta$ QTcF
Between-subject	SLT	11.3	6.4
	GRB	8.0	5.6
	QTinno	10.5	4.0
Within-subject	SLT	11.3	9.0
	GRB	6.6	7.4
	QTinno	7.3	4.8

Mixed model including factors for age, sex, dose, subject, day, and hour, and all interactions. All numerical entries are in milliseconds. SLT indicates single lead tangent; GRB, global representative beat.

Table 3

Hour-by-hour mean change in QTcF intervals after start of infusion of placebo or indicated dose of NCE1, relative to time-matched, placebo-corrected control

Day	Hour	NCE1 low dose			NCE1 high dose		
		QTinno	Global	Tangent	QTinno	Global	Tangent
Mean change in placebo-corrected QTcF (point estimates, in ms)							
1	1	−9.8	−2.2	−5.6	−4.4	−1.2	−5.1
	2	−4.7	−3.4	−1.4	8.5	4.8	4.8
	4	9.2	4.0	1.3	17.0	11.5	6.0
	6	10.6	9.3	6.2	14.0	6.8	6.7
	8	13.3	9.9	4.8	13.7	8.3	2.6
	12	6.0	4.8	−0.4	11.0	13.0	8.4
	24	10.8	6.4	10.5	6.2	5.2	14.3
15	1	6.3	6.2	10.9	10.4	8.2	12.4
	2	15.5	13.5	17.2	17.7	18.4	19.2
	4	23.3	16.1	12.9	23.0	16.5	19.7
	6	7.1	9.2	12.2	14.3	8.4	5.2
	8	26.5	19.5	20.4	20.2	18.5	14.1
	12	17.3	16.7	16.1	16.6	15.6	16.3
	24	3.8	3.3	10.4	8.3	7.9	11.8

QT intervals were measured by single lead tangent (tangent), global representative beat (global), or QTinno method, as indicated.

respectively). Fig. 2 shows Bland-Altman plots for differences in absolute QTcF and  $\Delta$ QTcF intervals between tangent and QTinno, from which the numerical data in the “Tangent – QTinno” columns of Table 1 were obtained. As seen by differences in absolute QTcF measurements, relative global and QTinno, tangent and QTinno were further apart in mean pairwise differences and demonstrated a substantially larger number of individual measurements where the difference between methods exceeded 20 milliseconds.

A frequency histogram of individual differences in QTcF is shown in Fig. 3. Comparing QTinno to global, 456 (95.8%) of 476 of the individually measured QTcF values were within 15 milliseconds of each other, whereas only 93 (19.6%) of 475 of the individually measured QTcF values by QTinno and tangent were within 15 milliseconds. Thus, this figure confirms close agreement between global and QTinno but a lesser degree of agreement between tangent and QTinno.

A frequency histogram for individual differences in time-matched QTcF change ( $\Delta$ QTcF) is shown in Fig. 4. Comparing QTinno to global, 306 (97.1%) of 315 of the individual  $\Delta$ QTcF measurements were within 15 millise-

conds of each other, whereas 292 (92.7%) of 315 of the individually measured QTcF values by QTinno and tangent were within 15 milliseconds. Thus, there was close agreement between QTinno and both global and tangent on this metric.

The intrinsic variability of the individual values produced by each measurement method for absolute QT and QTcF, as defined by between- and within-subject error terms (estimated SD), is shown in Table 2. Values for both between- and within-subject intrinsic variability were generally comparable between the 2 semiautomated measurement methods. However, the intrinsic variability of both  $\Delta$ QT and  $\Delta$ QTcF was lower with QTinno than either global or tangent, for both between- and within-subject variability.

Table 3 presents data on central tendency of time-matched, placebo-corrected change in QTcF in both NCE1 treatment groups at various time points in the study. For the NCE1 low-dose treatment group, all 3 methods identified hour 8 on day 15 as the point of maximum QTcF prolongation. For NCE1 high dose, tangent and QTinno identified the time point of maximum QTcF prolongation at

Table 4

Categorical outlier analysis

Measurement Method	Treatment	No. of subjects in category			Total
		Degree of QTcF Prolongation			
		<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 representative beat	Combined	465	11	0	476
	NCE1 low dose	113	6	0	119
	NCE1 high dose	107	5	0	112
	Untreated	245	0	0	245
Single lead 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

Frequency of time-matched change in QTcF detected by QTinno, global, and tangent measurement methods, by category (<30, 30–60, and >60 milliseconds).

hour 4 on day 15, whereas global identified maximum QTcF prolongation at hour 8 on day 15. The 90% confidence interval around both  $\Delta\Delta\text{QTcF}_{\text{max}}$  values excluded zero with the upper bound more than 10 milliseconds for all measurement methods (data not shown). In several instances, point estimates for time-matched, placebo-corrected change in QTcF diverged substantially between methods, an observation that likely reflects the relatively small number of data points at each time point ( $n = 6-9$ ).

In categorical outlier analysis (Table 4), 1 subject on NCE1 low dose had a maximum absolute QTcF of more than 450 milliseconds (452 milliseconds) when measured by global but not when measured by tangent or QTinno. No other subjects had QTcF of more than 450 milliseconds with any method (data not shown). Six subjects in the NCE1 low-dose group and 5 subjects in high-dose group had maximum  $\Delta\text{QTcF}$  values in the range of 30.1 to 60 milliseconds when measured by global; similar numbers were obtained with the QTinno method (5 and 5, respectively). The tangent method reported somewhat larger numbers (10 and 7, respectively) for each group. For untreated subjects, QTinno and global identified no instances of time-matched QTcF change of more than 30 milliseconds, whereas tangent identified 3 subjects in this category. For QTinno and global, no subjects had  $\Delta\text{QTcF}$  values of more than 60 milliseconds, whereas tangent identified 1 subject in this category.

## Discussion

This study evaluated the performance of a fully automated QT/QTc measurement method (QTinno) to 2 commonly used semiautomated methods (global and tangent) for measuring cardiac time intervals. Each has a distinct methodological approach. Global constructs a single “median beat” from all complexes in each lead and annotates a display in which all leads are superimposed. Tangent annotates 3 complexes in ECG lead II (or  $V_2$  or  $V_5$ , if lead II is unsatisfactory) and constructs a tangent-baseline intercept to define the end of the T wave. In both of the above methods, annotations are overreading and adjusted if necessary by trained human observers. The fully automated QTinno method measures cardiac time intervals on a single, computer-constructed vector magnitude lead, which combines input from all ECG leads and defines T-offset using baseline-independent curve-fitting techniques. There was no human overreading (although human overreading is provided as a program option for users that desire it).

Both global and tangent computerized measurements were overread by the same 3 cardiologists and adjusted where deemed necessary. In contrast, although the QTinno program identifies and flags potentially problematic ECGs (eg, those with high noise content) and provides an option for human overreading, the results presented here were fully automated and without human adjustments to illustrate the fully automated aspects of QTinno performance. Some studies suggest that when compared to fully automated, the human overreading has a substantial impact on the results of the central tendency analysis of drug-induced QTc prolonga-

tion. For example, in a recent TQTS, Malhotra et al<sup>14</sup> reported that key metrics, including mean QTcF prolongation, increased by more than 2-fold after human overreading, for all cohorts in the study, including 2 doses of active drug and the moxifloxacin-positive control group. Such effects, which are at present inconclusive, may have a significant impact on the future clinical development of an investigational drug.

In the current study, the absolute QT and QTcF intervals measured by QTinno were reasonably similar to those measured by global, whereas corresponding measurements by tangent were about 25 milliseconds shorter. The tangent method uses a single ECG lead to measure cardiac time intervals, global and QTinno use approaches that are distinctly different from tangent and from each other, but both measure QT intervals from the earliest Q onset to latest T-offset. Kligfield et al<sup>9</sup> have recently shown that the semiautomated QT measurement from a single lead returned shorter values than the global method, an observation likely to contribute to the explanation of the differences in QT measurement observed in this study. In contrast to the differences observed for absolute QT/QTcF, all 3 methods showed relatively close agreement in time-matched  $\Delta\text{QT}$  and  $\Delta\text{QTcF}$ . The widths of the 95% LOA for  $\Delta\text{QT}$  and  $\Delta\text{QTcF}$  were similar to those reported by other investigators.<sup>16,19,20</sup>

The QTinno method showed lower intrinsic variability than either tangent or global for  $\Delta\text{QT}$  and  $\Delta\text{QTcF}$ . Because the intrinsic variability of  $\Delta\text{QTcF}$  affects study power and sample size calculations, this observation suggests that measurement by QTinno could enable robust QTc evaluation at the International Committee on Harmonization E14 threshold of interest with smaller numbers of subjects or higher statistical power, assuming the accurate measurement of the absolute QT interval duration by this method. Additional clinical studies are needed to test this hypothesis.

For clinical trials evaluating drug QT effects, it is important to identify and quantify the largest time-matched, placebo-corrected change in QTcF ( $\Delta\Delta\text{QTcF}_{\text{max}}$ ) at any time point after dosing. All 3 measurement methods identified the same point for low-dose NCE1 (day 15, 8 hours postdose) and differed slightly for high-dose NCE1 (day 15, hour 4 for global and QTinno and hour 2 for tangent). In addition, the  $\Delta\Delta\text{QTcF}$  values had upper 90% confidence interval bounds of more than 10 milliseconds at most time points regardless of the QT interval measurement method. However, this study was not powered to the same level as a TQTS, and observed differences between  $\Delta\Delta\text{QTcF}$  values and the large confidence intervals associated with each point estimate are likely due to the small cohort size and the parallel group design. Despite these limitations, this study demonstrates that all 3 measurement methods robustly detected the maximum mean drug-induced QTc prolongation in a clinically significant range (15-30 milliseconds).

In addition to analyses of central tendency, the E14 guidance recommends several categorical analyses, including the reporting of instances where the QTc interval change from baseline is greater than 30 and 60 milliseconds. No subject was identified as having QTcF prolongation of more

than 60 milliseconds by the global and QTinno methods, whereas the tangent method identified a single subject having QTcF prolongation of more than 60 milliseconds. The global and QTinno methods were in close agreement on the number of subjects having QTc prolongation between 30 and 60 milliseconds, whereas tangent reported more subjects in this category than the other 2 methods.

In summary, this study investigated the performance of a fully automated program, QTinno, to 2 commonly used semiautomated methods for assessing the effect of drugs on QT interval. Although tangent diverged from global and QTinno in some metrics, the 3 methods showed good agreement in detecting time-matched QTcF changes from baseline ( $\Delta$ QTcF and  $\Delta\Delta$ QTcF). Relative to global and tangent, QTinno exhibited lower intrinsic variability for  $\Delta$ QT and  $\Delta$ QTcF, an observation that suggests that QTinno may be able to reduce sample size or increase statistical power for TQTS.

Key questions remaining to be investigated include the performance of QTinno in comparison to existing QT methods: (1) on a fully powered TQTS database; (2) the ability of this method to detect and quantify changes induced by a range of different drugs, including those that have minimal or marked effect on QTc, and those that substantially alter T-wave morphology; (3) the impact of manual overreading on semiautomated results and the detection and quantification of any data distortions or variability that might be associated with such an approach.

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