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Risk Factors for Recurrent Syncope and Subsequent Fatal or Near-Fatal Events in Children and Adolescents With Long QT Syndrome

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Objectives We aimed to identify risk factors for recurrent syncope in children and adolescents with congenital long QT syndrome (LQTS).

Background Data regarding risk assessment in LQTS after the occurrence of the first syncope episode are limited.

Methods The Prentice-Williams-Peterson conditional gap time model was used to identify risk factors for recurrent syncope from birth through age 20 years among 1,648 patients from the International Long QT Syndrome Registry.

Results Multivariate analysis demonstrated that corrected QT interval (QTc) duration (≥500 ms) was a significant predictor of a first syncope episode (hazard ratio: 2.16), whereas QTc effect was attenuated when the end points of the second, third, and fourth syncope episodes were evaluated (hazard ratios: 1.29, 0.99, 0.90, respectively; $p < 0.001$ for the null hypothesis that all 4 hazard ratios are identical). A genotype-specific subanalysis showed that during childhood (0 to 12 years), males with LQTS type 1 had the highest rate of a first syncope episode ($p = 0.001$) but exhibited similar rates of subsequent events as other genotype-sex subsets ($p = 0.63$). In contrast, in the age range of 13 to 20 years, long QT syndrome type 2 females experienced the highest rate of both first and subsequent syncope events ($p < 0.001$ and $p = 0.01$, respectively). Patients who experienced ≥1 episodes of syncope had a 6- to 12-fold ($p < 0.001$ for all) increase in the risk of subsequent fatal/near-fatal events independently of QTc duration. Beta-blocker therapy was associated with a significant reduction in the risk of recurrent syncope and subsequent fatal/near-fatal events.

Conclusions Children and adolescents who present after an episode of syncope should be considered to be at a high risk of the development of subsequent syncope episodes and fatal/near-fatal events regardless of QTc duration.
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Abbreviations and Acronyms

ACA = aborted cardiac arrest
ECG = electrocardiogram
ICD = implantable cardioverter-defibrillator
LQTS = long QT syndrome
LQT1 = long QT syndrome type 1
LQT2 = long QT syndrome type 2
PWP = Prentice, Williams, and Peterson
QTc = corrected QT interval
SCD = sudden cardiac death

Congenital long QT syndrome (LQTS) is an inherited cardiac arrhythmic disorder due to mutations affecting the cardiac ion channels resulting in delayed ventricular repolarization and a prolonged QT interval on an electrocardiogram (ECG). The associated arrhythmias may manifest as syncope, aborted cardiac arrest, or sudden cardiac death (SCD).

Thus far, studies on the risk stratification of LQTS have provided data on the clinical and genetic risk factors predicting the likelihood of a first cardiac event (1–3). However, these studies may not apply to patients with LQTS who present after their first episode of syncope. Specifically, children and adolescents with congenital LQTS were shown to have a high risk of a first cardiac event. However, currently, there are no data regarding risk factors for recurrent episodes of syncope in this population. We hypothesized that the traditional clinical, electrocardiographic, and genetic risk factors for a first syncope would exhibit a time-dependent change in predictive value for recurrent syncope. Accordingly, the primary aim of the present study was to investigate risk factors for recurrent syncope in children and adolescents who present for evaluation after a syncope episode. To further stress the importance of recurring syncope as a risk factor in LQTS, we also assessed the risk of fatal or near-fatal events after repeated episodes of syncope in this population.

Methods

Study population. The study population was drawn from the International LQTS Registry. Patients were included in the study if they had: 1) a corrected QT interval (QTc) duration assessed using Bazett's formula (4) of ≥450 ms; and/or 2) a documented LQTS-causing mutation by genetic testing. Subjects were excluded from the analysis if they: 1) had a QTc duration <450 ms on the baseline ECG without a genotype-positive mutation; 2) were from families with known LQTS mutations but did not have their family's LQTS mutation (the exclusion of such individuals might involve rare patients with an undetected second mutation); and 3) were enrolled in the registry after 20 years of age to enable complete data collection regarding events that occurred during the childhood and adolescence periods. The final sample consisted of 1,648 patients.

Data collection and management. On enrollment, a complete medical history was obtained, and patients were followed yearly for additional medical information. Prospectively designed forms were used to obtain clinical data from patients, their families, and physicians (by regular phone and mail contact), regarding individual and family history, demographic, electrocardiographic, therapeutic, and cardiac event information. On enrollment in the International LQTS Registry, a 12-lead ECG was obtained for each subject. Lead II was used for measuring the QT interval, which was adjusted for heart rate by Bazett's formula (4). Information on LQTS therapies was gathered prospectively at yearly intervals. Follow-up data regarding beta-blocker therapy included the starting date, type of beta-blocker, and discontinuation date in case it occurred. Among subjects who died, the use of a beta-blocker before death was determined retrospectively.

The LQTS genotype was determined by multiple established genetic laboratories using standard mutational analytic techniques. In this study sample, 738 patients were genetically tested and identified to have an LQTS-causing mutation. The LQTS Registry study was approved by the University of Rochester Institutional Review Board, and informed consent was obtained from study participants or their guardians. The first recorded ECG obtained at the time of patient enrollment in the LQTS Registry was used in the current analysis.

End points. The primary end point was the occurrence of recurrent syncope episodes after the first event (categorized as second through fourth episodes) from birth through age 20 years. Syncope was defined as a transient loss of consciousness with abrupt onset and offset. A subsequent syncope episode was defined as syncope occurring ≥7 days from the previous syncope episode. The 7-day separation period was included to distinguish a single event from a continuing event associated with specific triggers (i.e., fever, menses, medications), allowing patients to be clearly removed from the triggered event and stabilized on new therapies. Aborted cardiac arrest (ACA) and LQTS-related SCD served as end points for our analysis of the association between recurrent syncope and the risk of subsequent fatal or near-fatal events. ACA was defined as cardiac arrest with recovery after defibrillation, and SCD was defined as sudden and unexpected death due to LQTS.

Statistical analysis. The clinical characteristics of the study patients were categorized by the total number of syncope episodes experienced by the patients. Patients with different numbers of syncope episodes were compared using the chi-square test for categorical variables and analysis of variance for continuous variables.

The conditional model, proposed by Prentice, Williams, and Peterson (PWP), was used to simultaneously model the distribution of the time to first syncope episode and the gap times between subsequent syncope events as functions of risk factors of interest (5), with inference based on the robust sandwich estimator of the covariance matrix for the estimated model parameters to account for potential dependencies between the gap times. Unlike some other models for recurrent events, such as the marginal model of Wei et al. (6), the PWP model assumes that the risk of a second

Table 1 Clinical and Electrocardiographic Characteristics by the Number of Syncope Episodes During Follow-Up (n = 1,648)

Characteristic	Number of Episodes of Syncope				
	0	1	2	3	≥4
n	965	241	151	99	192
Male	515 (53)	119 (49)	74 (49)	40 (40)	79 (41)
Congenital deafness	6 (1)	6 (2)	6 (4)	7 (7)	23 (12)*†
Electrocardiogram (ms)					
QRS	76 ± 15	77 ± 18	78 ± 17	78 ± 16	75 ± 15
R-R	695 ± 205	819 ± 236	820 ± 218	832 ± 218	865 ± 208*
QTc duration, ms	478 ± 41	502 ± 54	514 ± 61	511 ± 57	514 ± 60*†
QTc >500 ms	174 ± 18	87 ± 36	64 ± 43	40 ± 40	78 ± 41*
LQTS-related therapies					
Beta-blockers	566 (59)	213 (88)	136 (90)	90 (91)	186 (97)*†
ICD	59 (6)	57 (24)	31 (21)	29 (29)	51 (27)*
PM	30 (3)	27 (11)	25 (17)	18 (18)	40 (21)*†
LCSD	6 (1)	7 (3)	2 (1)	11 (11)	44 (23)*†
Fatal/near-fatal events during follow-up‡					
ACA	27 (3)	23 (10)	16 (11)	16 (16)	30 (16)
SCD	34 (4)	13 (5)	10 (7)	10 (10)	21 (11)

Data are shown as n (%) or mean ± SD. *p value <0.05 for the difference among the 5 subgroups (comprising no syncope and 1 to 4 syncopal events); findings were similar when a p value for trend was assessed. †p value <0.05 for the difference among the 4 syncopal events subgroups. ‡No statistical test was performed to compare the frequency of fatal/near-fatal events among the syncope subgroups due to a different follow-up time in each subset. Adjusted results for the difference are shown in Table 4.

ACA = aborted cardiac arrest; ICD = implantable cardioverter-defibrillator; LCSD = left cardiac sympathetic denervation; PM = pacemaker; SCD = sudden cardiac death; QTc = corrected QT interval.

event is conditional on having a first event. Each ordered outcome (first, second, third, and fourth syncope episodes) is assigned to a separate time-dependent stratum, with its own baseline hazard function, and all covariates are interacted with each stratum, allowing each ordered outcome to effectively have its own unconstrained Cox model. Pre-specified covariates that were included as potential predictors of a first and recurrent syncope episodes included sex, age older than 13 years (except for the first syncope episode, where this main effect term was absorbed by the baseline hazard function because age is the time scale), sex × age older than 13 years interaction (to allow for separate hazard ratios for males and females among those younger than 13 and those 13 years of age and older [1]), the Bazett-corrected QT interval (dichotomized at QTc duration ≥500 ms in the primary analysis, and at the upper quartile [≥540 ms] in a secondary analysis), and beta-blocker therapy (modeled as a time-dependent binary covariate).

We also performed a genotype-specific subset analysis among the 644 long QT type 1 syndrome (LQT1) or long QT type 2 syndrome (LQT2) study patients to identify potential genotype-sex factors as predictors of the first and subsequent episodes of syncope. We focused on the LQT1 and LQT2 genotypes due to the limited number of patients with the other genotypes. Because previous studies showed a relationship between genotype, sex, and age (1), we performed Kaplan-Meier estimates of time to first and second events based on genotype-sex subsets (categorized as LQT1 males, LQT1 females, LQT2 males, and LQT2 females) and within pre-specified age groups (childhood: age 0 to 12 years; adolescence: age 13 to 20 years), with the log-rank test used for hypothesis testing. Multivariate analyses of these interactions were performed to analyze genotype and sex interactions within age groups. Due to a smaller sample size of genotyped patients, we limited the analyses in the genotype-specific models to a comparison of risk factors for the first and the second syncope episodes (i.e., all subsequent episodes were categorized into a single ≥2 events end point).

Wald tests were used for each joint hypothesis test that determined whether the covariate by event stratum interactions was significant.

The Cox model was used to evaluate the association between first and recurrent syncope episodes and the risk of subsequent ACA or SCD. The same covariates used to model recurrent syncope in the PWP model were used in this analysis, with the addition of the time-dependent number of previous syncope events. The Kaplan-Meier estimator was used to assess the 5-year cumulative probability of an ACA or SCD based on combined assessment of the number of syncope episodes experienced by an individual and QTc duration.

Statistical analysis was performed using SAS version 9.1.3 for Windows (SAS Institute, Cary, North Carolina).

Results

The clinical characteristics of the total study cohort and the genotype-positive patient subset by the number of episodes of syncope during follow-up are shown in Tables 1 and 2, respectively. Comparison of electrocardiographic parameters showed increasing QTc duration with an increasing

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Table 2 Clinical and Electrocardiographic Characteristics by the Number of Syncope Episodes During Follow-Up: Genotype-Positive Patients (n =738)

	Number of Episodes of Syncope					
	0	1	2	3	≥4	p Value*
n	467	115	58	35	63	
LQT1	236 (51)	54 (47)	30 (52)	14 (40)	40 (63)	
LQT2	161 (34)	41 (36)	20 (35)	17 (48)	15 (24)	
LQT3	59 (13)	15 (13)	2 (3)	1 (3)	3 (5)	0.04
LQT5–8	5 (1)	2 (2)	3 (5)	2 (6)	1 (2)	
>1 mutations†	6 (1)	3 (2)	3 (5)	1 (3)	4 (6)	

Values are n (%) unless otherwise specified. *p value for the overall difference for the distribution of genotypes among the syncope episode subgroups. †Includes patients who were genetically tested and identified as having >1 LQTS-causing mutation.

LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2; LQT3 = long QT syndrome type 3; LQT3 = long QT syndrome type 3; LST5–8 = long QT syndrome types 5 through 8.

number of syncope episodes. Notably, patients who experienced syncope had a very high frequency of beta-blocker use (≥88%). In addition, the frequency of implantable cardioverter-defibrillator (ICD) use was significantly higher among patients who experienced syncope, but similar among the 4 syncope subgroups (Table 1). Among the 738 genotype-positive patients, the LQT1 and LQT2 genotypes composed the majority (87%) identified LQTS genotypes (Table 2). The mean ages at which the first through fourth episodes of syncope occurred were 9, 10, 11, and 12 years (±6 years for all), respectively, and the majority (>80%) of subsequent events occurred within 5 years of the previous event. The frequency of patients who experienced ≥1 syncope events was similar between LQTS patients who did and did not undergo genetic testing (37% and 42%, respectively).

Risk factors for first and recurrent episodes of syncope. Patients with QTc duration ≥500 ms had a significantly higher cumulative probability of experiencing their first syncope as compared to patients with QTc duration <500 ms (75% vs. 48%, respectively; $p < 0.001$) from birth through age 20 years (Fig. 1A). However, among patients who experienced a first syncope, the rate of subsequent events was increased among those who had both QTc duration <500 ms and those with QTc duration ≥500 ms (74% and 76%, respectively; $p = 0.11$) at age 20 years (Fig. 1B). Similarly, among patients who experienced 2, 3, and 4 syncope episodes, the risk of a subsequent syncope episode was virtually identical between patients who had narrow or prolonged QTc duration (not shown). This was supported by the PWP model for recurrent events (Table 3), which showed that QTc duration ≥500 ms was a powerful independent predictor (>2-fold risk increase; $p < 0.001$) of a first syncope episode, whereas the risk associated with QTc duration was significantly attenuated when the end points of subsequent episodes of syncope were assessed (second syncope episode, hazard ratio [HR]: 1.29; third syncope episode, HR: 0.99; fourth syncope episode, HR: 0.90; interaction $p < 0.001$ for the null hypothesis that all 4 HRs are identical). The results regarding the association between QTc duration and the risk of a first episode and recurrent events were virtually identical when patients with congenital deafness (n = 48) and multiple mutations (n = 17) were excluded from the analysis. Furthermore, a secondary analysis, in which QTc duration was categorized at the upper quartile of the study population (≥540 ms [n = 425]) or as a continuous measure, consistently demonstrated that QTc was predictive only of a first event and not of subsequent events (not shown).

A sex-genotype specific analysis that was performed in a subset of 644 patients having either the LQT1 (n = 387) or LQT2 (n = 257) genotype showed age-dependent risk factors for first and subsequent cardiac events (Figs. 2 and 3). During childhood, males with LQT1 had the highest cumulative probability for a first cardiac event (36% during 10 years of follow-up [Fig. 2A]). In contrast, after the occurrence of a first event, the cumulative probability of a subsequent event during childhood was increased substantially in all genotype-sex subgroups (35% to 46% during only 2 years of follow-up [Fig. 2B]). Consistent with these findings, multivariate analysis showed that during childhood, males with LQT1 exhibited a significant increase in the risk of a first syncope episode ($p = 0.001$ for the overall difference among the subgroups) but did not show a statistically significant increase in the risk of subsequent events ($p = 0.34$ for the overall difference among the subgroups).

After the onset of adolescence, there was an age-sex risk reversal, and females with LQT2 showed the highest rate of both a first cardiac event (38% during 5 years of follow-up [Fig. 3A]) and subsequent events (58% during only 2 years of follow-up [Fig. 3B]). Similarly, multivariate analysis showed that females with the LQT2 genotype in the age range of 13 through 20 years exhibited a higher risk of both a first and subsequent events compared with the other sex-genotype groups ($p = 0.001$ and $p = 0.02$, respectively, for the overall difference).

Recurrent syncope and the risk of subsequent ACA or SCD. After adjustment for QTc duration, sex, and time-dependent beta-blocker therapy, the occurrence of recurring episodes of syncope was associated with a pronounced increase in the risk of subsequent ACA or SCD (Table 4). Compared with no events, having 1 or 2 syncope episodes was associated with a >6-fold ($p < 0.001$) increased risk of

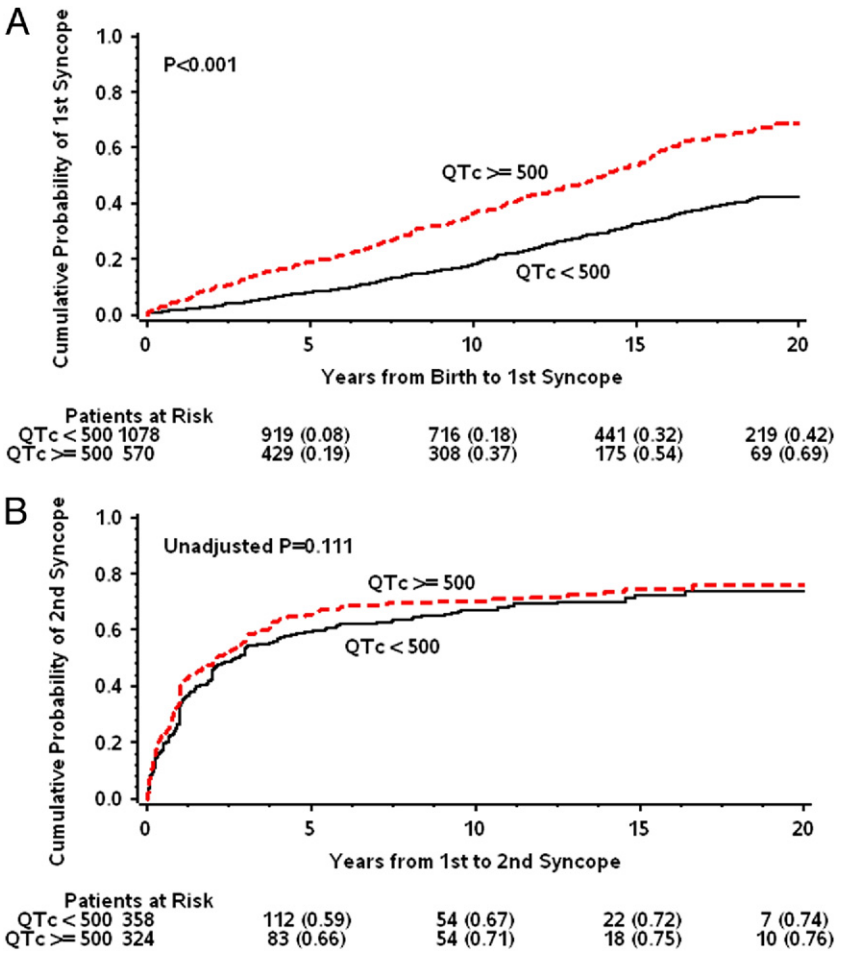

Figure 1 **Probability of Cardiac Events by QTc Duration**

Kaplan-Meier estimates of the probability of a first episode, of syncope (with follow-up time starting at birth) **(A)** and a second episode of syncope (among patients who experienced a first syncope episode, with follow-up time starting at the time of the first syncope event) **(B)** by corrected QT interval (QTc) duration (dichotomized at ≥500 ms).

subsequent ACA or SCD, and having >2 episodes was associated with a >12-fold ($p < 0.001$) relative risk of subsequent fatal or near-fatal events (Table 4). Combined assessment of the number of syncope episodes and QTc duration (Fig. 4) showed that the 5-year cumulative probability of ACA or SCD was lowest among those who did not experience syncope (1% and 5% in patients with QTc duration <500 ms and ≥500 ms, respectively), intermediate among those who experienced 1 or 2 syncope episodes (11% to 14%), and highest among those who experienced >2

Table 3 **Multivariate Analysis (Total Population): Predictors of First and Recurrent Syncopal Events***

	QTc Duration (≥500 ms vs. <500 ms)			Time-Dependent Beta-Blocker Effect		
End Point	HR†	95% CI	p Value	HR‡	95% CI	p Value
First event	2.14	1.84–2.49	<0.001	0.54	0.42–0.70	<0.001
Second event	1.32	1.07–1.62	0.009	0.22	0.17–0.28	<0.001
Third event	1.10	0.85–1.43	0.47	0.35	0.27–0.46	<0.001
Fourth event	1.01	0.82–1.26	0.91	0.44	0.35–0.54	<0.001

*See the Methods section for description of analytic technique; findings were further adjusted for corrected QT interval (QTc) duration ≥500 ms, sex, and sex × age interaction. †Omnibus p value for testing the null hypothesis that all 4 hazard ratios (HRs) equal 1 <0.001; p value for testing the null hypothesis that all 4 HRs are <0.001. ‡Omnibus p value for testing the null hypothesis that all 4 HRs equal 1 <0.001; p value for testing the null hypothesis that all 4 HRs are <0.001.

CI = confidence interval.

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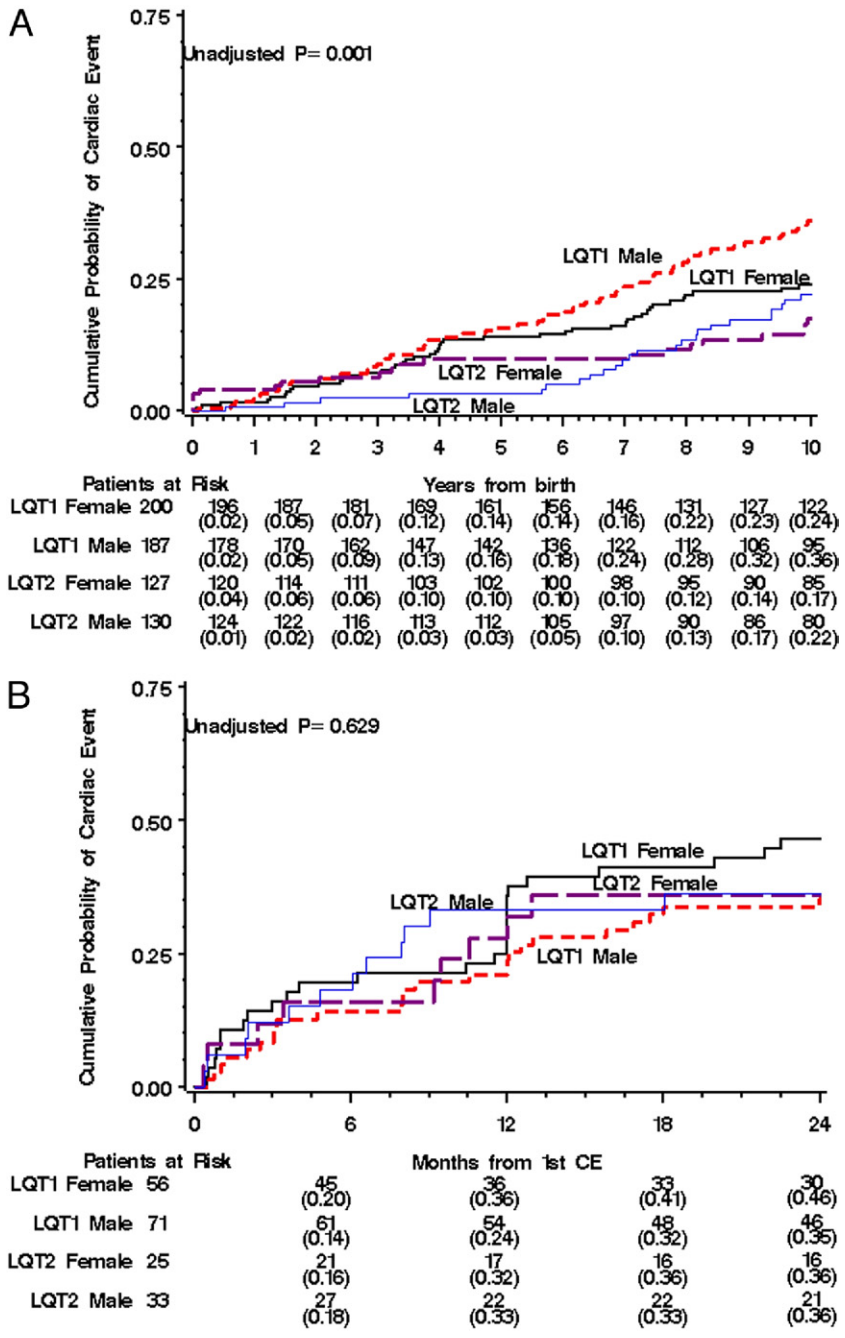

Figure 2 **Cumulative Probability of First and Second Syncope Episodes by Sex and Genotype During Childhood**

Kaplan-Meier estimates of the probability of a first **(A)** and second **(B)** syncope episode (among patients who experienced a first event, with follow-up time starting at the time of the first event) in genotype-sex subsets in the age range of 0 through 10 years. CE = cardiac event; LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2.

syncope episodes (17% to 21%). Notably, the effect of QTc duration on the risk of subsequent ACA or SCD was pronounced before the occurrence of a first syncope episode and attenuated after the occurrence of syncope (Fig. 4).

Beta-blocker therapy. Beta-blocker use was associated independently with a significant and a substantial reduction in the risk of both first and recurrent syncope episodes (Table 2). The magnitude of risk reduction associated with beta-blocker therapy was similar in LQT1 and LQT2 patients. Furthermore, treatment with beta-blockers was associated with a significant (>70%) reduction in the risk of subsequent fatal or near-fatal events among patients who

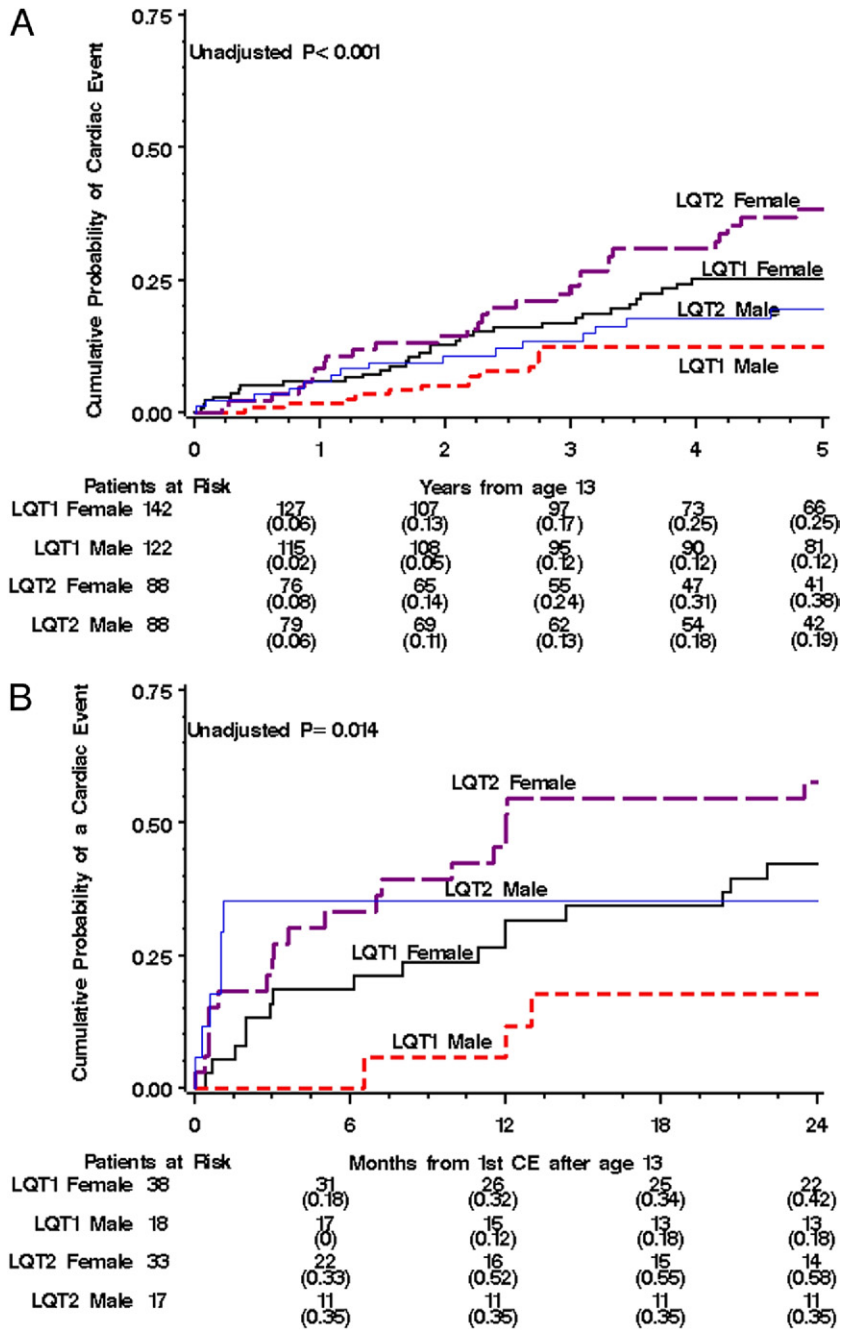

Figure 3 **Cumulative Probability of First and Second Syncope Episodes by Sex and Genotype During Adolescence**

Kaplan-Meier estimates of the probability of a first **(A)** and a second **(B)** syncope episode (among patients who experienced the first event, with follow-up time starting at the time of the first event) in genotype-sex subsets in the age range of 13 to 20 years. Abbreviations as in Figure 2.

experienced a first episode and recurrent episodes of syncope (Table 3).

Discussion

Previous studies on risk stratification in LQTS have been limited to identifying markers that predict the risk of a first cardiac event. Our study is the first to assess traditional risk markers for cardiac events in the LQTS populations as independent predictors of subsequent syncope. Unlike previous studies, we assessed recurrent syncope as an end point rather than a risk factor. We have shown that, in children and adolescents with congenital LQTS, there are important time-dependent changes in risk factors after a first syncope episode. Importantly, the present study shows that the risk

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Table 4 Multivariate Analysis (Cox Model): Recurrent Syncope as a Predictor of ACA/SCD*

	Adjusted Risk			Time-Dependent Beta-Blocker Effect†		
Variable	HR‡	95% CI	p Value	HR§	95% CI	p Value
First syncope event vs. no events	6.54	3.96–10.80	<0.001	0.25	0.11–0.55	0.001
Second syncope event vs. no events	6.69	6.65–12.25	<0.001	0.28	0.11–0.72	0.008
Third syncope event vs. no events	12.51	7.03–22.28	<0.001	0.22	0.08–0.57	0.002
≥4 Syncope events vs. no events	14.65	8.02–26.76	<0.001	0.20	0.10–0.44	<0.001

*Adjusted for significant covariates: QTc duration ≥500 ms, sex, age, sex × age interaction, and time-dependent beta-blocker use. †The efficacy of time-dependent beta-blocker therapy in reducing the risk of the end point in each risk group was evaluated by including a beta-blocker × syncope group interaction term in the multivariate model. ‡Omnibus p value for testing the null hypothesis that all 4 HRs equal 1 < 0.001; p value for testing the null hypothesis that all 4 HRs equal = 0.016. §Omnibus p value for testing the null hypothesis that all 4 HRs equal 1 = 0.014; p value for testing the null hypothesis that all 4 HRs = 0.959.

Abbreviations as in Table 3.

of subsequent syncope episodes after the occurrence of a first event is increased regardless of QTc duration, despite the high use of beta-blocker therapy (>90%) during this time period. Furthermore, our results confirm that recurrent syncope is a powerful predictor of subsequent fatal or near-fatal events, independently of QTc. These findings have important clinical and therapeutic implications for LQTS patients who present for evaluation after the occurrence of a first episode of syncope before 20 years of age.

QTc duration as a risk marker for first and recurrent events. The heart rate–QTc interval has been the basis for diagnostic criteria for LQTS (7) and is a known predictor of a first cardiac event in this population (3,8–11). Our results are consistent with previous observations, demonstrating that a QTc duration of ≥500 ms is an independent predictor of a first cardiac event. However, an LQTS patient who has already experienced a syncope episode should be considered at higher risk of a recurrent syncope episode and possibly even LQT-triggered ACA/SCD regardless of his or her QTc value. Notably, the proportion of patients with a lower-range QTc duration in the total population (65%) was higher than among patients who experienced recurrent events (approximately 50%). However, although in the former subgroup, a QTc <500 ms is indicative of a relatively lower risk of a first cardiac event (3,8–11), it is not a reassuring value after the occurrence of an LQTS cardiac event. It is possible that additional risk factors may be present in LQTS patients who present with a first syncope episode despite a lower-range QTc duration, including environmental factors, the presence of modifier genes, or high-risk ion channel properties of the LQTS-related mutation. Thus, risk assessment and management of clinically symptomatic children and adolescents with congenital LQTS should be independent of QTc. This impact on risk stratification requires careful evaluation to distinguish whether that first event stemmed from LQT's signature dysrhythmia of torsades or whether that fainting episode was simply a vasovagally mediated episode occurring in an LQTS host.

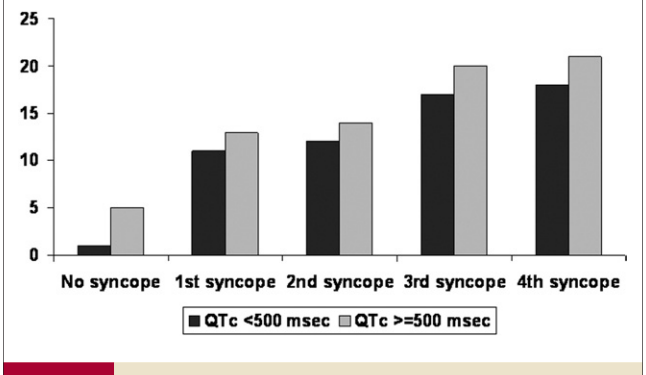

Figure 4 The 5-Year Cumulative Probability of ACA/SCD by the Number of Syncope Episodes and QTc Duration

Kaplan-Meier estimates of the 5-year cumulative probability of aborted cardiac arrest (ACA) and sudden cardiac death (SCD) before the occurrence of a first episode of syncope and after the first, second, third, and fourth episodes of syncope by corrected QT interval (QTc) duration. Follow-up was restarted after the occurrence of a syncopal event.

Sex, genotype, and age as risk markers for first and recurrent events. The effect of sex, genotype, and age on time to the first cardiac event has been well studied (1,7–9). During childhood, males with LQTS were shown to have an increased risk of a first cardiac event compared with their female counterparts (12) and to experience the events at a younger age (1). After the onset of adolescence, however, risk reversal occurs, and females were shown to exhibit a 2- to 3-fold increased risk of a first cardiac event compared with males throughout adulthood (10,12). Previous studies have also shown that there are also important genotype-sex interactions within the age groups. Thus, during childhood, males with LQT1 were shown to be at higher risk of a first cardiac event, whereas after the onset of adolescence, LQT2 females were shown to exhibit a higher risk (1,12). Consistent with previous data, our genotype-specific analysis also shows that males with LQT1 and females with LQT2 experienced the highest rate of first events during childhood and after the onset of adolescence, respectively. However, our findings extend those of previous studies and demonstrate that after the occurrence of a first cardiac event, rates are markedly increased during childhood regardless of genotype or sex (≥35% in all genotype-sex during only 2 years of follow-up), whereas the risk of recurrent events during the post-adolescence period remains higher among females with LQT2. Notably, women with the LQT2 genotype who experienced a first cardiac event exhibited an

extremely high rate of subsequent events (58% during only 2 years of follow-up), further stressing the importance of careful follow-up and timely therapeutic intervention in this high-risk population.

Recurrent syncope as a predictor of subsequent fatal or near-fatal events. Syncope, although nonfatal, is associated with comorbidities such as trauma and is a much more frequent cardiac event than ACA or SCD. The present study supports previous data regarding the importance of first and recurrent syncope episodes as a powerful predictor of subsequent fatal or near-fatal events in LQTS children and adolescents (8,9). We have shown that after the occurrence of a first syncope episode, LQTS patients exhibited a 6-fold increase in the risk of subsequent ACA or SCD, and the risk of fatal or near-fatal events was increased to >12-fold among patients who experienced ≥3 episodes of syncope. These findings were independent of QTc duration or age-sex interactions. Furthermore, patients who had 3 or 4 episodes of syncope before the age of 20 years (who composed approximately one-fifth of the total study population and 43% of symptomatic patients) experienced a very high rate of subsequent ACA or SCD during only 5 years of follow-up (in the range of 17% to 21%, regardless of QTc duration). Thus, the occurrence of recurrent nonfatal events has important prognostic implications in LQTS patients that are independent of the traditional risk factors previously reported in this population (1–3,7).

Therapeutic implications. The mainstay of LQTS treatment in arrhythmia prevention is beta-blocker therapy, which suppresses the adrenergic-mediated triggers (13). Beta-blockers reduce cardiac event rates in LQT1 and LQT2 patients in a risk-dependent fashion (14). Beta-blockers were shown to reduce lethal events by 70% in high-risk children (8) and by 64% in high-risk adolescents with recent syncope (9). However, previous studies have also suggested that beta-blocker therapy may have important limitations in LQTS patients, including a relatively high residual rate of cardiac events in patients with LQT2 and LQT3 (2) and a high residual rate of ACA or SCD among those who experience syncope during beta-blocker therapy (15). Our study confirms that beta-blocker therapy is associated with a significant reduction in the risk of a first cardiac event in children and adolescents with LQTS (8,9). Furthermore, our findings extend previous data and demonstrate that treatment with beta-blockers is associated with a pronounced (>70%) reduction in the risk of subsequent ACA or SCD among patients who experienced any number of previous syncope episodes. However, we have shown that the cumulative probability of ACA or SCD among patients who experienced >2 syncope episodes was approximately 20% at 5 years of follow-up, despite the fact that the majority of this population was treated with beta-blockers. Thus, based on the findings of the present study and previous reports, a management strategy among LQTS patients who present for risk assessment after a syncope episode may include the following: 1) initiation of beta-blocker therapy in those who experience a syncope event without therapy (16); 2) additional interventions, including primary ICD therapy (17) and/or left cardiac sympathetic denervation (18–20) in patients who experience syncope during beta-blocker therapy; 3) careful follow-up for residual symptoms or arrhythmias after the initiation of beta-blocker therapy, with consideration of ICD therapy for patients who experience >2 episodes of syncope during follow-up (who had a frequency of ICD implants similar to that of patients who experienced 1 or 2 episodes, but had a very high rate of subsequent of ACA or SCD at 5 years [approximately 20%]).

Study limitations. In analyzing recurrent syncope, we censored ACA and SCD in the cause-specific PWP model, which may have biased subsequent risk group analyses. We addressed this bias with a secondary analysis of predictors for ACA or SCD, ensuring consistency in the risk analysis.

Data for the present study were derived from patients enrolled in the International LQTS Registry. Thus, similar to previous registry studies, it is possible that there were some inaccuracies in the yearly data collection and an inconsistent follow-up of some study patients. Furthermore, despite the fact that cardiac events were reviewed carefully by the study specialists, confounding factors, including vasovagal, neurologic, and metabolic disturbances, cannot be ruled out as the mechanism that precipitated some of the syncope events in the present study.

It should be stressed that present findings regarding the lack of association between QTc duration and the risk of subsequent events are based on categorized data in a large study population. Thus, individual clinical assessment for therapeutic intervention is still important in this population (i.e., an extremely prolonged QTc duration in a symptomatic individual may still be considered as an additional marker for more aggressive intervention). Furthermore, it should be noted that the implications regarding risk factors for recurrent events that were identified in the present study are restricted to children and adolescents who experience a first syncope episode.

Our sample population had a more limited number of genotyped patients (n = 738), of whom the majority composed the LQT1 and LQT2 genotypes. Therefore, risk factors for recurrent events were not assessed for study patients with the less frequent LQT3 through 8 genotypes. Furthermore, due to a smaller sample size, we limited the analyses of the genotype-specific models to a comparison among risk factors for the first event and ≥2 cardiac events.

Conclusions

This study focused on recurrent syncope in children and adolescents with LQTS. We have shown that the predictive value of traditional LQTS risk markers change in patients who experience a first nonfatal cardiac event. QTc duration was shown to be a major predictor of a first syncope episode. However, the risk associated with this traditional electro-

cardiographic marker was attenuated among patients who experienced a first event. Furthermore, we have shown important age-related genotype and sex differences in the risk of recurrent events in LQT1 and LQT2 patients. These time-dependent clinical and genetic factors should be considered in risk assessment and the management of LQTS patients who present for evaluation after the occurrence of a first episode of syncope.

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Key Words: long QT syndrome ■ QTc interval ■ recurrent events ■ sudden cardiac death ■ syncope.