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Genotype-Specific QT Correction for Heart Rate and the Risk of Life Threatening Cardiac Events in Adolescents with the Congenital Long-QT Syndrome

Alon Barsheshet, MD^{*}, Derick R. Peterson, PhD[†], Arthur J. Moss, MD^{*}, Peter J. Schwartz, MD[‡], Elizabeth S. Kaufman, MD[§], Scott McNitt, MS^{*}, Slava Polonsky, MS^{*}, Jonathan Buber, MD^{*}, Wojciech Zareba, MD, PhD^{*}, Jennifer L. Robinson, MS^{*}, Michael J. Ackerman, MD^{||}, Jesaia Benhorin, MD[¶], Jeffrey A. Towbin, MD[#], G. Michael Vincent, MD^{**}, Li Zhang, MD^{**}, and Ilan Goldenberg, MD^{*}

^{*} Cardiology Division, University of Rochester Medical Center, Rochester, New York

[†] Department of Biostatistics and Computational Biology, University of Rochester Medical Center, Rochester, New York

[‡] Department of Lung, Blood and Heart, University of Pavia, Pavia; Department of Cardiology, Fondazione IRCCS Policlinico S. Matteo, Pavia; Laboratory of Cardiovascular Genetics, IRCCS Istituto Auxologico Italiano, Milan, Italy; Department of Family and Community Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia

[§] Heart and Vascular Research Center, MetroHealth Campus of Case Western Reserve University, Cleveland, Ohio

^{||} Department of Pediatrics, Division of Pediatric Cardiology, Mayo Clinic, Rochester, MN

[¶] Department of Cardiology, Tel Aviv University, Tel Aviv, Israel

[#] Department of Pediatrics, University of Cincinnati Children's Hospital, Cincinnati, Ohio

^{**} LDS Hospital, Salt Lake City, Utah

Abstract

Background—A prolonged QT interval corrected for heart rate (QTc) is a major risk factor in patients with the long-QT syndrome (LQTS). However, heart rate-related risk in this genetic disorder differs among genotypes.

Objective—We hypothesized that risk-assessment in LQTS patients should incorporate genotype-specific QT correction for heart rate.

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Address for correspondence: Alon Barsheshet, MD, Heart Research Follow-up Program, Box 653, University of Rochester Medical Center, Rochester, NY 14642, Tel: 585-276-5228; Fax: 585-273-5283, alon.barsheshet@heart.rochester.edu.

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Methods—The independent contribution of four repolarization measures (the absolute QT interval, Bazett's, Fridericia's, and Framingham's correction formulae) to the risk of aborted cardiac arrest or sudden cardiac death during adolescence, before and after further adjustment for the RR interval, was assessed in 727 LQT1 and 582 LQT2 patients. Improved QT/RR correction was calculated using a Cox model, dividing the coefficient on $\log(RR)$ by that on $\log(QT)$.

Results—Multivariate analysis demonstrated that in LQT1 patients 100 msec increments in the absolute QT interval were associated with a 3.3-fold increase in the risk of life-threatening cardiac events ($p=0.020$), and 100 msec decrements in the RR interval were associated with a further 1.9-fold increase in the risk ($p=0.007$), whereas in LQT2 patients, resting heart rate was not a significant risk factor ($HR=1.11$; $p=0.51$; p -value for heart rate $\times$ genotype interaction = 0.036). Accordingly, analysis of an improved QT correction formula showed that patients with the LQT1 genotype required a greater degree of QT correction for heart rate (improved $QTc=QT/RR^{0.8}$) than LQT2 patients (improved $QTc=QT/RR^{0.2}$).

Conclusions—Our findings suggest that risk stratification for life-threatening cardiac events in LQTS patients can be improved by incorporating genotype-specific QT correction for heart rate.

Keywords

Aborted cardiac arrest; Heart rate; Long QT syndrome; QT correction; Risk factor; Sudden cardiac death

Introduction

The identification of genes associated with the congenital long-QT syndrome (LQTS) has had a major impact on understanding the molecular basis for ventricular arrhythmias and sudden cardiac death (SCD) in young patients without structural heart disease.¹ Numerous advances have been made in the identification of risk factors for cardiac events in LQTS patients.^{2–6} However, there remains a substantial challenge to explain the widely observed genotype-phenotype variability of this genetic disorder.

A prolonged QT interval corrected for heart rate (QTc) is a major risk factor for cardiac events in LQTS patients,^{4–5, 7–8} and is usually assessed using the exponential Bazett⁹ and Fridericia¹⁰ correction formulae. However, heart rate-related risk of cardiac events in LQTS patients has been shown to occur in a gene-specific manner.^{3, 11–12} Specifically, 82% of the lethal arrhythmic episodes in LQT1 patients, who harbor mutations that impair the I_{Ks} current, are associated with exercise and faster heart rates, whereas in LQT2 patients, in whom I_{Ks} current is normal, symptoms occur mostly during night or with arousal triggers.¹¹ This may be due to the fact that the repolarizing current I_{Ks} activates during increased heart rate, and is essential for QT interval adaptation during tachycardia.¹³ Thus, it has been shown that faster heart rates are associated with increased arrhythmic risk in LQT1 patients^{12, 14} and it is possible that RR interval provides incremental prognostic information to mere assessment of QTc as currently calculated by QT correction formulae particularly in LQT1 patients with fast resting heart rates.

The present study was designed to evaluate whether risk stratification for life-threatening cardiac events in LQTS patients who carry the common LQT1 and LQT2 genotypes should incorporate a genotype-specific QT correction for heart rate.

Methods

Study Population

The study population was drawn from subjects enrolled in the International Long-QT Syndrome Registry,² for whom follow-up data were available from age 10 through 20 years. Genetic testing was performed on 3,374 members of 443 families enrolled in the registry, and identified 1309 patients with the LQT1 (727 patients from 165 proband-identified families with the *KCNQ1* mutations) and LQT2 (582 patients from 176 proband-identified families with the *KCNH2* mutations) genotypes. Patients with a mutation in both *KCNQ1* and *KCNH2* genes were not included in the current analysis. Mutations were identified by standard genetic tests.^{15–16} Informed consent for genetic and clinical studies was obtained from all subjects.

Data collection and management

For each patient, data on personal and family history, cardiac events, and therapy were systematically recorded at each visit or medical contact. Clinical data were recorded on prospectively designed forms and included patient and family history and demographic, electrocardiogram (ECG), therapeutic, and cardiac event information. Upon enrollment in the Long QT Registry, a 12-lead ECG was obtained from each patient. From the first recorded ECG, the duration of the QT and RR intervals were assessed from lead II. The observer who made the QT and RR measurements was blinded to clinical status of patients. Follow-up data regarding β -blocker therapy included the starting date, type of β -blocker, and discontinuation date in case it occurred. Among patients who died, the usage of a β -blocker before death was determined retrospectively. The reported analyses used the LQTS analytic database version 18.

End point

The primary end point of the study was time to aborted cardiac arrest ([ACA] requiring external defibrillation as part of the resuscitation) or LQTS-related SCD (death abrupt in onset without evident cause, if witnessed, or death that was not explained by any other cause if it occurred in a nonwitnessed setting), whichever occurred first, from age 10 through 20 years. We focused on life threatening events during adolescence, which is a time period with a high event risk among the LQTS population as demonstrated previously.⁷

Repolarization and heart rate measures

We analyzed the risk associated with the following four repolarization measures: the absolute QT interval (Model 1); the QT interval corrected for heart rate using Bazett's formula (Model 2: $QTc[b] = QT/RR^{1/2}$); the QT interval corrected for heart rate using Fridericia's formula (Model 3: $QTc[f] = QT/RR^{1/3}$); and the QT interval corrected for heart rate using the linear Framingham formula¹⁷ (Model 4: $QTc[fram] = 0.154(1 - RR) + QT$). To evaluate the incremental prognostic contribution of heart rate to the analyzed repolarization parameters among carriers of each genotype, all models were analyzed before- (Models A) and after- (Models B) further adjustment for the RR interval.

Assessment of an improved QT correction for heart rate

Bazett⁹ and Fridericia¹⁰ derived their QT correction formulae by regressing $\log(QT)$ on $\log(RR)$ in a population of normal subjects, and observing that the slope was $-1/2$ and $-1/3$, respectively. These analyses result in the following log-transformed formulae: $\log(QTc(b)) = \log(QT) - 1/2\log(RR)$; and $\log(QT(f)) = \log(QT) - 1/3\log(RR)$. We fit a Cox model that included both $\log(QT)$ and $\log(RR)$. If Bazett's formula were optimal for risk stratification among LQT1 and LQT2 genotype carriers, the estimated coefficient on $\log(RR)$ should

equal $-1/2$ times that on $\log(QT)$; if Fridericia's formula were to provide optimal risk stratification, then the estimated coefficient on $\log(RR)$ would be $-1/3$ times that on $\log(QT)$. But neither Bazett's nor Fridericia's correction formula was specifically designed for risk stratification based on a specific endpoint, and it is possible that improved correction for heart rate might differ, depending on the intended use of the correction formula.

Using this methodology we also estimated an "improved" QT correction for heart rate among carriers of each genotype, by using the derived coefficients from the $\log(QT)$ and $\log(RR)$ model, using the following formula: $QTc_{[new]} = QT/RR^\alpha$ ($\alpha = -\beta_{\log(RR)}/\beta_{\log(QT)}$). By "improved," we refer here to risk stratification for SCD or ACA.

Statistical analysis

The clinical characteristics of study patients by genotype were compared using the chi-square test and the Fisher's exact test for categorical variables, and the t-test or the Mann-Whitney-U test for continuous variables.

Cox proportional hazards regression models were used to assess the independent contribution of each of the four repolarization measures, with and without further adjustment for the RR interval, to the development of ACA or SCD during follow-up in LQT1 and LQT2 patients. Prespecified covariates included in each of the models were: syncope (defined as transient loss of consciousness that was abrupt in onset and offset), treatment with β -blockers, and gender (male age 10–15 years). The development of syncope and the administration of β -blocker therapy from age 10 through 20 years in an affected individual were evaluated in a time-dependent manner. We checked the proportional hazards assumption and found insufficient evidence of any violations of proportional hazards ($p > 0.05$ for each predictor interacted with time) after allowing gender to interact with age, since this particular violation of the proportional hazards assumption has already been well documented in our prior work.^{6–7} In a secondary analysis we standardized all QTc measures to have the same unit, analyzed hazard ratios (HR) per standard deviation (SD) of QTc and reported these data in the supplementary appendix.

To assess and compare the discriminatory ability of the models among carriers of each genotype, we calculated Harrell-Kremers generalized c-index of concordance¹⁸ (<http://mayoresearch.mayo.edu/mayo/research/biostat/upload/80.pdf>) for each of the time-dependent adjusted Cox models (without including RR in the models), and compared this to the c-index based on replacing QTc by QTc(new).

Grouped jackknife estimates of standard errors were compared with the standard large-sample estimates assuming independence in order to determine whether adjusting inferences for the potential dependencies due to family membership appeared necessary.¹⁹ A 2-sided $p < 0.05$ significance level was used for hypothesis testing. The statistical software used for the analyses was SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Baseline clinical and ECG characteristics and cardiac events during follow-up in carriers of the LQT1 and LQT2 genotypes are shown in Table 1. Gender distribution and the frequency of a family history of a LQTS-related SCD were similar in the 2 genotype groups. Baseline heart rates and the corrected QT intervals were similar among LQT1 and LQT2 patients, whereas the absolute QT interval was significantly longer among LQT2 patients as compared with LQT1 patients. The baseline RR and QT intervals were normally distributed in both LQT1 and LQT2 patients (Figure 1).

Association between repolarization measures and outcome before further adjustment for the RR interval

Multivariate analysis showed that the exponential Bazett formula was the only correction method that independently predicted the risk of life-threatening events among LQT1 patients, whereas among LQT2 patients all analyzed QT correction formulae exhibited a similar association with outcome (Table 2A). Thus, among LQT1 patients 100 msec increments in QTc(b) were associated with a significant 2.8-fold increase in the risk of life threatening cardiac events, whereas among LQT2 patients 100 msec increments in QTc(b), QTc(f) and QTc(fram) were associated with a similar (2.1–2.2 fold) increase in the risk of ACA or SCD (Table 2A).

Association between repolarization measures and outcome after further adjustment for the RR interval

When the RR interval was included as an additional covariate in each of the 4 models, the effects of heart rate were shown to be significantly different between LQT1 and LQT2 patients (Table 2B).

In LQT1 patients, each of the 4 repolarization measures was demonstrated to be a more powerful (>3-fold risk increase) and significant predictor of outcome in the models that included the RR interval compared with the respective models that did not include heart rate as a covariate. Multivariate analysis in LQT1 patients showed that 100 msec increments in the absolute QT interval were associated with a 3.3-fold increase in the risk of ACA or SCD ($p=0.020$), and 100 msec decrements in the RR interval were associated with a further 1.9-fold increase in the risk ($p=0.007$; Table 2B). Further adjustment for heart rate improves risk stratification for LQT1 patients, compared with currently used QT correction formulae.

In LQT2 patients, the risk associated with each repolarization measure was similar before and after adjustment for heart rate, and the RR interval was not a significant predictor of outcome in any of the models (Table 2B). Further adjustment for heart rate does not improve risk stratification for LQT2 patients, compared with currently used heart-rate corrected QT formulae.

Similar results were found when we standardized all QTc measures to have the same unit (standard deviation of each QT corrected formula) before running the Cox models as reported in the supplementary appendix (Tables 1S and 2S).

A significant heart rate x genotype interaction was shown in the adjusted model that included the absolute QT and RR intervals (Table 2B). This finding indicates that the heart rate associated risk is significantly greater in LQT1 patients ($HR = 1.88$) as compared with LQT2 patients ($HR = 1.11$; p -value for heart rate x LQT1/LQT2 interaction = 0.036).

Genotype-specific QT correction for heart rate

The ratio of the estimated coefficients on $\log(QT)$ and $\log(RR)$ in the Cox models were different for LQT1 vs. LQT2 patients (Table 3). In LQT1 patients, the ratio of the estimated coefficients was about 0.8, significantly different from the ratio implied by the correction of either Bazett (0.5) or Fridericia (0.33), neither of which sufficiently corrects for RR. In LQT2 patients, the ratio of the estimated coefficients on $\log(RR)$ and $\log(QT)$ was about 0.2 (Table 3). This was not statistically significantly different from the ratio implied by either Bazett's (0.5) or Fridericia's formula (0.33), though it is obviously closer to Fridericia than to Bazett. Thus, although we have insufficient evidence to reject any of the currently used QTc formulae for LQT2 patients, Fridericia's (and the Framingham) correction appears

slightly superior to Bazett's, and the data hints that all might slightly over-correct for heart rate among LQT2 patients.

The differences in the c-indices between models based on various QTc measures are relatively small in absolute terms, but QTc(new) is the best measure overall; wstatistically significant (Supplementary data, Table 3s). The mean (SD) values of QT and the various versions of QTc, stratified by whether or not ACA/SCD was observed, are presented in Table 4. QTc(new) appears better separated as compared with other correction formulae. Among potential dichotomizations of QTc(new), a threshold of 550ms resulted in the best model fit (the highest c-index) for predicting life threatening events.

Discussion

Several important clinical implications emerge from the current study of LQTS patients: 1) resting heart rate is an independent predictor of life-threatening cardiac events in LQT1, but not LQT2 patients, with a statistically significant difference in heart rate-related risk between genotypes; 2) current formulae that correct the QT interval duration for heart rate have important limitations for risk assessment in LQT1 patients; and 3) risk stratification for life-threatening cardiac events in LQTS patients may be improved by incorporating a genotype-specific correction of the QT interval for heart rate.

The identification that genes responsible for LQTS encode different ion channels involved in the control of repolarization has led to important advancements in current knowledge regarding genotype-phenotype correlation in hereditary arrhythmogenic disorders. Data from the International LQTS Registry have shown that life-threatening arrhythmias in LQTS patients occur under specific circumstances and in a gene-specific manner.¹¹ It has been shown that, despite the fact that LQT1 and LQT2 patients harbor mutations that affect the potassium channels, triggers for life-threatening cardiac events among carriers of these 2 genotypes are distinctly different. Patients with the LQT1 genotype have been consistently reported to have a high frequency of arrhythmic events during activities that are associated with increased sympathetic activity and faster heart rates, such as vigorous exercise and swimming, whereas patients with the LQT2 genotype have been shown to be at a relatively low risk during exercise.^{11, 20–22} The difference in heart rate-related risk between genotypes may reflect that different potassium currents are involved in these two LQTS genotypes. I_{Ks} shortens ventricular repolarization with fast heart rates and catecholamines; in LQT1, there is a reduction in this compensatory response. Fast heart rates have been shown to lead to accumulation of I_{Ks} , even in the absence adrenergic stimulation.¹³ Thus, impaired I_{Ks} accumulation in LQT1 patients, as a result of malfunction of channels containing a mutant subunit, may contribute to reduced adaptation of action potential duration to increasing heart rates. This concept is supported by an experimental model for LQT1, in which I_{Ks} blockade greatly enhances the probability of torsade de pointes in the presence of catecholamines,²³ and by the fact that LQT1 patients have an exaggerated QTc interval prolongation during physical activity.²⁴ Our findings are consistent with previous observations regarding the effect of impaired I_{Ks} function on the relationship between heart rate and the duration of ventricular repolarization in LQT1 patients. However, in contrast to previous studies that evaluated the QT – RR relationship during exercise testing,^{24–25} we have shown that increasing resting heart rate is an independent risk factor for life-threatening cardiac events in LQT1 patients. In addition, Schwartz et al.¹² and Brink et al.¹⁴ have previously reported that resting heart rate plays a significant modulating role on the risk for cardiac events among carriers of a specific KCNQ1 mutation (A341V); the present study extends these findings to a wide range of KCNQ1 mutation carriers.

Importantly, although the Bazett's correction formula was identified in the present study as the best predictor of life-threatening events among known formulae for LQT1 patients, our data suggest that currently available QT correction for heart rate do not provide sufficient risk-assessment among carriers of the LQT1 genotype. We have shown that risk-assessment among carriers of this genotype can be improved by incorporating a genotype-specific QT correction formula that assumes a more linear relationship between the duration of ventricular repolarization and heart rate than that provided by QTc(b) or QTc(f). Our data demonstrate a significant heart rate x genotype interaction effect, indicating that the risk associated with resting heart rate is significantly different between LQT1 and LQT2 patients. Thus, in LQT2 patients, in whom I_{Ks} function is not affected, a QTc exponential formula of $QT/RR^{0.2}$ appears to describe accurately the relationship between heart rate and ventricular repolarization, whereas in LQT1 patients risk stratification is improved by using a much stronger $QT/RR^{0.8}$ correction formula. All models in the present study were adjusted for baseline and time-dependent risk factors and showed that 100msec increase in QTc [new] was associated with 2.9-fold ($p=0.004$) and 2.1-fold ($p=0.013$) increased risk for ACA/SCD among LQT1 and LQT2 patients respectively, in addition to the effects of gender, time dependent syncope, and beta blockers.

When a baseline ECG is assessed in a non-genotyped LQTS patient, we suggest using Bazett's correction formula; however, an important implication for a patient who has been diagnosed as a carrier of the LQT1 genotype would be that the RR interval provides incremental prognostic information to mere assessment of QTc by Bazett's correction formula. Thus, we recommend using the improved QT correction formulae when the specific genotype is known. It should be noted that any given value of QTc means something different for each correction formula as the scales are not identical. When using the new correction formulae, a threshold of QTc (new) of 550 ms was associated with the best model fit for predicting life threatening events.

Limitations

In the present study we evaluated risk factors for LQTS-related life-threatening cardiac events during adolescence, a time-period that has been shown to be associated with the highest event rate in patients with this genetic disorder⁷ and when heart rates are usually faster than 60 bpm. However, the phenotypic expression of LQTS has been shown to be age-dependent.⁷⁻⁸ Thus, it is possible that the risk associated with heart rate may be different in older LQTS patients. Further studies are needed to validate the current findings in different age-groups of affected LQTS patients.

Due to sample size limitations, we did not exclude patients treated with β -blockers; nevertheless, all multivariate models included adjustment for time-dependent β -blocker therapy. In a secondary analysis excluding patients treated with β -blockers, we observed consistent results regarding the QT-RR relationship and the suggested improved QT correction formulae among LQT1 and LQT2 patients. Our study is underpowered to assess the yield of the new formulae and event rates within fixed time-periods by dichotomizing survival time and is also underpowered to calculate the sensitivity and specificity of the new formulae.

The current study population, despite being the largest genotyped population to assess QT/RR relation to arrhythmic risk, is not sufficient for validation of specific correction formulae without validations in independent populations. The present study is an overall risk assessment, whereas in clinical practice risk assessment should be individualized since some lethal events can occur in LQT1 patients in the absence of rapid heart rate. QTc alone should not be viewed as a complete diagnostic test, as there are several other important and known risk factors.

Conclusions

Investigations of clinical aspects and basic causal mechanisms of the LQTS have provided novel and important insight into the fundamental nature of the electrical activity of the human heart and to the relationship between disturbances in ion flow and cardiac disease. Our findings suggest that an understanding of the genotype-phenotype relationship in this genetic disorder can lead to improved criteria for risk stratification for life-threatening arrhythmic events in affected patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

List of abbreviations

ACA	Aborted cardiac arrest
ECG	Electrocardiogram
ICD	Implantable Cardioverter Defibrillator
LCSD	Left cardiac sympathetic denervation
LQTS	Long QT Syndrome
LQT1	Long QT Syndrome Type 1
LQT2	Long QT Syndrome Type 2
QTc	Corrected QT interval
SCD	Sudden Cardiac Death

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Figure 1.
Distribution of the QT and RR intervals among LQT1 patients (panels A and B) and among LQT2 patients (panels C and D).

Table 1

Baseline characteristics and clinical course of study patients by genotype

CHARACTERSTIC	LQT1 (N=727)	LQT2 (N=582)
Female, n (%)	429(59)	329(57)
Family history of SCD, n (%)	77(11)	48(8)
Baseline ECG data		
QT, msec (mean $\pm$ SD)	444 $\pm$ 68	452 $\pm$ 79 *
QTc(b), msec (mean $\pm$ SD)	483 $\pm$ 50	486 $\pm$ 56
QTc(f), msec (mean $\pm$ SD)	469 $\pm$ 50	473 $\pm$ 59
QTc(fram), msec (mean $\pm$ SD)	466 $\pm$ 50	470 $\pm$ 59
RR, msec (mean $\pm$ SD)	857 $\pm$ 197	878 $\pm$ 219
Clinical history (prior to age 10)		
<i>Treatment</i>		
β -blocker therapy, n (%)	133(18)	84(14)
LCSD (%)	8(1)	2(0)
Pacemaker, n (%)	4(1)	11(2) *
ICD, n (%)	7(1)	6(1)
<i>Events</i>		
Syncope, n (%)	133(18)	64(11)
Aborted cardiac arrest, n (%)	5(1)	5(1)
Clinical course during adolescence		
<i>Treatment</i>		
β -blocker therapy, n (%)	262(36)	204(35)
LCSD, n (%)	6(1)	6(1)
Pacemaker, n (%)	5(1)	19(3) *
ICD, n (%)	40(6)	37(6)
<i>Events</i>		
Syncope, n (%)	193(27)	150(26)
Aborted cardiac arrest, n (%)	9(1)	13(2)
Aborted cardiac arrest or sudden cardiac death	12(2)	18(3)

*
p<0.05

ICD = implantable cardioverter defibrillator; LCSD = left cervical sympathetic denervation; LQT1 = long-QT syndrome type 1; LQT2 = long-QT syndrome type 2. QTc(b),(f),(fram) = corrected QT interval using Bazett's, Fridericia's, and Framingham's formulae, respectively.

Table 2

Adjusted models: Risk of ACA or SCD by genotype for each repolarization measure

A. Without including the RR interval as a covariate.*				
	LQT1		LQT2	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Model 1A				
QT	1.08 (0.49–2.38)	0.858	1.86 (1.12–3.10)	0.017
Model 2A				
QTc(b)	2.78 (1.18–6.54)	0.019	2.06 (1.08–3.92)	0.029
Model 3A				
QTc(f)	2.00 (0.87–4.61)	0.105	2.13 (1.16–3.89)	0.015
Model 4A				
QTc(fram)	1.72 (0.74–3.97)	0.206	2.17 (1.21–3.89)	0.010

B. Including the RR interval as a covariate*				
	LQT1		LQT2	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Model 1B				
QT	3.28 (1.20–8.93)	0.020	2.13 (1.14–4.00)	0.018
RR [†]	1.88 (1.19–2.98)	0.007	1.11 (0.82–1.49)	0.507
Model 2B				
QTc(b)	3.05 (1.20–7.74)	0.019	2.04 (1.07–3.86)	0.029
RR	1.31 (0.98–1.76)	0.066	0.90 (0.72–1.13)	0.372
Model 3B				
QTc(f)	3.22 (1.24–8.33)	0.016	2.07 (1.10–3.90)	0.025
RR	1.49 (1.08–2.06)	0.015	0.96 (0.76–1.22)	0.764
Model 4B				
QTc(fram.)	3.28 (1.20–8.93)	0.020	2.13 (1.14–4.00)	0.018
RR	1.57 (1.10–2.24)	0.013	0.98 (0.77–1.26)	0.898

* Hazard ratios are per 100 msec increase in the QT and QTc intervals; and per 100 msec decrease in the RR interval; findings in each model were also adjusted for the additional covariates: time-dependent syncope, gender (male age 10–15 years), and time-dependent medical therapy with β -blockers.

[†] p-value for genotype x heart rate interaction = 0.036

ACA= aborted cardiac arrest; SCD=sudden cardiac death; QTc(b) = corrected QT Bazett; QTc(f) = corrected QT Friderichia; QTc(fram) = corrected QT Framingham.

Table 3

Adjusted models: Risk of ACA or SCD by genotype specific new correction formulae

A. LQT1 patients*			
	HR	95% CI	P-VALUE
RR not included in model			
QTc(new): QT/RR ^{0.8}	2.85	1.41–5.78	0.004
RR included in the model			
QTc(new): QT/RR ^{0.8}	2.65	1.13–6.25	0.026
RR	1.05	0.75–1.47	0.762

B. LQT2 patients*			
	HR	95% CI	P-VALUE
RR not included in model			
QTc(new): QT/RR ^{0.2}	2.06	1.16–3.63	0.013
RR included in the model			
QTc(new): QT/RR ^{0.2}	2.10	1.11–3.96	0.022
RR	1.02	0.79–1.32	0.890

* Hazard ratios are per 100 msec increase in the QT and QTc intervals; and per 100 msec decrease in the RR interval; findings in each model were also adjusted for the additional covariates: time-dependent syncope, gender (male age 10–15 years), and time-dependent medical therapy with β -blockers.

ACA= aborted cardiac arrest; SCD=sudden cardiac death; QTc(b) = corrected QT Bazett; QTc(f) = corrected QT Friderichia; QTc(fram) = corrected QT Framingham.

Table 4
Absolute values of corrected QT among patients with and without life threatening cardiac events.

	LQT1			LQT2		
	ACA/SCD	No ACA/SCD	Δ mean	ACA/SCD	No ACA/SCD	Δ mean
QT	461±63	443±68	18	512±110	450±77	62
QTc(b)	521±57	482±49	38	524±77	484±54	40
QTc(f)	500±54	468±50	32	519±87	471±57	47
QTc(fram.)	493±53	465±50	27	519±91	469±57	50
QTc(new)	564±75	511±68	53	516±95	462±64	53

Data are presented as mean±SD msec unless otherwise specified.

ACA= aborted cardiac arrest; SCD=sudden cardiac death; QTc(b) = corrected QT Bazett; QTc(f) = corrected QT Friderichia; QTc(fram) = corrected QT Framingham; QTc(new) for LQT1 = $QT/RR^{0.2}$; QTc(new) for LQT2 = $QT/RR^{0.8}$