Interplay Between Genetic Substrate, QTc Duration, and Arrhythmia Risk in Patients With Long QT Syndrome

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Abstract

Background Long QT syndrome (LQTS) is a common inheritable arrhythmogenic disorder, often secondary to mutations in the *KCNQ1*, *KCNH2*, and *SCN5A* genes. The disease is characterized by a prolonged ventricular repolarization (QTc interval) that confers susceptibility to life-threatening arrhythmic events (LAEs).

ObjectivesThis study sought to create an evidence-based risk stratification scheme to personalize the quantification of the arrhythmic risk in patients with LQTS.

MethodsData from 1,710 patients with LQTS followed up for a median of 7.1 years (interquartile range [IQR]: 2.7 to 13.4 years) were analyzed to estimate the 5-year risk of LAEs based on QTc duration and genotype and to assess the antiarrhythmic efficacy of beta-blockers.

ResultsThe relationship between QTc duration and risk of events was investigated by comparison of linear and cubic spline models, and the linear model provided the best fit. The 5-year risk of LAEs while patients were off therapy was then calculated in a multivariable Cox model with QTc and genotype considered as independent factors. The estimated risk of LAEs increased by 15% for every 10-ms increment of QTc duration for all genotypes. Intergenotype comparison showed that the risk for patients with LQT2 and LQT3 increased by 130% and 157% at any QTc duration versus patients with LQT1. Analysis of response to beta-blockers showed that only nadolol reduced the arrhythmic risk in all genotypes significantly compared with no therapy (hazard ratio: 0.38; 95% confidence interval: 0.15 to 0.93; p = 0.03).

Conclusions The study provides an estimator of risk of LAEs in LQTS that allows a granular estimate of 5-year arrhythmic risk and demonstrate the superiority of nadolol in reducing the risk of LAEs in LQTS.

Key Words: beta-blockers**;** genetics**;** inherited arrhythmias**;** life-threatening arrhythmic events**;** long QT syndrome**;** sudden cardiac death

Abbreviations and Acronyms

CI confidence interval
HR hazard ratio
LAE life-threatening arrhythmic event
LQTS long QT syndrome
QTc corrected QT interval
RCS restricted cubic spline

The genetic background of long QT syndrome (LQTS), an inherited disease that predisposes young patients to sudden cardiac death (1), was largely discovered between 1995 and 1996 when Mark Keating's laboratory identified the first 3 genes associated with the disease: *KCNQ1* (LQT1) (2), *KCNH2* (LQT2) (3), and *SCN5A* (LQT3) (4).

In the first 10 years after the discovery of these major LQTS genes (1995 to 2006), efforts were dedicated to identifying novel mutations and characterizing their functional effect. These studies paved the way for the development of the contemporary risk stratification strategy in LQTS, which is based on the early evidence that arrhythmic risk is modulated by the duration of corrected QT (QTc) interval and the genetic substrate 5, 6. In the following decade (2007 to 2017), next-generation sequencing allowed for the identification of novel genes and established genetic testing as a pivotal element in the clinical management of patients. As of today, 17 genes have been associated with LQTS, although the majority of patients carry mutations in 3 genes: *KCNQ1*, *KCNH2*, or *SCN5A* (7). Despite the innovation introduced by genetic screening, the

management of patients has advanced slowly, and the target of a personalized approach to treatment has not yet achieved a level of evidence sufficient for its incorporation in the guidelines for critical practice.
In the present study, we analyzed data from our cohort of 1,710 patients with LQTS to characterize the diversity of clinical manifestations of the disease, propose a granular model for the assessment of arrhythmic risk, and compare the effect of different beta-blockers in reducing the occurrence of life-threatening arrhythmias. This latter point has a high clinical relevance, because even though nadolol is the treatment recommended by several tertiary referral centers (8), no evidence-based data exist on whether it is superior to other beta-blockers in reducing the occurrence of sudden cardiac death and cardiac arrest.

Methods

Study population

The study was conducted on 1,710 individuals from 812 families followed up at our clinics and genotyped as carriers of a single mutation in one of the major LQTS genes: *KCNQ1*, *KCNH2*, or *SCN5A*. Patients who were carriers of double mutations (e.g., those with Jervell and Lange-Nielsen syndrome) and those who carried genetic variants adjudicated as benign or likely benign according to the criteria proposed by the American College of Medical Genetics and Genomics (9) were excluded from the current study. Clinical data were filed in a custom-made registry and included demographic information, personal and family history of symptoms, arrhythmic events, electrocardiographic parameters, and therapies at enrollment and during follow-up.
For the measurement of electrocardiographic parameters, we adopted the methodology introduced by the Long QT Syndrome International Registry (10) that is now largely adopted in the field (11). Accordingly, we obtained the first available 12-lead electrocardiogram (paper speed 25 mm/s and voltage settings 10 mm/mV) before therapy when accessible, at stable heart rates close to 60 beats/min during daylight hours to limit the confounding effect of diurnal variability of QT interval (12). The QT interval duration was measured in lead DII or V5 and corrected for the heart rate using the Bazett formula.
The study protocol was approved by the ethics committee of the IRCCS (Institute for Research and Health Care), ICS (Clinical Science Institute) Maugeri, Pavia, Italy. All patients or their guardians provided written consent to grant access to their clinical data for investigational purposes.

Genetic analysis

Genetic analysis was performed at our institution, either by Sanger sequencing (ABI PRISM 330, Thermo Fisher, Waltham, Massachusetts) or next-generation sequencing (Ion Torrent Personal Genome Machine, Thermo Fisher, Waltham, Massachusetts) on the 3 key genes associated with LQTS, in accordance with the current recommendations (13). The genetic variants included in the study were evaluated independently by 2 groups (Molecular Cardiology Laboratory at ICS Maugeri and Health in Code, La Coruña, Spain) according to the criteria proposed by the American College of Medical Genetics and Genomics (9). Eighty-nine percent of patients included in the study had a pathogenic or likely pathogenic mutation, and 11% of patients had a variant of uncertain significance.

Statistical analysis

Statistical analysis (V.B., E.P.) was performed with SAS version 9.4 (SAS Institute, Cary, North Carolina). Data are expressed as percentage or mean ± SD. Continuous variables were compared with unpaired Student's *t*-test, and categorical variables were compared with the chi-square test.
The cumulative incidence of a first life-threatening arrhythmic event (LAE) (sudden cardiac death, aborted cardiac arrest, and hemodynamically nontolerated polymorphic ventricular tachycardia) during follow-up was defined from the date of LQTS diagnosis to the first LAE. Deaths attributable to nonarrhythmic causes were considered competing events. In instances with no events, the observation was censored at the last visit. The Gray test was used to assess the difference in the cumulative incidence of the first LAE between subgroups of patients (14). Multivariable Cox proportional hazards models were used to evaluate the effects of sex, genotype, QTc duration, history of LAEs before diagnosis of LQTS, occurrence of syncope, and beta-blocker therapy on the risk of experiencing an LAE.
Initiation of beta-blocker therapy was considered a time-dependent covariate in the models to account dynamically for patients who initiated, switched, or stopped beta-blocker therapy. The effects of nadolol, propranolol, and selective beta-blockers (i.e., metoprolol, atenolol, bisoprolol, carvedilol, nebivolol) were compared with no beta-blocker use. The occurrence of syncope during follow-up was also treated as a time-dependent covariate. The heterogeneity of sex, QTc duration, syncope, and beta-blocker therapy effects on risk of LAEs among genotypes was assessed by including interaction terms between the

factor of interest and the genotype in expanded Cox models. In cases with 2 or fewer events among strata, the exact Poisson regression model was used. A robust sandwich estimator for the covariance matrix of the Cox regression coefficients was used to adjust for clustering caused by the inclusion in the cohort of probands and members of the same family.

Departure from linearity in the relationship between QTc duration (treated as a continuous variable) and the hazard of an LAE was investigated with restricted cubic spline (RCS) models (15). Briefly, an RCS describes the relationship between a response variable and a continuous covariate using smoothly joined piecewise cubic polynomials, which were restricted to be linear in the tails. The likelihood ratio test was used to determine whether the RCS model significantly increased the likelihood function compared with a simpler model that assumed a linear relationship.

We estimated the cumulative incidence of a first LAE after initial diagnosis of LQTS, while not taking beta-blockers, by QTc duration and genotype. The cumulative incidence was derived from the regression coefficients from a multivariable Cox model that included QTc duration (10-ms increments) and genotype as covariates and from the baseline cumulative hazard function calculated with the Breslow estimator (16). Only periods free of beta-blocker therapy were considered. These periods were defined as time lags during which interruption of treatment was related either to patient's decision, other physicians' suggestion, or contraindication for concomitant medical conditions (such as depression).

For all analyses, 2-tailed p values were calculated with significance set at $p < 0.05$.

Results

LQTS phenotypical manifestations in the post-genomic era

The characteristics of the 1,710 patients with LQTS are presented in Table 1. Interestingly, in this cohort, the mean QTc interval was significantly shorter than in our previously published data (17) (QTc interval 471 ± 45 ms vs. 492 ± 47 ms; $p < 0.0001$). This apparent discrepancy can be explained by dividing the patients into 3 groups according to the date of diagnosis: before 1995 (n = 129), between 1995 and 2006 (n = 836), and between 2007 and 2016 (n = 745) and comparing the mean QTc changes across the 3 periods. As shown in Online Table 1 and Online Figure 1, over time the cohorts presented with shorter mean QTc intervals ($p < 0.001$), smaller proportions of patients with a QTc interval ≥500 ms ($p < 0.001$), and lower probabilities of experiencing an LAE after 5 years of follow-up ($p = 0.005$). Conversely, the percentage of patients with concealed LQTS (QTc interval ≤460 ms) increased significantly ($p < 0.001$). Overall, patients with concealed LQTS constituted 42% of the population in the study (Table 1), and compared with patients with the overt form of the disease (QTc interval >460 ms), they showed a different genotype distribution, with an increased share of LQT1 and a reduced proportion of LQT2 and LQT3 ($p < 0.001$). Furthermore, patients with concealed LQTS displayed a minimal arrhythmic risk, with an annual rate of LAEs of 0.088% versus 0.72% in the overt LQTS group ($p < 0.001$). During follow-up, only 5 of 719 patients with concealed LQTS (0.7%) experienced an LAE (3 LQT2, 1 LQT1, 1 LQT3), compared with 63 of 991 patients with overt LQTS (6.4%; 14 LQT1, 31 LQT2, 18 LQT3; $p < 0.001$). Of note, all 5 patients with concealed LQTS who experienced an LAE during follow-up had elected not to be treated.

Table 1. Characteristics of the Study Population (N = 1,710) by QTc Duration at Diagnosis

	Overall Population (N = 1,710)	Baseline QTc Duration ≤460 ms (n = 719)	Baseline QTc Duration >460 ms (n = 991)	p Value
Female sex	893 (52)	314 (44)	579 (58)	<0.001
Genotype				
LQT1	963 (56)	452 (63)	511 (52)	<0.001
LQT2	551 (32)	198 (27)	353 (36)	
LQT3	196 (12)	69 (10)	127 (13)	
QT interval, ms	471 ± 45	436 ± 21	497 ± 39	<0.001

	Overall Population (N = 1,710)	Baseline QTc Duration ≤460 ms (n = 719)	Baseline QTc Duration >460 ms (n = 991)	p Value
Symptoms				
History of LAEs before diagnosis	71 (4)	5 (1)	66 (7)	<0.001
History of syncope	269 (16)	64 (9)	205 (21)	<0.001
Follow-up duration	9 ± 7	8 ± 6	9 ± 8	0.0048
Annual rate of LAEs at follow-up	0.47	0.088	0.72	<0.001

Values are n (%) or mean ± SD. Patients were divided according to duration of QTc interval. Patients diagnosed after genetic screening whose QTc intervals were ≤460 ms were included in the concealed LQTS group (n = 719). Conversely, patients with QTc duration >460 ms were included in the overt LQTS group (n = 991). LAE = life-threatening arrhythmic event; LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2; LQT3 = long QT syndrome type 3; LQTS = long QT syndrome; QTc = corrected QT interval.

To determine whether concealed LQTS was associated with specific mutations, we identified all mutations with 6 or more carriers and observed the QTc interval duration among patients. As depicted in Figure 1, all mutations (except for G628S in the *KCNH2* gene) were present in at least 1 patient with concealed LQTS, which suggests that the severity of the functional modification caused by a mutation is not the sole determinant of QTc duration.

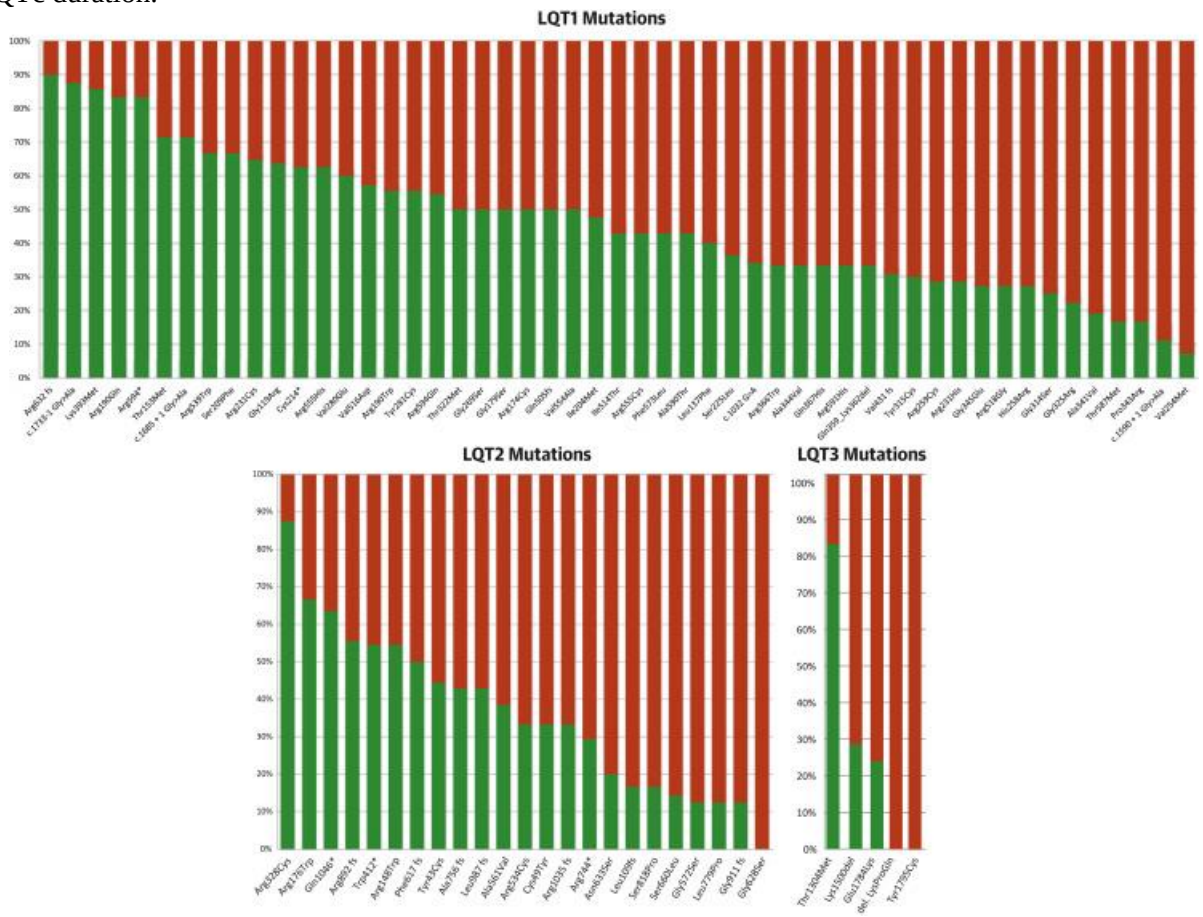


Figure 1. Penetrance of LQT Syndrome Phenotype According to Genotype

The penetrance of LQT syndrome phenotype was calculated for each mutation for which the study population included ≥6 carriers. The proportion of patients with overt LQT syndrome is illustrated in **red**, whereas the percentage of patients with concealed LQT syndrome is depicted in **green**. LQT = long QT.

Dissecting the relationship between QTc interval, genotype, and risk of LAEs

As a next step, we analyzed the correlation between QTc interval duration and the risk of LAE in a subset of 1,070 treatment-naïve patients who experienced 29 LAEs over 5,150 person-years of observation. We first explored whether the relationship between QTc interval and the hazard of LAEs would be better represented by a linear or a nonlinear function. As shown in Online Figures 2A and 2B, the nonlinear function failed to significantly improve the fit of the model; therefore, we adopted the linear function to represent the relationship between the hazard of experiencing an LAE and the duration of QTc interval in the absence of beta-blockers. We then assessed whether the correlation between QTc duration and LAEs was affected by genotype, and we observed that the relationship was similar in all 3 genotypes (p for interaction = 0.09). These results suggest that both genotype and QTc duration act independently to determine the arrhythmic risk in patients with LQTS. To provide clinicians with an estimate of LAE risk in patients with overt LQTS stratified by discrete QTc values and genotype, we calculated the absolute risk of LAEs at 5 years while patients were off therapy using a multivariable Cox model that considered these 2 parameters as independent factors. As shown in Table 2, the estimated risks increased by 15% for each 10-ms increment of the QTc duration for all 3 genotypes (e.g., from 1.7% in the 481- to 490-ms group to 2.0% in the 491- to 500-ms group for LQT1). As for the intergenotype comparison, the risk for patients with LQT2 and LQT3 increased by 130% and 157%, respectively, compared with patients with LQT1 at any QTc duration (e.g., in the 481- to 490-ms category, it increased from 1.7% in LQT1 to 3.9% in LQT2 and to 4.4% in LQT3).

Table 2. Effect of QTc Duration on Risk of Experiencing LAEs at 5 Years Off Beta-Blockers Stratified by Genotype

QTc Duration, ms	LQT1		LQT2		LQT3	
	n	5-Yr Risk (95% CI), %	n	5-Yr Risk (95% CI), %	n	5-Yr Risk (95% CI), %
461–470	78	1.3 (0.3–2.3)	44	3.0 (0.8–5.2)	18	3.4 (0.7–6.0)
471–480	63	1.5 (0.3–2.7)	26	3.4 (1.0–5.8)	16	3.8 (0.8–6.8)
481–490	50	1.7 (0.4–3.0)	39	3.9 (1.3–6.5)	15	4.4 (1.0–7.7)
491–500	32	2.0 (0.5–3.5)	21	4.5 (1.5–7.4)	7	5.0 (1.2–8.7)
501–510	15	2.3 (0.5–4.0)	15	5.1 (1.8–8.3)	9	5.7 (1.3–9.9)
511–520	11	2.6 (0.6–4.6)	17	5.9 (2.2–9.5)	6	6.5 (1.5–11.3)
521–530	5	3.0 (0.7–5.2)	10	6.7 (2.5–10.7)	7	7.5 (1.7–12.9)
531–540	5	3.4 (0.7–6.0)	6	7.6 (2.9–12.2)	3	8.5 (1.8–14.7)
541–550	6	3.9 (0.8–6.9)	4	8.7 (3.3–13.8)	2	9.7 (1.9–16.8)
551–560	2	4.4 (0.8–7.9)	5	9.9 (3.7–15.7)	3	11.0 (2.0–19.2)

QTc Duration, ms	LQT1		LQT2		LQT3	
	n	5-Yr Risk (95% CI), %	n	5-Yr Risk (95% CI), %	n	5-Yr Risk (95% CI), %
>560	14	5.1 (0.8–9.1)	22	11.3 (4.1–17.9)	7	12.5 (2.1–21.9)

Increase in risk of experiencing an LAE off beta-blockers in patients with increasing QTc interval durations (10-ms increments). Estimates were based on the occurrence of 29 LAEs during 5,150 person-years of observation free from beta-blocker therapy (n = 1,070) and were calculated using a multivariable Cox model that considered genotype as a categorical covariate and QTc interval as a continuous covariate.
CI = confidence interval; other abbreviations as in Table 1.

Identification of predictors of LAEs at follow-up

We subsequently searched for additional predictors of LAEs at follow-up in a multivariable Cox model (Table 3). In addition to confirming the importance of QTc duration, we found that the following parameters were also independently associated with increased risk of experiencing a first LAE: a history of LAEs before the diagnosis of LQTS (hazard ratio [HR]: 2.56; 95% confidence interval [CI]: 1.24 to 5.29; p = 0.01), LQT2 and LQT3 genotypes versus LQT1 (HR: 2.23; 95% CI: 1.14 to 4.37; p = 0.02 and HR: 4.00; 95% CI: 1.89 to 8.47; p < 0.001), female sex (HR: 1.70; 95% CI: 1.00 to 2.88; p = 0.048), and the occurrence of syncope (HR: 2.52; 95% CI: 1.38 to 4.61; p = 0.003).

Table 3. Predictors of Arrhythmic Risk at Follow-Up

	n	Events/PY	HR	95% CI	p Value
Sex					
Male	817	21/6,630	Ref.		
Female	893	47/7,694	1.70	1.00–2.88	0.048
LQTS genotype					
LQT1	963	15/7,913	Ref.		
LQT2	551	34/4,672	2.23	1.14–4.37	0.02
LQT3	196	19/1,739	4.00	1.89–8.47	<0.001
Basal QTc duration, ms					
≤460	719	5/5,643	Ref.		
461–499	669	23/5,661	3.28	1.20–9.02	0.02
≥500	322	40/3,020	8.44	3.14–22.7	<0.001
Syncope (time dependent)					
No	*	53/13,119	Ref.		
Yes		15/1,205	2.52	1.38–4.61	0.003
BB (time dependent)					

	n	Events/PY	HR	95% CI	p Value
No BB		29/5,150	Ref.		
Nadolol		10/4,480	0.38	0.15–0.93	0.03
Propranolol		13/1,432	0.74	0.32–1.68	0.47
Selective		15/3,159	0.79	0.35–1.77	0.56
Episode of life-threatening arrhythmias before diagnosis					
No	1,639	54/13,635	Ref.		
Yes	71	14/689	2.56	1.24–5.29	0.01

Estimates from multivariable Cox regression models predicting life-threatening arrhythmic events after presentation in 1,710 patients.
BB = beta-blockers; PY = person-years; Ref. = referent; other abbreviations as in Tables 1 and 2.

*
A total of 269 patients experienced syncope before diagnosis of LQTS; 117 patients had syncope at follow-up.

Finally, we used the multivariable model to test whether treatment with different beta-blockers would influence the occurrence of an LAE. Data demonstrated that nadolol was associated with a significant 62% risk reduction (HR: 0.38; 95% CI: 0.15 to 0.93; p = 0.03) compared with no treatment; interestingly, this effect demonstrated no significant interaction with genotype (p = 0.092). Notably, neither propranolol (HR: 0.74; 95% CI: 0.32 to 1.68; p = 0.47) nor the selective beta-blockers (HR: 0.79; 95% CI: 0.35 to 1.77; p = 0.56) conferred a significant reduction in the risk of LAEs at follow-up (Table 3). Interestingly, data showed that the mean dosage of each of the 3 compounds was aligned with that reported by Abu-Zeitone et al. (18) (Online Table 2). Furthermore, we assessed whether the difference in efficacy in favor of nadolol could be confirmed in the subgroup of patients treated with therapeutic doses of nadolol, metoprolol, and propranolol, corresponding to 50% or more of the recommended daily dose (i.e., nadolol ≥0.5 mg/kg, metoprolol ≥1.0 mg/kg, and propranolol ≥1.5 mg/kg). In this group, we confirmed that patients treated with therapeutic doses of propranolol or metoprolol were at greater risk of LAE than patients treated with high doses of nadolol (HR for propranolol/metoprolol vs. nadolol: 2.77; 95% CI: 1.11 to 6.94; p = 0.03).

Discussion

A diagnosis of LQTS can cause major distress in patients and family members alike; this concern is rooted in the assumption that all individuals with the diagnosis are exposed to a high risk of sudden cardiac death. However, it is known that the risk of having an arrhythmic event is not equal for all patients (10). The challenge for clinicians resides in the ability to identify patients at lower risk of arrhythmic events versus those at higher risk. In the past 10 years, recommendations for risk stratification proposed by guidelines 19, 20, 21 have been based on evidence that patients with LQT2 and LQT3 have a greater risk of events than LQT1 patients and that individuals with QTc duration >500 ms are at higher risk than subjects with shorter QTc duration (6).
In the attempt to achieve a more refined approach to risk stratification, we analyzed data from 1,710 patients with LQTS followed up at our center and assessed the risk of developing a hard arrhythmic endpoint that included sudden cardiac death, resuscitated cardiac arrest, and hemodynamically nontolerated polymorphic ventricular tachycardia.

Evolution of LQTS: One-half of the patients have a normal QTc interval

The first observation that caught our attention was that with the increased availability of genetic testing, the percentage of individuals with concealed LQTS has increased from 23% to 50% (Online Table 1). This means

that today, clinicians are likely to find a large number of patients with concealed LQTS among their patients with LQTS, and they should be aware that as initially suggested by Goldenberg at al. (10), their arrhythmic risk is remarkably lower than in patients with overt LQTS. As shown in Table 1, patients with concealed LQTS showed an annual rate of LAEs of 0.088%, or 8 times lower than the risk of patients with prolonged QTc duration. Interestingly, we also found that the normal QTc duration in these patients was not associated with specific mutations; rather, all mutations can be found in patients with a broad range of QTc durations (Figure 1).

The interplay between QTc duration and genotype modulates arrhythmic risk in patients with overt LQTS

Guidelines for clinical practice recommend estimating arrhythmic risk in patients with LQTS based on QTc duration and genotype 19, 20, 21. Although QT measurement has been criticized for its variability and low interobserver reproducibility, it has been unanimously confirmed as a strong predictor of outcome in worldwide registries 10, 22. On the other hand, although genotype was initially heralded as the novel predictor for risk stratification, the dream of elaborating mutation-specific management strategies remains out of reach, in part because of the inexplicably variable penetrance of mutations.

On the basis of these considerations, we thought that to advance the field, we would have to sharply depart from current approaches and instead dissect the interplay between QTc duration and genotype. Convinced that the QTc duration was the pivotal element for risk stratification in LQTS, we explored the mathematical relationship between QTc interval and genotype to quantify their additive effect on the risk of LAEs before therapy. Our results provide a new model to estimate risk of LAEs in beta-blocker–naïve patients with LQTS (Table 2). This model is clinically relevant because it enables discussion with patients of their therapeutic options based on a personalized estimate of the 5-year risk of LAEs when treatment with beta-blockers is refused or adopted with poor compliance.

Refining the use of beta-blockers in LQTS

A very important modulator of the risk of LAEs in LQTS is the initiation of beta-blocker treatment, but unfortunately, whether differences exist in the reduction of risk conferred by different beta-blockers remains unclear. The International Registry of LQTS produced 2 studies 18, 23 that compared efficacy among beta-blockers that produced conflicting results, possibly because of different-sized patient cohorts. The larger study (18) included 1,530 patients with LQT1 and LQT2 treated with selective beta-blockers, propranolol, or nadolol and assessed the occurrence of a composite endpoint that included syncope, aborted cardiac arrest, and sudden death. The 4 agents produced a similar reduction of events, with HRs between 0.70 and 0.50 compared with patients without therapy. The study supported the superiority of nadolol among patients with LQT2, but it was not designed to address the response of patients with LQT3. Other major limitations were the small cohort of only 259 patients treated with nadolol and the inclusion of syncope among the endpoints. Wilde et al. (11) reported data on an international cohort of patients with LQT3, but despite the fact that 391 patients were included in the study, the event rate at follow-up was low, especially among males. Consequently, it was only possible to demonstrate the efficacy of beta-blockers in preventing arrhythmias in females, and the study was not powered to provide a conclusive answer on whether beta-blockers were effective in preventing life-threatening events in patients with LQT3 regardless of sex. Accordingly, the most relevant finding of the study is the documentation of the absence of adverse events (proarrhythmic events) related to beta-blockers in LQT3, which finally removes the concern that has prevented the use of beta-blockers in patients with LQT3 for decades (24).

Recently, a meta-analysis on the efficacy of beta-blockers in LQT1, LQT2, and LQT3 was published (25). Despite the fact that this study pulled data from the largest LQTS registries in the world, it was not able to provide a conclusive statement on the role of beta-blockers in LQT3. The reason for this unexpected failure lies in the fact that data on patients with LQT3 were limited to 2 studies published by Moss et al. (26) in 2000 and by Priori et al. (17) in 2004: the 2 studies represented a small population of patients with LQT3 in whom 20 events occurred off therapy and 13 on therapy. On these bases, the authors concluded that the meta-analysis was underpowered to assess the efficacy of beta-blockers in LQT3. Interestingly, however, they confirmed the finding by Wilde et al. (11) that no signal of the occurrence of proarrhythmic events was detected, which confirms that there is no evidence to contraindicate the use of beta-blockers in LQT3.

This brief overview highlights the paucity of data available in the medical literature about the efficacy of beta-blockers in patients with LQT3. Our study, by providing single-center data comparing the occurrence of LAEs over a total observation period of 4,480 person-years among patients taking nadolol to 5,150 person-years

among patients who were off therapy, documents the efficacy of nadolol 0.9 mg/kg/day in preventing the occurrence of life-threatening arrhythmias in all 3 genotypes and represents the first demonstration of the efficacy of a beta-blocker in patients with LQT3. Furthermore, the evidence provided in our study of the superiority of nadolol over the other beta-blockers in preventing life-threatening events highlights the need to ensure that nadolol remains on the market and is available worldwide as the first choice of treatment for patients with LQTS.

A novel scheme to estimate 5 year-risk of LAEs

Current risk-stratification methods for LQTS are based on a correct but coarse set of parameters 19, 20, 21. Accordingly, clinicians who are tasked with determining treatment for patients have to base their decision on few elements, such as the higher risk associated with having a QTc duration >500 ms and LQT2 or LQT3 genotypes. More refined distinctions, such as determining who is at higher risk between an LQT1 patient with QTc duration of 540 ms and an LQT2 patient with QTc duration of 490 ms, are not supported by evidence-based data. The risk-stratification scheme derived from our cohort allows a more detailed assessment of risk based on the integration between QTc duration and genotype.

As a first step, patients with LQT1, LQT2, and LQT3 with QTc duration ≤460 ms should be regarded as a subset with a benign outcome, so no further risk stratification based on QTc duration and genotype is indicated, although avoidance of drugs that prolong QT-interval duration should be strictly indicated. For patients with overt LQT1, LQT2, or LQT3, the scheme that we propose could enable estimation of the risk of life-threatening arrhythmias before therapy with a 10-ms QTc granularity and the identification of the likelihood of LAEs for each combination of QTc duration and genotype (Figure 2, Central Illustration).

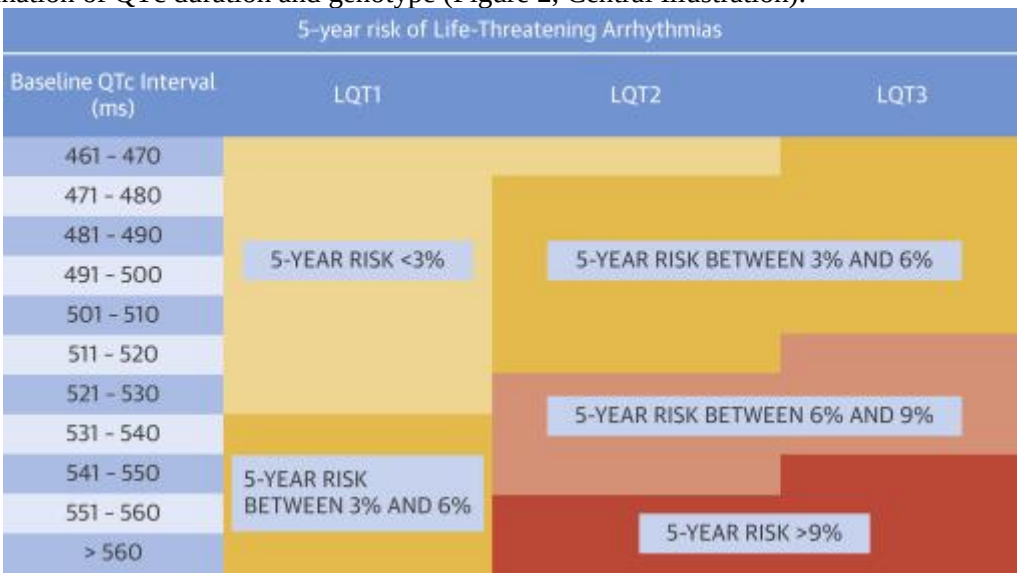
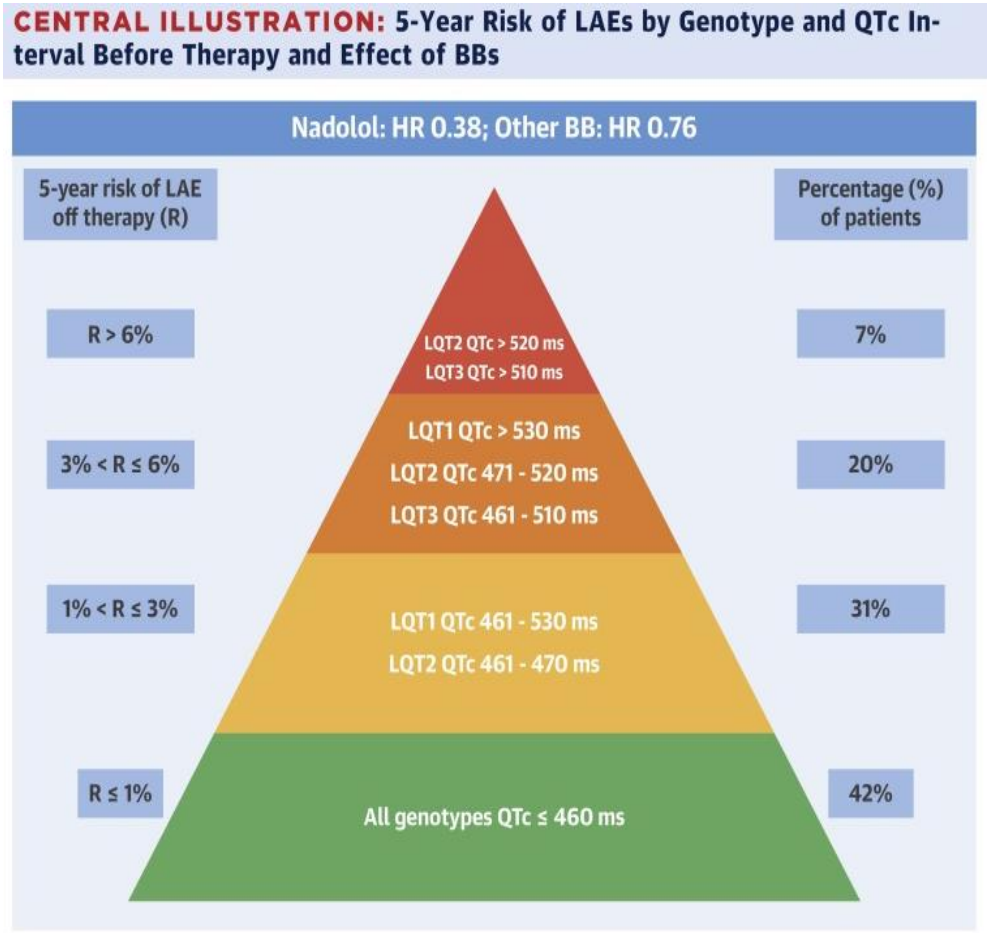


Figure 2. 5-Year Risk of Life-Threatening Arrhythmic Events by Genotype for Each 10-ms Increment of QTc Duration for Patients Who Are Not Receiving Beta-Blockers

Visualization of the 5-year relative risk for patients with each genotype and for each QTc duration. The 4 colors group patients within the same 5-year risk of life-threatening arrhythmic events. This scheme can be used to personalize the risk estimate of patients at diagnosis in the absence of beta-blocker therapy and to estimate the risk of life-threatening arrhythmic events in patients who are not compliant with treatment. QTc = corrected QT interval.



Central Illustration. 5-Year Risk of LAEs by Genotype and QTc Interval Before Therapy and Effect of BBs Visualization of 5-year risk of LAEs by genotype and QTc interval before and after therapy according to models derived from the patient population of the present study. The **column to the left** indicates the cutoff of the 5-year risk of LAEs that corresponds to each color-coded group of patients characterized by QTc duration and genotype (from **green** [lower risk] to **red** [higher risk]). The **column to the right** indicates the percentage of patients in each color-coded category present in the cohort. The **bar on the top** shows the HR of patients treated with nadolol (HR: 0.38) and other BBs (selective BBs and propranolol; HR: 0.76) and can be used to estimate the residual risk for each group of patients when treated with BBs. BB = beta-blocker; HR = hazard ratio; LAEs = life-threatening arrhythmic events; QTc = corrected QT interval.

Finally, on the basis of our analysis of outcomes at follow-up (Table 3), it is possible to integrate the HRs for different beta-blockers (Central Illustration) into our risk-stratification scheme, thereby enabling physicians to explore residual risk during treatment with nadolol, propranolol, or selective beta-blockers and to determine whether an implantable cardioverter-defibrillator is needed in addition to pharmacological therapy.

Study limitations

Our study presented limitations inherent to registries. Specifically, at variance with prospective studies that have a short duration, registries enroll patients who are followed up for decades, which makes it difficult to ensure rigorous control of compliance with therapy or adherence to lifestyle recommendations, such as restriction of exercise and avoidance of stressful environments.

Conclusions

Our findings provide an estimator of risk of LAEs in LQTS that allows a granular estimate of 5-year arrhythmic risk and demonstrate the superiority of nadolol in reducing the risk of LAEs in LQTS.

Perspectives

COMPETENCY IN PATIENT CARE: In patients with LQTS, the risk of life-threatening arrhythmias increases by 15% for each 10-ms increment in QTc duration, and arrhythmic risk for those with the LQT2 and LQT3 genotypes was 130% and 157% greater, respectively, than for those with LQT1. Of the most commonly used beta-blocker drugs, only nadolol significantly reduced arrhythmic risk in all genotypes. **TRANSLATIONAL OUTLOOK:** Further studies are needed to enhance and integrate personalized risk stratification into clinical management strategies for patients with LQTS and other types of inherited arrhythmias.

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