Circulation

ORIGINAL RESEARCH ARTICLE

Determination and Interpretation of the QT Interval

Comprehensive Analysis of a Large Cohort of Long QT Syndrome Patients and Controls

BACKGROUND: Long QT syndrome (LQTS) is associated with potentially fatal arrhythmias. Treatment is very effective, but its diagnosis may be challenging. Importantly, different methods are used to assess the QT interval, which makes its recognition difficult. QT experts advocate manual measurements with the tangent or threshold method. However, differences between these methods and their performance in LQTS diagnosis have not been established. We aimed to assess similarities and differences between these 2 methods for QT interval analysis to aid in accurate QT assessment for LQTS.

METHODS: Patients with a confirmed pathogenic variant in *KCNQ1*(LQT1), *KCNH2*(LQT2), or *SCN5A*(LQT3) genes and their family members were included. Genotype-positive patients were identified as LQTS cases and genotype-negative family members as controls. ECGs were analyzed with both methods, providing inter- and intrareader validity and diagnostic accuracy. Cutoff values based on control population's 95th and 99th percentiles, and LQTS-patients' 1st and 5th percentiles were established based on the method to correct for heart rate, age, and sex.

RESULTS: We included 1484 individuals from 265 families, aged 33±21 years and 55% females. In the total cohort, $QT_{Tangent}$ was 10.4 ms shorter compared with $QT_{Threshold}$ (95% limits of agreement±20.5 ms, $P<0.0001$). For all genotypes, $QT_{Tangent}$ was shorter than $QT_{Threshold}$ ($P<0.0001$), but this was less pronounced in LQT2. Both methods yielded a high inter- and intrareader validity (intraclass correlation coefficient >0.96), and a high diagnostic accuracy (area under the curve >0.84). Using the current guideline cutoff (QTc interval 480 ms), both methods had similar specificity but yielded a different sensitivity. QTc interval cutoff values of $QT_{Tangent}$ were lower compared with $QT_{Threshold}$ and different depending on the correction for heart rate, age, and sex.

CONCLUSION: The QT interval varies depending on the method used for its assessment, yet both methods have a high validity and can both be used in diagnosing LQTS. However, for diagnostic purposes current guideline cutoff values yield different results for these 2 methods and could result in inappropriate reassurance or treatment. Adjusted cutoff values are therefore specified for method, correction formula, age, and sex. In addition, a freely accessible online probability calculator for LQTS (www.QTcalculator.org) has been made available as an aid in the interpretation of the QT interval.

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Clinical Perspective

What Is New?

- Long QT syndrome (LQTS) can be a challenging diagnosis, partly because the optimal method for QT assessment is not unequivocally established.
- This has large implications for the accuracy of a LQTS diagnosis, which impacts patient management including both noninvasive and invasive treatment as well as possible diagnostic miscues.
- In this study, we present the results of a large cohort of LQTS patients and controls with a comprehensive evaluation of QTc cutoff values specified for QT interval measurement method, including corrections for heart rate, age, and sex.
- A freely accessible online probability-calculator of LQTS (www.QTcalculator.org) has been made available for use by physicians and allied professionals worldwide.

What Are the Clinical Implications?

- With this study we show that the 2 methods for manual QT interval assessment, the tangent and threshold method, both have high diagnostic accuracy and validity, but need different cutoff values for use in practice.
- With the development of a probability-calculator for LQTS (www.QTcalculator.org), including instructions for the assessment of the QT interval, we provide additional guidance in accurate decision-making in LQTS and in the prevention of inappropriate reassurance or treatment.

The congenital long QT syndrome (LQTS) is an inheritable cardiac arrhythmia disorder with a prevalence of 1 per 2000 persons, and is associated with sudden cardiac death attributable to malignant ventricular arrhythmias.[1,2] Prolongation of the QT interval corrected for heart rate (QTc interval) is the hallmark of the clinical diagnosis of LQTS,[3] mirroring a prolonged repolarization caused by mutations in genes encoding key cardiac ion channels. Besides a prolonged QTc interval, there are 2 more cornerstones for diagnosing LQTS: (1) the presence of clinical and electrocardiographic features that are associated with LQTS and (2) the presence of a confirmed pathogenic variant.[3] Importantly, all 3 elements in the diagnosis of LQTS bear clinical challenges. For example, there is a large variability between readers in the assessment of the QT interval and its correction for heart rate,[4,5] whereas the risk for malignant arrhythmias and sudden cardiac death is considered to be dependent on the magnitude of prolongation of the QTc interval.[6] Furthermore, symptom interpretation as either benign or malignant remains difficult[7,8] and distinguishing pathogenic variants from innocuous rare variants can be very complex, especially in the current era of DNA panels and whole-genome sequencing.[9] Importantly, therapeutic decisions such as lifestyle advice, the introduction of β-blocker therapy, and invasive therapy such as implantable defibrillators and left cardiac sympathetic denervation are based on these 3 elements.[3]

Current guidelines focus on QTc interval cutoff values in the diagnosis of LQTS. A QTc interval >480–500 ms on repeated ECGs is considered diagnostic for LQTS, whereas a value >460–480 ms on repeated ECGs in the presence of unexplained syncope is sufficient to make the diagnosis. Both criteria suggest a need for treatment.[3,10] It should be noted that these cutoff QTc-interval values for diagnosing LQTS are not age- or sex-specific, although age and sex are known modulating factors of the QTc interval.[11]

Despite the importance of the degree of QT interval prolongation, no standard method for its measurement and correction for heart rate has been unequivocally established.[3] Although the QT interval can be assessed automatically, LQTS experts advocate manual measurements[12] using either the tangent or threshold method.[5] When both methods were applied to ECGs of non-LQTS patients, the tangent method consistently measures shorter QT intervals than the threshold method.[13–15] The differences between both methods in LQTS patients is not known, but interestingly, world-renowned LQTS experts measure the QTc interval in LQTS patients with a variation up to 70 ms.[4] This could be attributable to the use of different methods. Besides, in many LQTS studies, including large gene-association studies, the use of method for QTc interval assessment is not even mentioned.[6,16–18] It is therefore conceivable that there will be variability of a similar scale in the assessment of the QTc interval in these studies.

Our aim was to provide insights into the differences between the tangent and threshold method, their validity, and their method-specific cutoff values in diagnosing LQTS, by performing a comprehensive analysis in a large cohort of LQTS patients and controls.

METHODS

The data, analytic methods, and study materials are available to other researchers for purposes of reproducing the results. Study materials are securely housed at the Academic Medical Center in Amsterdam and can be made available after completion of a research proposal to the authors, including a data use agreement.

Study Design, Setting, and Population

A multicenter retrospective cohort study was performed including families of patients with a confirmed pathogenic variant in *KCNQ1* (LQTS type 1, LQT1), *KCNH2* (LQTS type 2, LQT2), and *SCN5A* (LQTS type 3, LQT3) genes. LQT1-3 are the three most common LQTS-types and account for ≈95%

of all genotype-positive LQTS patients.[2] Patients with LQT1, LQT2, and LQT3 were identified as cases and their genotype-negative family members as controls. LQTS type was defined as a confirmed pathogenic variant in the coding genes of either *KCNQ1*, *KCNH2*, or *SCN5A* detected using either direct Sanger sequencing of regions of interest, single-stranded conformational polymorphism analysis, or denaturing high-performance liquid chromatography, followed by sequencing of only those fragments with abnormal profiles. Family information (cosegregation) or functional analysis was needed to classify a variant as pathogenic.[19,20] All LQTS patients and their family members seen in the Academic Medical Center in Amsterdam, The Netherlands, were included. Because LQT3 is less prevalent than LQT1 and LQT2, the LQT3 cohort was enhanced by adding LQT3 patients seen in the University Hospital of the Ludwig-Maximilians-University in Munich, Germany. Inclusion was closed in December 2016. The study was approved by the Academic Medical Center Review Board, and informed consent of the individuals was waived as this study used retrospective data from regular care.

Data Collection and Management

ECGs and Additional Data

From all subjects, the first recorded 12-lead resting ECG was sought. When the first ECG was not available, a later ECG was used, preferably when the patient was not on medication. Data on filter settings, paper speed, and sensitivity were collected. ECGs recorded in the presence of a ventricular paced rhythm, arrhythmias (eg, atrial fibrillation, multiple premature ventricular complexes), or conduction disorders (eg, complete left or right bundle-branch block, 2:1 atrioventricular block) were excluded from the analysis because these elements complicate accurate QT assessment. In addition, ECGs of patients using class III antiarrhythmic drugs, patients with (concomitant) cardiomyopathies, or ECGs that were insufficient because of very low quality were also excluded. All ECGs were digitalized and blinded for patient characteristics.

Patient characteristics were collected including date of birth, sex, reason for genetic testing, and presence of cardiac events at baseline. At time of the ECG recording the presence of β-blocker therapy was also documented.

Measurements

To avoid differences in outcome based on the use of different leads or different P-QRS-T complexes, one electrophysiologist (P.P.) first marked 3 consecutive complexes in a period without a pronounced sinus arrhythmia. Preferably, lead II was used for analyses, and alternatively lead V5. When both lead II and V5 were deemed unsuitable, 1 of the remaining leads was chosen. If it was not possible to mark 3 consecutive complexes, ≤2 complexes were chosen. No particular effort was made to select ECGs or complexes with the longest or the shortest QT intervals. Therefore, more intermediate and borderline QT intervals were selected for this study, aiming at a better understanding of the importance of QT-measurement methods for intermediate and borderline QT intervals. Additional assessment of the PQ interval, QRS duration, and RR interval/heart rate was performed to provide a reference for the results on the QT interval. The PQ interval was selectively excluded in case of an atrial rhythm, an atrial paced rhythm, low voltage P waves, or fusion of P waves with the preceding T or U wave hampering meaningful PQ measurement.

To determine inter- and intrareader validity for the measurements, 3 readers (S.V., B.N., and K.L.) with experience in analyzing ECGs of LQTS patients independently assessed the time scale per ECG for calibration and subsequently determined the PQ interval, QRS duration, RR interval/heart rate, and the QT interval in the marked complexes using on-screen digital calipers in public available software (Image J version 1.45 k, National Institute of Mental Health, Bethesda, MD). The QT interval was measured from the onset of the QRS complex to the end of the T wave using both the tangent method ($QT_{Tangent}$) and the threshold method ($QT_{Threshold}$). The second component of the T wave (T2) was always included in the QT interval, and a U wave was always excluded from QT interval analyses. The end of the T wave by the tangent method was defined as the point where the tangent on the steepest point of the terminal limb of the T wave intersects with the isoelectric baseline (Figure 1). For the threshold method, the end of the T wave was defined as the intersection of the terminal limb of the T wave with the isoelectric baseline (Figure 1). For the threshold method, when a U wave interrupted the T wave before it returned to baseline, the end of the QT interval was defined as the nadir between the T and U wave. The isoelectric baseline was obtained by connecting the TP segment (segment between T wave and P wave) of the complex in which the QT interval was measured with the TP segment of the preceding complex. The RR interval between the measured and the preceding complex was used to obtain the QTc interval with both the Bazett[21] $\left(\frac{QT_{(ms)}}{\sqrt{RR_{(sec)}}}\right)$ and Fridericia[22] $\left(\frac{QT_{(ms)}}{\sqrt[3]{RR_{(sec)}}}\right)$ correction formulas for the main analyses. Additionally, for LQTS-diagnosis cutoff values are determined for the Framingham,[23] Rautaharju,[24] and Hodges[25] formulas. The 3 measured complexes were averaged per reader.

All 3 readers analyzed the complete set of ECGs, with an interval of ≥1 week between the tangent and the threshold method for individual ECGs to prevent the possible influence of memorizing marker settings. To assess intrareader validity, 1 of the readers (S.V.) additionally reanalyzed $QT_{Tangent}$ and $QT_{Threshold}$ in a randomly selected set of 10% of all ECGs from each genotype-subgroups (controls, LQT1, LQT2, and LQT3), after an interval of ≥1 week.

Data Verification

The measurements of the 3 readers were verified by comparing the heart rate measurements. Because we assumed that the heart rate measurements should be identical between the readers with similar time calibration, ECGs with a heart rate difference of ≥5 beats per minute had to be reanalyzed by the reader who was the outlier (with the assumption of erroneous time calibration).

Statistical Analysis

All data were entered into an IBM SPSS statistics database (IBM Corp, Released 2011, IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY) and analyzed with R version 3.4.3 (The Foundation for Statistical Computing, Vienna, Austria). Baseline

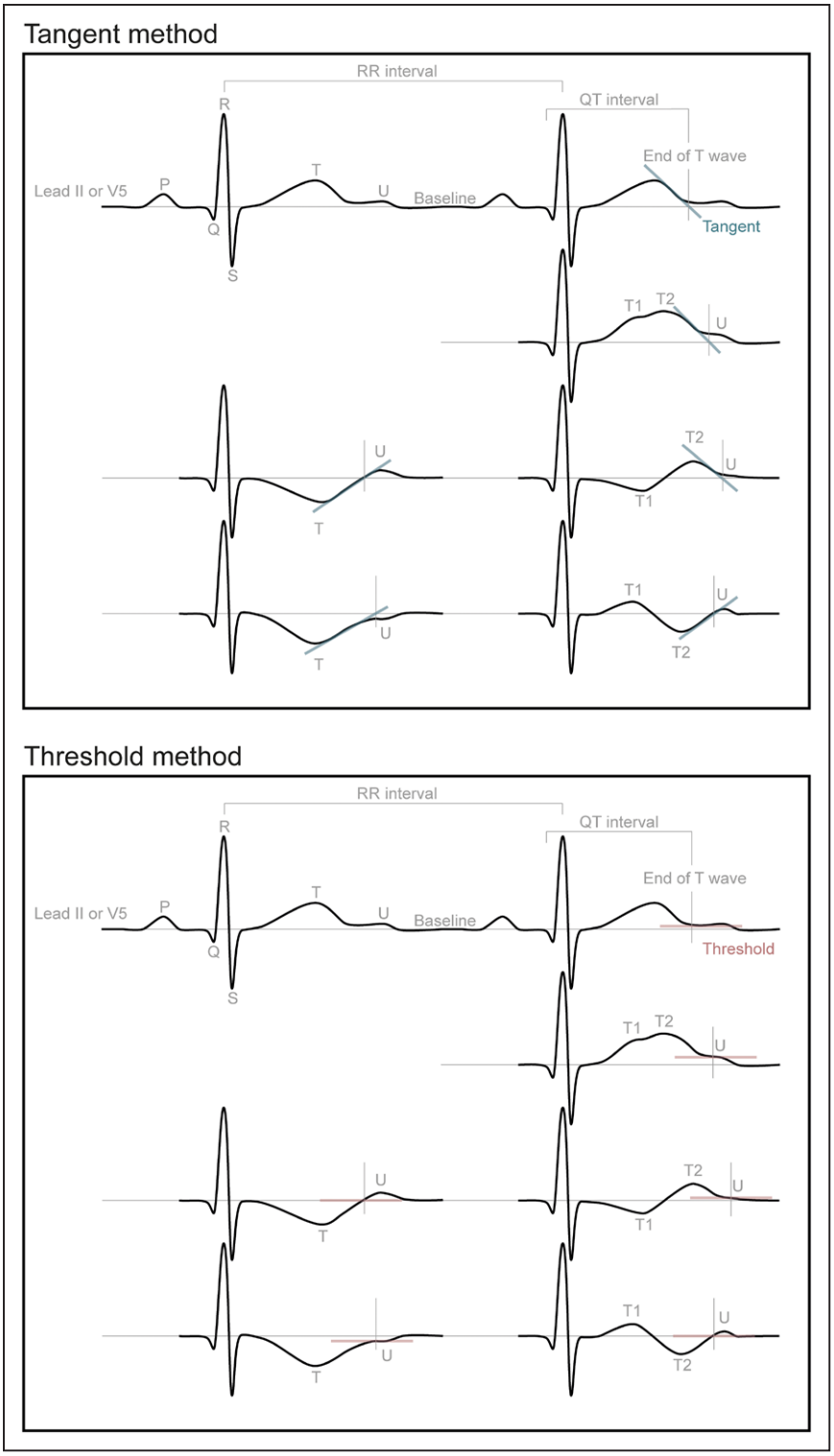

Figure 1. Illustration of the tangent and the threshold method.
The second component of the T wave (T2) was included, and the U wave was excluded from QT interval analyses.

and ECG characteristics were presented as numbers (percentage, %) for categorical variables and mean (±SD) for continuous variables, stratified by genotype (ie, control, LQT1, LQT2, and LQT3). Mean ECG parameters (ie, PQ interval, QRS duration, and heart rate), $QT_{Tangent}$, and $QT_{Threshold}$ were presented as averaged measurements of the 3 readers together. Stratification by genotype was performed on the patients who were genotyped, because particular T wave ECG patterns have been associated with specific underlying genotypes.[26–28] Differences between controls, LQT1, LQT2, and LQT3 were tested using a χ^2 test or a Fisher Exact test for categorical variables as appropriate, and with a 1–way ANOVA test for continuous variables.

To put the differences between $QT_{Tangent}$ and $QT_{Threshold}$ in perspective, the repeatability for PQ interval, QRS duration, and heart rate were presented including all ECGs based on the average measurements of the 3 readers. Repeatability of

the ECG parameters PQ interval, QRS duration, and heart rate, as well as differences between $QT_{Tangent}$ and $QT_{Threshold}$, were analyzed using Bland-Altman analyses[29] and were compared using a paired samples *t* test. The differences between $QT_{Tangent}$ and $QT_{Threshold}$ were additionally stratified by genotype.

Including all ECGs, inter- and intrareader validity was expressed as the intraclass correlation coefficient for multiple measurements based on a 2-way agreement (inter reader validity) and consistency (intrareader validity) model according to Cicchetti[30] and Fleiss.[31] Bland-Altman analyses[29] were performed to assess bias and 95% limits of agreement.

Receiver-operating characteristic curves were constructed and the area under the curve was provided for the identification of LQTS by $QTc_{Tangent}$ and $QTc_{Threshold}$ for both the Bazett and Frederica correction formulas. Sensitivity and specificity were calculated for specific QTc interval cutoff values[3,32,33] for both methods.

A normalized distribution of QTc intervals for LQTS patients (LQT1-3 together and separate) and controls was provided for $QTc_{Tangent}$ and $QTc_{Threshold}$ corrected by both the Bazett and Fridericia formula based on the number of patients, mean, and SD per group. Probability plots were constructed for QTc intervals corrected by both the Bazett and Fridericia formula to represent percentiles for LQTS patients and controls. The normalized distributions and probability plots were stratified by age and sex: (1) children <12 years, (2) males ≥12 years, and (3) females ≥12 years. The age of 12 years was chosen to separate children from adults, because the average onset of puberty is approximately around this age.[34] Children <12 years were not stratified by sex, because there are no significant sex differences in QTc interval in prepubertal children.[11] Based on the distributions, rounded cutoff values were presented based on the 95th and 99th percentile of the controls and the 1st and 5th percentile of the LQTS patients using the Bazett, Friderica, Framingham, Rautaharju, and Hodges formulas.

Sampling uncertainty was quantified with 95% confidence intervals (CI) and *P* values. $P<0.05$ was considered to be statistically significant.

RESULTS

Population Characteristics

From a total of 1577 individuals who were eligible for the study, 6% had to be excluded mainly because of rhythm and conduction disorders as well as for technical errors. The remaining 1484 individuals were included in the analysis. The flowchart of the inclusion is shown in Figure I in the online-only Data Supplement.

The included 1484 individuals originated from 265 different families and had a mean age of 33±21 years at time of the ECG. There was a slight female predominance (55%). Table 1 shows the characteristics of the individuals stratified by genotype. The controls were somewhat older compared with the LQTS-patients, but there was an equal distribution of sex in all the four genotype-subgroups.

Table 1. Baseline Characteristics of the Patients by Genotype

	Controls n=592	LQT1 n=301	LQT2 n=370	LQT3 n=138	*P* Value
No. of families, n	141	115	96	44	NA
Age at ECG, y, mean (±SD)	39 (±20)	29 (±22)	29 (±21)	30 (±20)	<0.001
Female sex, n (%)	311 (53)	176 (58)	209 (56)	75 (54)	0.351
Proband, n (%)	0 (0)	81 (27)	71 (19)	34 (26)	NA
Beta-blocker therapy at ECG, n (%)	18 (4)	37 (14)	53 (17)	9 (7)	<0.001
Symptomatic at diagnosis, n (%)	2 (0.3)	23 (8)	18 (5)	7 (5)	<0.001

ECG Parameters, $QTc_{Tangent}$, and $QTc_{Threshold}$

ECG-parameters for the 4 subgroups stratified by genotype are shown in Table 2. Please note that 83 LQTS patient family members of the total of 1484 individuals were not genetically tested and could therefore not be divided into a genotype subgroup. Hence, 1401 individuals were stratified based on genotype (ie, controls. LQT1, LQT2, and LQT3). There was no statistically significant difference between the genotype subgroups for heart rate. The PQ interval ($P=0.001$) and QRS duration ($P<0.001$) were significantly different between the genotypes, where LQT3-patients had the longest PQ interval (149±30 ms) and QRS duration (87±17 ms). As expected, both the QT and the QTc interval were longer in LQT1, LQT2, and LQT3 patients compared with controls.

Table 2. Baseline ECG Characteristics

	Controls n=592	LQT1 n=301	LQT2 n=370	LQT3 n=138	*P* Value
PQ, ms (±SD)	148 (±24)	145 (±29)	142 (±25)	149 (±30)	0.001
QRS, ms (±SD)	84 (±13)	79 (±13)	78 (±13)	87 (±17)	<0.001
Heart rate, bpm (±SD)	73 (±19)	74 (±20)	76 (±22)	73 (±23)	0.126
QT-interval					
Tangent, ms (±SD)	367 (±37)	411 (±56)	415 (±60)	408 (±71)	<0.001
Threshold, ms (±SD)	379 (±38)	422 (±57)	421 (±61)	418 (±69)	<0.001
$QTc_{Tangent}$					
Bazett, ms (±SD)	399 (±26)	447 (±40)	457 (±42)	435 (±44)	<0.001
Fridericia, ms (±SD)	387 (±23)	434 (±38)	442 (±42)	425 (±49)	<0.001
$QTc_{Threshold}$					
Bazett, ms (±SD)	412 (±25)	459 (±39)	464 (±41)	447 (±42)	<0.001
Fridericia, ms (±SD)	400 (±23)	445 (±39)	448 (±42)	436 (±47)	<0.001

LQTS indicates long QT.

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Repeatability of ECG Parameters and Differences Between $QT_{Tangent}$ and $QT_{Threshold}$

Including all the ECGs of the 1484 individuals, there was a small systematic error in the repeatability for the ECG-parameters (eg, PQ interval, QRS duration, and heart rate). In addition, $QT_{Tangent}$ was 10.4 ms shorter compared with $QT_{Threshold}$ with a 95% limits of agreement in a range of 20.5 ms (P<0.0001). QT interval measurements by genotype subgroup also showed a shorter $QT_{Tangent}$ compared to $QT_{Threshold}$ in all groups (P<0.0001 for all groups). Measurements in LQT2 patients had the lowest difference between the 2 methods but a higher variability compared with the other subgroups. Bland-Altman plots for the differences between $QT_{Tangent}$ and $QT_{Threshold}$ for all ECGs and for each genotype subgroup are shown in Figure II in the online-only Data Supplement, together with a description of the repeatability of the other ECG parameters.

Interreader and Intrareader Validity for ECG Parameters, $QT_{Tangent}$, and $QT_{Threshold}$

Table I in the online-only Data Supplement shows the interreader validity for the ECG parameters and the QT interval measured with the tangent and threshold method. For the ECG parameters, there was very high agreement between readers, with a small systematic error. For both $QT_{Tangent}$ and $QT_{Threshold}$ there was also a high agreement ($QT_{Tangent}$ intraclass correlation coefficient >0.98, $QT_{Threshold}$>0.96) and a small systematic error (ranging for $QT_{Tangent}$ 1–8 ms and $QT_{Threshold}$ 2–15 ms). Both methods had a 95% limits of agreement ranging from ±20ms to ±30ms.

Table II in the online-only Data Supplement shows the intrareader validity, which was also high for all the ECG-parameters and both $QT_{Tangent}$ (intraclass correlation coefficient =0.99) and $QT_{Threshold}$ (intraclass correlation coefficient =0.99). The systematic error for both the $QT_{Tangent}$ and $QT_{Threshold}$ was 4 ms, with a 95% limits of agreement of approximately ±20 ms.

$QTc_{Tangent}$ and $QTc_{Threshold}$ in Diagnosing LQTS

The discriminating value of $QTc_{Tangent}$ and $QTc_{Threshold}$ in diagnosing LQTS is shown in Figure III in the online-only Data Supplement. For the Bazett correction, both methods had a similarly high area under the curve of 86% and 85%, respectively. Correction by Fridericia yielded a similar area under the curve compared with Bazett.

Using the current guideline-based QTc interval cutoff value of 480 ms for the diagnosis of LQTS, Bazett-correction showed a similar specificity for $QTc_{Tangent}$ and $QTc_{Threshold}$ (100% versus 99%, respectively) but a higher sensitivity for $QTc_{Threshold}$ (19% versus 26%). Using the Fridericia formula, there were similar findings for the specificity ($QTc_{Tangent}$ 100% and $QTc_{Threshold}$ 100%) and sensitivity ($QTc_{Tangent}$ 13% and $QTc_{Threshold}$ 16%).

$QTc_{Tangent}$ and $QTc_{Threshold}$ in Diagnosing LQTS Stratified by Age and Sex

Figure 2 shows the normalized distributions of both the Bazett- and Fridericia-corrected $QTc_{Tangent}$ and $QTc_{Threshold}$ in LQTS patients and controls stratified by age and sex. The group of children <12 years of age included 216 LQTS patients and 83 controls. In the group aged ≥12 years, 242 LQTS patients and 237 controls were male, and 348 LQTS patients and 271 controls were female. For all groups stratified by age and sex, there was a considerable overlap for both the Bazett-corrected QTc intervals and the Fridericia-corrected QTc intervals between LQTS patients and controls. The normalized QTc interval distributions for the 4 genotype subgroups stratified by age, sex, QT interval measuring method, and correction formula are shown in Figures IV and V in the online-only Data Supplement. There were no statistically significant differences by genotype.

In Figures 3 and 4, QTc intervals corrected with the Bazett and Fridericia correction formula, respectively, are plotted separately for LQTS patients and controls in ascending order with corresponding percentiles shown on the horizontal axis (probability plots). Using these plots, a measured QTc interval can be evaluated for the likelihood that this specific QTc interval is from a LQTS patient or a control.

Rounded cutoff values for the diagnosis of LQTS based on the 95th and 99th percentiles of the control population and the 1st and 5th percentile of the LQTS patients are provided in Table 3, for 5 methods to correct for heart rate.

In Figures VI and VII in the online-only Data Supplement the sensitivity, specificity, and misclassification (false negatives and false positives) for 4 different clinical cutoffs (ie, 480 ms, QTc intervals used for screening, 99th percentile of the controls and Youden's index) are shown stratified by age, sex, QT interval measuring method, and correction formula.

Website: www.QTcalculator.org

The application of the presented knowledge base was translated to a dedicated new website, www.QTcalculator.org (screenshot in Figure 5) for free use by physicians and allied professionals worldwide. With this website, a provided QT and RR interval or heart rate is the starting input for the calculator. Because of the impact of the measurement method (tangent or threshold), the age of the patient (<12 years or ≥12years), sex (>12 years:

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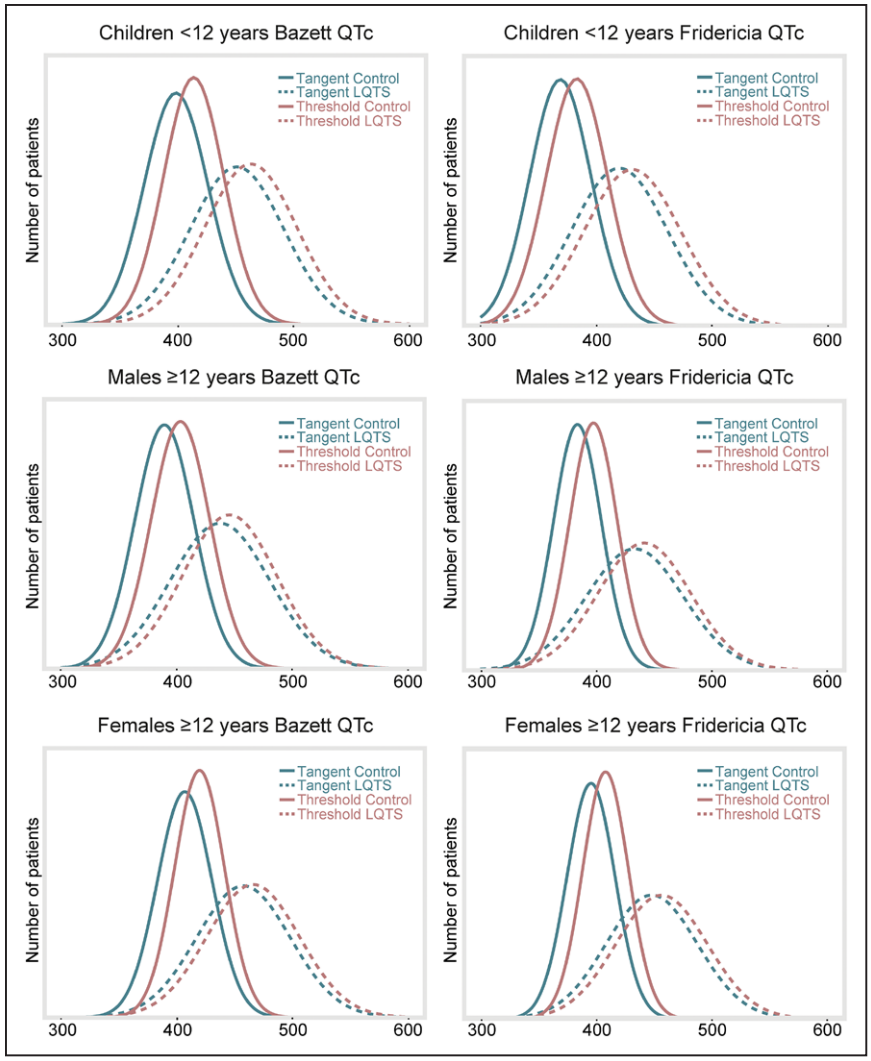

Figure 2. Normalized distributions of $QTc_{Tangent}$ and $QTc_{Threshold}$ using Bazett correction formula (3 left panels) and Friderica correction formula (3 right panels) for controls and LQTS patients in 3 groups stratified by age and sex.

males or females), and the correction formula for heart rate (ie, Bazett, Fridericia, Framingham, Rautaharju and Hodges), these elements also need to be specified. Subsequently, the calculator produces the probability score in percentiles, providing the user with a measure of the likelihood that the calculated QTc interval belongs to a LQTS patient or a non-LQTS patient based on the normalized data from the current study. Additional assistance is provided on the website, including instructions for the assessment of the QT interval.

DISCUSSION

Main Findings

The present study is the first to analyze the QT interval using both the tangent and threshold method in a large cohort of LQTS patients and their family members. We found that measuring the QT interval by the tangent method results in considerably shorter QT intervals compared with the threshold method, and that the extent of the shortening is genotype dependent (probably influenced by T wave morphology). Both methods have a high inter- and intrareader validity, and provide a good discrimination between LQTS patients and controls based on the QTc interval. When QTc interval cutoff values from the most recent guidelines were used, both methods had a similar specificity for LQTS diagnosis, but yielded different sensitivities depending on the method used for the heart rate correction. Furthermore, our study is the first to present reliable cutoff values to distinguish normal, borderline, and prolonged QTc intervals for different heart rate correction formulas.

Current Clinical Practice

Over the past decade, many efforts have been made to increase the awareness for LQTS, a treatable but potentially lethal syndrome. However, this increased awareness brought along the pitfall of incorrect QTc-interval assessment and misinterpretation of the normal distribution of QTc values, which contributed to under- and overdiagnosis, inappropriate distress or reassurance, inappropriate noninvasive and inva-

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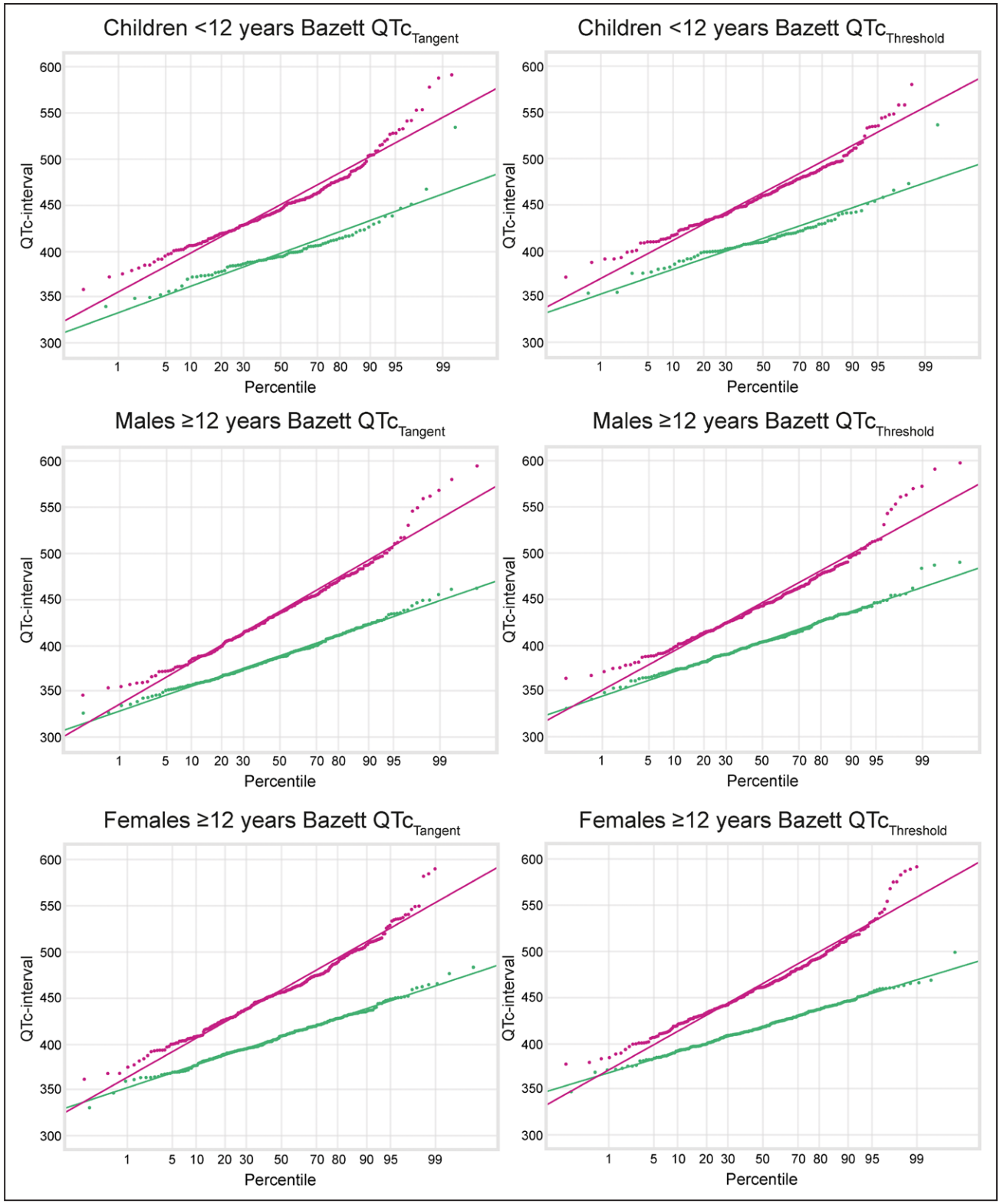

Figure 3. Probability plot for $QTc_{Tangent}$ (3 left panels) and $QTc_{Threshold}$ (3 right panels) using Bazett's correction formula in 3 groups stratified by age and sex.

QTc intervals are plotted on the *y* axis for controls (green) and LQTS patients (pink). The *x* axis indicates the Gaussian percentiles, based on the rank of the observation within its category. If the points follow roughly a straight line, the distribution is considered Gaussian, as is the case in the current data (where only the extreme values show deviation from a normal Gaussian distribution). Note that in the children aged <12 years, a non-LQTS individual has a QTc interval >500 ms. This individual received an ECG on the day of birth.

Table 3. Cutoff QTc Interval Values Based on the Rounded 95th and 99th Percentiles of the Control Population and 1st and 5th Percentiles of the LQTS Population, by Age and Sex for 5 Different Correction Methods

Sample	Tangent Method					Threshold Method				
	Bazett	Fridericia	Framingham*§	Rautaharju†§	Hodges‡§	Bazett	Fridericia	Framingham*§	Rautaharju†§	Hodges‡§
Children <12 y										
95th Control	440	400	390	390	430	450	410	400	400	440
99th Control	480	440	400	400	450	480	450	410	410	450
1st LQTS	380	340	250	250	370	390	360	270	270	370
5th LQTS	400	360	280	280	380	410	370	290	290	390
Males ≥12 y										
95th Control	430	420	420	430	420	450	430	440	450	430
99th Control	450	440	440	450	430	470	460	460	460	450
1st LQTS	360	360	330	340	360	370	370	330	340	370
5th LQTS	370	370	350	360	370	390	380	360	370	390
Females ≥12 y										
95th Control	450	430	420	420	430	460	440	440	440	440
99th Control	460	440	450	450	440	470	460	450	450	450
1st LQTS	380	380	340	340	380	390	390	340	340	390
5th LQTS	400	390	360	360	390	410	400	370	370	400

*Framingham correction method [QT+0.154(1−RR)][23] with RR interval in seconds.

†Rautaharju correction method [QT−0.185(RR−1)+*k*][24] with RR interval in seconds and *k*=+0.006 s for males and *k*=+0 s for females. This method is not validated for children, *k*=+0 s was chosen in this group.

‡ Hodges correction method [QT+1.75(HR−60)].[25]

§These correction formulas were originally not developed in a pediatric population.

LQTS indicates long QT syndrome.

sive interventions, and significant morbidity.[35] Previous work has shown that the majority of physicians worldwide, including many cardiologists, do not correctly recognize a prolonged QT interval when present.[4] Remarkably, even world-renowned LQTS experts measure the QTc interval with a variation up to 70 ms.[4] So even when the QT interval should be measured from the beginning of the QRS complex to the end of the T wave and must be corrected for the heart rate, this seemingly innocuous definition is fraught with problems.[36]

Previous Studies

Manual measurements of the tangent and threshold method have been compared head to head in only a limited number of studies and only in non-LQTS patients.[13–15] These studies describe a shorter $QT_{Tangent}$ compared with $QT_{Threshold}$, with an absolute mean difference ranging from 9–27 ms, with a low mean interreader difference ranging from 10–13 ms for $QT_{Tangent}$ and 12–19 ms for $QT_{Threshold}$. The mean intrareader difference was described in 1 study,[14] ranging from 3–7 ms for $QT_{Tangent}$ and 4–5 ms for $QT_{Threshold}$. It should be noted that in neonatal and infant non-LQTS patients, QT interval measurements have a lower inter- and intrareader validity[37,38] when compared with adult non-LQTS patients. In this study, performed in mostly LQTS adults and older children, the inter- and interobserver validity was also higher compared with neonatal and infant non-LQTS patients. Unfortunately, there are no studies on the comparison of $QT_{Tangent}$ to $QT_{Threshold}$ in this specific age group of neonates and infants.

In our total cohort, we found an absolute mean difference between $QT_{Tangent}$ and $QT_{Threshold}$ of 10.4 ms, which is in line with the lowest differences in the previously published studies.[14] This result, and the minimal inter- and intrareader differences, could be explained by the readers in our study who were trained in measuring QT intervals in LQTS patients and by the fact that we preselected the complexes that had to be measured. In addition, we analyzed the averaged QT interval and heart rate of 3 consecutive complexes in a single lead from a 12-lead ECG, rather than measuring only 1 complex in several leads[15] or an averaged complex using orthogonal leads.[13]

Effect of T Wave Morphology and a Prominent U Wave

Several studies have shown that the morphology of the T wave has an effect on the QT interval, and that this effect is different depending on the method chosen for measuring the QT interval. Two decades ago, it was found that an increased height of the T wave confers a

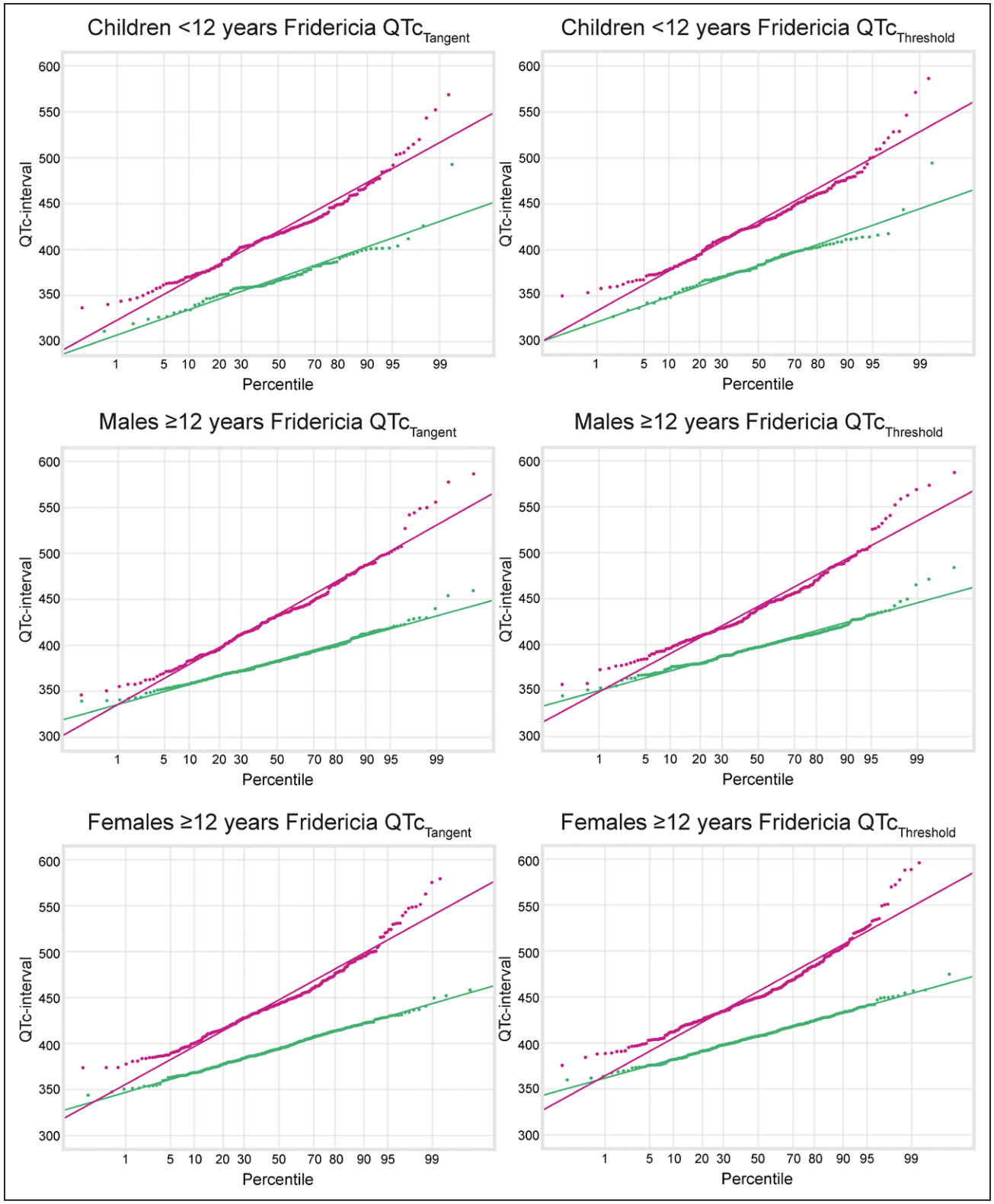

Figure 4. Probability plot for $QTc_{Tangent}$ (3 left panels) and $QTc_{Threshold}$ (3 right panels) using Fridericia correction formula in 3 groups stratified by age and sex.

QTc intervals are plotted on the *y* axis for controls (green) and LQTS patients (pink). The *x* axis indicates the Gaussian percentiles, based on the rank of the observation within its category. If the points follow roughly a straight line, the distribution is considered Gaussian, as is the case in the current data (where only the extreme values show deviation from a normal Gaussian distribution). Note that in the children aged <12 years, a non-LQTS individual has a QTc interval >500 ms. This individual received an ECG on the day of birth.

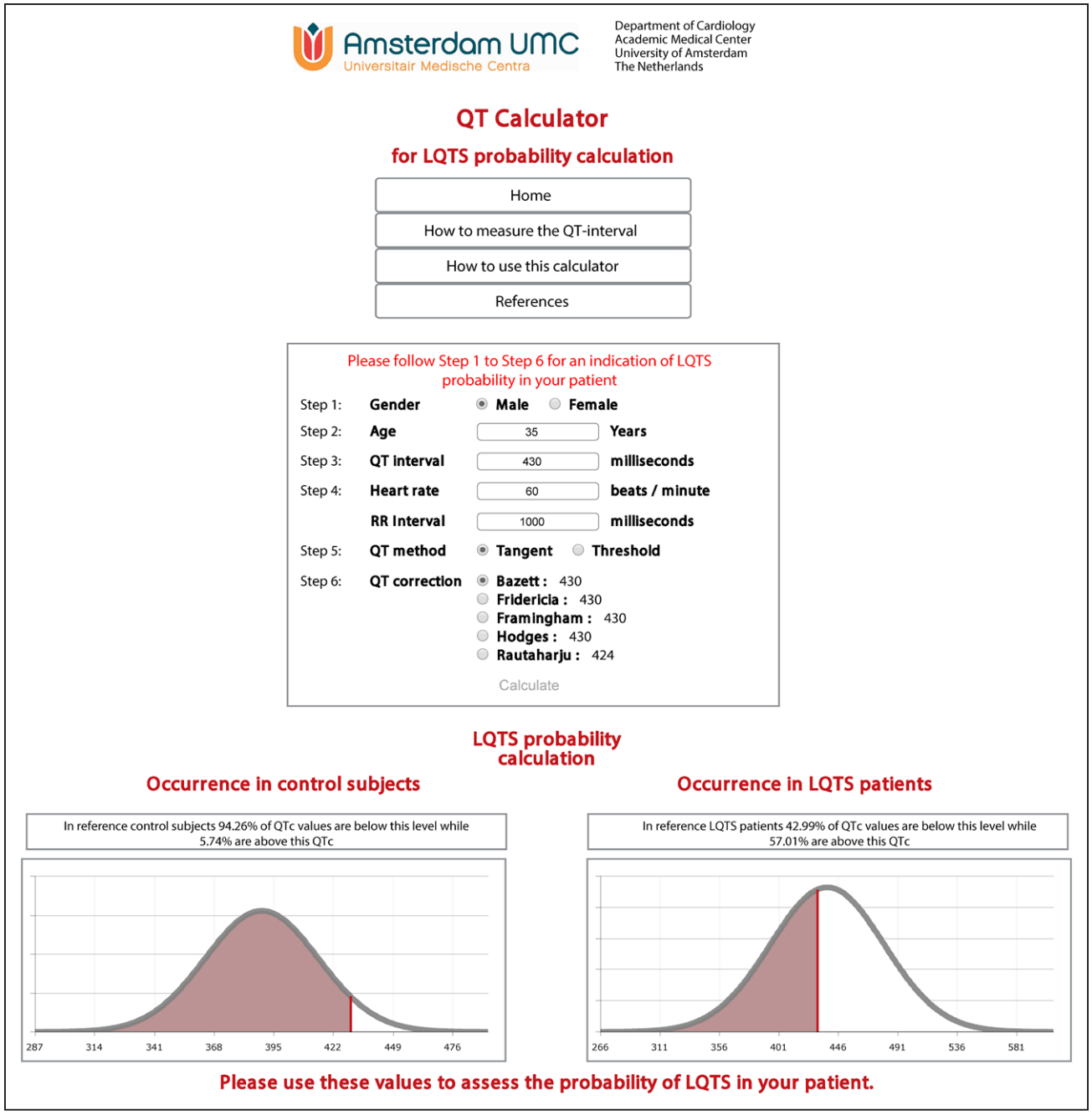

Figure 5. Sreenshot from www.QTcalculator.org.

tendency toward an increasing $QT_{Threshold}$.[39] In the presence of flattened and prolonged T wave, as during hypoglycemia, $QT_{Tangent}$ is longer compared with $QT_{Threshold}$ with an absolute mean difference of 13 ms.[13] When a prominent U wave is present, as during quinine-induced QT interval prolongation, $QT_{Tangent}$ is also longer compared with $QT_{Threshold}$.[14]

LQT2 patients can have low amplitude, moderately delayed or notched T waves,[26–28] which could explain the smaller difference between $QT_{Tangent}$ and $QT_{Threshold}$ in our study and the more pronounced variation between both methods when these ECGs were compared with ECGs of LQT1 patients, LQT3 patients, and controls.

Discriminating LQTS Patients From Controls

We found that with trained observers, both $QT_{Tangent}$ and $QT_{Threshold}$ have a high inter- and intrareader validity and provide a good discrimination between LQTS patients and controls. However, it is important to keep in mind that $QT_{Tangent}$ is consistently shorter compared with $QT_{Threshold}$, and that correction for heart rate by Bazett or

Fridericia results in a different effect on the QTc interval. Different cutoff values may therefore be detrimental in discriminating normal from prolonged QTc intervals. These cutoff values should preferably be based on the method chosen to measure the QT interval, the formula used for the correction for heart rate, age, and sex. We suggest cutoff values based on the rounded 99th percentiles of the control population as shown in Table 3 to conservatively diagnose LQTS. Based on these cutoff values, a prolonged QTc interval on repeated 12-lead ECGs in the absence of secondary causes or QT interval prolongation may be sufficient to diagnose LQTS. In contrast, there are LQTS patients with rather short QTc intervals, as exemplified in this study and previously by others.[2] It might well be that (multiple) modifier genes result in short, instead of long, QTc intervals in these patients with a pathogenic LQTS mutation. Whether this results in a compromised repolarization reserve in these patients, or in a protective repolarization reserve, is currently unknown. Still, their offspring may display prolonged QTc intervals when the mutation is inherited, indicating the value of a LQTS mutation status in these patients with a normal, or rather short, QTc interval at 50% risk of LQTS.

For further guidance on discriminating LQTS patients from non-LQTS patients, the newly developed website www.QTcalculator.org can be used, which contains the data of the present study and enables interactive QT-interval evaluation based on a probability score in percentiles. With this website we aim to provide additional guidance to the community for accurate decision making in a LQTS evaluation and in the prevention of inappropriate reassurance or treatment.

Strengths and Limitations of the Study

We analyzed a very large number of ECGs of LQTS patients and controls, including difficult T-wave morphologies and ECGs with diverse paper speed, gain, noise, and quality, which resulted in a real-life approach. However, our study was limited to retrospective data, which meant that an ECG off β-blocker therapy, was not always available for inclusion.

The included LQTS patients were all diagnosed based on a variant in the proband (first affected family member) that cosegregated through a pedigree which makes the pathogenicity of these variants secure. By using genotype-negative family members as controls, we have selected a well-defined control population. Moreover, as compared with the general population, our controls may be more likely to have QT interval modifier genes, and as a consequence may have even longer QT intervals compared with random healthy controls. Population controls are thus more likely to have even lower QT intervals and it might therefore be reasonable to expect that the sensitivity and specificity would be even better if LQTS patients were compared with random healthy controls. However, considering the absence of included individuals from the general population, the cutoff values suggested in this study are more relevant in a setting with a high (eg, 50%) a priori probability for LQTS. Hence, these data give the possibility to assess the likelihood of the carrier-status in an individual patient at risk for LQTS.

The readers in our study were trained, so the results of our study are particularly relevant for physicians trained in measuring QT intervals. However, the use of our figures for assessment of the end of the T wave should result in an easy and accurate QTc evaluation also for less experienced readers, as we have shown previously in medical students for the tangent method.[40] In addition, because we made no particular effort to select ECGs or complexes with the longest QT intervals, we included more intermediate and borderline QT intervals. Therefore, discriminating abnormal from normal is more challenging because obviously long (or short) QT intervals are easier to recognize and to interpret as such. For this reason, diagnosing LQTS, particularly in borderline cases, should preferably be performed by experts in the field.

Conclusions

The length of the QT interval is different depending on the method used for its assessment. The tangent method measures a shorter QT interval compared with the threshold method, yet both the tangent and threshold method have a high validity. However, for diagnostic purposes current guideline cutoff values yield different results for these 2 methods and may result in inappropriate reassurance or treatment. Adjusted cutoff values are therefore provided, specified for method, correction formula, age, and sex. In addition, a freely accessible online probability-calculator for LQTS (www.QTcalculator.org) has been made available to provide further guidance in appropriate QT interval assessment for users worldwide.

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Disclosures

Dr Wilde is a member of the scientific advisory board of LivaNova. However, LivaNova did not participate in this study in any way. The remaining authors report no conflicts.

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