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ORIGINAL RESEARCH

Risk Prediction in Male Adolescents With Congenital Long QT Syndrome: Implications for Sex-Specific Risk Stratification in Potassium Channel-Mediated Long QT Syndrome

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BACKGROUND: Sex-specific risk management may improve outcomes in congenital long QT syndrome (LQTS). We recently developed a prediction score for cardiac events (CEs) and life-threatening events (LTEs) in postadolescent women with LQTS. In the present study, we aimed to develop personalized risk estimates for the burden of CEs and LTEs in male adolescents with potassium channel-mediated LQTS.

METHODS AND RESULTS: The prognostic model was derived from the LQTS Registry headquartered in Rochester, NY, comprising 611 LQT1 or LQT2 male adolescents from age 10 through 20 years, using the following variables: genotype/mutation location, QTc-specific thresholds, history of syncope, and β-blocker therapy. Anderson-Gill modeling was performed for the end point of CE burden (total number of syncope, aborted cardiac arrest, and appropriate defibrillator shocks). The applicability of the CE prediction model was tested for the end point of the first LTE (excluding syncope and adding sudden cardiac death) using Cox modeling. A total of 270 CEs occurred during follow-up. The genotype–phenotype risk prediction model identified low-, intermediate-, and high-risk groups, comprising 74%, 14%, and 12% of the study population, respectively. Compared with the low-risk group, high-risk male subjects experienced a pronounced 5.2-fold increased risk of recurrent CEs (P<0.001), whereas intermediate-risk patients had a 2.1-fold (P=0.004) increased risk . At age 20 years, the low-, intermediate-, and high-risk adolescent male patients had on average 0.3, 0.6, and 1.4 CEs per person, respectively. Corresponding 10-year adjusted probabilities for a first LTE were 2%, 6%, and 8%.

CONCLUSIONS: Personalized genotype–phenotype risk estimates can be used to guide sex-specific management in male adolescents with potassium channel-mediated LQTS.

Key Words: adolescence ■ genetics ■ long QT syndrome ■ male sex ■ QT interval ■ sudden cardiac death ■ syncope

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CLINICAL PERSPECTIVE

What Is New?

- The burden of cardiac events in male patients with potassium channel-mediated long QT (LQT) syndrome is increased after the onset of adolescence.
- Risk prediction model incorporating genotype and phenotype data delineates 3 risk groups of male adolescents with either LQT1 or LQT2.
- Male adolescents with LQT1 who harbor a cytoplasmic loop mutation exhibit the highest risk for cardiac event burden and life-threatening events despite variable phenotypic expression.

What Are the Clinical Implications?

- Risk stratification in adolescents with potassium channel-mediated LQT syndrome should incorporate sex-specific genotype–phenotype data.
- The development of a male-specific risk prediction model, in addition to the already published female-specific model, provides clinicians with a foundation for risk-tailored management of male and female adolescents with either LQT1 or LQT2.

Nonstandard Abbreviations and Acronyms

CE	cardiac events
C-loop	cytoplasmic loop
LTE	life-threatening event

Long QT syndrome (LQTS) is an inherited genetic disorder caused by monogenic mutations in several ion channels in cardiac myocytes, often manifesting in QT interval prolongation and predisposition to malignant arrhythmias and sudden cardiac death (SCD).[1] The 2 most common genetic variants are type 1 long QT (LQT1) and type 2 long QT (LQT2). The mutation in the *KCNQ1* gene, which encodes Kv7.1 ion channels regulating slow repolarizing potassium currents (I_{Ks}) in patients with LQT1, and the mutation in the *KCNH2* gene, which encodes Kv11.1 ion channels affecting rapid repolarizing potassium current (I_{Kr}) in patients with LQT2, are responsible for delay in ventricular repolarization and QT prolongation.[2] Furthermore, specific mutation locations with a higher risk for cardiac events (CEs) have been identified. The cytoplasmic loop (C-loop) mutations that localize between the Kv7.1 channel's transmembrane spanning domains and the pore-localizing mutations in the Kv11.1 channels are associated with higher arrhythmogenic potential.[3,4]

Age and sex have different effects on the probability of CEs and electrocardiographic presentations in LQT1 and LQT2 patients.[5] Male sex tends to be associated with higher risk during preadolescence, whereas, after the onset of adolescence, women have higher CE risk through adulthood.[5–7] Sex hormone modulation of the cardiac ion channels' function appears to be the mechanism related to the difference in QT duration and arrhythmogenic risk with the onset of adolescence.[8,9] We have recently reported a novel risk prediction model for LQTS in women after the onset of puberty that incorporates genotype and phenotype data.[10] However, due to the differential effects of sex hormones on arrhythmic risk, the same model is not applicable in men. Furthermore, the Rochester, New York LQTS Registry data (Figure S1) show that, despite the possible protective effects of testosterone in men with LQTS, the burden of recurrent CEs remains relatively high in boys with LQT1 and LQT2 during the high-risk adolescence period, reaching an average rate of 0.8 CEs per person per year at age 20 years, suggesting a need for improved risk stratification in male adolescents with LQTS who harbor mutations in cardiac potassium channels.[11,12]

In the present study, comprising 611 genetically confirmed male patients with LQT1 and LQT2 from the Rochester LQTS Registry, we aimed to (1) develop a male-specific risk prediction model for CE burden during adolescence by incorporating genotype (genotype and mutation location) and phenotype characteristics (QTc duration threshold and history of syncope before age 10); and (2) assess the applicability of the CE burden risk prediction model in predicting the first occurrence of a life-threatening event (LTE). The development of a male-specific risk prediction model in addition to our already published female-specific model[10] is aimed to provide clinicians with a foundation for sex-specific risk-tailored management of male and female adolescents with either LQT1 or LQT2.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The study population consisted of male patients with either genetically confirmed LQT1 or LQT2 who were enrolled in Rochester, New York's International LQTS Registry (n=1743). To be included in this study, patients needed to have been at least 10 years of age when study data were analyzed. Thus, baseline and follow-up were available for all patients in this study from age 10 years. Follow-up was through age 20 years or was censored earlier if the subject died between ages 10 and 20 years or had not yet reached their 20th birthday. Patients with either multiple LQTS-causative mutations, the R148W variant, or missing data were excluded (Figure 1). Through August 2020, 611 male

subjects with LQT1 (N=304) and LQT2 (N=307) met our inclusion and exclusion criteria. The Institutional Review Board of the University of Rochester approved the registry and all patients provided informed consent for participation.

Data Collection and Management

At enrollment, we collected patients' demographic characteristics, past medical and family history, previous CEs, electrocardiogram findings, and therapies. Thereafter, on a yearly basis, prospectively designed forms with information on demographic characteristics, personal and family medical history, electrocardiogram findings, medical therapies, left cardiac sympathetic denervation, implantation of a pacemaker or an implantable cardioverter-defibrillator, and the occurrence of presumed/proven LQTS-triggered CEs was recorded. The QT interval was corrected for heart rate using Bazett's formula to derive the patient's QTc value.[13] The routine approach for QTc assessment in the registry is based on a paper copy of baseline ECG using lead II and manually measured the nadir between T wave and isoelectric line or between T wave and U wave if present. Alternatively, lead V5 was used if QT measurement cannot be done in lead II.

Genotype Characterization and Genotype/Mutation Location Groups

The *KCNQ1* and *KCNH2* mutations were identified with the use of standard genetic tests conducted in academic molecular genetic laboratories, including the Functional Genomics Center, University of Rochester Medical Center, Rochester, NY; Baylor College of Medicine, Houston, TX; and Boston Children's Hospital, Boston, MA. Mutation definitions and categorizations are provided in Data S1, and the specific mutations included in the present study, by location, type, and number of patients (percentage), are detailed in Table S1.

Based on our prior studies, we prespecified 4 genotype and mutation-location groups: higher-risk mutation locations were defined as missense C-loop juxtaposed between the transmembrane spanning domains for LQT1 and pore-loop for LQT2; and lower-risk mutation locations were defined as non-C loop for LQT1 and non-pore-loop for LQT2 for each respective genotype.[3,4,14,15]

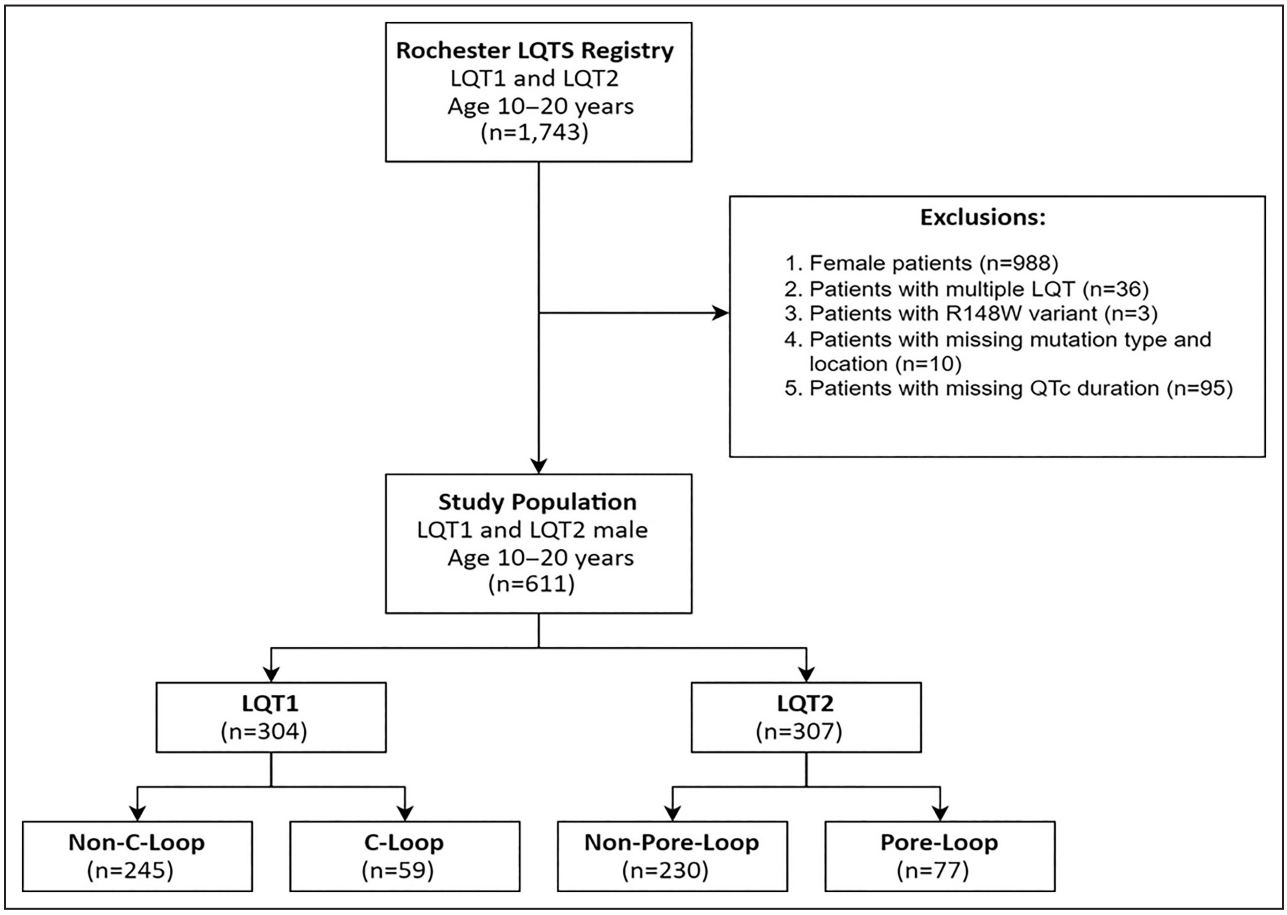

Figure 1. Study population.
C-loop indicates cytoplasmic-loop; LQT1, long QT type 1; LQT2, long QT type 2; and LQTS, long QT syndrome.

End Point Definitions

The primary end point was recurrent CEs, defined as syncope (transient loss of consciousness being abrupt in onset and offset), aborted cardiac arrest requiring defibrillation as part of resuscitation, or appropriate implantable cardioverter-defibrillator shocks. The secondary end point was the first occurrence of a LTE, defined as the first occurrence of aborted cardiac arrest, appropriate implantable cardioverter-defibrillator shock, or LQTS-related SCD (defined as abrupt death without evident cause, if witnessed, or death that was not explained by any other cause if it occurred in a nonwitnessed setting such as sleep).

Statistical Analysis

Patient baseline characteristics, treatments, and cardiac episodes before age 10 years, and treatments and cardiac episodes during follow-up period were summarized as mean±SD for continuous variables and frequency (percentage) for categorical variables across 4 pre-specified genotype and mutation-location groups. Continuous variables were compared by genotype and mutation location using Wilcoxon rank-sum tests (2-sample test) or Kruskal–Wallis tests (test for more than 2 independent groups), and categorical variables were compared using chi-square tests.

Because the goal was to explore the burden of recurrent CEs among genotype–phenotype associations, 16 different combinations were created based on the 4 genotype and mutation locations, a history of syncope before age 10 years (no versus yes), and a binary QTc threshold (< or ≥500 ms). Ghosh–Lin curves were used to illustrate and compare the mean cumulative recurrent events.[16] Furthermore, Andersen–Gill recurrent events regression model for CEs was performed to explore 16 risk groups adjusting for time-dependent β-blocker therapy.[17] Robust SEs were used to account for clustering of patients within a family. Using Wald test statistics, these risk groups were further combined based on both similar estimated beta coefficients and clinical guidance of the investigators, which resulted in 3 risk groups.

A granular multivariable Cox proportional hazards model for the end point of CE was estimated which included risk group covariates representing all combinations of (1) genotype mutation group, (2) QTc dichotomized at 500ms, and (3) history/no history of syncope and that used LQT2 subjects with pore-loop mutation, QTc <500 msec, and no history of syncope as the reference group. The hazard ratios fell roughly into 3 distinct groups, which suggested 3-tier risk strata and allowed easier interpretation. All findings were adjusted for time-dependent β-blocker therapy. In addition, the effect of time-dependent β-blocker therapy within each of the 3 risk groups was assessed by performing an interaction test. The discriminative performance of the model was quantified by Harrell's concordance c-statistics.[18] Lastly, this risk prediction model for CEs, which included the 3 risk groups and time-dependent β-blocker therapy covariates, was applied to a first occurrence LTE outcome using Cox proportional hazards regression modeling with robust SEs.[19] Adjusted probability curves for LTE based on the average of covariate vectors across 3 risk groups were displayed across age in years using baseline β-blocker therapy before age 10 years instead of time-dependent β-blocker therapy.[20] All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

RESULTS

Baseline Clinical Characteristics

A total of 304 male adolescents with LQT1 and 307 with LQT2 were studied. The clinical characteristics of study patients by genotype and mutation-location groups are shown in the Table. When comparing male patients with LQT1 versus LQT2, those with LQT1 were more likely to have experienced a syncopal event before 10 years of age and been started on β-blocker therapy before 10 years of age, whereas those with LQT2 had a longer QTc. When considering the mutation location, LQT1 with C-loop mutation, as well as patients with LQT2 with a pore-loop localizing mutations, were more likely to have been treated with a β-blocker at baseline and to have experienced syncope before age 10 years.

Cardiac Events During Follow-Up

During a total follow-up duration of 9.9±2.5 years, there were a total of 270 recurrent CEs. Specifically, there were 79 CEs in 245 patients with LQT1 non-C loop mutations, 69 CEs in 59 patients with LQT1 C-loop mutations, 67 CEs in 230 patients with LQT2 and non-pore-loop mutations and 55 CEs in 77 patients with LQT2 pore-loop mutations. Overall, among the 611 male patients, 71 (12%) had 1 CE, and 57 (9.3%) had 2 or more CEs.

Development of the Risk Prediction Model for the Burden of CEs

By combining estimated beta coefficients from Andersen–Gill regression models, 16 genotype–phenotype groups were categorized into 3 risk strata. The genotype–phenotype groups within each risk stratum are shown in Figure 2 and Table S2.

The lowest risk group has the most patients (n=452 [74%]) with the majority of study population in these categories: (1) LQT1 with a non-C-loop mutation,

Table. Clinical Characteristics of the Study Population by Genotype and Mutation Location

Clinical characteristics*	LQT1		LQT2		*P* value		
	Non-C-loop (N=245)	C-loop (N=59)	Non-pore-loop (N=230)	Pore-loop (N=77)	LQT1	LQT2	All 4 groups
ECG parameters							
RR, ms†	864±214	798±253	859±255	864±227	0.058	0.830	0.305
QTc, ms	467±47	492±51	472±53	499±47	<0.001	<0.001	<0.001
QTc >500 ms	42 (17)	19 (32)	43 (19)	33 (43)	0.010	<0.001	<0.001
Prior treatment before 10 y of age							
β-blockers	58 (24)	25 (42)	48 (21)	28 (36)	0.004	0.006	<0.001
Non-selective/ selective β-blockers	43/15	22/3	35/13	28/2	0.003	0.005	<0.001
LCSD	0	0	0	0	NA	NA	NA
Pacemaker	3 (1)	0	2 (1)	4 (5)	1.000	0.037	0.070
ICD	3 (1)	1 (2)	3 (1)	4 (5)	0.580	0.069	0.133
Prior cardiac events before 10 y of age							
Syncope	38 (16)	24 (41)	19 (8)	19 (25)	<0.001	<0.001	<0.001
ACA	1 (0)	0	1 (0)	1 (1)	1.000	0.439	0.648
Appropriate ICD shock	0	0	0	1 (1)	NA	0.251	0.223
Therapies during follow-up after 10 y of age							
β-blockers	108 (44)	32 (54)	98 (43)	38 (49)	0.160	0.303	0.358
Pacemaker	2 (1)	0	6 (3)	3 (4)	1.000	0.696	0.154
ICD	18 (7)	2 (3)	12 (5)	8 (10)	0.385	0.111	0.310
LCSD	2 (1)	1 (2)	1 (0)	1 (1)	0.478	0.439	0.459
First cardiac events during follow-up after 10 y of age							
Syncope	51 (21)	26 (44)	29 (13)	18 (23)	<0.001	0.023	<0.001
ACA	1 (0)	3 (5)	2 (1)	1 (1)	0.024	1.000	0.046
Sudden cardiac death	3 (1)	0	3 (1)	1 (1)	1.000	1.000	1.000
Appropriate ICD shocks	2 (1)	0	1 (0)	3 (4)	1.000	0.050	0.110

ACA indicates aborted cardiac arrest; C-loop, cytoplasmic-loop; implantable cardioverter-defibrillator; LCSD, left cardiac sympathetic denervation; LQT1, long QT type 1; LQT2, long QT type 2; NA, not applicable; QTc, Bazett's heart-rate corrected QT value.

*Data are presented either as mean±SD or number (percentage); *P* value for selective/nonselective comparisons are among patients who were treated with β-blockers.

†RR interval is determined as the time interval (in ms) between two consecutive R waves on the surface ECG.

QTc<500 ms, and without history of syncope; (2) LQT2 with a non-pore-loop mutation, regardless of the QTc or history of syncope; and (3) LQT2 with a pore-loop mutation, QTc<500 msec, and without history of syncope.

The intermediate-risk group consisted of 86 (14%) patients with (1) LQT1 with a non-C loop mutation, and either QTc ≥500 ms or history of syncope; (2) LQT1 with C-loop mutations and QTc<500 ms without history of syncope; (3) LQT2 with a pore-loop mutation, including those with QTc<500 with history of syncope or those with QTc ≥500 ms without history of syncope. Intermediate-risk male patients experienced 2-fold increased risk of recurrent CEs when compared with those in the low-risk group (hazard ratio [HR], 2.06 [95% CI, 1.27–3.36]), Figure 2.

Of the total of 611 patients included in the analysis, 73 (12%) were identified as being at high risk for a CE. The highest-risk group included patients with: (1) LQT1 with a C-loop mutation, QTc≥500 ms, or history of syncope; (2) LQT2 with a pore-loop mutation and both QTc≥500 ms and history of syncope. The prediction model showed that, compared with the low-risk group, high-risk male patients had a 5.2-fold increased risk of recurrent CEs (HR, 5.17, [95% CI, 3.06–8.72]).

The mean cumulative CE rate according to the risk groups is presented in Figure 3. The Ghosh–Lin analysis showed that at 20 years of age, the low-, intermediate-, and high-risk male adolescents had on average 0.3, 0.6, and 1.4 events per person, respectively.

No significant interactions were found between the β-blocker therapy used in these patients and the risk

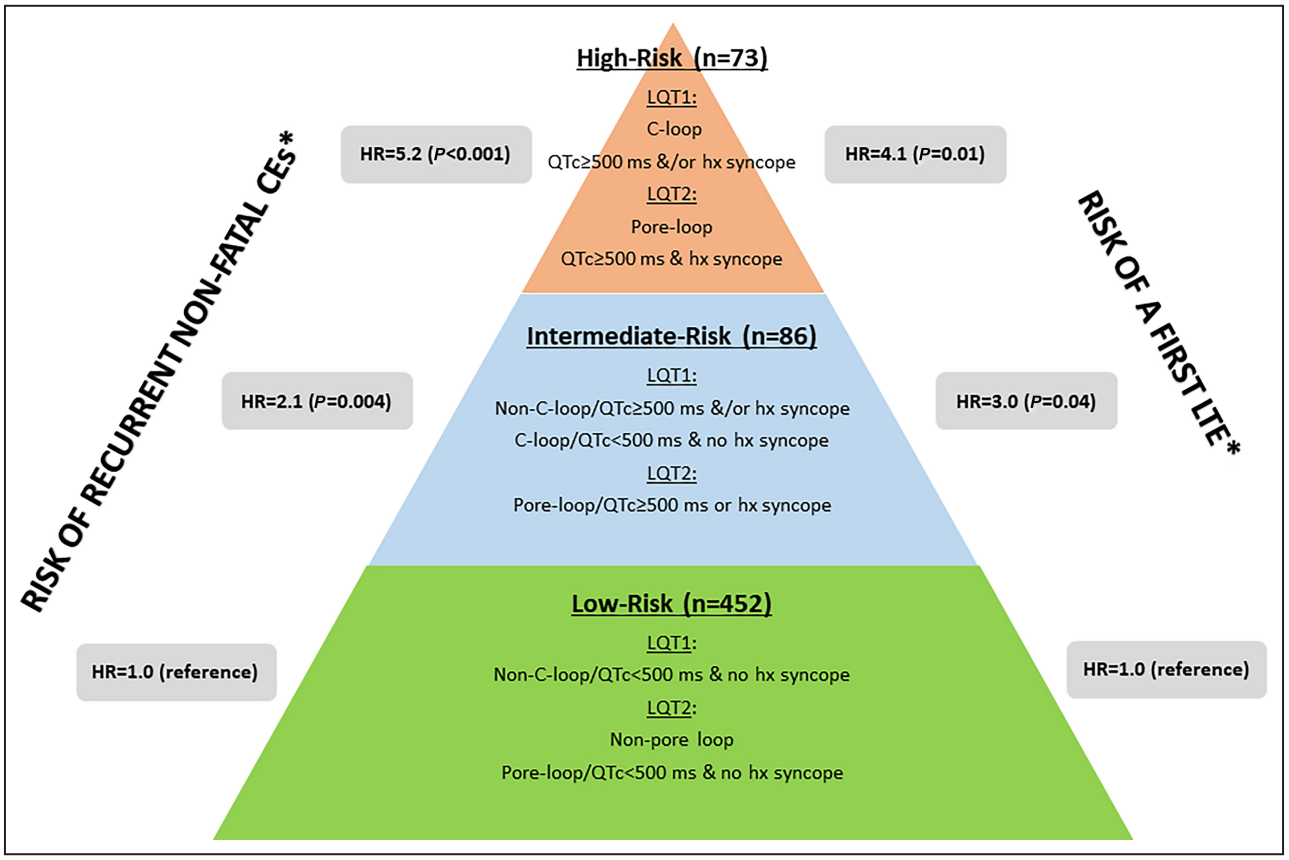

Figure 2. Risk groups for recurrent cardiac events (CEs) and first occurrence life-threatening event (LTE) in male patients with long QT syndrome.
*Findings are further adjusted for time-dependent β-blocker therapy. C-loop indicates cytoplasmic-loop; HR, hazard ratio; hx, history; LQT1, long QT type 1; and LQT2, long QT type 2.

strata (global *P* value for interaction=0.13), suggesting that allocation to the risk group is not modified by β-blocker use. Consistently, the CE burden within the 3 risk groups was similar regardless of β-blocker therapy (Table S3). Harrell's concordance statistic for the model was 0.76.

Applicability of the Risk Prediction Model for a First Occurrence of a Life-Threatening Event Including SCD

To evaluate the applicability of the risk prediction model, the model was applied to the first occurrence of LTE, which included SCD. The risk of LTE was 4.1-fold higher in the high-risk group versus the low-risk group (HR, 4.05 [95% CI, 1.36–12.05]) and 3-fold higher in the intermediate-risk group versus the low-risk group (HR, 3.03 [95% CI, 1.04–8.86]). There was no significant interaction between β-blocker use and the risk strata with respect to LTEs. These results were consistent with those observed for CEs. The 10-year prediction of an LTE after age 10 of the low-, intermediate-, and high-risk groups were 2%, 6%, and 8%, respectively, Figure 4.

DISCUSSION

This is the first study to describe risk stratification of male adolescents with potassium channel-mediated congenital LQTS founded on a combined assessment of genotype and phenotype data. In this study, we focused on a novel and clinically relevant end point for risk stratification, namely the burden of CEs during the high-risk adolescence period, rather than the risk of a first event. In addition, we further applied the risk model for the more severe end point of LTE that included tragic SCD in male adolescents with LQT1 or LQT2. Our main findings are (1) male patients with LQT1, regardless of mutation location, and male patients with LQT2 with a pore-loop mutation and phenotypic characteristics such as QTc>500 ms or prior syncope, exhibit the highest burden of recurrent events, experiencing an average cumulative number of CEs of 1.4 per person at age 20 years and a corresponding 8% chance of a LTE at age 20 years; and (2) LQT1 and LQT2 without the aforementioned high-risk mutations based on channel topology and phenotypic expression were recognized as low-risk characteristics. Such low-risk male subjects comprised the majority of the study population

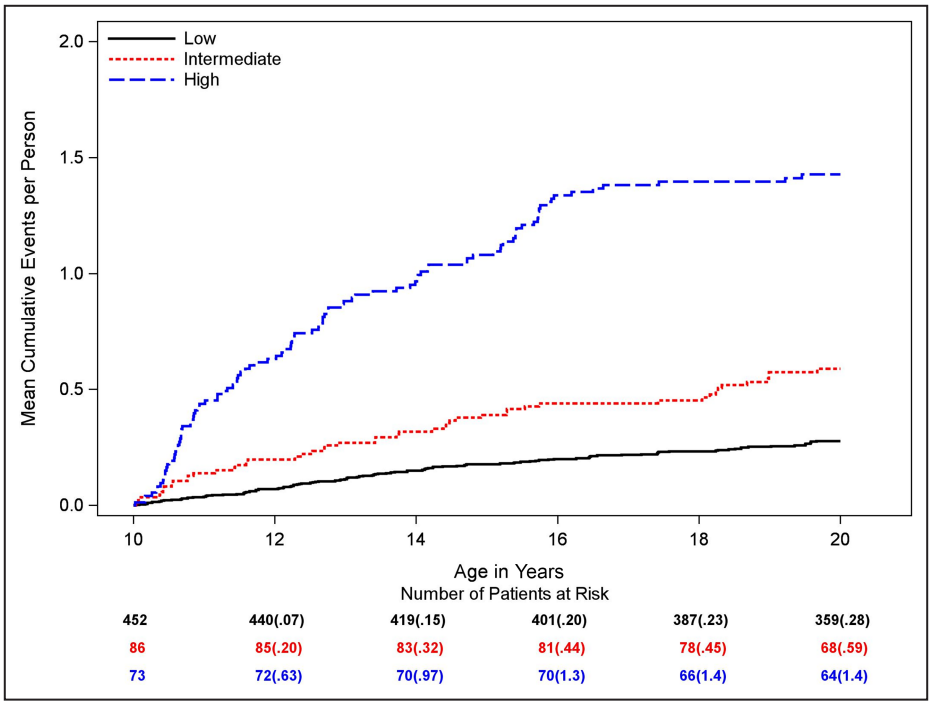

Figure 3. Time to recurrent cardiac events curves by risk group.

(74%) and had an average cumulative number of CEs of 0.3 at age 20 years and demonstrated a 10-year LTE risk of 2% after age 10 years. Recognizing sex differences in LQTS genotype expressivity and phenotype pleiotropy, a sex-specific risk-tailored approach is warranted to provide optimal management of the patient population with LQTS.

Interplay of Sex, Genotype, Mutation Location, and Phenotype

We have previously shown that C-loop mutations in the Kv7.1 ion channels, which harbor PKA (protein kinase A) phosphorylation sites under adrenergic stimulation, are associated with greater risk for CEs in patients with LQT1.[3,21] In patients with LQT2, pore-lope mutations in the Kv11.1 channels were shown to be associated with a higher arrhythmogenic potential.[4] In the present study, we extend prior data and show that adolescents with LQT1 who harbor a C-loop mutation exhibit the highest risk for CE burden and LTE despite variable phenotypic expression (ie, with or without a combination of prior syncope or a very prolonged QTc [Figure 2]). Testosterone was shown to shorten action potential duration and ventricular repolarization in male patients with LQTS, thereby reducing the propensity for CEs after the onset of adolescence.[8,9] Our findings suggest that the presence of C-loop mutations continues to increase susceptibility for arrhythmic events triggered by adrenergic stimulation in male adolescents with LQT1, despite hormonal changes. In contrast, we show that male patients with LQT2 with pore-loop mutations require the additional combination of QTc ≥500 ms and prior syncope to be identified as high risk (Figure 2). This finding may be due to the fact mutations in Kv11.1 ion channels are less affected by adrenergic activity. Therefore, additional phenotypic risk markers, beyond pore-loop location, may be required to exhibit a higher risk among male adolescents with LQT2 in the presence of the protective effects of testosterone.

In contrast to male adolescents with LQTS, our previous adolescent female-specific risk prediction model showed that the LQT2 versus LQT1 genotype is the strongest determinant of high risk for CE and LTE, regardless of the mutation location, possibly due to the more pronounced effect of female sex hormones on the Kv11.1 ion channels.[9] These data are consistent with our recent report, showing that the effect of the estrogen to progesterone ratio on QTc duration is enhanced in women with LQT2 compared with LQT1.[22]

Taken together, the findings from our previous report on risk stratification in women with LQT1 or LQT2 after the onset of adolescence,[10] and from the current study on the corresponding risk of male adolescents, suggest that risk assessment in patients with congenital LQTS after the onset of adolescence should be sex specific.

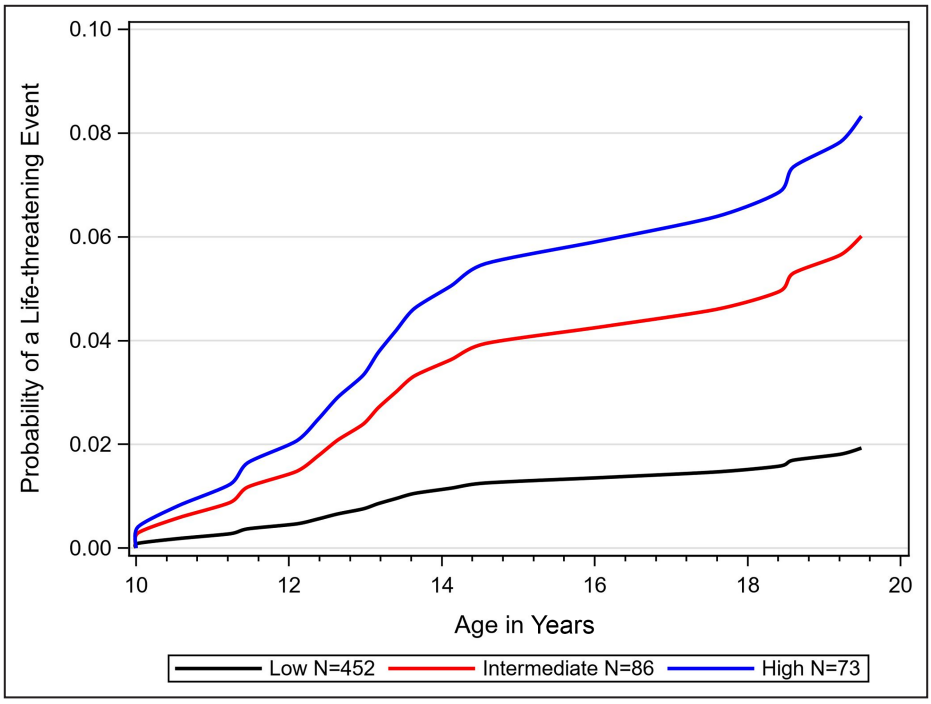

Figure 4. Adjusted risk prediction of the first occurrence of a life-threatening event from age 10 to 20 years.
Risk-adjusted for life-threatening events by risk group adjusting for mean baseline β-blocker use before age 10 for each risk group.

CE Burden as a Novel Concept for Risk Assessment in LQTS

Our understanding of the risk factors and outcomes in LQTS is based mostly on studies that have evaluated the end point of a first occurrence of CE or LTE in a binary fashion (present or absent) and have not investigated the burden of CEs in this population (defined in the present study as the total number of syncope, aborted cardiac arrest, and appropriate defibrillator shock events during follow-up). CE burden was shown to be associated with increased risk of mortality[12] and reduced quality of life in patients with LQTS. Importantly, our data show that the burden of CEs in male patients with LQT1 or LQT2 is increased after the onset of adolescence (Figure S1), which is in contrast to evidence from prior studies showing that the risk of a first CE and LTE is attenuated during this time period in male patients due to the protective effects of testosterone on the cardiac potassium channel.[5–7] These data stress the importance of CE burden assessment in men and women with LQTS, which may be different than the risk determined solely for the end point of a first CE.

β-Blocker Therapy

We have previously shown that the efficacy of β-blockers in preventing a first CE is more pronounced in patients with LQT1 and C-loop mutations, which are associated with PKA response to adrenergic stimulation[3] (although β-blockers were not shown to alter QTc during exercise in these patients[23]). In the present study, allocation to the risk group was not modified by β-blocker use when assessing the risk of recurrent CEs. This may possibly be because once a patient with LQTS experiences a first CE despite β-blocker treatment, the risk of subsequent events is not modified by continued treatment with the same drug (even among patients who are more likely to respond to the drug, such as patients with LQT1 and C-loop mutations). Therefore, following a first CE despite β-blocker treatment, verification of appropriate β-blocker drug, dose optimization, and validation of adherence to β-blocker therapy should be performed. Importantly, based on the apparent lack of signal of therapeutic efficacy with β-blocker therapy in this registry-based cohort and the very low event rates reported in large, single-center observation studies that use almost exclusively the nonselective β-blockers of either nadolol or propranolol, we would discourage the use of β-blockers like metoprolol and atenolol for the treatment of patients with LQTS.

Of note, in the present registry-based cohort, the rate of β-blocker use at baseline (age 10 years) was relatively low (26%), and selective agents were used at a relatively high rate (20%; Table). Furthermore, nearly half of recurrent CE in the present study occurred while patients were off β-blocker therapy at the time of the

event (Table S3); and among those who were treated with a β-blocker at the time of the CE, 34% received either a selective agent (most commonly atenolol) or lower than recommended dosages of nonselective β-blockers for LQTS (mean dose of nadolol: 44 mg/d, propranolol: 102 mg/d). These data further highlight the importance of appropriate β-blocker selection and dosing in patients with congenital LQTS.[24]

A Novel Scheme to Identify Low- and High-Risk Patients With LQTS and Mutations in the Potassium Cardiac Channel and Management Implications

More accessible cascade genetic screening for LQTS has led to a 2-fold increase in the number of patients with so-called normal ECG LQTS, alternatively referred to as electrocardiographically concealed LQTS.[25] Approximately one-fourth of patients with genetically confirmed LQTS have a resting QTc residing in the normal range of QTc values; therefore, a low probability of LTEs.[26] LQTS diagnosis portending SCD risks could carry significant mental distress to the patients. Given this, a risk stratification approach is warranted to enable optimal management of patients with LQTS. Figure 5 shows a summarization of our results with their potential treatment implications and possible interventions for consideration. The highest risk patients may require treatment intensification beyond β-blocker therapy.[24] Although there did not appear to be demonstrable effect of β-blocker therapy on the end points of CE or first occurrence LTE, the profound heterogeneity of β-blocker therapy used among these 611 male patients from the plethora of physicians treating these patients and the nature of this registry-based study may have prevented the clear experiential and demonstrated superiority of the nonselective β-blockers of nadolol and propranolol to emerge. Accordingly, for patients with recurrent CEs while apparently on β-blocker therapy, we recommend stepwise treatment intensification, consisting of

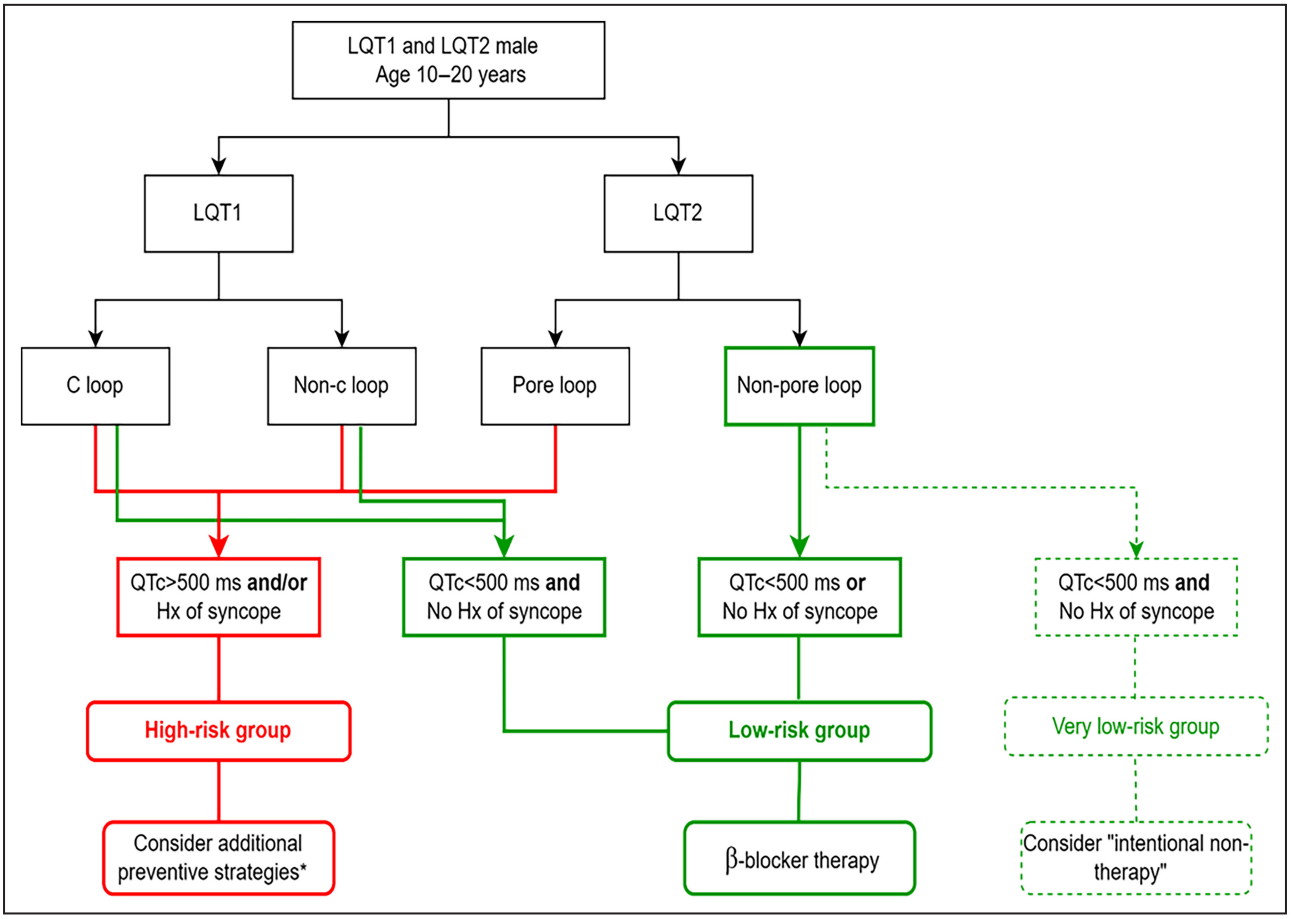

Figure 5. A novel scheme to identify low- and high-risk male adolescent patients with LQTS and mutations in either the Kv7.1 (LQT1-associated) or Kv11.1 (LQT2-associated) cardiac potassium channels and management implications.
*Stepwise treatment intensification in high-risk patients: (1) verification of appropriate β-blocker drug (nadolol or propranolol), β-blocker dose, and medication adherence; (2) intensification with left cardiac sympathetic denervation (LCSD); (3) intensification with mexiletine as combination drug therapy with β-blocker (LQT2); (4) use of intentional atrial pacing therapy (LQT2); and (5) ultimate SCD counterattack with an implantable cardioverter-defibrillator (ICD). C-loop indicates cytoplasmic-loop; Hx, history; LQT1, long QT type 1; LQT2, long QT type 2; LQTS, long QT syndrome; and SCD, sudden cardiac death.

verification of an appropriate β-blocker drug (nadolol or propranolol), dose, and adherence first and foremost, followed with left cardiac sympathetic denervation if the CE occurred while adherent with a decent dose of 1 of those 2 β-blockers,[27] then the addition of mexiletine in patients with LQT2,[28] atrial pacing (especially in patients with LQT2),[29] and lastly consideration of implantable cardioverter-defibrillator implantation.[30] Among the aforementioned management strategies, the importance of using only nonselective β-blocker with proven efficacy at target dosages, as well as the early use of left cardiac sympathetic denervation in case of a recurrent CE while on appropriate β-blocker therapy, should be stressed to avoid the need for long-term device therapy (and its associated complications) in this medically manageable inherited arrhythmic disorder.

On the other hand, we have shown that male adolescents without high-risk mutation- locations and phenotypic characteristics (ie, without prior syncope and with QTc<500 ms) are at very low risk for recurrent CEs (Table S2). The concept of "an intentional nontreatment strategy" was recently proposed by Ackerman and his team, wherein only preventative measures that may be considered for these patients.[31] As the quality of life of patients with LQTS is significantly disrupted,[32,33] this scheme could guide clinicians and patients for informed shared-decision making and potentially alleviate some of the distresses coming with receiving the LQTS diagnosis. The specific impact of these treatments when targeted in this manner toward these identified patient groups merits further investigation.

Future Directions

The LQTS genotype–phenotype approach presents one of the best efforts toward precision medicine. Sex-specific risk stratification models can help us identify patients with the lowest and highest risk for LTEs. However, the intermediate-risk category represents significant room for improvement. Further stratification within the intermediate-risk group would help delineate which patients required escalation of therapy or closely monitored. Additionally, the potential incorporation of broadly available Food and Drug Administration-approved mobile ECG applications in the surveillance of very low- or low-intermediate risk patients could help us detect ECG changes and timely referral to risk stratification reassessment and appropriate management.

Limitation

This study has several limitations that should be considered while interpreting the findings. First, we did not examine the direct interaction of sex hormones and the different potassium channel mutation location. Second, without external validation, the proposed risk stratification scheme should be considered as a proof of concept. Third, the number of LTEs in the present study population was relatively low (n=68). Nevertheless, our data show that the identified risk groups that were developed for the recurrent end point of the burden of CEs are applicable to the more severe, and potentially tragic, end point of the first occurrence of an LTE, which rarely included not only LTEs but tragically life-ending ones also.

CONCLUSIONS

This is the first risk prediction model that provides risk estimates for recurrent CEs and the occurrence of a sentinel LTE, including death after diagnosis, in male adolescents with either LQT1 or LQT2 based on personalized genotype–phenotype data. Our prediction model shows that the 10-year predicted risk of LTEs after age 10 years increases from 2% to 6% to 8% in the low-, intermediate-, and high-risk groups, respectively. These projected risk estimates can be used to guide sex-specific management in LQTS.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
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