ORIGINAL ARTICLE

Clinically significant incidental QTc prolongation is subject to within-individual variability

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Abstract

Background: Prolonged QTc interval observed in daily practice is often deemed to be drug induced and might result in drug discontinuation, with possible therapeutic consequences. However, whether clinically significant prolonged QTc may be due to within-individual variability occurs has yet to be described.

Methods: A retrospective cohort study documenting within-individual QTc variability in subjects attending annual routine medical evaluation. At each visit, QT interval was measured and corrected for heart rate using Bazett and three other commonly used formulae. Outcome measures were rates of $\Delta\text{QTc} \geq 60$ msec, absolute $\text{QTc} \geq 500$ msec and $\text{QTc} \geq 25\%$ from baseline.

Results: A total of 188 subjects [54 (29%)] females were recruited. Mean age at first ECG was 54 ± 12.8 years with mean time interval of 12.2 ± 1.1 months between measurements. Mean Bazett QTc was higher compared to the other 3 formulae: 412 ± 20 vs. 400 ± 16 msec. Using Bazett formula, 18/188 (9.6%) and 5/188 (2.7%) subjects showed at least one measurement with $\Delta\text{QTc} \geq 60$ msec and $\text{QTc} \geq 500$ msec, respectively. Of the former, 5/18 (27.8%) showed $\text{QTc} \geq 25\%$ prolongation. In multivariate analysis, $\text{QTc} \geq 500$ msec was significantly associated with number of measurements (HR: 5.01, 95%CI: 1.21–20.78, $p = .026$) with no effect of other known confounders. Lower rates were demonstrated with the other three formulae.

Conclusion: In clinical practice, significant prolonged QTc may be attributed to within-individual variability, particularly when adjusting the QT interval with Bazett correction. This should be taken into consideration when decisions on changing current drug regimens are to be made.

KEYWORDS

drug induced, QTc prolongation, within-individual variability

1 | METHODS

Drug-induced ventricular arrhythmias, and torsade des pointes (TdP) in particular, are of major concern in clinical practice as in drug development and postmarketing surveillance (Straus et al.,

2005; Wisniewska, Tylutki, Wyszogrodzka, & Polak, 2016). Since the occurrence of drug-induced TdP is rare, rate corrected QT (QTc) prolongation serves as a surrogate marker for increased arrhythmia risk (Straus et al., 2005; Yu et al., 2017; Sijs et al., 2009).

In clinical practice, acquired QTc prolongation is mostly attributed to drug exposure and often results in discontinuation of essential drugs with QT-prolonging potential, even if they are important for continued patient health and well-being. This QTc prolongation is commonly determined by comparison to a previous ECG, or in the presence of an abnormally prolonged interval exceeding an absolute value independent of previous measurements. The causality of QTc prolongation following exposure to various drugs is based on experience from drug development phases and further supported by large population-based studies (Briasoulis, Agarwal, & Pierce, 2011; Gueta et al., 2017; Isbister & Page, 2013; Maljuric et al., 2015; Viskin, Havakuk, & Schwaber, 2015; Wisniowska et al., 2016). However, whether clinically significant incidental QTc prolongation occurs within an individual over the years, independent of drug exposure, has yet to be described. The objective of the current study is to examine the rate and extent of clinically significant QTc prolongation which may be attributed solely to within-individual variability.

1.1 | Study design

A retrospective cohort study in individuals attending routine yearly medical evaluation for insurance purposes. As part of the annual evaluation, each visit included an ergometric stress test preceded by a resting ECG in the supine position, conducted between 8 a.m. and noon. All visits took place at the Institute for Medical Screening of the Chaim Sheba Medical Center, a large academic tertiary center. The study was approved by the Institutional Review Board.

1.2 | Cohort definition and data extraction

We reviewed the medical records and ECG recordings of all subjects aged ≥ 18 years, examined between 2003 and 2015. Only subjects with at least three consecutive annual visits were included. Exclusion criteria were chronic atrial fibrillation, documented conduction abnormalities, or unclear T-wave morphology. At each visit data recorded by health questionnaire included: demographics, risk factors, chronic diseases, and daily medications. Blood was sampled for complete blood count and chemistry panel, followed by resting ECG, preceding the ergometric stress test. Medications taken within the 48 hr prior to the ECG recording were documented and included cardiovascular agents (α -blockers, β -blockers, and calcium channel blockers), loop and thiazide diuretics and drugs known to prolong the QT interval (Isbister & Page, 2013). Subjects were followed until they reached six consecutive visits or when the yearly sequence was interrupted.

1.3 | QT interval determination and correction

For each subject on each visit, resting heart rate was recorded using the output calculated by the ECG machine. Lead II QT intervals were manually measured and averaged. All ECGs were standard 12-lead resting ECG (25 mm/s paper speed, 10 mm/mV amplitude) and recorded using the Quinton® Q4500 Stress Test Machine–Quinto®

MedTrack® treadmill. For the entire cohort, all QT values were measured by a single observer (IG) using a standard ECG ruler with 20-ms scale marks. The end of the T wave was determined as previously described (Goldenberg, Moss, & Zareba, 2006). To evaluate the accuracy of the QT measurements, 37 ECG recordings were randomly chosen (explained below under sample size determination) for QT interval measurement by a second observer (YP). Bland–Altman plot with calculation of bias and limits of agreement was used to test differences between both observers.

Each QT interval was adjusted to heart rate by four commonly used formulae (Vandenberk et al., 2016):

1. Bazett: $QTcB = QT/RR^{1/2}$
2. Fridericia: $QTcFri = QT/RR^{1/3}$
3. Framingham: $QTcFra = QT + 0.154 (1 - RR)$
4. Hodges: $QTcH = QT + 0.00175 ([60/RR] - 60)$

QTc prolongation (ΔQTc) was determined by subtracting the QTc value of the preceding year from the current ECG, that is, the difference between every two consecutive visits. Thus, each subject had 3–6 QTc values (calculated with each formula and independent of the previous measurements) with 2–5 ΔQTc values.

1.4 | Outcome definition

QTc prolongation was defined based on the International Conference of Harmonization (ICH) guidelines (ICH expert working group the clinical evaluation of QT, QTc interval prolongation, & proarrhythmic potential for nonantiarrhythmic drugs E 2015, 2015), and subjects were classified accordingly (with each formula) into two groups:

1. Prolongers: A: At least one $\Delta QTc \geq 60$ msec vs. non-prolongers (all $\Delta QTc < 60$ msec).
B: At least one QTc measurement $\geq 25\%$ from baseline (to account for the potential effect of baseline QTc) vs. non-prolongers (all measurement without QTc prolongation of $\geq 25\%$).
2. Exceeders (at least one absolute QTc value ≥ 500 msec) vs. non-exceeders (all QTc < 500 msec).

Within-individual (absolute) QTc variability was expressed as the coefficient of variation (CV) (standard deviation divided by mean multiplied by 100).

1.5 | Sample size determination

Sample size was calculated based on a pilot study comprising the first 100 subjects, of whom 14% had at least one $\Delta QTcB \geq 60$ msec. Based on this prevalence, we calculated the final sample size with 5% margin of error and 95% confidence interval to be 186 subjects.

Sample size for the Bland–Altman analysis was performed using MedCalc® software bvba (version 18.6) based on Lu et al., (2016). The expected between-observer mean difference and standard deviation were 0 and 10 msec, respectively. The latter

was chosen to define a 95% confidence interval of 40 msec or 1 mm (ECG speed 25 mm/s): a value precise enough to be measured with the naked eye using an ECG ruler. Maximally allowed difference between observers was defined as 30 msec, the lowest Δ QTc limit described as being of clinical significance (ICH E2015, 2015). Accordingly, we calculated that a sample size of at least 34 ECG recordings would provide 80% power to assess between-observer agreement.

1.6 | Data analysis

Maximal Δ QTc and maximal QTc values were identified for each subject, with each formula, and defined as dependent variables for analysis. Confounders (comorbidities, medications, electrolytes, and number of annual visits) were referred to the visit at which the maximal values were recorded (e.g., maximal Δ QTc with confounders at visits to which the Δ value was calculated, and maximal QTc value with the corresponding visit). Heart rate and serum electrolyte variability were expressed as CV. Comparisons between groups were conducted using paired *t* tests or Mann-Whitney U tests for parametric and nonparametric analysis, respectively. Categorical variables were compared using Chi-square or Fisher's exact tests. Bland-Altman plot with calculation of bias and limits of agreement were performed to illustrate inter-observer differences. Multivariate analyses were employed to examine the associations between various confounders and prolonged QTc values: these included both logistic regression and Cox regression. The former accounted for the total number of measurements while in the latter subjects were censored by the outcome (QTcP as defined). In order to investigate whether age and heart rate have significant impact on the risk for QTc prolongation, further analysis was conducted in which the cohort was divided into quartiles. Finally, Kaplan-Meier analysis was employed to examine the rate of QTc change over time by baseline age and heart rate. Data are presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR) as appropriate for continuous variables and proportions for categorical variables. All analyses were two-tailed and a *p*-value $\leq .05$ was considered significant. Statistical analyses were performed using SPSS software (version 21 IBM®, SPSS® Inc).

2 | RESULTS

2.1 | Study cohort

One hundred eighty-eight participants (134 [71%] males, 54 [29%] females) with 801 resting ECG recordings were analyzed. Of them 54 (28.7%) had 3 and 4 measurements, 57 (30.3%) had 5 recordings and 23 (12.2%) had six consecutive measurements. Mean age at first ECG recording was 55 ± 12.8 years, and mean BMI was 26 ± 3.8 kg/m². Meantime interval between each recording was $12.2 (\pm 1.1)$ months, that is, each measurement represents one-year of follow-up. Baseline characteristics are presented in Table S1 in the supplementary data.

2.2 | Corrected QT interval

Mean uncorrected QT interval was 379 ± 25.6 msec with a mean heart rate (HRate) of 72 ± 11 beats per minute (bpm). Mean QT corrected with Bazett correction (QTcB) was 412 ± 20 msec. Females had non-significantly shorter uncorrected QT (375 ± 20 vs. 381 ± 27 msec, *p* = .094) with a higher heart rate (74 ± 9 vs. 70 ± 11 , *p* = .009), resulting in longer QTcB (416 ± 17 vs. 410 ± 21 msec, *p* = .03). Mean Δ QTcB was $(-1) \pm 11$ msec with mean maximal Δ QTcB of 28 ± 25 msec and maximal QTcB of 436 ± 29 msec.

With the three other correction formulae, mean QTcFri, QTcFra, and QTcH were identical: 400 ± 17 , 400 ± 16 and 400 ± 16 msec, respectively. Conversely, paired comparisons between mean QTcB and each of the other three demonstrated significant differences (*p* < .001, Table S2). Linear regression analysis confirmed that only Bazett correction was significantly correlated with heart rate (*r*² = .248, *p* < .001, Table S3).

2.3 | Prolongers vs. non-prolongers

With Bazett correction, 18/188 (9.6%) individuals showed at least one measurement with Δ QTcB ≥ 60 msec. Univariate comparisons between *prolongers* and *non-prolongers* (Table 1) demonstrated older age among the former (66 vs. 51.5 years old, *p* = .002) and higher heart rate difference between the two consecutive measurements (Δ HRate of 12.1 vs. 5.2, *p* = .007). *Prolongers* also had more ECG recordings (median of 5 vs. 4, *p* = .036). Logistic regression (Table 2) demonstrated that age and Δ HRate were significantly associated with Δ QTcB ≥ 60 msec (HR: 1.06, 95% CI: 1.02–1.1 and HR: 1.06, 95% CI: 1.02–1.12, respectively). No interaction was observed age at first measurement and the number of measurements. These two covariates were also significantly associated when analyzed using Cox regression (HR: 1.06, 95% CI: 1.02–1.1, *p* = .003 and HR: 1.05, 95% CI: 1.01–1.1, *p* = .016).

Using the other three formulae revealed lower rates of *prolongers*: 11/188 (5.9%), 9/188 (4.8%), and 7 (3.7%) for QTcFri, QTcFra, and QTcH, respectively. Univariate analyses demonstrated similar exposure rates to cardiovascular agents, QT-prolonging agents and serum electrolyte concentrations between *prolongers* and *non-prolongers*. Heart rate did not differ between groups (data not shown). Logistic regression showed that for all three other formulae, the only significant determinant of Δ QTc ≥ 60 msec was number of measurements, that is, years of follow-up (Table 3). Cox regression analysis demonstrated non-significant association between QTc prolongation ≥ 60 msec and Δ HRate. Age at first measurement was associated only with Framingham correction (HR: 1.1, 95%CI: 1.03–1.17, *p* = .004).

Kaplan-Meier analysis showed that mean time for QTcB prolongation ≥ 60 msec among individuals ≥ 54 years old vs. those <54 years old was 65.9 and 54.8 months, respectively (*p* = .009). Similarly, delta heart rate above median values demonstrated shorter mean time to QTcB prolongation (58.3 vs. 64.8 months, *p* = .01). Further analysis in which age at first measurement and Δ HRate were divided to quartiles demonstrated significant higher odds for QTcB prolongation

TABLE 1 QTc non-prolongers vs. prolongers and non-exceeders vs. exceeders using Bazett correction

	Non-prolongers	Prolongers	<i>p</i>	Non-exceeders	Exceeders	<i>p</i>
No.	170	18		183	5	
Median (Δ) QTc, (IQR)	23 (11, 35)	73 (63, 95)	<.001	433 (415, 450)	530 (505, 548)	<.001
Age, median (IQR), years	51.5 (44, 63)	66 (54.3, 73.8)	.002	53 (44, 64)	66 (64.5, 80)	.005
Female (%)	49 (28.8)	5 (27.8)	1.0	54 (29.5)	0	.324
Delta heart rate, mean (SD), beats/min	5.2 (10.1)	12.1 (10.7)	0.007	-	-	
Heart rate, mean (SD), beats/min	-	-		74 (65, 83)	89 (79, 99)	.020
Ischemic heart disease (%)	13 (7.6)	2 (11.1)	.641	17 (9.3)	0 (0)	1.0
Hypertension (%)	52 (30.6)	10 (55.6)	.038	59 (32.2)	3 (60)	.334
Diabetes mellitus (%)	20 (11.8)	0 (0)	.226	20 (10.9)	0 (0)	1.0
Dyslipidemia (%)	70 (41.2)	12 (66.7)	0.047	79 (43.2)	5 (100)	.017
Cardiovascular agents ^b (%)						
At baseline	22 (12.9)	7 (38.9)	.01	29 (15.8)	2 (40)	.191
At 2 ^b measurement ^c	2 (1.2)	0 (0)	1.0	-	-	
Diuretic use ^d (%)						
At baseline	4 (2.4)	1 (5.6)	.4	7 (3.8)	0 (0)	1.0
At 2 ^d measurement ^c	0 (0)	2 (11.1)	.009	-	-	
QTc prolonging agents ^e (%)						
At baseline	12 (7.1)	3 (16.7)	.161	14 (7.7)	2 (40)	.059
At 2 ^c measurement ^c	1 (0.6)	0 (0)	1.0	-	-	
Electrolytes, median (IQR)						
Serum potassium ^a , mEq/L	-0.1 (-0.2, 0.3)	0.1 (-0.3, 0.3)	.588	4.3 (4.1, 4.5)	4.2 (4.2, 4.4)	.782
Serum calcium ^a , mg/dl	0 (-0.2, 0.3)	0.1 (-0.1, 0.2)	.944	9.6 (9.3, 9.8)	9.7 (9.4, 9.8)	.728
# of Measurements, median (IQR)	4 (3, 5)	5 (3, 6)	.036	4 (3, 5)	6 (5, 6)	.004

^aData for prolongers vs. non-prolongers and exceeders vs. non-exceeders represents Δ and absolute values, respectively.

^b α -blockers, β -blockers, and calcium channel blockers.

^cParticipants with newly prescribed medications compared to previous ECG.

^dLoop and thiazide diuretics.

^eIsbister, & Page (2013).

among older age quartile (>65 years old: HR: 8.55, 95% CI: 1.63–44.98, $p = .011$). No interaction was observed between the two variables. Similar analysis for the other three formulae did not reveal any significant association.

2.4 | Rate of $\geq 25\%$ prolongation

Of the 18 patients with ≥ 60 ms prolongation using Bazett correction, only 5/188 (2.7%) demonstrated $\geq 25\%$ prolongation

compared to baseline. The other three QT correction formulae showed only 2/188 (1.1%) subjected with $\geq 25\%$ prolongation. Univariate analysis showed similar proportions of females in both groups (prolongers vs. non-prolongers) for all correction formulae [with Bazett: 1/5 (20%) vs. 53/183 (29%), $p = 1.0$]. Similarly to the results of absolute change, prolongers were older (66.4 vs. 55 years old, $p = .042$), showed a non-statistical significance higher Δ HRate (15.8 vs. 5.6, $p = .07$), and had more ECG recordings (median of 6 vs. 4, $p = .04$). Logistic regression showed that only the

TABLE 2 Multivariate analysis for *prolongers* and *exceeders* as dependent variable using Bazett correction

	p value	HR	95% CI
Prolongers			
Age at first measurement, years	.007	1.06	1.02–1.10
Δ Heart rate, beats/min	.025	1.06	1.02–1.12
Number of measurements	.079	1.57	0.95–2.60
Exceeders			
Age at first measurement, years	.040	1.15	1.01–1.30
Heart rate, beat/min	.556	0.97	0.88–1.07
Number of measurements	.026	5.01	1.21–20.78

number of measurements was significantly associated with Bazett QTcP $\geq 25\%$ (OR: 4.25, 95% CI: 1.02–17.78, $p = .047$). No significant interaction between the latter and age at first measurement was observed.

When using Fridericia, Hodges and Framingham corrections, age did not significantly differ between groups. However, the former two showed smaller Δ HRate among *prolongers* ($p = .033$ with each).

2.5 | Exceeders vs. non-exceeders

Five of 188 subjects (2.7%) demonstrated at least one measurement with QTcB ≥ 500 msec, of whom 4/5 were also *prolongers*. Univariate comparisons (Table 1) showed that *exceeders* were older (66 vs. 53 years, $p = .005$), had faster HRate (89 vs. 74 bpm, $p = .02$) and more ECG measurements (6 vs. 4, $p = .004$). Cox regression demonstrated age at first measurement and heart rate to be significantly associated with QTcB ≥ 500 msec (HR: 1.15, 95% CI: 1.02–1.29, $p = .02$ and HR: 1.08, 95% CI: 1.00–1.16, $p = .04$, respectively). Logistic regression showed that only age and number of measurements were associated with QTcB ≥ 500 msec (HR: 1.15, 95% CI: 1.01–1.3 and HR: 5.01, 95% CI: 1.21–20.78, respectively), with no interaction between the two. Importantly, lower rates of *exceeders* were demonstrated using the other three formulae: 2/188 (1.1%), 0/188 and 1/188 (0.5%) for QTcFri, QTcFra, and QTcH, respectively. Multivariate analysis for each formula showed that number of measurements was the only significant variable associated with QTc ≥ 500 msec (Table 3).

2.6 | QTc coefficient of variation

Median CV (IQR) was 4.3% (3.0, 6.3), 3.6% (2.5, 5.0), 3.6% (2.5, 4.8), and 3.5% (2.3, 5.0) for QTcB, QTcFri, QTcFra, and QTcH, respectively. For all four formulae, CV was positively associated with number of measurements ($p < .05$, Table 4). Linear regression showed that QTc CV was also significantly associated with age at the first measurement, heart rate coefficient of variation (Table S4 and Table S5 in supplementary data) but not with electrolyte variability or gender.

2.7 | Between-observer agreement

Mean between-observer difference in QT measurements was -1.35 ± 13.16 msec (Figure S1 in supplementary data). Limits of agreement using Bland-Altman plot were demonstrated to be between 24.44 and -27.14 with no proportional bias ($p = .55$).

3 | DISCUSSION

Our study demonstrates that nearly 10% of subjects routinely checked once a year manifested at least one clinically significant QTc prolongation during follow-up of 3 to 6 years. This finding was observed when using the Bazett correction, whereas the three other formulae demonstrated much lower rates. All QTc prolongations were independent of comorbidities, electrolyte abnormalities, or drug exposures and therefore are probably attributed to within-individual variability. We also found that more measurements (i.e., each reflecting one annual visit and hence longer follow-up) were associated with higher within-individual QTc variability. In daily practice, such prolongation could be easily attributed by a concerned physician to a particular concurrent drug (or drug combination). This concern is mostly based on post-marketing surveillance, data from case reports, cases series, and large retrospective studies which inherently cannot account for within-individual variability. Low within-individual QTc variability has been addressed in many studies mostly in the context of early drug development, in small cohorts of healthy subjects followed up for up to 30 days and under well-controlled conditions (Batchvarov et al., 2002; Malik, 2001; Malik, Färbom, Batchvarov, Hnatkova, & Camm, 2002), features that can hardly reflect this variability seen in daily practice.

TABLE 3 Multivariate analysis for *prolongers* as dependent variable using Fridericia, Framingham, and Hodges

Prolongers	QTc Fridericia			QTc Framingham			QTc Hodges		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age at first measurement, years	1.03	0.98–1.08	.249	1.10	1.02–1.19	.01	1.02	0.96–1.08	.557
Number of measurements	3.71	1.64–8.43	.002	3.77	1.52–9.38	.004	8.96	1.99–40.41	.004

	Slope	95% CI slope	Constant, msec	95% CI Constant	p value
QTcB ^a	0.5	0.1–0.9	2.7	1.1–4.3	.008
QTcFri ^b	0.4	0.2–0.7	2.1	0.8–3.4	.003
QTcFra ^c	0.4	0.2–0.7	1.9	0.7–3.1	.001
QTcH ^d	0.4	0.1–0.7	2.2	1.0–3.5	.009

^aBazett correction.

^bFridericia correction.

^cFramingham correction.

^dHodges correction.

TABLE 4 QTc coefficient of variation as function of number of measurements

The appropriate formula for correcting the QT interval to heart rate has been the subject of debate for many decades (Chan, Isbister, Kirkpatrick, & Dufful, 2007; Indik, Pearson, Fried, & Woosley, 2006; Van de Water, Verheyen, Xhonneux, & Reneman, 1989). This issue is again well-demonstrated in the present findings. Bazett, the most commonly used adjustment, has long been criticized for it is over- and under-correction given tachycardia or bradycardia, respectively (Indik et al., 2006). Indeed, mean QTc was significantly longer with Bazett compared to all three other formulae and was significantly dependent on heart rate. Accordingly, rates of *prolongers* differed by the correction formula used: Bazett resulted in the highest rate of *prolongers* (9.6%). Accordingly, Bazett correction incompletely adjusts the QT interval for heart rate and might result in clinically significant false prolongation of the QTc interval.

With regard to variability of absolute QTc values, within-individual variability was shown to be significantly dependent on the number of measurements, by all formulae. Bazett correction gave the highest rate of *exceeders* (2.7%) compared to the other three formulae. Taken together, Bazett results in QTc overestimation that may have clinical significance when values are close to the accepted upper limit of normal. In daily practice, physicians often encounter a prolonged QTc interval without having a previous recording to compare it to. Thus, Bazett overestimation might lead to unnecessary discontinuation of an agent suspected to be the cause, or to withholding of a necessary treatment due to a falsely prolonged QTc interval.

Several limitations to our findings were: our definition of prolonged intervals that was based on ICH guidelines. In the real world, a prolonged QTc is often a concern when exceeding 450 ms and 470 for men and women, respectively. Hence, our results might underestimate the true prevalence of subjects with a prolonged interval due to within-subject variability. In that regard, absolute change in QTc may also dependent on baseline QTc measurement. Therefore, we also defined QTc prolongation as a 25% increase in QTc compared to the baseline measurement. Of note, a 25% QTc prolongation was associated with older age and higher delta heart rate quartiles as shown in the univariate and Kaplan–Meier analysis. Nevertheless, accounting for these covariates in the multivariate model (both logistic and Cox regression) demonstrated non-significant association with some of the correction formulae (e.g., Fidericia and Hodges), with negligible contribution with

others (e.g., Framingham). Additional limitations are also noteworthy: determining the end of the T wave is subject to within- and between-observer variation and may have biased our results. To minimize these potential errors only subjects with clear T-wave morphology were included and between-observer agreement was tested and found acceptable. Conversely, our method does reflect daily practice in which physicians often deem an interval to be prolonged based on QT measurements using a ruler with 20-ms increments. This method allows the precision of 10 ms at best and as shown in Bland–Altman analysis and is well-reflected by the mean difference between observers. In addition, comorbidities and drug exposure on the days of ECG recordings were based on self-reports and hence subject to reporting bias. Finally, the study cohort was subjects of higher socioeconomic level attending their routine annual medical evaluation and probably under better routine medical care. Hence, our results cannot be generalized to other populations.

In conclusion, physicians often encounter significant QTc prolongation attributed to drug exposure. Our results show that these changes might only be background noise, due to within-individual variability over time rather than drug effect. As clinically significant variability was mainly seen with Bazett correction, in the presence of faster heart rates physicians should attempt to correct the QT using other formulae and be aware of the potential clinical consequences of using the former.

ACKNOWLEDGEMENTS

The authors thank Ms. Ella Arenbayev for her administrative assistance.

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REFERENCES

- Batchvarov, V. N., Ghuran, A., Smetana, P., Hnatkova, K., Harries, M., Dilaveris, P., ... Malik, M. (2002). QT-RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. *American Journal of Physiology Heart and Circulatory*

- Physiology*, 282, H2356–2363. <https://doi.org/10.1152/ajpheart.00860.2001>
- Briasoulis, A., Agarwal, V., & Pierce, W. J. (2011). QT prolongation and torsade de pointes induced fluoroquinolone: Infrequent side effects from commonly used medications. *Cardiology*, 120, 103–110. <https://doi.org/10.1159/000334441>
- Chan, A., Isbister, G. K., Kirkpatrick, C. M., & Dufful, S. B. (2007). Drug-induced QT prolongation and torsades de pointes: Evaluation of a QT nomogram. *An International Journal of Medicine*, 100, 609–615. <https://doi.org/10.1093/qjmed/hcm072>
- Goldenberg, I., Moss, A. J., & Zareba, W. (2006). QT interval: How to measure it and what is “normal”. *Journal of Cardiovascular Electrophysiology*, 17, 333–336. <https://doi.org/10.1111/j.1540-8167.2006.00408.x>
- Gueta, I., Loebstein, R., Markovits, N., Kamari, Y., Halkin, H., Livni, G., & Yarden-Bilavsky, H. (2017). Voriconazole-induced QT prolongation among hemato-oncologic patients: Clinical characteristics and risk factors. *European Journal of Clinical Pharmacology*, 73, 1181–1185. <https://doi.org/10.1007/s00228-017-2284-5>
- ICH expert working group the clinical evaluation of QT, QTC interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs E14. (2015). *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*. Retrieved from <https://www.ich.org/products/guidelines/efficacy/efficacy-single/article/the-clinical-evaluation-of-qtqt-interval-prolongation-and-proarrhythmic-potential-for-non-antiarrh.html>
- Indik, J. H., Pearson, E. C., Fried, K., & Woosley, R. L. (2006). Bazett and Fridericia QT correction formulas interfere with measurement of drug-induced changes in QT interval. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, 3, 1003–1007. <https://doi.org/10.1016/j.hrthm.2006.05.023>
- Isbister, G. K., & Page, C. B. (2013). Drug induced QT prolongation: The measurement and assessment of the QT interval in clinical practice. *British Journal of Clinical Pharmacology*, 76, 48–57. <https://doi.org/10.1111/bcp.12040>
- Lu, M. J., Zhong, W. H., Liu, X. Y., Miao, H. Z., Li, Y. C., & Ji, M. H. (2016). Sample size for assessing agreement between two methods of measurements by Bland-Altman method. *The International Journal of Biostatistics*, 12, <https://doi.org/10.1515/ijb-2015-0039>
- Malik, M. (2001). Problems of heart rate correction in assessment of drug-induced QT interval prolongation. *Journal of Cardiovascular Electrophysiology*, 12, 411–420. <https://doi.org/10.1046/j.1540-8167.2001.00411.x>
- Malik, M., Färbon, P., Batchvarov, V., Hnatkova, K., & Camm, A. J. (2002). Relation between QT and RR intervals is highly individual among healthy subjects: Implications for heart rate correction of the QT interval. *Heart*, 87, 220–228. <https://doi.org/10.1136/heart.87.3.220>
- Maljuric, N. M., Noordam, R., Aarts, N., Niemeijer, M. N., van den Berg, M. E., Hofman, A., ... Visser, L. E. (2015). Use of selective serotonin re-uptake inhibitors and the heart rate corrected QT interval in a real-life setting: The population-based Rotterdam Study. *British Journal of Clinical Pharmacology*, 80, 698–705. <https://doi.org/10.1111/bcp.12681>
- Straus, S. M. J. M., Sturkenboom, M. C. J. M., Bleumink, G. S., Dieleman, J. P., Lei, J. V. D., Graeff, P. A. D., ... Stricker, B. H. C. (2005). Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. *European Heart Journal*, 26, 2007–2012. <https://doi.org/10.1093/eurheartj/ehi312>
- Van de Water, A., Verheyen, J., Xhonneux, R., & Reneman, R. S. (1989). An improved method to correct the QT interval of the electrocardiogram for changes in heart rate. *Journal of Pharmacological and Toxicological Methods*, 22, 207–217. [https://doi.org/10.1016/0160-5402\(89\)90015-6](https://doi.org/10.1016/0160-5402(89)90015-6)
- van der Sijs, H., Kowlesar, R., Klootwijk, A. P., Nelwan, S. P., Vulto, A. G., & van Gelder, T. (2009). Clinically relevant QTc prolongation due to overridden drug-drug interaction alerts: A retrospective cohort study. *British Journal of Clinical Pharmacology*, 67, 347–354. <https://doi.org/10.1111/j.1365-2125.2008.03357.x>
- Vandenberk, B., Vandael, E., Robyns, T., Vandenberghe, J., Garweg, C., Foulon, V., ... Willems, R. (2016). Which QT correction formulae to use for QT monitoring? *Journal of the American Heart Association*, 5, e003264 <https://doi.org/10.1161/JAHA.116.003264>
- Viskin, S., Havakuk, O., & Schwaber, M. J. (2015). Pro-arrhythmic effects of noncardiac medications: Lessons from Macrolide Antibiotics. *Journal of the American College of Cardiology*, 66, 2185–2188. <https://doi.org/10.1016/j.jacc.2015.09.027>
- Wisniewska, B., Tylutki, Z., Wyszogrodzka, G., & Polak, S. (2016). Drug-drug interactions and QT prolongation as a commonly assessed cardiac effect- comprehensive overview of clinical trials. *BMC Pharmacology and Toxicology*, 17, 12. <https://doi.org/10.1186/s40360-016-0053-1>
- Yu, H., Zhang, L. I., Liu, J., Liu, Y., Kowey, P. R., Zhang, Y., ... Xia, Y. (2017). Acquired long QT syndrome in hospitalized patients. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, 14, 974–978. <https://doi.org/10.1016/j.hrthm.2017.03.014>

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Gueta I, Klempfner R, Markovits N, et al. Clinically significant incidental QTc prolongation is subject to within-individual variability. *Ann Noninvasive Electrocardiol*. 2020;25:e12699. <https://doi.org/10.1111/anec.12699>